We would like to dedicate this book
to all family physicians who deliver care in austere environments,
especially our colleagues in uniform, and the families that support them.

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Preface

Current Diagnosis & Treatment in Family Medicine is the third edition of this single-source reference for house staff and practicing family physicians who provide comprehensive and continuous care of individuals of both sexes throughout the lifespan. The text is organized according to the developmental lifespan, beginning with childhood and adolescence, encompassing a focus on the reproductive years, and progressing through adulthood and the mature, senior years.

OUTSTANDING FEATURES

- Evidence-based recommendations
- Culturally related aspects of each condition
- Conservative and pharmacologic therapies
- Complementary and alternative therapies when relevant
- Suggestions for collaborations with other health care providers
- Attention to the mental and behavioral health of patients as solitary as well as comorbid conditions
- Recognition of impact of illness on the family
- Patient education information
- End-of-life issues

INTENDED AUDIENCE

Primary care trainees and practicing physicians will find this text a useful resource for common conditions seen in ambulatory practice. Detailed information in tabular and text format provides a ready reference for selecting diagnostic procedures and recommending treatments. Advanced practice nurses and physician's assistants will also find the approach provided here a practical and complete first resource for both diagnosed and undifferentiated conditions, and an aid in continuing management.

Unlike smaller medical manuals that focus on urgent, one-time approaches to a particular presenting complaint or condition, this text was envisioned as a resource for clinicians who practice continuity of care and have established a longitudinal, therapeutic relationship with their patients. Consequently, recommendations are made for immediate as well as subsequent clinical encounters.
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We wish to thank our many contributing authors for their diligence in creating complete, practical, and readable discussions of the many conditions seen on a daily basis in the average family medicine and primary care practice. Furthermore, the vision and support of our editors at McGraw-Hill for creating this resource for primary care have been outstanding and critical to its completion.

Jeannette E. South-Paul, MD, FAAFP
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Evelyn L. Lewis, MD, MA
ESSENTIALS OF WELL CHILD CARE

Providing comprehensive medical care for children is an integral and enjoyable part of family medicine that defines a critical distinction between the family physician and other medical specialists. The provision of well child care through a series of periodic examinations forms the foundation for the family physician to build lasting relationships with entire family and their community and to establish the patient's medical home.

Better nutrition, safety methods, and immunizations have significantly improved the health of US children, but serious childhood health problems persist. Inadequate or delayed prenatal care, childhood obesity, failure to optimize intellectual potential, and poor management of developmental delay are examples of remaining critical issues. Barriers to health care such as insufficient health literacy and lack of insurance coverage compound these issues. One of the key reference guides for pediatric health promotion is the third edition of Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents, which was funded by the US Department of Health and Human Services. Bright Futures outlines a system of care that addresses basic concerns of child rearing such as nutrition, parenting, safety, and infectious disease prevention with focused attention on evidenced-based health components and interventions.

The components of routine well child care include the following:

- History taking
- Monitoring physical parameters of growth
- Developmental/behavioral assessment
- Physical examination
- Screening tests and procedures
- Anticipatory guidance
- Administration of immunizations

The underlying purpose is to identify concerns about a child’s development and to intervene with early prevention or treatment to optimize eventual capabilities. Family physicians need to comfortably identify common normal variants as well as abnormal findings that may require referral.

One widely accepted schedule for the periodicity of routine well child visits (Table 1-1) provides ample opportunities to observe the child and family at critical junctures during a child’s growth and development. The periodicity table can be downloaded for direct clinical use from http://brightfutures.aap.org/clinical_practice.html. It provides a structured framework for anticipatory guidance and developmental screening recommendations at appropriate intervals.

Any encounter, even for an acute illness, is an opportunity to update health screening, provide anticipatory guidance, and administer immunizations. Recognized problems such as growth delay can necessitate additional checkups for more intense follow-up. Supplemental visits may also be required if the child is adopted or living with surrogate parents; is at high risk for medical disorders as suggested by the pregnancy, delivery, or neonatal history; exhibits psychological disorders as suggested by speech delay, persistent temper tantrums, or poor school performance; or if the family is socially or economically disadvantaged; or if the parents request/require additional education or guidance. Table 1-2 lists some developmental “red flags” that necessitate additional visits.


GENERAL APPROACH

A general principle for well child examinations (ages, newborn to 4 years old) is to perform maneuvers from least to most invasive. Clinicians should first make observations about the child-parent(s) interaction, obtain an interval history, and then perform a direct examination of the child, reserving the
Table 1-1. Proposed schedule of routine well-child care visits.

### Recommendations for Preventive Pediatric Health Care

**Bright Futures/American Academy of Pediatrics**

Each child and family is unique; therefore, these Recommendations for Preventive Pediatric Health Care are designed for the care of children who are receiving competent parenting, have no manifestations of any important health problems, and are growing and developing in satisfactory fashion. Additional visits may become necessary if circumstances suggest variations from normal.

Developmental, psychosocial, and chronic disease issues for children and adolescents may require frequent counseling and treatment visits separate from preventive care visits. These guidelines represent a consensus by the American Academy of Pediatrics (AAP) and Bright Futures. The AAP continues to emphasize the great importance of continuity of care in comprehensive health supervision and the need to avoid fragmentation of care.

The recommendations in this statement do not constitute an exclusive or standard course of treatment or standard of medical care. Variations, taking into account individual circumstances, may be appropriate.


<table>
<thead>
<tr>
<th>AGE</th>
<th>INFANCY</th>
<th>EARLY CHILDHOOD</th>
<th>MIDDLE CHILDHOOD</th>
<th>ADOLESCENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Initial/interval</td>
<td>Initial/interval</td>
<td>Initial/interval</td>
<td>Initial/interval</td>
</tr>
<tr>
<td>Measurements</td>
<td>Length/height/size</td>
<td>Head Circumference</td>
<td>Weight for length</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>SENSORY SCREENING</td>
<td>Hearing</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>DEVELOPMENTAL/BEHAVIORAL ASSESSMENT</td>
<td>Developmental Screening</td>
<td>Autism Screening</td>
<td>Developmental Screening</td>
<td>Psychosocial/Behavioral Assessment</td>
</tr>
<tr>
<td>PROCEDURES</td>
<td>Newborn Mantoux/Hemoglobin Screening</td>
<td>Immunization</td>
<td>Hemoglobin/Hemocrit</td>
<td>Lead Screening</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tuberculosis Screening</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dysptension Screening</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cervical Dysplasia Screening</td>
</tr>
<tr>
<td>ORAL HEALTH</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>ANTICIPATORY GUIDANCE</td>
<td></td>
<td></td>
<td></td>
<td>**</td>
</tr>
</tbody>
</table>

**KEY**
- To be performed
- Risk assessment to be performed, with appropriate action to follow, if positive
- Range during which a service may be provided, with the symbol indicating the preferred age
use of any specialized instruments until the end. Some parts of the examination are best accomplished when the infant is quiet so they may be done “out of order.” Although most of the communications and decisions about the child’s health are between the physician and the parents, clinicians should attempt to communicate directly with the patient to gauge whether he or she is developmentally appropriate and to develop familiarity directly with the patient. Patient-physician communication is particularly important during adolescence to gain the patient’s trust and to assess comprehension and compliance. A child’s medical record must be kept meticulously. A checklist-based system is an efficient way to ensure completeness in physical and developmental examinations. A table or flow sheet, as found in an electronic medical record, is helpful for tracking immunizations and screening tests. Parents should be encouraged to maintain their own records, especially for immunizations and growth, for each child.

Well child care ideally begins in the preconception period. Family physicians have a unique opportunity to provide such counseling since women routinely present for gynecological examinations before and after pregnancy. Prospective parents should be counseled about appropriate nutrition, including 0.4 mg of folic acid supplementation daily for all women of childbearing age. Prior to conception, referral for genetic screening and counseling should be offered on the basis of age, ethnic background, or family history. Prescription drug and supplement use should be reviewed. Potential exposures to cigarette smoke, alcohol, illicit drugs, or chemicals such as pesticides should be discouraged strongly. Immunizations against hepatitis B, pertussis, tetanus, rubella, and varicella should be completed, and clinicians should discuss prevention of infection with toxoplasmosis, cytomegalovirus, and parvovirus B19.

Prior medical problems such as diabetes, epilepsy, depression, or hypertension warrant special management prior to conception, especially since medications may need to be changed before pregnancy. The “prenatal” visit is an opportunity to discuss occupational and financial issues related to pregnancy, to gather information about preparations for the child’s arrival, to discuss plans for feeding and child care, and to screen for domestic violence. A family’s decision about feeding the infant, often made long before the child is born, is often based on cultural beliefs and value judgments rather than medical knowledge. The prenatal visit is a good opportunity to promote breast-feeding, emphasizing the health benefits for both mother and infant. Having gained familiarity with the family’s background, the physician can dedicate visits with the newborn infant to providing parents with specific guidance about child care.


### HEALTH MAINTENANCE AND DISEASE PREVENTION

A brief developmental assessment using the Clinical Neonatal Behavioral Assessment System (CLNBAS), a neurobehavioral assessment, in the presence of the parents can educate them about the capacities of their new child. The CLNBAS consists of 18 behavioral and reflex items designed to examine newborn physiologic and motor states that have an impact on parents’ care given in relation to sleep, feeding, crying, and consolability. Furthermore, parents obtain valuable information regarding their infant’s individuality and temperament, which can enable them to adjust care to better suit the infant’s needs.

#### Nutrition (See Also Chapter 4)

During the newborn period, all mothers should be strongly encouraged to breast-feed their infants. A widely accepted goal is exclusive breast-feeding for the first 6 months of life. Vitamin D supplement (400 U/d) may be indicated for some breast-fed children. Parents who choose to bottle-feed their newborn have several choices in formulas, but should avoid cow’s milk, because of risks like anemia. Commercial formulas are typically fortified with iron and vitamin D and some contain fatty acids such as docosahexaenoic acid (DHA) and arachidonic acid (ARA) theoretically, but they are not proven to promote nervous system development. Soy or lactose-free formulas can be used, but they do not offer any specific benefit.

### Table 1-2. Developmental “red flags.”

<table>
<thead>
<tr>
<th>Age (mo)</th>
<th>Clinical Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Not turning toward sights or sounds</td>
</tr>
<tr>
<td>4-5</td>
<td>No social smiling or cooing</td>
</tr>
<tr>
<td>6-7</td>
<td>Not reaching for objects</td>
</tr>
<tr>
<td>8-9</td>
<td>No reciprocating emotions or expressions</td>
</tr>
<tr>
<td>12</td>
<td>No imitative sound exchange with caregivers</td>
</tr>
<tr>
<td>18</td>
<td>No signs of complex problem-solving interactions (following 2-step directions)</td>
</tr>
<tr>
<td>24</td>
<td>No using words to get needs met</td>
</tr>
<tr>
<td>36-48</td>
<td>No signs of using logic with caregivers Not pretending playing with toys</td>
</tr>
</tbody>
</table>

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*Serious emotional difficulties in parents or family members at any time warrant full evaluation.

An appropriate weight gain is 1 oz/d during the first 6 months of life and 0.5 oz/d during the next 6 months. This weight gain requires a caloric intake of 120 kcal/kg/d during the first 6 months and 100 kcal/kg/d thereafter. Breast milk and most formulas contain 20 cal/oz. Caregivers need to be questioned at every visit about the amount and duration of the child’s feedings. Initially, the child should be fed on demand or in some cases as for twins on a partial schedule. Solid foods such as cereals or strained, pureed baby foods such as vegetables and fruits are introduced at 4-6 months of age when the infant can support his or her head and the tongue extrusion reflex has extinguished. Delaying introduction of solid foods until this time appears to limit the incidence of food sensitivities. The child can also continue breast- or bottle-feeding, limited to 30 oz/d, because the solids now provide additional calories. Around 1 year of age when the infant can drink from a cup, bottle-feeding should be discontinued to protect teeth from caries. No specified optimum age exists for weaning a child from breast-feeding. After weaning, ingestion of whole or 2% cow’s milk may promote nervous system development.

Older infants can tolerate soft adult foods such as yogurt and mashed potatoes. A well-developed pincer grasp allows children to self-feed finger foods. With the eruption of primary teeth at 8-12 months of age, children may try foods such as soft rice or pastas.

With toddlers, mealtimes can be a source of both pleasure and anxiety as children become “fjnicky.” The normal child may exhibit specific food preferences or be disinterested in eating. An appropriate growth rate and normal developmental milestones should reassure frustrated parents. Coping strategies include offering small portions of preferred items first and offering limited food choices. Eating as a family gives toddlers a role model for healthy eating and appropriate social behaviors during mealtimes.

**Elimination**

Regular patterns for voiding and defecation provide reassurance that the child is developing normally. Newborn infants should void within 24 hours of birth. An infant urinates approximately 6-8 times a day. Parents may count diapers in the first few weeks to confirm adequate feeding. The older child usually voids 4-6 times daily. Changes in voiding frequency indicate the child’s hydration status, especially when the child is ill.

Routine circumcision of male infants is not currently recommended so parents who are considering circumcision require additional guidance. Although a circumcised boy has a decreased incidence of urinary tract infections (OR 3-5) and a decreased risk of phimosis and squamous cell carcinoma of the penis, some clinicians raise concerns about bleeding, infection, pain of the procedure, or damage to the genitalia (incidence of 0.2%-0.6%). Therefore, the decision about circumcision is based on the parents’ personal preferences and cultural influences. When done, the procedure is usually performed after the second day of life, on a physiologically stable infant. Contraindications include ambiguous genitalia, hypospadias, HIV, and any overriding medical conditions. The denuded mucosa of the phallus appears raw for the first week post-procedure, exuding a small amount of serosanguineous drainage on the diaper. Infection occurs in less than 1% of cases. Mild soap and water washes are the best method of cleansing the area. By the 2-week checkup, the phallus should be completely healed with a scar below the corona radiata. The parents should note whether the infant’s urinary stream is straight and forceful.

Newborns are expected to pass black, tarry meconium stools within the first 24 hours of life. Failure to pass stool in that period necessitates a workup for Hirschsprung disease (aganglionic colon) or imperforate anus. Later on the consistency of the stool is usually semisolid and soft, with a yellow-green seedy appearance. Breast-fed infants typically defecate after each feeding or at least two times a day. Bottle-fed infants generally have a lower frequency of stooling. Occasionally, some infants may have only one stool every 2 or 3 days without discomfort. If the child seems to be grunting forcefully with defecation or is passing extremely hard stools, treatment with lubricants like glycerin can be advised. Any appearance of blood in the stools is abnormal and warrants investigation. Anal fissure is common.

With the introduction of solid foods, stool becomes more solid and malodorous. Increased dietary intake of certain fruits, vegetables, and water often relieves constipation. Treatment of mild to moderate constipation may include the use of Karo syrup mixed in with feedings (1-2 teaspoonfuls in 2 oz of milk) or psyllium seed or mineral oil (15-30 mL) for older children. Children who are severely constipated may require referral to a gastroenterologist.

**Sleep**

An important issue for new parents is the development of proper sleeping habits for their child. Newborns and children cycle through different stages of sleep/wakefulness including deep, light, or rapid eye movement sleep; indeterminate state; wide-awake, alert state; fussy; and crying. On average, a baby goes through the states every 3-4 hours and new parents’ first job is to learn their baby’s unique style. Newborns sleep an average of 18-20 h/d.

At first, feeding the baby whenever he wakes is the most appropriate response. So the tiring nighttime awakenings are commonplace due to frequent feedings because babies often have their days and nights “reversed.” When the baby gets to be 3 or 4 weeks old, feedings can be delayed for a bit of play and interaction. Parents can try to keep the baby awake at the end of each cycle and then introduce the last feeding earlier in the evening. The goal is to space out the baby’s awake time to 3 or more hours between feedings and a long sleep at night.

By 2-3 months, baby’s pattern of sleeping and feeding should be more predictable and parents can start to institute some routines which allow the child to self-comfort.
After feeding, rocking, and soothing, parents should be encouraged to lay the baby down in the crib when he or she is quiet but not asleep. A soothing, consistent bed time ritual allows babies to learn to settle down by themselves and lays the foundation for other independent behaviors in the future.

All newborn infants should be placed on their backs to sleep to reduce the risk of sudden infant death syndrome (SIDS). Risk factors include prone and side positions for infant sleep, smoke exposure, soft bedding and sleep surfaces, and overheating. Recent studies also show that cosleeping (bed sharing) slightly increases the overall risk of SIDS and is greatest for infants less than 11 weeks old. The issue of cosleeping is often difficult to address as it is viewed as a common and necessary practice in some cultures. Evidence also suggests that pacifier use at sleep time and room sharing (without bed sharing) are associated with decreased risk of SIDS. Although the cause of SIDS is unknown, immature cardiorespiratory autonomic control and failure of arousal responsiveness from sleep are important factors. With the Back to Sleep campaign, prone sleeping among all US infants has decreased to less than 20%, and the incidence of SIDS has decreased 40%.


### Developmental/Behavioral Assessment

Watching a newborn develop from a dependent being to a communicative child with a unique personality is an amazing process that caregivers and clinicians can actively promote. Early identification of developmental disorders is critical for the well-being of children and their families. Unfortunately, primary care physicians fail to identify and appropriately refer many developmental problems, even though screening tools are available. Because the period of most active development occurs during the first 3 years, clinicians must ensure that developmental surveillance is performed and documented for every preventive care visit and at every office visit regardless of purpose. Surveillance includes asking parents if they have any concerns about their child’s development, keeping a developmental history, observing the child, identifying any risk factors for developmental delay, and accurately tracking the findings and progress. If the family shows concerns through this periodic surveillance, reassurance and reexamination is appropriate if the child is at low risk.

Table 1-3. Prevalence of developmental disorders.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Cases Per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention-deficit/hyperactivity disorder</td>
<td>75-150</td>
</tr>
<tr>
<td>Learning disabilities</td>
<td>75</td>
</tr>
<tr>
<td>Behavioral disorders</td>
<td>60-130</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>25</td>
</tr>
<tr>
<td>Autism spectrum disorders</td>
<td>2-10</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>2-3</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>0.8-2</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>0.3-0.6</td>
</tr>
</tbody>
</table>


Either as a result of concerns identified during surveillance or specifically at the 9-, 18-, 30-month visits, a formal developmental screening tool should be administered to uncover problems such as those listed in Table 1-3. These visits were chosen as they represent junctures where strides in the different developmental domains can be readily observed by parents and clinicians. Broadly, the developmental domains include fine and gross motor skills, language and communication, problem solving/adaptive behavior, and personal-social skills. These developmental tests screen children who are apparently normal, confirm any concerns the clinician may have uncovered, and offer a way to monitor children at high risk for developmental delay. Each test approaches the task of identifying children in a different way; no screening tool is universally deemed appropriate for all populations and all ages.

Between the 18- and 24-month visits, clinicians should formally screen for autism spectrum disorders (ASD). The increasing public awareness and concern about ASD has made this recommendation key. Autistic disorder is a pervasive developmental disorder resulting in social, language, or sensorimotor deficits. Incidence is approximately 6 in 10,000 persons. One-third of autistic persons can achieve some degree of independent living, making early diagnosis and intervention very important. The differential diagnosis includes other psychiatric and pervasive developmental disorders; profound hearing loss; metabolic disorders, such as lead poisoning; or associated genetic disorders, such as fragile X syndrome and tuberous sclerosis. Studies have consistently demonstrated no causal link between the MMR (measles-mumps-rubella) vaccine and autism. The M-CHAT or Modified Checklist for Autism in Toddlers is a widely used, validated autism-specific screening tool.

Table 1-4 lists several useful developmental screening tests. Although historically held to be the gold standard, the Denver Developmental Screening Test—revised requires trained personnel about 20-30 minutes of office time to administer. Proper use is not widespread in practice.
The Parents’ Evaluation of Developmental Status, the Ages and Stages Questionnaire, and the Child Development Review-Parent Questionnaire are all parent-completed tools which take less than 15 minutes to complete and may be easily used in a busy clinical practice. Shortened, customized lists of developmental milestones may result in some increased recognition of delay but should not replace periodic use of validated developmental assessment tests.

If the screening tool results are concerning, the physician should inform the parents and schedule the child for further developmental or medical evaluation or referral to pediatric subspecialists such as neurodevelopmental pediatricians, pediatric psychiatrists, speech-language pathologist, and physical and occupational therapists. Identification of an etiology through medical testing, such as genetic evaluation, serum metabolites, and brain imaging, occurs in approximately one-fourth of cases.

If screening is normal, the physician has an opportunity to focus on optimizing the child’s potential. Parents can be encouraged to read to their children on a regular basis, sing and play music, limit television altogether in toddlers and to no more than 2 hours daily for older children, and directly engage in age-appropriate stimulating activities such as exercise or game playing. Clinicians should encourage the parents and patients to report on positive behaviors and activities at every visit.


<table>
<thead>
<tr>
<th>Test</th>
<th>Age</th>
<th>Time (min)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Office Administered</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denver II</td>
<td>0-6 y</td>
<td>30</td>
<td><a href="http://www.denverii.com">www.denverii.com</a></td>
</tr>
<tr>
<td>Battelle Developmental Inventory Screening Tool (BDI-ST)</td>
<td>Birth to 8 y</td>
<td>15</td>
<td><a href="http://www.riverpub.com">www.riverpub.com</a></td>
</tr>
<tr>
<td>Brigance Screens-II</td>
<td>0-90 mo</td>
<td>15</td>
<td><a href="http://www.curriculumassociates.com">www.curriculumassociates.com</a></td>
</tr>
<tr>
<td>Bayley Infant Neuro-Developmental Screen (BINS)</td>
<td>3-24 mo</td>
<td>10</td>
<td><a href="http://www.harcourttassessment.com">www.harcourttassessment.com</a></td>
</tr>
<tr>
<td><strong>Parent Administered</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ages &amp; Stages Questionnaires (ASQ)</td>
<td>4-60 mo (every 4 mo)</td>
<td>15</td>
<td><a href="http://www.brookespublishing.com">www.brookespublishing.com</a></td>
</tr>
<tr>
<td>Parents’ Evaluation of Development Status (PEDS)</td>
<td>0-8 y</td>
<td>&lt;5</td>
<td><a href="http://www.pedstest.com">www.pedstest.com</a></td>
</tr>
<tr>
<td>Child Development Inventory (CDI)</td>
<td>18 mo-6 y</td>
<td>45</td>
<td><a href="http://www.childdevrev.com">www.childdevrev.com</a></td>
</tr>
<tr>
<td><strong>Language and Cognitive Screening</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Language Milestone (ELM)</td>
<td>0-3 y</td>
<td>5-10</td>
<td><a href="http://www.proedinc.com">www.proedinc.com</a></td>
</tr>
<tr>
<td>Capute Scales (Cognitive Adaptive Test/Clinical Linguistic Auditory Milestone Scale [CAT/CLAMS])</td>
<td>3-36 mo</td>
<td>15-20</td>
<td><a href="http://www.brookespublishing.com">www.brookespublishing.com</a></td>
</tr>
<tr>
<td>Modified Checklist for Autism in Toddlers</td>
<td>16-48 mo</td>
<td>5-10</td>
<td><a href="http://www.firstsigns.com">www.firstsigns.com</a></td>
</tr>
</tbody>
</table>


Oral Health

As other health outcomes improve, the poor state of oral health in children is now emerging as a major concern. Tooth decay remains one of the most common chronic diseases of childhood, even more common than asthma. Medically and developmentally compromised children and children from low-income families are at highest risk, and affected children remain at higher risk for cavities throughout their childhood and adulthood. To minimize the incidence of early childhood caries, children should not be put to sleep with a bottle or by breast-feeding. Parents should also be discouraged from inappropriately using the bottle or “sippy” cup as a pacifier. Dietary sugars along with cariogenic bacteria, most often acquired from the mother who should never clean off a pacifier by inserting it into her own mouth, lead to accelerated decay in the toddler’s primary teeth.

Current recommendations encourage an initial oral evaluation to establish a dental home before the first birthday, around 6-9 months of age, at least within 6 months of the eruption of the first primary tooth. Children should continue with regular biannual dental appointments thereafter. Primary prevention includes provision of a diet high in calcium and prescription of fluoride supplementation for those with an unfluoridated water supply (<0.6 ppm). Once primary teeth erupt, parents should use a soft-bristled brush or wash-cloth with water to clean the teeth at least daily. Infants should drink from a cup and be weaned from the bottle at around 12-14 months of age. Pacifiers and thumb sucking are best limited after teeth have erupted. All children, toddler to school age, need limits on the intake of high-sugar drinks and juices, especially between meals. (For further discussion and recommendations relating to oral health, see Chapter 45.)

CLINICAL FEATURES

History and Physical Examination

The prenatal and neonatal records should be reviewed for gestational age at birth; any abnormal maternal obstetric laboratory tests; maternal illnesses such as diabetes, preeclampsia, depression, or infections that occurred during the pregnancy; maternal use of drugs or exposure to teratogens; date of birth; mode of delivery; Apgar scores at 1 and 5 minutes; and birth weight, length, and head circumference. A social history should include the family structure (caregivers, siblings, etc) and socioeconomic status.

A physical examination of the newborn should include the following:

- **General observation:** Evidence of birth trauma, dysmorphic features, respiratory rate, skin discolorations, or rashes.
- **Head, ears, eyes, nose, and throat (HEENT) examination:** Mobile sutures, open fontanelles, ears, bilateral retinal red reflexes, clarity of lens, nasal patency, absence of cleft palate or lip, and palpation of clavicles to rule out fracture.
- **Cardiovascular examination:** Cardiac murmurs, peripheral pulses, capillary refill, and the presence of cyanosis.
- **Pulmonary examination:** Use of accessory muscles and auscultation of breath sounds.
- **Abdominal examination:** Masses, distention, and the presence of bowel sounds.
- **Extremity examination:** Number and abnormalities of digits and toes, and screening for congenital dislocation of the hips using Ortolani and Barlow maneuvers.
- **Genitourinary examination:** Genitalia and anus.
- **Neurologic examination:** Presence of newborn reflexes (ie, rooting, grasping, sucking, stepping, and Moro), resting muscle tone.

To track the child’s physical and developmental progress, a comprehensive interval history and physical examination is important at each encounter, even if the parents do not report concerns. The child’s weight (completely undressed), length, and head circumference (until 3 years of age) are measured and plotted on standard CDC growth charts at each visit. A child’s rate of growth will usually follow one percentile (25th, 50th, etc) from birth through school age. A child can appropriately cross percentiles upward (eg, a premature infant who then “catches up”) or inappropriately (eg, a child who becomes obese). Any child who drops more than two percentiles over any period of time may be diagnosed with failure to thrive (see Chapter 2).

By 15 months of age, children experience stranger anxiety and are much less likely to be cooperative. Clinicians can minimize the child’s adverse reactions by approaching the child slowly and performing the examination while the child is in the parent’s arms, going from least to most invasive task. Touching the child’s shoe or accompanying stuffed animal first and then gradually moving up to the chest while distracting with a toy or otoscope light is often helpful. After the first year of life, the pace of the infant’s growth begins to plateau. At the 15- to 18-month visit, the infant most likely will be mobile and may want to stand during the examination. To engage the child, the clinician should ask where to do the examination or which body part to examine first.

Beginning at 2 years of age, the body mass index (BMI) is plotted; at age 3 years the child’s blood pressure is measured. Eye examinations for strabismus allow early treatment. By age 4 or 5 years, documentation of visual acuity should be attempted. Hearing, now tested at birth, is informally evaluated until the age of 5 years, when audiometry should be attempted. At least 75% of speech in 3-year-olds should be intelligible. Speech delay should trigger referral. Physicians need to assess gait, spinal alignment, and injuries, looking particularly for signs of child abuse or neglect. Table 1-5 highlights the important components of the physical examination at each age. The examiner should concentrate on and comment on the child’s psychological and intellectual development.
Table 1-5. Highlights of physical examination by age.

<table>
<thead>
<tr>
<th>Age of Child</th>
<th>Essential Components of Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 wk</td>
<td>Presence of bilateral red reflex</td>
</tr>
<tr>
<td></td>
<td>Auscultation of the heart for murmurs</td>
</tr>
<tr>
<td></td>
<td>Palpation of the abdomen for masses</td>
</tr>
<tr>
<td></td>
<td>Ortolani/Barlow maneuvers for hip dislocation</td>
</tr>
<tr>
<td></td>
<td>Assessment of overall muscle tone</td>
</tr>
<tr>
<td></td>
<td>Reattainment of birth weight</td>
</tr>
<tr>
<td>2 mo</td>
<td>Observation of anatomic abnormalities or congenital malformations (effects of birth trauma resolved by this point)</td>
</tr>
<tr>
<td></td>
<td>Auscultation of the heart for murmurs</td>
</tr>
<tr>
<td>4-6 mo</td>
<td>Complete musculoskeletal examination (neck control, evidence of torticollis)</td>
</tr>
<tr>
<td></td>
<td>Extremity evaluation: eg, metatarsus adductus</td>
</tr>
<tr>
<td></td>
<td>Vision assessment (conjugate gaze, symmetric light reflex, visual tracking of an object to 180°)</td>
</tr>
<tr>
<td></td>
<td>Bilateral descent of testes</td>
</tr>
<tr>
<td>9 mo</td>
<td>Pattern and degree of tooth eruption</td>
</tr>
<tr>
<td></td>
<td>Assessment of muscle tone</td>
</tr>
<tr>
<td></td>
<td>Presence of bilateral pincer grasp</td>
</tr>
<tr>
<td></td>
<td>Observation of crawling behavior</td>
</tr>
<tr>
<td>12 mo</td>
<td>Range of motion of the hips, rotation and leg alignment</td>
</tr>
<tr>
<td></td>
<td>Bilateral descent of the testes</td>
</tr>
<tr>
<td>15-18 mo</td>
<td>Cover test for strabismus</td>
</tr>
<tr>
<td></td>
<td>Signs of dental caries</td>
</tr>
<tr>
<td></td>
<td>Gait assessment</td>
</tr>
<tr>
<td></td>
<td>Any evidence of injuries</td>
</tr>
</tbody>
</table>

Table 1-6. Commonly screened components of newborn screening panels.

<table>
<thead>
<tr>
<th>Diseases Screened</th>
<th>Incidence of Disease in Live Births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital hypothyroidism</td>
<td>1:4000</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>1:4500</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>1:10,000-1:18,000</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>1:14,000</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>1:30,000</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1:44,000-1:80,000 (depending on population)</td>
</tr>
<tr>
<td>Biotinidase deficiency</td>
<td>1:60,000</td>
</tr>
</tbody>
</table>

*Screening panel requirements vary in each state. Sources: Kaye CI; and the Committee on Genetics. Technical report: Newborn Screening Fact Sheets. Available at: www.pediatrics.org/cgi/content/full/118/3/1304. See National Newborn Screening Status Report (http://genes-r-us.uthscsa.edu/nbsdisorders.pdf) for complete listing of disease tests by state (accessed 6/28/09).

Screening Laboratory Tests

Every state requires newborns to undergo serologic screening for inborn errors of metabolism (Table 1-6). Requirements vary from state to state. Most institutions routinely screen newborns for hearing loss, but the US Preventive Services Task Force has not recommended for or against universal screening (Level I recommendation).

Screening for anemia with finger stick hemoglobin levels begins between the ages of 9 and 12 months. Due to the high prevalence of iron deficiency anemia in toddlers, repeat screenings has been recommended approximately 6 months after the first screening. Measurement of hemoglobin or hematocrit levels alone detects only those patients with iron levels low enough to become anemic. For this reason, some authorities recommend screening by ferritin levels or red cell distribution width (RDW) to identify iron deficiency earlier. A positive screening test is an indication for a therapeutic trial of iron to establish a diagnosis of iron deficiency. Thalassemia minor is the major differential consideration. A sickle cell screen is indicated in all African American children.

Annual lead screening begins at age 9 months to 1 year if the child is considered to be at high risk. Risk factors include exposure to chipping or peeling paint in buildings built before 1950, frequent contact with an adult who may have significant lead exposure, having a sibling who is being treated for a high lead level, and location of the home near an industrial setting likely to release lead fumes. Many agencies require a one-time universal lead screening at 1 year of age because high-risk factors are often absent in children with lead poisoning.

Tuberculosis (TB) screening using a purified protein derivative (PPD) is offered to high-risk children at 1 year of age. Routine testing of children without risk factors is not indicated. Children require testing if they have had contact with persons with confirmed or suspected cases of infectious TB, have emigrated from endemic countries (Asia or the Middle East), or have any clinical or radiographic findings suggestive of TB. HIV-infected children need to have PPD tests annually. Children at risk for HIV due to exposure to high-risk adults (HIV positive, homeless, institutionalized, etc) are retested every 2-3 years. Children without specific risk factors for tuberculosis but who live in high-prevalence communities may be retested twice: once at ages 4-6 years and again at ages 11-12 years.

A cholesterol level may be obtained after age 2 years if the child has a notable family history of early coronary artery disease. The National Cholesterol Education Program (NCEP) recommends screening in a child with a parent who has a total cholesterol of 240 mg/dL or greater or a parent or
grandparent with onset of cardiovascular disease before age 55 years. Clinical evaluation and management of the child are to be initiated if the low-density lipoprotein (LDL) cholesterol level is 130 mg/dL or greater.

Although formal audiometry and visual acuity testing can begin as early as age 3 years, failure to meet informal developmental milestones should trigger earlier referral. A screening urinalysis is not indicated.

<table>
<thead>
<tr>
<th>CONCERNS IN NORMALLY DEVELOPING CHILDREN</th>
</tr>
</thead>
</table>
The majority of child behaviors are considered to be normal if the child is growing normally and meeting developmental milestones. Anticipatory guidance can be helpful and reassuring to caregivers when their child exhibits variations from ideal behavior. Selected behavioral issues that are commonly encountered include infantile colic, temper tantrums, and reluctant toilet training.

► Infantile Colic

Colic is a term often used to describe an infant who is difficult to manage or fussy despite being otherwise healthy. Colic may be defined as 3 or more hours of uncontrollable crying or fussing at least three times a week for at least 3 weeks. Other symptoms include facial expressions of pain or discomfort, pulling up of the legs, passing flatus, fussiness with eating, and difficulty falling or staying asleep. Symptoms classically worsen during the evening hours. Because the diagnosis depends on parental report, the incidence of colic varies from 5% to 20%. It occurs equally in both sexes and peaks around 3-4 weeks of age.

The underlying cause of colic is unknown, but organic pathology is present in less than 5% of the cases. Possible etiologies include an immature digestive system sensitive to certain food proteins, an immature nervous system sensitive to external stimuli, or a mismatch of the infant’s temperament and those of caregivers. Feeding method is probably unrelated to incidence. Clinicians can provide reassurance to caregivers of children with colic by informing them that colicky children continue to eat and gain weight appropriately, despite the prolonged periods of crying and that the syndrome is self-limited and usually dissipates once the child reaches 3-4 months of age. Colic has no known long-term consequences; therefore, the main problem for caregivers is to cope with anxiety over the crying child. A stressed caregiver who is unable to handle the situation is at risk for abusing a child.

No definitive treatment can be offered for colic. Little evidence supports the use of simethicone or acetaminophen drops. Switching to a hypoallergenic (soy) formula is effective when the child has other symptoms suggestive of cow’s milk protein allergy. Breast-feeding mothers can attempt to make changes in their diets (eg, avoidance of cruciferous vegetables such as broccoli and cabbage) to see if the infant improves. Both clinicians and caregivers have proposed many “home remedies.” Reducing the amount of stimulation or sometimes changing the scenery with a car ride or walk outdoors is recommended. Frequent burping, swaddling the infant, infant massage, or the use of a crib vibrator or increasing background noise from household appliances or white noise generator have been shown to be moderately effective. Rigorous study of these techniques is difficult, but clinicians can suggest any or all because the potential harm is minimal.

► Temper Tantrums

A normal part of child development temper tantrums encompass excessive crying, screaming, kicking, thrashing, head banging, breath-holding, breaking or throwing objects, and aggression. Between the ages of 1 and 3 years, a child’s growing sense of independence is in conflict with physical limitations and parental controls and hampered because of limited vocabulary and inability to express feelings or experiences. This power struggle sets the stage for the expression of anger and frustration through a temper tantrum. Tantrums can follow minor frustrations, occur for no obvious reason, and are mostly self-limited. A child’s tendency toward impulsivity or impatience or a delay in the development of motor skills or cognitive deficits and parental inconsistency—excessive restrictiveness, overindulgence, or over reaction—may increase the incidence of tantrums. Tantrums that produce a desired effect have an increased likelihood of recurrence.

As much as possible, parents should provide a predictable home environment. Consistency in routines and rules will help the child know what to expect. Parents should prepare the child for transitions from one activity to another, offer some simple choices to satisfy the child’s growing need for control, acknowledge the child’s wants during a tantrum, and act calmly when handling negative behaviors to avoid reinforcement. Physical punishment is not advised.

Most importantly, ignoring attention-seeking tantrums and not giving in to the demands of the tantrum will, in time, decrease the recurrence. Children who are disruptive enough to hurt themselves or others must be removed to a safe place and given time to calm down in a nonpunitive manner. Most children learn to work out their frustrations with their own set of problem-solving and coping skills, thus terminating tantrums. Persistence of tantrums beyond age 4 or 5 years requires further investigation and usually includes referral or group education and counseling.

► Toilet Training

Some indicators of readiness for toilet use include an awareness of impending urination or defecation, prolonged involuntary dryness, and the ability to walk easily, to pull clothes on and off easily, to follow instructions, to identify body parts, and to initiate simple tasks. These indicators are not likely to be present until 18-30 months of age. Once the child
becomes interested in bathroom activities or in watching his or her parents use the toilet, parents should provide a potty chair. Parents can then initiate toilet training by taking the diaper off and sitting the child on the potty at a time when she or he is likely to urinate or defecate. Routine sittings on the potty at specified times, such as after meals when the gastrocolic reflex is functional, may be helpful. The child who is straining or bending at the waist may be escorted to the bathroom for a toileting trial. If the child eliminates in the potty or toilet, praise or a small reward may be given to reinforce that behavior. Stickers, storybooks, or added time with the parents can be used for motivation.

With repeated successes transitional diapers or training pants may be used until full continence is achieved. The training process may take days to months, and caregivers can expect accidents. Accidents need to be dealt with plainly; the child should not be punished or made to feel guilty or forced to sit on the toilet for prolonged periods.

Table 1-7. Medical problems commonly diagnosed in childhood.

<table>
<thead>
<tr>
<th>Problem</th>
<th>Definition</th>
<th>Prevalence</th>
<th>Risk Factors</th>
<th>Assessment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental dysplasia of hips</td>
<td>Spectrum of abnormalities that cause hip instability, ranging from dislocation to inadequate development of acetabulum</td>
<td>8-25 cases in 1000 births</td>
<td>Female gender Breech delivery Family history Possibly birth weight &gt;4 kg</td>
<td>Screening clinical examination at birth and well child visits of marginal use</td>
<td>Abduction splints in infants &lt;6 mo; open or closed reduction more effective in those &gt;6 mo Optimal treatment remains controversial; consider orthopedic referral</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>Major: large VSDs, severe valvular stenosis, cyanotic disease, large ASDs</td>
<td>5-8 cases in 1000 newborns, 50% with major disease and 50% with minor disease</td>
<td>Maternal diabetes or connective tissue disease Congenital infections (CMV, HSV, rubella, etc) Drugs taken during pregnancy Family history Down syndrome</td>
<td>Major disease presents shortly after birth Minor disease can present with murmur, tachycardia, tachypnea, pallor, peripheral pulses; ECG, CXR, echocardiogram</td>
<td>Cardiology evaluation; medication; surgical treatment options</td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>Testicles are absent (agenesis, vascular compromise) or undescended</td>
<td>2-5% of full-term and 30% of premature male infants Prevalence varies geographically</td>
<td>Disorders of testosterone secretion Abdominal wall defects Trisomies</td>
<td>Increased risk of inguinal hernia, testicular torsion, infertility, and testicular cancer</td>
<td>Hormonal or surgical treatment, or both; can start at age 6 mo; complete before age 2 y</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
<td>Hypertrophic (elongated, thickened) pylorus, progresses to obstruction of gastric outlet</td>
<td>3 cases in 1000 live births</td>
<td>Male infants First-born infants Unconjugated hyperbilirubinemia</td>
<td>Diagnosis by clinical examination, ultrasound, or upper GI series Electrolyte abnormalities (metabolic alkalosis)</td>
<td>Surgical repair; fluid, electrolyte resuscitation</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>Ventral location of urethral meatus (anywhere from proximal glans to perineum)</td>
<td>~1 case in 250 male births</td>
<td>Advanced maternal age Maternal diabetes mellitus Caucasian ethnicity Delivery before 37 weeks' gestation</td>
<td>Check for other abnormalities (cryptorchidism) and intersex conditions (congenital adrenal hyperplasia)</td>
<td>Circumcision contraindicated Urology referral, usually within 3-6 mo</td>
</tr>
<tr>
<td>Strabismus</td>
<td>Anomaly of ocular alignment (one or both eyes, any direction)</td>
<td>~2%-4% of population</td>
<td>Family history Low birth weight Retinopathy of prematurity Cataract</td>
<td>Clinical tests: corneal light reflex, red reflex, cover test, and cover/uncover test</td>
<td>Child should be referred to pediatric ophthalmologist for early treatment to reduce visual loss (amblyopia)</td>
</tr>
</tbody>
</table>

VSD, ventricular septal defect; ASD, atrial septal defect; CMV, cytomegalovirus; HSV, herpes simplex virus; GI, gastrointestinal; ECG, electrocardiogram; CXR, chest x-ray
*1999-2000 data. (http://www.cdc.gov/)
Significant constipation can be treated medically, because it may present a barrier to training. About 80% of children achieve success at daytime continence by 30 months of age.

As with many child-rearing issues, consistency and a nurturing environment give the child a sense of security. Training should not start too early or during times of family stress. Parents can be asked to describe specific scenarios so concrete anticipatory guidance may be given to deal with any barriers. Toilet training, as with most behavior modification, has a higher chance of success if positive achievements are rewarded and failures are not emphasized.

**MEDICAL PROBLEMS**

Beyond the normal variations in child development, the family physician may need to identify and treat significant medical problems. Early diagnosis and referral lead to prevention of potentially serious sequelae and improved quality of life. Some of the major abnormalities detected in the young child (Table 1-7) underscore the importance of regular and thorough well child-care visits with the family physician.
Failure to Thrive

Deborah Auer Flomenhoft, MD

ESSENTIALS OF DIAGNOSIS

- Persistent weight loss over time.
- Growth failure associated with disordered behavior and development.
- Weight less than third percentile for age.
- Weight crosses two major percentiles downward over any period of time and continues to fall.
- Median weight for age of 76%-90% (mild undernutrition), 61%-75% (moderate undernutrition), or <61% (severe undernutrition).

General Considerations

Failure to thrive (FTT) is an old problem that continues to be an important entity for all practitioners who provide care to children. Growth is one of the essential tasks of childhood and is an indication of the child’s general health. Growth failure may be the first symptom of serious organ dysfunction. Most frequently, however, growth failure represents inadequate caloric intake. Malnutrition during the critical period of brain growth in early childhood has been linked to delayed motor, cognitive, and social development. Developmental deficits may persist even after nutritional therapy has been instituted.

FTT was first described by Holt in 1897; he describes a group of children who suddenly “ceased to thrive” and became “wasted skeletons” when weaned after the first 4-6 weeks of life. More than 100 years later there is no consensus definition of FTT. Residents and medical students need to be familiar with several definitions of FTT. Practitioners must also recognize the limitations of each definition. Competing definitions of FTT include the following:

- **Persistent weight loss over time.** Children should steadily gain weight. Weight loss beyond the setting of an acute illness is pathological. However, the assessment and treatment for FTT need to be addressed before the child has had persistent weight loss.
- **Growth failure associated with disordered behavior and development.** This old definition is useful because it reminds the practitioner of the serious sequelae and important alarm features in children with undernutrition. Currently, FTT is more commonly defined by anthropometric guidelines alone.
- **Weight less than the third percentile for age.** This is a classic definition. However, this definition includes children with genetic short stature and children whose weight transiently dips beneath the third percentile with an intercurrent illness.
- **Weight crosses two major percentiles downward over any period of time.** Thirty percent of normal children will drop two major percentiles within the first 2 years of life as their growth curve shifts to their genetic potential. These healthy children will continue to grow on the adjusted growth curve. Children with FTT do not attain a new curve, but continue to fall. The most accurate assessment for failure to thrive is a calculation of the child’s median weight for age. This quick calculation enables the clinician to assess the degree of undernutrition and plan an appropriate course of evaluation and intervention. The median weight for age is determined by the United States Centers for Disease Control and Prevention (CDC) growth charts. The median should not be adjusted for race, ethnicity, or country of origin. Differences in growth are more likely due to inadequate nutrition in specific geographic or economically deprived populations. Determinations of nutritional status are as follows:
  - **Seventy-six to 90% median weight for age represents mild undernutrition.** These children are in no immediate danger and may be safely observed over time (Table 2-1).
  - **Sixty-one to 75% median weight for age is moderate undernutrition.** These children warrant immediate evaluation and intervention with close follow-up in an outpatient setting.
Observe as outpatient when causes are identified in 10% of children with FTT.

Degree of undernutrition:
- **Mild**
  - 76%-90%
  - Observe as outpatient
- **Moderate**
  - 61%-75%
  - Urgent outpatient evaluation
  - Close weight follow-up
- **Severe**
  - <61%
  - Hospitalization
  - Nutrition support
  - In-hospital evaluation

### Pathogenesis

When diagnosing FTT it is essential to consider the etiology. Historically there has been a dichotomy: organic versus nonorganic FTT. Either children had major organ dysfunction (organic) or psychosocial problems led to inadequate nutrition (nonorganic). Over the past decades FTT has been better understood as a mixed entity in which both organic disease and psychosocial factors influence each other. With this understanding, the old belief that a child who gains weight in the hospital has nonorganic FTT has been debunked.

### A. Organic FTT

Organic causes are identified in 10% of children with FTT. In-hospital evaluations reveal an underlying organic etiology in about 30% of children. These data are misleading, however. More than two-thirds of these children are diagnosed with gastroesophageal reflux disease (GERD). The practitioner risks one of two errors in diagnosing GERD as the source of failure to thrive: physiological reflux is found in at least 70% of infants. It may be a normal finding in an infant who is failing to thrive for other reasons. Further, undernutrition causes decreased lower esophageal segment (LES) tone, which may lead to reflux as an effect rather than a cause of FTT.

### B. Nonorganic FTT

Nonorganic FTT, weight loss in which no physiological disease is identified, constitutes 80% of cases. Historically, the responsibility for this diagnosis fell on the caretaker. Either the parent was unable to provide enough nutrition or the parent was emotionally unavailable to the infant. In either circumstance the result was unsuccessful feeding. Psychosocial stressors were thought to create a neuroendocrine milieu preventing growth even when calories were available: increased cortisol and decreased insulin levels in undernourished children inhibit weight gain.

### C. Mixed FTT

Most FTT is neither purely organic nor nonorganic, but rather mixed: there is a transaction between both physiological and psychosocial factors that creates a vicious cycle of undernutrition. For example, a child with organic disease may initially have difficulty eating for purely physiological reasons. However, over time, the feedings become fraught with anxiety for both parents and child and are even less successful. The child senses the parents’ anxiety and eats less and more fretfully than before. The parents, afraid to overtax the “fragile” child, may not give the child the time needed to eat. They may become frustrated that they are not easily able to accomplish this most basic and essential care for the child. Parents of an ill child may perceive that other aspects of care are more important than feeding, such as strict adherence to a medication or therapy regimen.

Children with organic disease underlying FTT often gain weight in the hospital when fed by emotionally uninvolved parties such as nurses, volunteers, or physicians: these people do not feel that the child’s difficulties represent personal failure and may be more patient. They are also not the sole providers for all of the child’s needs. This happy circumstance (weight gain in the hospital) should not be mistaken for parental neglect in the home; rather, the primary care provider should pay close attention to the psychosocial stressors on the feeding dyad.

Conversely the child who seems to be failing to thrive for purely psychosocial reasons often has complicating organic issues. The undernourished child is lethargic and irritable, especially at feeding times. As noted above, undernutrition decreases LES tone and may worsen reflux: the undernourished child is more difficult to feed and holds down fewer calories. Poor nutrition adversely affects immunity: children with FTT often have recurrent infections that increase their caloric requirements and decrease their ability to meet them.

The mixed model reminds the clinician that FTT is an interactive process involving physiological and psychosocial
elements and, more importantly, both parent and child. The child's attributes affect the relationship as surely as the parents’. A fussy child may be more difficult for a particular parent to feed. A “good” or passive baby may not elicit enough feeding. Physical characteristics also affect parent-child relationships: organic disease may not only make feeding difficult but may engender a sense of failure or disappointment in the parent. It is crucial to remember that each child is different; parents have unique relationships with each of their children. Therefore, a parent whose first child is diagnosed with FTT is not doomed to repeat the cycle with the second child. Conversely, an experienced parent who has fed previous children successfully is not immune from the specter of FTT.

D. Causes of FTT

All failure to thrive is caused by undernutrition. The mechanism varies. The child may have increased caloric requirements because of organic disease. The child may have inadequate intake either because not enough food is made available or there is mechanical difficulty in eating.

Thirdly, adequate calories may be provided but the child is unable to utilize them either because the nutrients cannot be absorbed across the bowel wall or because of inborn errors of metabolism.

The astute clinician will note that there may be overlap between these mechanisms. For example, a child with cystic fibrosis has increased caloric requirements associated with chronic respiratory tract infections. However, shortness of breath may make it difficult for the child to eat sufficient quantities. And associated pancreatic insufficiency limits nutrient absorption.

Prevention

FTT may be prevented by good communication between the primary care provider and the family. The practitioner should regularly assess feeding practices and growth and educate parents about appropriate age-specific diets. As a general rule, infants who are feeding successfully gain about

- 30 g/d at 0-3 months
- 20 g/d at 3-6 months
- 15 g/d at 6-9 months
- 12 g/d at 9-12 months
- 8 g/d at 1-3 years

In addition, growth parameters need to be recorded at every visit, sick or well. Weight should be documented for all children. Recumbent length is measured for children younger than 2 years old. Height is measured for children older than 3 years old. Between the ages of 2 and 3 years either height or length may be recorded. Length measurements exceed heights by an average of 1 cm. With a good growth chart in hand, the primary care provider can monitor growth and intervene early if problems arise.

Clinicians should investigate the economic stresses on families. In a family struggling with recent unemployment or underemployment, referral to a walk-in clinic or other social support programs may prevent hunger and subsequent FTT.

Clinical Findings

A. Symptoms and Signs

The importance of a complete, long-term growth curve in making the diagnosis of FTT cannot be overemphasized. Acute undernutrition manifests as “wasting”; the velocity of weight gain decreases while height velocity continues to be preserved. The result is a thin child of normal height. Chronic undernutrition manifests as “stunting”; both height and weight are affected. The child may appear proportionately small. Review of a growth curve may reveal that weight was initially affected and increase the suspicion for FTT.

Children should be plotted on an appropriate growth curve. Growth curves are gender specific and are available at the CDC Web site. Growth curves should not be used for specific countries of origin. Specific growth curves are available for children with genetic disorders such as Trisomy 21 or Turner syndrome. However, these curves are not well validated. These curves draw from a small group of children and the nutritional status of the participants was not assessed. These curves may be useful for the clinician in discussing an affected child’s growth potential with a family, but are not necessary. These growth curves must also be used with care.

B. History

The clinician’s most valuable tool in the diagnosis of FTT is the history. While taking the history health care providers have the opportunity to establish themselves as the child’s advocate and the parents’ support. Care must be taken not to establish an adversarial relationship with the parents. It is useful to begin by asking the parents their perception of their child’s health; many parents do not recognize FTT until the clinician brings it to their attention.

The history and physical examination are more valuable than any standard battery of tests in uncovering significant organ dysfunction contributing to growth failure. For example, the child who feeds poorly may have a physical impediment to caloric intake such as cleft palate or painful dental caries. Poor suck may also raise concerns for neurological disease. Recurrent upper or lower respiratory tract infections may suggest cystic fibrosis (CF), human immunodeficiency virus (HIV), or immunodeficiency. Sweating during feeding should prompt consideration of an underlying cardiac problem with or without cyanosis. Chronic diarrhea indicates malabsorption: chronic infection, eosinophilic disease, celiac disease, and pancreatic insufficiency should be evaluated.

The health care provider must elicit more subtle aspects of past medical history as well: particular attention must be paid to developmental history and intercurrent illnesses.
Delay in achievement of milestones should prompt a close neurologic examination: inborn errors of metabolism and cerebral palsy can present with growth failure. A history of recurrent serious illness may be the only indicator of inborn errors of metabolism. Recurrent febrile illness without a clear source may also indicate urinary tract infection. A history of snoring or sleep disturbances should prompt an evaluation for tonsillar and adenoidal hypertrophy, which has been identified as a cause of FTT.

Past medical history must include a complete perinatal history (Table 2-2). Children with lower birth weights and those with specific prenatal exposures are at higher risk for growth problems. Forty percent of children with FTT had birth weights below 2500 g; only 7% of all births are below 2500 g.

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<th>Table 2-2. History taking.</th>
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<tr>
<td><strong>Questions</strong></td>
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<tr>
<td>Perinatal Infection Movement</td>
</tr>
<tr>
<td>Feeding behavior Diaphoreosis Poor suck, swallow Time to eat</td>
</tr>
<tr>
<td>Diet history Infant Breastfeeding: time of nursing, sensation of let down, fullness of breasts Formula fed: assess how parents are mixing formula, feeding techniques</td>
</tr>
<tr>
<td>Older children 24-h diet history Prospective 72-h diet diary Dysphagia</td>
</tr>
<tr>
<td>Growth history Onset in infancy Onset of failure to thrive after addition of solids Onset after infancy, recent drop</td>
</tr>
<tr>
<td>Stooling history Diarrhea Constipation</td>
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Low birth weights may be caused by infection, drug exposure, or other maternal and placental factors. The child with symmetric growth retardation is of particular concern. Infants exposed in utero to rubella, cytomegalovirus (CMV), syphilis, toxoplasmosis, or malaria are at high risk for low birth weight, length, and head circumference. These measurements portend poor catch-up growth potential. Short stature is often accompanied by developmental delay and mental retardation in these children.

Children with asymmetric intrauterine growth retardation (preserved head circumference) have better potential for catch-up growth and appropriate development. Fetal growth is affected by both maternal factors and exposure to toxins. Drugs of abuse such as tobacco, cocaine, and heroin have been correlated with low birth weight. Placental insufficiency caused by hypertension, preeclampsia, collagen vascular disease, or diabetes may result in an undernourished baby with decreased birth weight. And, finally, intrauterine physical factors may reduce the fetus’s growth: uterine malformation, multiple gestation, and fibroids may all contribute to smaller babies.

A careful investigation of the health of the mother is warranted. Maternal HIV is a significant risk factor for FTT. Most children born to HIV-positive mothers have normal birth weights and lengths. However, children who are infected frequently develop FTT within the first year of life.

Family history is essential. A family history of atopy, eczema, or asthma raises the suspicion of eosinophilic enteritides. A family history of autoimmune disease should heighten the concern for celiac. Metabolic diseases are generally recessive, and an absence of family history should not be regarded as reassuring.

An examination of the family’s relationships with the child and one another can uncover valuable information. Children described as “difficult” or “unpredictable” by their mothers have been noted to be slow or poor feeders by independent observers. Maternal depression and history of abuse are strong risk factors for FTT; addressing these issues is integral to establishing a functional feeding relationship between parent and child. Finally, a thorough assessment of economic supports may reveal that nutritious foods are unobtainable or difficult to access. Social financial supports are often inadequate to meet children’s needs. Tenuous housing or homelessness may make it impossible to keep appropriate foods readily available.

**C. Feeding History**

A careful feeding history constitutes the history of present illness; it often sheds more light on the problem than a battery of laboratory tests. When assessing an infant, it is essential to know what formula the infant is taking, what volume, and how frequently. Caregivers should describe the preparation of formula. Pictograms on the back of powdered formulas routinely show a single scoop of formula being added to a full bottle of water: families that are non-English speaking or
have low literacy skills may be inadvertently mixing dilute formula. In calculating caloric intake, the practitioner should remember that breast milk and formula have 20 cal/oz. Baby foods range from 40 to 120 cal/jar; a good rule is 80 cal/4-oz jar.

How the baby eats is as important as how much the baby eats. The examiner should ask how long it takes the baby to eat: slow eating may be associated with poor suck or decreased stamina secondary to organic dysfunction. Parental estimation of the infant’s suck may also be helpful. Parents should be asked both if the baby is spitty and if the baby vomits frequently as they may endorse one symptom and deny the other. The clinician should inquire about feeding techniques: bottle propping may indicate a poor parent-child relationship or an overtaxed parent.

The breast-fed baby merits special mention. The sequelae of unsuccessful breast-feeding are profound. Infants may present with severe dehydration: normal infants have been neurologically devastated and even died. Parents rarely recognize that the infant is failing to thrive. Mothers are often discharged from the hospital before milk is in and may be unsure about what to expect or misinterpret their experience in the hospital as successful nursing.

The neonatal period is the most critical period in the establishment of breast-feeding. The primary care provider should educate the breast-feeding mother prior to hospital discharge. Milk should be in by day 3 or 4. The neonate should feed at least eight times in a 24-hour period and should not be sleeping through the night. A “good” baby, an infant who sleeps through the night, should arouse concerns of possible dehydration. Breast-fed babies should have at least six wet diapers a day. Whereas formula-fed infants may have many stool patterns, the successful breast-fed neonate should have at least four yellow seedy stools a day. After 4 weeks of life stool pattern may change to once a day or less.

Breast-fed babies should be seen within the first week of life to evaluate infant weight and feeding success. Weight loss is expected until day 5 of life. Infants should regain their birth weight by the end of the second week of life. Any weight loss greater than 8% should elicit concern: weight loss greater than 10%-12% should prompt evaluation for dehydration, that is, serum sodium. Primary care providers should ask about the infant’s suck and whether the mother feels her breasts are emptied at the feeding. The successful infant should empty the mother’s breast and be contented at the end of the nursing session.

The evaluation of older children also requires a thorough diet history. An accurate diet history begins with a 24-hour diet recall: parents should be asked to quantify the amount their child has eaten of each food. The 24-hour recall acts as a template for a 72-hour diet diary, the most accurate assessment of intake: the first 48 hour of a diet diary are the most reliable. All intakes must be recorded including juices, water, and snacks. The child who consumes an excessive amount of milk or juice may not have the appetite to eat more nutrient-rich foods: a child needs no more than 16-24 oz of milk and should be limited to less than 12 oz of juice per day.

It is as important to assess mealtime habits as the meals themselves. Activity in the household during mealtime may be distracting to young children. Television watching may preempt eating. Excessive attention to how much the child eats can increase the tension and ultimately decrease the child’s intake. Most toddlers cannot sit for longer than 15 minutes: prolonging the table time in the hopes of increasing the amount eaten may only exacerbate the already fragile parent-child relationship. And although many toddlers graze throughout the day, some are unable to take in appropriate calories with this strategy.

The primary care provider should also discuss the family’s beliefs about a healthy diet. Some families have dietary restrictions, either by choice or culturally, that affect growth. Many have read the dietary recommendations for a healthy adult diet, but a low-fat, low-cholesterol diet is not an appropriate diet for a toddler. Until the age of 2 years children should drink whole milk and their fats should not be limited. Only after the age of 5 years is it appropriate to move to a Step 1 diet. This may seem counterintuitive to many parents.

### D. Physical Examination

In addition to reviewing the growth curve the clinician must complete a physical examination. A weight, length, or height as appropriate for the child’s age, and head circumference are indicated for all children. Growth parameters may be roughly interpreted using the following guidelines:

- **Acute undernutrition:** low weight, normal height, normal head circumference
- **Chronic undernutrition:** short height, normal weight for height, normal head circumference
- **Acute or chronic undernutrition:** short height, proportionately low weight for height, normal head circumference
- **Congenital infection or genetic disorder impairing growth:** short height, normal to low weight for height, small head circumference

The general examination provides a wealth of information. Vital signs should be documented: bradycardia and hypotension are worrisome findings in the malnourished child and should prompt immediate hospitalization. It is important to document observations of the parent-child interaction in the physical examination: are the parent and child responsive to one another or is the child lying unattended on the examining table? In the same vein, it is useful to note both the parent’s and the child’s affect: parental depression has been associated with higher risk of FTT. And, as noted above, the child’s disposition is integral in shaping the parent-child relationship. Occasionally the examiner may find subtle indications of neglect such as a flat occiput indicating that the child is left alone for long periods. However, in this day of “back to sleep” a flat occiput may be a normal finding.

Children with undernutrition often have objective findings of their nutritional state. Unlike the genetically small child, children with FTT have decreased subcutaneous fat. If undernutrition has been prolonged they will also have muscle...
wasting; in infants it is easier to assess muscle wasting in the calves and thighs rather than in the interosseous muscles. It is also important to remember that infants suck rather than chew, therefore they will not have the characteristic facies of temporal wasting. Nail beds and hair should be carefully noted as nutritional deficiencies may cause pitting or lines in the nails. Hair may be thin or brittle. Skin should be examined for scaling and cracking, which may be seen with both zinc and fatty acid deficiencies. Presence of eczema may indicate allergic diathesis and eosinophilic enteritis.

The physical examination should be completed with special attention directed to the organ systems of concern uncovered in the history. However, examination of some organ systems may reveal abnormalities not elicited through history. A thorough abdominal examination is of particular importance: organomegaly in the child with FTT raises the possibility of inborn errors of metabolism and requires laboratory evaluation. The examiner should note the genitourinary (GU) examination: undescended testicles may indicate panhypopituitarism; ambiguous genitalia may indicate congenital adrenal hyperplasia (CAH). A careful neurologic examination may reveal subtly increased or decreased tone consistent with cerebral palsy and, therefore, increased caloric requirements or inability to coordinate suck and swallow, respectively.

Children with undernutrition have been repeatedly shown to have behavioral and cognitive delays. Unfortunately the Denver Development Screen II is an inadequate tool to assess the subtle but real delays in these children. It has been suggested that the Bayley Test may be a more sensitive tool when assessing these children. Even with nutritional and social support, behavioral and cognitive lags may not correct. Children who have suffered FTT remain sensitive to undernutrition throughout childhood: one study found a significant decrease in fluency in children with a remote history of undernutrition when they did not eat breakfast. Children with a normal nutritional history were not found to be similarly affected.

The immune system is affected by nutritional status. Children with FTT may present with recurrent mucosal infections: otitis media, sinusitis, pneumonia, and gastroenteritis. Immunoglobulin A (IgA) production is extremely sensitive to undernutrition. With this in mind, the clinician must be sensitive to the growth parameters of children presenting frequently for intercurrent illness. Children with more severe malnutrition may be lymphopenic (lymphocyte count <1500) or anergic.

Undernourished children are frequently iron deficient, even in the absence of anemia. Iron and calcium deficiencies enhance the absorption of lead. In areas in which there is any concern for lead exposure, lead levels should be performed as part of the workup for FTT.

**E. Laboratory Findings**

No single battery of laboratory tests or imaging studies can be advocated in the workup of FTT. Testing should be guided by the history and physical examination. Less than 1% of “routine laboratory tests” ordered in the evaluation of FTT provide useful information for treatment or diagnosis.

Tests that have been advocated as markers of nutritional status have limitations. Albumin has an extremely long half-life (21 days) and is a poor indicator of recent undernutrition. Prealbumin, which has been touted as a marker for recent protein nutrition, is decreased in both acute inflammation and undernutrition.

Laboratory evaluation is indicated when the history and physical examination suggest underlying organic disease. Children with developmental delay and organomegaly or severe episodic illness should have a metabolic workup including urine organic and serum amino acids: there is a 5% yield in this subset of patients. Children with a history of recurrent respiratory tract infections or diarrhea should have a sweat chloride performed at a cystic fibrosis center. Less experienced laboratories offer unreliable results. A history of poorly defined febrile illnesses or recurrent “viral illness” may be followed up with a urinalysis, culture, and renal function to evaluate for occult urinary tract disease. In children with diarrhea, it may be useful to send stool for *Giardia* antigen, qualitative fat, white blood cell (WBC) count, occult blood, ova and parasites (O&P), rotavirus, and α₁-antitrypsin. Rotavirus has been associated with a prolonged gastroenteritis and FTT. Elevated α₁-antitrypsin in the stool is a marker for protein enteropathy.

For children who develop FTT after the addition of solid foods, an evaluation for celiac disease is warranted whether or not diarrhea is present. Fifteen percent of celiac patients present with constipation. Antigliadin antibody is appropriate for screening infants and toddlers; tissue transglutaminase is insensitive in this age group (Table 2-3).

Infectious diseases need to be specifically addressed. Worldwide, tuberculosis (TB) is one of the most common causes of FTT. A Mantoux test and anergy panel must be

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<td><strong>CBC with diff</strong></td>
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<td><strong>CMP</strong></td>
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<td><strong>Antigliadin Ab</strong></td>
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<td><strong>Tissue transglutaminase</strong></td>
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<td><strong>Urinalysis</strong></td>
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<td><strong>Sweat chloride</strong></td>
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placed on any child with risk factors for TB exposure. HIV must also be entertained. FTT is frequently a presenting symptom of HIV in the infant. Testing for HIV is not legally required in prenatal assessment: mothers may not know their children are at risk. Any suspicion of HIV merits testing. Less ominous infectious etiologies can also cause FTT: persistent giardiasis and rotavirus are two common toddler infections that cause poor growth.

**Differential Diagnosis**

It is essential to differentiate a small child from the child with FTT. No criterion is specific enough to exclude those who are small for other reasons. Included in the differential diagnosis of FTT are familial short stature, Turner syndrome, normal growth variant, prematurity, endocrine dysfunction, and genetic syndromes limiting growth.

Here, too, a good growth chart is of great utility. The child with FTT has a deceleration in weight first. Height velocity continues unaffected for a time. Children with familial short stature have a simultaneous change in their height and weight curves. Height velocity slows first (it can even plateau) in endocrine disorders such as hypothyroidism. The preterm infant’s growth parameters need to be adjusted for gestational age: head circumference is adjusted until 18 months, weight until 24 months, and height through 40 months.

The family history is helpful in differentiating the child with FTT from the child with constitutional growth delay or familial short stature. Midparental height, which can be calculated from the family history, is a useful calculation of probable genetic potential:

- For girls: \((\text{father’s height in inches} - 5 + \text{mother’s height})/2\ ± 2\ in\)
- For boys: \((\text{mother’s height in inches} + 5 + \text{father’s height})/2\ ± 2\ in\)

If the child’s current growth curve translates into an adult height that falls within the range of midparental height reassurance may be offered.

It is most difficult to differentiate the child with constitutional growth delay from the child with FTT. These children typically have reduced weight for height as do children with FTT. However, unlike children with FTT they ultimately gain both weight and height on a steady curve. Family history is often revealing in constitutional growth delay. Querying parents about the onset of their own pubertal signs may seem intrusive, but often gives the clinician the information needed to reassure parents about their child’s growth.

Breast-feeding infants may be growing normally and not follow the CDC growth curves. After 4-6 months their weight may decrease relative to their peers. After 12 months their weight catches up to that of age-matched formula-fed infants. However, a decrease in weight in early infancy is a symptom of unsuccessful breast-feeding and should be interpreted as FTT.

**Complications**

Developmental delay may persist in children with FTT well past the period of undernutrition. Studies have repeatedly shown that these children, as a group, have more behavioral and cognitive problems in school than their peers, even into adolescence. One caveat about these studies is that many defined failure to thrive by that classic definition: growth failure associated with disordered behavior and development. These studies do not doom every child with FTT to scholastic and social failure, but the clinician must be vigilant and act as the child’s advocate. Formal developmental screening is especially important in the child with a history of FTT. Intervention should be offered early rather than waiting “to see if the child catches up.” Children with FTT can be successful but may need specific supports on the road to achieving that success.

**Treatment**

**A. Nutrition**

The cornerstone of therapy is nutrition. The goal of treatment is catch-up growth. Children with FTT may need 1.5 to 2 times the usual daily calories to achieve catch-up growth. For an infant this is roughly 150-200 cal/kg/d. There are many formulas for calculating caloric requirements: one simple estimate is

\[
\text{kcal/kg} = 120 \times \text{median weight for current height/weight (kg)}
\]

It is important that this nutrition include adequate protein calories. Children with undernutrition require 3 g protein/kg body weight/d to initiate catch-up growth and may need as much as 5 g/kg. (In the literature from the developing world some malnourished children have required as much as 12 g protein/kg/d!) High-calorie diets should continue until the child achieves an age-appropriate weight for height.

It is almost impossible for any child to take in two times the usual volume of food. Some solutions are to offer higher-calorie formulas (24-30 cal/oz) to infants. For older children it is possible to replace or add higher-calorie foods. Heavy cream may be substituted for milk on cereal or in cooking. Cheese may be added to vegetables. Instant breakfast drinks may be offered as snacks. It is advisable to enlist a dietician in designing a high-calorie diet for the child with FTT.

Occasionally tube feedings are indicated in the child with FTT. Some children may benefit from nighttime feedings through a nasogastric or a percutaneous endoscopic gastroscopy tube. This solution is particularly useful in children with underlying increased caloric requirements, for example, children with cystic fibrosis and cerebral palsy. Children with mechanical feeding difficulties may also require tube feeding for some period of time. The child who is primarily tube fed should have early intervention with an occupational or speech therapist. Without therapy the child may develop oral aversions or fail to develop...
appropriate oral-motor coordination; both issues will worsen FTT when oral feeding is reinstituted.

Parents need to be educated at the onset of nutritional therapy. Catch-up growth is expected within the first month. However, some children may not show accelerated weight gain until after the first 2 weeks of increased nutrition. Children usually gain 1.5 times their daily expected weight gains during the catch-up phase. Children’s weight improves well before their height increases; parents may expect their previously skinny child to become cherubic and even plump. This change in body habitus does not indicate overfeeding but successful therapy. It does not matter how quickly the child gains; the composition of weight gain will be 45%-65% lean body mass.

B. Medications

Few medications are indicated in the treatment of FTT. Those few are nutritional supports. Children with FTT should be supplemented with iron. Zinc has also been shown to improve linear growth. It is sufficient to supplement children with a multivitamin containing zinc and iron. Vitamin D supplementation should also be considered. Vitamin D replacement is especially important in dark-skinned children and in children who are not regularly exposed to sunlight.

C. Social Support

Beyond nutritional support the importance of social support has already been alluded to. The services offered must be tailored to the family and the child. Certainly frequent visits with the primary care provider are useful: weight gain can be measured and concerns addressed. Home visits by social services have been shown to decrease hospitalizations and improve weight gain. Children with developmental delay need early assessment and intervention by the appropriate therapists.

The primary care provider plays a critical role in recognizing and assessing FTT. These seemingly simple interventions made early in childhood have lasting ramifications throughout the life span.

D. Indications for Referral or Admission

Most FTT can and should be managed by the primary care provider. A trusting relationship between the clinician and the family is an invaluable asset in the treatment of failure to thrive. Parents struggling with the diagnosis often believe that the health care system views them as neglectful. This anxiety creates barriers to open and honest communication about the child’s feeding and developmental status. However, suspicions may be allayed when primary care providers enlist themselves as allies in the treatment.

The primary indication for referral is the treatment of an underlying organ dysfunction, for example, cystic fibrosis, that requires specialized care. Referral should also be made when the primary care provider feels specialized testing is needed: for example, endoscopic biopsies for the further evaluation of celiac disease or eosinophilic enteritis. The clinician may also wish to reevaluate the child who fails to begin catch-up growth after 1-2 months of nutritional intervention.

Most children with FTT can be managed in the outpatient setting; a few may need hospitalization at some point during their evaluation. Indications for admission at initial evaluation are bradycardia or hypotension, indicators of severe malnutrition. Children who are less than 61% of the median weight for their age should be admitted for nutritional support. Children with hypoglycemia should be admitted: low serum glucose is worrisome for severe malnutrition and metabolic disease.

The majority of families of children with FTT are neither abusive nor neglectful. However, if the clinician suspects abuse or neglect the child should be admitted: about 10% of children with FTT are abused. These children ultimately experience poorer developmental outcomes than other children with FTT if left in the home. When abuse is documented social services must be involved.

The third group of children who may be considered for hospital admission are those who have failed to initiate catch-up growth with outpatient management. A hospital stay of several days will allow the clinician to observe feeding practices and enable the family to internalize the plan of care. Further testing for organ dysfunction may be indicated during this hospitalization. It can also be a time to enlist other health professionals in the treatment plan: occupational therapists and social workers are often helpful allies in the treatment of FTT.
Neonatal Hyperbilirubinemia

Andrew B. Symons, MD, MS
Martin C. Mahoney, MD, PhD, FAAFP

General Considerations

Nearly every infant is born with a serum bilirubin level higher than that of the normal adult. Approximately 60% of newborns are visibly jaundiced during the first week of life. The diagnostic and therapeutic challenge for the physician is to differentiate normal physiologic jaundice from pathologic jaundice, and to institute appropriate evaluation and therapy when necessary.

Table 3-1 lists several maternal and neonatal factors that increase the risk of developing severe hyperbilirubinemia among infants of 35 or more weeks’ gestation. Among the most significant clinical characteristics associated with severe hyperbilirubinemia are predischarge levels in the high-risk zone on the serum bilirubin nomogram (Figure 3-1). The following factors (in order of decreasing importance) are associated with decreased risk of significant jaundice: total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) level in the low-risk zone, gestational age greater than 41 weeks, exclusive bottle-feeding, black race, and discharge from the hospital after 72 hours.

Pathogenesis

A. Physiologic Jaundice

The three classifications of neonatal hyperbilirubinemia are based on the following mechanisms of accumulation: increased bilirubin load, decreased bilirubin conjugation, and impaired bilirubin excretion. In the newborn, unconjugated bilirubin is produced faster and removed more slowly than in the normal adult due to immaturity of the glucuronyl transferase enzyme system. The main source of unconjugated bilirubin is the breakdown of hemoglobin in senescent red blood cells. Newborns have an increased erythrocyte mass at birth (average hematocrit of 50% vs 33% in the adult) and a shorter life span for erythrocytes (90 days vs 120 days in the adult). The newborn cannot readily excrete unconjugated bilirubin, and much of it is reabsorbed by the intestine and returned to the enterohepatic circulation.

Increased production and decreased elimination of bilirubin lead to a physiologic jaundice in most normal newborns. Bilirubin is a very effective and potent antioxidant, and physiologic jaundice may provide a mechanism for protecting the newborn from oxygen free-radical injury. The average full-term white newborn experiences a peak serum bilirubin concentration of 5-6 mg/dL (86-103 μmol/L), which begins to rise after the first day of life, peaks on the third day of life, and falls to normal adult levels by days 10-12. African American infants tend to have slightly lower peaks in serum bilirubin. In Asian infants, serum bilirubin levels rise more quickly than in white infants and tend to reach higher peaks on average (8-12 mg/dL; 135-205 μmol/L). This leads to a longer period of physiologic jaundice among Asian and Native American newborns. Preterm infants (<37 weeks’ gestation) of all races may take 4-5 days to reach peak serum bilirubin levels, and these peaks may be twice that observed among full-term infants.

B. Breastfeeding and Breast Milk Jaundice

Infants who are breast-fed may experience exaggerated bilirubin levels due to two separate phenomena associated with breastfeeding and breast milk.

Breast-fed infants may experience relative starvation in the first few days of life due to delayed release of milk by the mother or difficulties with breastfeeding. This nutritional inadequacy can result in increased enterohepatic circulation of bilirubin, leading to elevated serum bilirubin levels in the first few days of life. Termed breastfeeding jaundice, this finding is considered abnormal and can be overcome by offering frequent feedings (10-12 times per day) and by avoiding water supplementation in breast-fed infants.

Breast milk is believed to increase the enterohepatic circulation of bilirubin; however, the specific factor(s) in breast milk that are responsible for this action are unknown. For the first 5 days of life, the serum bilirubin level in breast-fed infants parallels that in non-breast-fed infants. Beginning at approximately day 6, breast milk jaundice occurs in breast-fed...
Table 3-1. Risk factors for development of severe hyperbilirubinemia in infants of 35 or more weeks’ gestation.\(^a\)

<table>
<thead>
<tr>
<th>Major Risk Factors</th>
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<tbody>
<tr>
<td>PredischARGE TSB or TcB level in the high-risk zone (see Figure 3-1)</td>
</tr>
<tr>
<td>Jaundice observed in the first 24 h of life</td>
</tr>
<tr>
<td>Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency), elevated ETCO</td>
</tr>
<tr>
<td>Gestational age of 35-36 wk</td>
</tr>
<tr>
<td>Previous sibling who received phototherapy</td>
</tr>
<tr>
<td>Cephalohematoma or significant bruising</td>
</tr>
<tr>
<td>Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive</td>
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<tr>
<td>East Asian race</td>
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<table>
<thead>
<tr>
<th>Minor Risk Factors</th>
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<tbody>
<tr>
<td>PredischARGE TSB or TcB level in the high intermediate-risk zone</td>
</tr>
<tr>
<td>Gestational age of 37-38 wk</td>
</tr>
<tr>
<td>Jaundice observed before discharge</td>
</tr>
<tr>
<td>Previous sibling with jaundice</td>
</tr>
<tr>
<td>Macrosomic infant of diabetic mother</td>
</tr>
<tr>
<td>Maternal age &gt;25 y</td>
</tr>
<tr>
<td>Male gender</td>
</tr>
</tbody>
</table>

\(\text{TSB, total serum bilirubin; TcB, transcutaneous bilirubin; G6PD, glucose-6-phosphate dehydrogenase; ETCO, end-tidal carbon monoxide.}\)

\(\text{\(^a\)Listed in approximate order of importance.}\)

\(\text{\textit{Source: Reproduced, with permission, from American Academy of Pediatrics Subcommitteee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004;114:297.}}\)

Infants as serum bilirubin either rises a little for a few days or declines more slowly. Approximately two-thirds of breast-fed infants may be expected to have hyperbilirubinemia from 3 weeks to 3 months of age, with as many as one-third exhibiting clinical jaundice. Breast milk jaundice (unlike breastfeeding jaundice) is considered a form of normal physiologic jaundice in healthy, thriving breast-fed infants.

C. Pathologic Jaundice

Exaggerated physiologic jaundice occurs at serum bilirubin levels between 7 and 17 mg/dL (104-291 μmol/L). Bilirubin levels above 17 mg/dL in full-term infants are no longer considered physiologic, and further investigation is warranted.

The onset of jaundice within the first 24 hours of life or a rate of increase in serum bilirubin exceeding 0.5 mg/dL/h (8 μmol/L/h) is potentially pathologic and suggestive of hemolytic disease. Conjugated serum bilirubin concentrations exceeding 10% of total bilirubin or 2 mg/dL (35 μmol/L) are also not physiologic and suggest hepatobiliary disease or a general metabolic disorder.

Table 3-2 summarizes factors that may indicate that jaundice is pathologic as opposed to physiologic, warranting further evaluation. Important historical features include family history of hemolytic disease, onset of jaundice in the first 24 hours of life, a rapid rise in serum bilirubin levels, and ethnicity, as well as infant feeding patterns, stool and urine appearance, and activity levels. Clinical assessment requires careful attention to vital signs, weight loss, general appearance, pallor, and hepatosplenomegaly.

The primary concern with severe hyperbilirubinemia is the potential for neurotoxic effects as well as general cellular injury, which can occur at TSB levels exceeding 20-25 mg/dL. The term kernicterus refers to the yellow staining of the basal ganglia observed postmortem among infants who died with severe jaundice. (Bilirubin deposition in the basal ganglia can also be imaged using magnetic resonance techniques.) The American Academy of Pediatrics (AAP) has recommended that the term acute bilirubin encephalopathy be used to describe the acute manifestations of bilirubin toxicity seen in the first weeks after birth and that the term kernicterus be reserved for the chronic and permanent clinical sequelae of bilirubin toxicity.

Although a common complication of hyperbilirubinemia in the 1940s and 1950s due to Rh erythroblastosis fetalis and ABO hemolytic disease, kernicterus is rare today with the use of Rh immunoglobulin and with the intervention of phototherapy and exchange transfusion. With early discharge to home, however, a small resurgence of kernicterus has been observed in countries in which this complication had essentially disappeared. For instance, although no cases of kernicterus were identified in Denmark during the 20 years preceding 1994, six cases were diagnosed between 1994 and 1998. Although a few isolated cases of kernicterus have been reported in the United States in the last two decades, no published data on the incidence or prevalence of kernicterus in the United States are available.

Bilirubin can interfere with DNA synthesis as well as protein synthesis and protein phosphorylation. Bilirubin also interferes with neuroexcitatory signals and impairs nerve conduction, particularly in the auditory nerve. Hyperbilirubinemia may also impair cerebral glucose metabolism in the brain.

The concentration of bilirubin in the brain and the duration of exposure are important determinants of the neurotoxic effects of bilirubin. Bilirubin can enter the brain when not bound to albumin, so infants with low albumin are at increased risk of developing kernicterus. Conditions that alter the blood-brain barrier such as infection, acidosis, hypoxia, sepsis, prematurity, and hyperosmolarity may affect the entry of bilirubin into the brain.

In infants without hemolysis, serum bilirubin levels and encephalopathy do not correlate well. In infants with hemolysis, TSB levels higher than 20 mg/dL are associated with worse neurologic outcomes, although some infants with concentrations of 25 mg/dL are normal. Kernicterus was detected in 8% of infants with associated hemolysis who had TSB levels of 19-25 mg/dL, 33% of infants with levels of 25-29 mg/dL, and 73% of infants with levels of 30-40 mg/dL. It should be noted that the majority of cases of kernicterus described in recent years have been among neonates who had
Table 3-2. Factors that may indicate a pathologic cause of jaundice among newborns.

<table>
<thead>
<tr>
<th>General considerations</th>
<th>Clinical signs suggesting possibility of other diseases (e.g., sepsis, galactosemia) in which jaundice may be one manifestation</th>
<th>Signs of cholestatic jaundice suggesting the need to rule out biliary atresia or other causes of cholestasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of significant hemolytic disease</td>
<td>Vomiting</td>
<td>Dark urine or urine positive for bilirubin</td>
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<tr>
<td>Onset of jaundice before age of 24 h</td>
<td>Lethargy</td>
<td>Light-colored stools</td>
</tr>
<tr>
<td>Rise in serum bilirubin levels of more than 0.5 mg/dL/h</td>
<td>Poor feeding</td>
<td>Persistent jaundice of more than 3 weeks’ duration</td>
</tr>
<tr>
<td>Pallor, hepatosplenomegaly</td>
<td>Hepatosplenomegaly</td>
<td>TSB, total serum bilirubin; G6PD, glucose-6-phosphate dehydrogenase.</td>
</tr>
<tr>
<td>Rapid increase in TSB level after 24-48 h (consider G6PD deficiency)</td>
<td>Excessive weight loss</td>
<td>Source: Adapted, with permission, from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004;114:297.</td>
</tr>
<tr>
<td>Ethnicity suggestive of inherited disease (G6PD deficiency, etc)</td>
<td>Aperature</td>
<td></td>
</tr>
<tr>
<td>Failure of phototherapy to lower TSB level</td>
<td>Temperature instability</td>
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**Figure 3-1.** Nomogram for designation of risk in 2840 well newborns of 36 or more weeks’ gestational age with birth weight of 2000 g or more or 35 or more weeks’ gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin value. (Reproduced, with permission, from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004;114:297.)
TSB levels higher than 30 mg/dL at the time of diagnosis, which is well above the recommended treatment thresholds of 15 or 20 mg/dL.

It is estimated that up to 15% of infants with kernicterus have no obvious neurologic signs or symptoms. In its acute form, kernicterus (eg, acute bilirubin encephalopathy) may present in the first 1-2 days with poor sucking, stupor, hypotonia, and seizures. During the middle of the first week, hypotonia of extensor muscles, opisthotonus (backward arching of the trunk), retrocollis (backward arching of the neck), and fever may be observed. After the first week, the infant may exhibit generalized hypotonia. Some of these changes disappear spontaneously or can be reversed with exchange transfusion. In most infants with moderate (10-20 mg/dL) to severe (>20 mg/dL) hyperbilirubinemia, evoked neurologic responses return to normal within 6 months. A minority of infants (ranging between 6% and 23%) exhibit persistent neurologic deficits.

In its chronic form, kernicterus may present in the first year with hypotonia, active deep tendon reflexes, obligatory tonic neck reflexes, dental dysplasia, and delayed motor skills. After the first year, movement disorders, upward gaze, and sensorineural hearing loss may develop. It has been suggested that long-term effects of severe hyperbilirubinemia on intelligence quotient (IQ) are more likely in boys than in girls. Seidman and colleagues studied 1948 subjects from Hadasah Hebrew University Medical Center in Jerusalem born in 1970-1971 and drafted into the army 17 years later and found a significantly higher risk of lowered IQ (<85) among males with a history of TSB exceeding 20 mg/dL (OR 2.96; 95% CI 1.29-6.79).

Clinical Findings

The American Academy of Family Physicians offers no clinical policy on neonatal hyperbilirubinemia. In 2004, the AAP issued an updated practice parameter for the management of hyperbilirubinemia among newborns of 35 or more weeks’ gestation. Elements of these recommendations are summarized below and can be accessed in full at http://www.aap.org.

A. Symptoms and Signs

Clinically, jaundice usually progresses from head to toe. The TSB level can be estimated by the degree of caudal extension: face, 5 mg/dL; upper chest, 10 mg/dL; abdomen, 12 mg/dL; palms and soles, more than 15 mg/dL. However, visual estimates of total bilirubin are prone to error, especially in infants with pigmented skin. TSB or total cutaneous bilirubin (TcB) levels should be measured in infants who develop jaundice within the first 24 hours, and all bilirubin levels should be interpreted according to the infant’s age (in hours). TcB measurement devices may provide an alternative to frequent blood draws for the accurate assessment of serum bilirubin. Current guidelines indicate variability in the accuracy of TcB instruments from different manufacturers.

Evaluation of infants who develop abnormal signs such as feeding difficulty, behavior changes, apnea, and temperature changes is recommended regardless of whether jaundice has been detected in order to rule out underlying disease. Clinical protocols for evaluating jaundice, with assessments to be performed no less than every 8-12 hours in the newborn nursery, should be in place.

B. Laboratory Findings

When a pathologic cause for jaundice is suspected, laboratory studies should be promptly completed:

- When jaundice is noticed within the first 24 hours, clinicians should consider a sepsis workup, evaluation for rubella and toxoplasmosis infection, assessment of fractionated serum bilirubin levels, and blood typing to rule out erythroblastosis fetalis. Results of thyroid and galactosemia testing, obtained during the newborn metabolic screening, also should be reviewed.

- If the level of conjugated bilirubin is higher than 2 mg/dL, a reason for impaired bilirubin excretion should be sought. If conjugated bilirubin is lower than 2 mg/dL, hemoglobin levels and reticulocyte counts should be evaluated. A high hemoglobin concentration indicates polycythemia whereas a low hemoglobin concentration with an abnormal reticulocyte count suggests hemolysis. If the reticulocyte count is normal, the infant must be evaluated for a nonhemolytic cause of jaundice.

- Infants with a poor response to phototherapy and those whose family history is consistent with the possibility of glucose-6-phosphate dehydrogenase (G6PD) deficiency require further testing.

- Maternal prenatal testing should include ABO and Rh (D) typing and a serum screen for unusual isoimmune antibodies. If the mother has not had prenatal blood grouping, or is Rh negative, a direct Coombs test, blood type, and Rh (D) type of the infant’s cord blood should be performed. Institutions are encouraged to save cord blood for future testing, particularly when the mother’s blood type is group O.

C. Neonatal Jaundice after Hospital Discharge

Follow-up should be provided to all neonates discharged less than 48 hours after birth. This evaluation by a health care professional should occur within 2-3 days of discharge.

Approximately one-third of healthy breast-fed infants have persistent jaundice after 2 weeks of age. A report of dark urine or light stools should prompt a measurement of direct serum bilirubin. If the history and physical examination are normal, continued observation is appropriate. If jaundice persists beyond 3 weeks, a urine sample should be tested for bilirubin, and a measurement of total and direct serum bilirubin should be obtained.

Prediction & Prevention

Shorter hospital stays after delivery limit the time for hospital-based assessment of infant feeding, instruction about breastfeeding, and the detection of jaundice. Hyperbilirubinemia
and problems related to feeding are the main reasons for hospital readmission during the first week of life. Of 29,934 infants discharged between 1988 and 1994 from a large suburban hospital in Michigan, just 0.8% were readmitted by the age of 14 days. Of those readmitted, 51% were diagnosed with hyperbilirubinemia and 31% with sepsis.

Because bilirubin levels usually peak on day 3 or 4 of life, and most newborns are discharged within 48 hours, most cases of jaundice occur at home. It is therefore important that infants be seen by a health care professional within a few days of discharge to assess for jaundice and overall well-being. This is particularly important in near-term infants (35-36 weeks' gestation) who are at particular risk for hyperbilirubinemia due to both relative hepatic immaturity and inadequate nutritional intake.

Measuring TSB before discharge and then plotting this value on a nomogram (see Figure 3-1) can be useful for predicting the risk of subsequent moderately severe hyperbilirubinemia (>17 mg/dL) and can guide physicians in identifying neonates for whom close follow-up is warranted. Neonates in the high-risk group (95th percentile for TSB) at 18-72 hours of life had a 40% chance of developing moderately severe hyperbilirubinemia upon discharge, whereas for those in the low-risk group (40th percentile for TSB) the probability for subsequently developing moderately severe hyperbilirubinemia was zero. However, it should be noted that there are no evidence-based guidelines that endorse this approach.

Carbon monoxide is a by-product resulting from the breakdown of heme. Measuring end-tidal carbon monoxide (ETCO) in neonates has been proposed as a potential tool for predicting the development of severe hyperbilirubinemia; however, the value of routine measurements of ETCO has been questioned. At present, ETCO measurements to assess hyperbilirubinemia are not yet validated for use in clinical settings.

Treatment

A. Suspected Pathologic Jaundice

The decision whether to intervene in cases of elevated bilirubin levels during the neonatal period is tempered by clinical judgment, and the physician team (including the family physician and consultants) is encouraged to discuss management options with the parents or guardians of the infant. Treatment decisions for both phototherapy (Figure 3-2) and exchange transfusion (Figure 3-3) are based on TSB levels. Intensive phototherapy should produce a decline in TSB of 1-2 mg/dL within 4-6 hours, and the decline should continue thereafter. If the TSB does not respond appropriately to intensive phototherapy, exchange transfusion is recommended. If levels are in the range that suggests the need for exchange transfusion (see Figure 3-3), intensive phototherapy should be attempted while preparations for exchange transfusion are made. Exchange transfusion is also

![Figure 3-2. Guidelines for phototherapy in hospitalized infants of 35 or more weeks’ gestation. (Reproduced, with permission, from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004;114:297.)](image-url)
recommended in infants whose TSB levels rise to exchange transfusion levels despite intensive phototherapy. In any of the preceding situations, failure of intensive phototherapy to lower the TSB level strongly suggests the presence of hemolytic disease or other pathologic processes and strongly warrants further investigation or consultation.

In infants with isoimmune hemolytic disease, administration of intravenous gamma globulin (0.5-1 g/kg over 2 hours) is recommended if the TSB is rising despite intensive phototherapy or the TSB is within 2-3 mg/dL of the exchange level. If necessary, this dose can be repeated in 12 hours.

Figure 3-2 summarizes the management strategy for hyperbilirubinemia in infants of 35 or more weeks’ gestation. Management decisions regarding phototherapy (see Figure 3-2) and exchange transfusion (see Figure 3-3) are based on the infant’s age, risk factors, and TSB levels.

B. Phototherapy and Exchange Transfusion

1. Phototherapy—Hospital-based studies in the United States have shown that 5-40 infants per 1000 term and late-preterm infants receive phototherapy prior to discharge from the nursery, and an equal number are readmitted for phototherapy after discharge. Phototherapy involves exposing the infant to high-intensity light in the blue-green wavelengths. Light interacts with unconjugated bilirubin in the skin, converting it to less toxic photoisomers that are excreted in the bile and urine without conjugation. The efficacy of phototherapy is strongly influenced by the energy output in the blue spectrum, the spectrum of the light, and the surface area of the infant exposed to phototherapy. Phototherapy units contain several fluorescent tubes that are either freestanding or part of a radiant warming device.

Fiberoptic systems have been developed that deliver light through a fiberoptic blanket. The phototherapy tubes (designated F20 T12/BB) make the infants look blue, which may be bothersome to health care workers and make clinical evaluation of jaundice difficult. However, this problem can be mitigated by using four special blue tubes and two daylight fluorescent tubes in the unit. Eye protection is placed on the infant, and the bank of lights is placed 15-20 cm from the infant. The infant is placed naked in a bassinet. Exposure is increased by placing a fiberoptic blanket under the infant, by placing lighting units all around the infant, or by putting a white sheet around the bassinet to serve as a reflecting surface. If slight warming of the infant is noted, the tubes can be moved away a bit. Phototherapy may be interrupted briefly for parental visits or breastfeeding.

In infants with TSB levels higher than 25 mg/dL, phototherapy should be administered continuously until a response is documented, or until exchange therapy is initiated. If the TSB is not responding to conventional phototherapy (a response is defined as a sustained reduction in TSB of 1-2 mg/dL in 4-6 hours), the intensity should be increased by adding more lights; the intensity of the lights should also be increased while exchange transfusion is prepared. With commonly used light sources, overdose is impossible, although the infant may experience loose stools. Phototherapy is continued until the TSB level is lower than 14-15 mg/dL. The infant may be discharged after the completion of phototherapy. Rebound of TSB following cessation of phototherapy is usually less than 1 mg/dL.

2. Exchange transfusion—Exchange transfusion rapidly removes bilirubin from the circulation. Circulating antibodies against erythrocytes are also removed. Exchange transfusion is
particularly beneficial in neonates with hemolysis. One or two central catheters are placed. Small aliquots of blood (8-10 mL per pass) are removed from the infant’s circulation and replaced with equal amounts of donor red cells mixed with plasma. The procedure is repeated until twice the infant’s blood volume is replaced (~160-200 mL/kg). Serum electrolytes and bilirubin are measured periodically during the procedure. In some cases the procedure must be repeated to lower serum bilirubin levels sufficiently. Infusing salt-poor albumin at a dose of 1 g/kg 1-4 hours before exchange transfusion has been shown to increase the amount of bilirubin removed during the procedure.

Complications of exchange transfusion include thrombocytopenia, portal vein thrombosis, necrotizing enterocolitis, electrolyte imbalance, graft-versus-host disease, and infection. Mortality from exchange transfusion approaches 2%, and an additional 12% of infants may suffer serious complications. Therefore, exchange transfusion should be reserved for neonates who have failed intensive phototherapy and should be performed by clinicians and facilities with proper experience.

Measurement of serum albumin levels in an infant suspected of jaundice is an option, considering levels less than 3.0 g/dL as one risk for lowering the threshold for phototherapy. If exchange transfusion is being considered, the bilirubin/albumin ratio is used in conjunction with the TSB level and other factors in determining the need for exchange transfusion (see Figure 3-3).

C. Suspected Nonpathologic Jaundice

For the management of breastfeeding jaundice, interruption of breastfeeding in healthy term newborns is generally discouraged. Frequent breastfeeding sessions (at least 8-10 times in 24 hours) are advised. However, if the mother and physician wish, they may consider using supplemental formula feedings or temporarily interrupting breastfeeding and replacing it with formula feedings. Phototherapy may be initiated, depending on TSB levels.

As previously discussed, breast milk jaundice is seen initially after day 6 of life in the majority of healthy breast-fed infants between 3 weeks and 3 months of age. This is a form of normal physiologic jaundice.

Conclusions

Because up to 60% of all newborns are noted to be clinically jaundiced, all family physicians who care for neonates will encounter this common clinical entity. In the overwhelming majority of cases, this jaundice is entirely benign. However, it is important that the family physician recognize cases in which jaundice could represent a pathologic process or the risk for development of severe hyperbilirubinemia.

As in the treatment of other conditions such as fever in the neonate, close monitoring and surveillance are important, and strategies for assessing risk must be used. Infants who are discharged prior to 48 hours of age, particularly those who are born at less than 35 weeks’ gestation, should be seen in the office within a few days of discharge to evaluate jaundice and overall clinical status.

The possibility of jaundice should be discussed with parents before hospital discharge. Parents of newborns should be assured of the generally benign nature of most cases of jaundice, especially breastfeeding jaundice and breast milk jaundice. Parental education should emphasize the need to monitor the infant for jaundice and associated symptoms such as poor feeding, lethargy, dark urine, and light-colored stools. Family physicians should encourage parents to contact the office with specific questions and concerns. An example of a parent information sheet in English and Spanish is available at http://www.aap.org/family/jaundicefaq.htm.

NEONATAL HYPERBILIRUBINEMIA


ESSENTIALS OF DIAGNOSIS

- Visible yellowing of the skin, ocular sclera, or both are present in neonatal jaundice; however, because visual estimates of total bilirubin are prone to error, quantitative testing (serum or transcutaneous) should be completed in infants noted to be jaundiced within the first 24 hours of life.

- Risk of subsequent hyperbilirubinemia can be assessed by plotting serum bilirubin levels onto a nomogram; all bilirubin levels should be interpreted according to the infant’s age (in hours).
General Considerations

Nutrition is a critical capstone for the proper growth and development of infants. Breastfeeding of term infants by healthy mothers is the optimal mechanism for providing the caloric and nutrient needs of infants. Preterm infants can also benefit from breast milk and breastfeeding although supplementation and fortification of preterm breast milk may be required. Barring some unique circumstances, human breast milk can provide nutritional, social, and motor developmental benefits for most infants.

Despite increased emphasis on breastfeeding education, according to the 2005 National Immunization Survey conducted by the Center for Disease Control, approximately 75% of women chose to initiate breastfeeding. Of these women, only 43.1% were still breastfeeding at 6 months, and 21.4% of infants were still receiving breast milk at 1 year. The Department of Health and Human Services Healthy People 2010 initiative proposes to increase these numbers to 50% and 25% for infants at 6 and 12 months, respectively. The rates of women who were exclusively breastfeeding without formula supplementation were even lower with only 31.5% and 11.9% of infants ages 3 and 6 months, respectively, doing so. There are still, however, disparities associated with these rates, specifically for African American women. Breastfeeding rates are about 50% lower among all ages regardless of income or educational level in comparison to Caucasian women. Education of practitioners as well as their patients is an integral component of this initiative.

Most women presently of childbearing age were not breast-fed and report having no maternal relatives who breast-fed their children. Because evidence clearly suggests familial influences in the development of infant feeding practices, practitioners may find it difficult to encourage breastfeeding behaviors among women with no direct familial breastfeeding experience.

Efforts to alter knowledge, attitudes, and behaviors regarding breastfeeding must effectively address the numerous psychosocial barriers. Health care providers are critical conduits for maternal and familial education. All members of the health care team, including physicians, midwives, and nurses, are valuable sources of important evidence-based information as well as psychological support for mothers in search of guidance regarding infant feeding practices. Unless health care practitioners are properly educated regarding breastfeeding practices and barriers, efforts to achieve the Healthy People 2010 objectives will remain suboptimal.

Numerous studies have shown the superiority of breast milk and the health advantages that breast-fed children have. The literature has shown that infants who are breast-fed have fewer episodes of diarrheal illness, ear infections, and allergies. Exclusive breastfeeding for at least 4 months in infants at risk for developing atopic disease decreases the cumulative incidence of atopic dermatitis. Lower rates of childhood obesity, type 2 diabetes, sudden infant death syndrome (SIDS) and leukemia have also been associated with breastfeeding. There are likewise financial advantages to breastfeeding. Other somewhat controversial investigations suggest higher intelligence among breast-fed infants.

There are also Maternal benefits to breastfeeding. Mothers who breast-feed are less likely to develop premenopausal breast cancer. An association with decreased rates of Type 2 diabetes and ovarian cancer also exists. Studies are also looking at the relationship between breastfeeding and rates of postpartum depression and cardiovascular disease. Most importantly, however, is the bonding relationship breastfeeding promotes between mother and infant.

All major maternal-child health professional organizations recommend exclusive breastfeeding for the first 6 months prior to the introduction of age-appropriate solid foods and advise continued breastfeeding for the first year of life.

The American Academy of Pediatrics (AAP) Committee on Nutrition recommends breastfeeding for the first year of life with supplemental vitamin D at birth and the addition of supplemental iron at age 4 months and possible addition of fluoride at age 6 months for infants living in regions in which
water is low in fluoride. Vitamin D supplementation is particularly applicable in regions with limited sunlight and for infants of mothers with decreased daily intake of cow’s milk. Further recommendations include delaying introduction of cow’s milk until after 1 year and delaying addition of reduced-fat milk until 2 years of age. To this end, new mothers should be encouraged to continue prenatal vitamins containing supplemental iron, calcium, and vitamin D. Supplemental solid foods should be considered at or around 6 months of age once the infant demonstrates appropriate readiness.

**Anatomy of the Human Breast & Breastfeeding**

Women are able to produce milk by the age they are able to bear children. There is no evidence that breast function, breast milk production, or composition is different among younger women. The principal external structures of the mature human female breast are the nipple, areola, and Montgomery tubercles. The areola is the darker part of the breast, with the nipple being the central-most structure through which milk ducts open and milk is expressed. Within the areola are Montgomery tubercles, through which sebaceous and sweat glands (Montgomery glands) open, producing lubricating substances for the nipple.

Underlying structures include adipose tissue, mammary gland cells, and contractile myoepithelial cells surrounding the gland cells (allowing for milk ejection). Milk produced within the alveoli is ejected into the milk ducts which open out directly to the nipple. It was thought previously that milk was stored in lactiferous sinuses, however recent research has concluded that these sinuses do not exist.

Infant breastfeeding draws the nipple and areola into the mouth, causing elongation of the nipple. The elongated nipple is compressed between the palate and the tongue and milk is expressed less than 0.05 seconds after the nipple has elongated. Stimulation of the areola is essential for the oxytocin-mediated hormonal cascade that controls milk ejection.

**Physiology of Breastfeeding**

Two principal hormones are required for breast milk production—oxytocin and prolactin—controlled by the hypothalamic-pituitary axis. Oxytocin production and secretion are under the control of the posterior pituitary and are stimulated by suckling. Oxytocin production in response to suckling is intermittent and stimulates ejection (“let down”) of breast milk. Oxytocin does not appear to affect breast milk production, although numerous stressors can negatively impact breast milk let down. Evidence suggests that lactogenesis may be delayed and let down reduced following stressful vaginal delivery or cesarean section.

Milk production is controlled primarily by the release of prolactin. Prolactin secretion is through a feedback loop under dopaminergic control with the primary action on prolactin receptors on mammary epithelium. Suckling likewise stimulates prolactin release. Furthermore, prolactin acts as an inhibitor of ovulation through hormonal feedback control, although breastfeeding is considered a relatively unreliable contraceptive mechanism.

Several additional hormones are required for milk production: cortisol, human growth hormone, insulin, thyroid and parathyroid hormones, and feedback inhibitor of lactation (FIL). Not entirely understood, FIL appears to act at the level of breast tissue to inhibit continued breast milk production when the breast is not completely emptied.

Milk production begins during the postpartum period with prolactin production and concomitant decreased estrogen and progesterone production following placental delivery. Milk production will persist under this hormonal control for the first several days; however, continued milk production beyond the initial 48 hours postpartum requires suckling. Although mothers will continue to produce milk between feedings once suckling has initiated the feedback loop, milk production significantly rises during breastfeeding.

**Breast Milk**

**A. Stages of Production**

Production of human breast milk among healthy mothers who deliver full-term infants occurs in three phases—colostrum, transitional milk, and mature milk. Colostrum is a thick, yellow substance produced during the first several days postpartum. Healthy mothers produce approximately 80–100 mL daily. Colostrum is rich in calcium, antibodies, minerals, proteins, potassium, and fat-soluble vitamins. This milk has immunologic qualities that are vital to the infant and it possesses gastrointestinal properties to aid in secretion of meconium. Production of colostrum is followed for the next 5–6 days with transitional milk, which provides essential components more closely resembling mature breast milk. Most women will notice a significant change evidenced by the fullness of their breasts and the change in the consistency of the milk. True milk is white and sometimes has a bluish tint. The consistency is similar to cow’s milk with a sweet taste. Mature breast milk, produced beginning at or near postpartum day 10, produces key components, discussed in the next section.

Numerous factors may affect the supply of breast milk, including anxiety, medications, maternal nutritional status, sleep, exercise, breastfeeding frequency, tactile stimulation, and fluid intake. Breastfeeding mothers should be encouraged to consume generous amounts of fluids and express breast milk every 2–3 hours. The hormonal feedback loop that controls the production and release of prolactin and oxytocin is initiated by suckling or other tactile stimulation of the breast. The greater the amount of suckling or other tactile breast stimulation, the greater the milk supply.
B. Components

Mature human breast milk contains protein, carbohydrate, and fat components and provides approximately 20 kcal/oz and 1 g of protein. The principal protein elements of both mature and premature breast milk are casein (40%) and whey (60%). Breast milk contains approximately 2.5 g/L of casein. Also called “curds,” this protein forms calcium complexes. Higher concentrations of this protein are found in cow’s milk. Whey (approximately 6.4 g/L) is a protein component composed of α-lactalbumin, lactoferrin, lysozyme, immunoglobulins, and albumin.

Free nitrogen, vital for amino acid synthesis, is also a significant component of mature breast milk and is integral for multiple biochemical pathways, including production of uric acid, urea, ammonia, and creatinine. It is also a key component of insulin and epidermal growth factor.

There are approximately 70 g/L of lactose, the primary carbohydrate in mature breast milk. Composed of galactose and glucose, the lactose concentration continues to increase throughout breastfeeding. Human milk fat likewise increases with continued breastfeeding. Mature breast milk provides approximately 40 g/L and includes triacylglycerides, phospholipids, and essential fatty acids.

The principal electrolytes in breast milk are sodium, potassium, magnesium, and calcium. Calcium appears to be mediated through the parathyroid hormone–related protein, which allows for mobilization of calcium stores from bone in otherwise healthy women. Bone calcium levels return to normal after termination of breastfeeding. Regulation of sodium and potassium concentrations in breast milk occurs through corticosteroids.

Iron absorption is particularly high in newborns and infants, although the relative concentration of iron in mature breast milk is low. For infants younger than 6 months of age, the concentration of iron in breast milk is sufficient and supplementation is not necessary; however, recommendations for infants older than 6 months include supplemental iron from green vegetables, meats, and iron-rich cereals. The recommended amount of supplemental elemental iron is 1 mg/kg/d. Iron is an essential component in the synthesis of hemoglobin.

Vitamin K, a lipid-soluble vitamin and important component in the clotting cascade, is routinely provided in the immediate postpartum period as a 1-mg intramuscular injection. There is evidence that oral vitamin K may produce similar benefit as well as maternal supplementation of 5 mg/d of oral vitamin K for 12 weeks following delivery.

Another lipid-soluble component, vitamin D, is essential for bone formation. Women who have limited exposure to sunlight or suboptimal vitamin D intake will produce little or no vitamin D in breast milk. The recommended daily intake of vitamin D is 400 IU/d. Practitioners must be cognizant of mothers with special diets (ie, vegetarian diets) whose low vitamin D intake might indicate a need for supplemental vitamin D.

Other elemental minerals in breast milk (eg, zinc, copper, selenium, manganese, nickel, molybdenum, and chromium) are found in trace amounts but nonetheless are essential for a multitude of biochemical processes.

C. Composition of Preterm Breast Milk

The composition of breast milk in mothers of preterm infants is different from that in mothers of term infants. This difference persists for approximately 4 weeks before the composition approaches that of term infant breast milk. The difference in preterm milk composition reflects the increased nutrient demands of preterm infants. Preterm breast milk contains higher concentrations of total and bound nitrogen, immunoglobulins, sodium, iron, chloride, and medium-chain fatty acids. However, it may not contain sufficient amounts of phosphorus, calcium, copper, and zinc. Preterm infants are more likely to require fortification with human milk fortifiers (HMF) to correct these deficiencies.

Breastfeeding Technique

Preparation for breastfeeding should begin in the preconception period or at the first contact with the patient. Most women choose their method of feeding prior to conception. Psychosocial support and education may encourage breastfeeding among women who might not otherwise have considered it. Evidence for this strategy, however, is anecdotal and requires further investigation.

There are numerous potential supports available to women who are considering feeding behaviors. Practitioners are encouraged to identify members of the patient’s support network and provide similar education to minimize the potential barriers posed by uninformed support individuals.

One commonly perceived physical barrier is nipple inversion. Women who have inverted nipples will have difficulty with the latch-on process (discussed in section Breastfeeding Technique, later). Nipple shields are relatively inexpensive devices that can draw the nipple out. Manual or electric breast pumps may also be used to draw out inverted nipples, typically beginning after delivery.

Adoptive mothers represent another group with perceived potential barriers to breastfeeding. Feeding of the infant must be discussed once the decision to adopt has been made. Adoptive mothers can be medicated to simulate pregnancy and stimulate production of milk. Despite these hormonal adjuncts, these mothers sometimes will have an inadequate response and subsequent inadequate milk supply. There are several types of supplemental feeding systems that women can wear while breastfeeding that attach to the nipple to provide additional nutrition along with the breast milk.

Breastfeeding should begin immediately in the postpartum period, ideally in the first 30–40 minutes after delivery. This is easier to accomplish if the infant is left in the room with the mother before being bathed and before the newborn examination is performed. It is also safe to allow breastfeeding...
before administration of vitamin K and erythromycin ophthalmic ointment.

Clinical situations arise that preclude initiation of breastfeeding in the immediate postpartum period (i.e., cesarean delivery, maternal perineal repair, maternal or fetal distress). In such cases breastfeeding should be initiated at the earliest time possible. Only when medically necessary should a supplemental feeding be initiated. If mothers have expressed a desire to breast-feed, the practitioner should coordinate an interim feeding plan, emphasizing that bottle feeding not be started. Acceptable alternatives include spoon, cup, or syringe feeding.

Breast-fed children commonly feed at least every 2-3 hours during the first several weeks postpartum. Infants should not be allowed to sleep through feedings; however, if necessary, feeding intervals may be increased to every 3-4 hours overnight. The production of breast milk is on a supply-demand cycle. Breast stimulation through suckling and the mechanism of breastfeeding signals the body to make more milk. When feedings are missed or breasts are not emptied effectively, the feedback loop decreases the milk supply. As the infant grows, feedings every 3-4 hours are acceptable. During growth spurts, the amount of milk needed for the rate of growth often exceeds milk production. Feeding intervals often must be adjusted to growth periods until the milk supply “catches up.”

Although feeding intervals may be increased during nighttime periods, a common question becomes when to stop waking the infant for night feedings. Anecdotal evidence suggests that after the first 2 weeks postpartum, in the absence of specific nutritional concerns, the infant can determine its own overnight feeding schedule. Typically, most infants will begin to sleep through the night once they have reached approximately 10 lb.

Positioning of the infant is critical for effective feeding in the neonatal period, allowing for optimal latch-on. In general, infant and mother should face each other in one of the following three positions: the cradle, the most common, the football, or the lay/side. The cradle hold allows the mother to hold the infant horizontally across the front of the chest. The infant’s head can be on the left or right side of the mother depending on which side he or she is feeding. The infant’s head should be supported with the crook of the mother’s arm. The football hold is performed with the mother sitting on a bed or chair, the infant’s bottom against the bed or chair and its body lying next to the mother’s side, and the infant’s head cradled in her hand. The side position allows the mother to lay on her left or right side with the infant lying parallel to her. Again, the infant’s head is cradled in the crook of the mother’s elbow. This position is ideally suited for women postcesarean delivery as it reduces the pain associated with pressure from the infant on their incisions. It must be stressed that choice of position is based on mother and infant comfort. It is not unusual to experiment with any or all positions prior to determining the most desirable. It is likewise not uncommon to find previously undesirable positions more effective and comfortable as the infant grows and the breastfeeding experience progresses. All breastfeeding positions should allow for cradling of the infant’s head with the mother’s hand or elbow allowing for better head control in the latch-on stage. The infant should be placed at a height (often achieved with a pillow) appropriate for preventing awkward positioning, maximizing comfort, and encouraging latch-on.

Many of the difficulties with breastfeeding result from improper latch-on. Latch-on problems are often the source of multiple breastfeeding complaints among mothers, ranging from engorgement to sore cracked nipples. Many women discontinue breastfeeding secondary to these issues. The latch-on process is governed by primitive reflexes. Stroking the infant’s cheek will cause the infant to turn toward the side on which the cheek was stroked. This reflex is useful if the infant is not looking toward the breast. Tickling the infant’s bottom lip will cause his or her mouth to open wide in order to latch-on to the breast. The mother should hold her breast to help position the areola to ease latch-on. It is important that the mother’s fingers be behind the areola so as not to provide a physical barrier to latch-on. Once the infant’s mouth is opened wide, the head should be pulled quickly to the breast. The infant’s mouth should encompass the entire areola to compress the milk ducts. If this is done improperly, the infant will compress the nipple, leading to pain and eventually cracking, with minimal or no milk expression. The mother should not experience pain with breastfeeding. If this occurs the mother should break the suction by inserting a finger into the side of the infant’s mouth and then latch the infant on again. This process should be repeated as many times as necessary until proper latch-on is achieved.

One issue that continually concerns parents is whether the infant is receiving adequate amounts of breast milk. Several clinical measures can be used to determine if infants are receiving enough milk. Weight is an excellent method of assessment. Pre- and postfeed measurement of an infant with a scale that is of high quality and measures to the ounce is a very accurate means of determining weight. The problem is that this type of scale is not available to most families. Weight can also be evaluated on a longer-term basis. Infants should not lose more than about 8% of their birth weight after delivery and should gain this weight back in 2 weeks.

Most infants with difficulties, however, will decompensate before this 2 week period. Breast-fed infants should be evaluated 2-3 days after discharge, especially if discharged prior to 48 hours postdelivery. A more convenient way to determine the adequacy of the infant’s intake of milk is through clinical signs such as infant satisfaction postfeeding and bowel and bladder amounts. In most cases infants who are satisfied after feeding will fall asleep. Infants who do not receive enough milk will usually be fussy or irritable or continuously want to suck at the breast, their finger, and so on. Breast-fed infants usually will stool after most feeds but at a minimum five to six times a day. After the first couple of days, the stool should turn from meconium-like to a mustard-colored seedy type. If breast-fed infants are still passing
meconium or do not have an adequate amount of stool, parents and health care team should evaluate whether they are taking in enough milk. Infants should also urinate approximately three or four times a day. This may be hard to assess with the era’s superabsorbent diapers; therefore, careful examination of the diaper should be made.

**Problems Associated with Breastfeeding**

An inadequate milk supply can lead to disastrous outcomes if not identified and treated. There are two types of milk inadequacies—the inability to make milk and the inability to keep the supply adequate. The first type of milk inadequacy is quite rare but examples include surgeries in which the milk ducts are severed or Sheehan syndrome. There is no specific treatment to initiate milk production in affected women. The inability to maintain an adequate milk supply has numerous etiologies, ranging from dietary deficiencies to engorgement. The key in preventing adverse events is early recognition and effective treatment. One of the mainstays of treatment is working with the body’s own feedback loop of supply and demand to increase the supply. As more milk is needed, more milk will be produced. This is effectively done by using a breast pump. Pumping should be performed after the infant has fed.

Engorgement is caused by inadequate or ineffective emptying of the breasts. As milk builds up in the breasts they become swollen. If the condition is not relieved, the breasts can become tender and warm. Mastitis can also develop. The mainstay of treatment is emptying the breasts of milk, either by the infant or if that is not possible by mechanical means. Usually when the breast is engorged, the areola and nipple are affected and proper latch-on becomes difficult if not impossible. A warm compress may be used to help with let down, and the breast can be manually expressed enough to allow the infant to latch-on. If this is not possible or is too painful the milk can be removed with an electrical breast pump. Between feedings a cold pack can be used to decrease the amount of swelling. There have been reports that chilled cabbage leaves used to line the bra can act as a cold pack that conforms to the shape of the breast and can reduce the pain and swelling. However, there is no evidence of any medicinal properties in the cabbage that affect engorgement. Mastitis, if occurring, is treated with antibiotics. Mothers can continue to breast-feed with the affected breast so care should be taken to choose an antibiotic that is safe for the infant.

Sore nipples are a common problem for breastfeeding mothers. In the first few weeks there may be some soreness associated with breastfeeding as the skin gets used to the constant moisture. There should not be pain with breastfeeding; if there is pain it is usually secondary to improper latch-on, which resolves with correction. With severe cracking there will occasionally be bleeding. Breastfeeding can be continued with mild bleeding, but if severe bleeding occurs the breast should be pumped and the milk discarded to prevent gastrointestinal upset in the infant. There are some remedies that can be used in the event of cracking. Keeping the nipples clean and dry between feedings can help prevent and heal cracking. The mother’s own milk or a pure lanolin ointment can also be used as a salve. Mothers should be warned not to use herbal rubs or vitamin E because of the risk of absorption by the infant. Another cause of sore nipples is candidal infection. This usually occurs when an infant has thrush. Sometimes treating the infant will resolve the problem, but occasionally the mother will need to be treated as well. Taking the same nystatin liquid dose that the infant is using twice a day will resolve the infection. Again, keeping the nipples clean and dry can help.

Blebs, a small pimple or blister-like lesion on the nipple, can also be a cause of sore nipples. This occurs secondary to the opening of the milk duct being covered by new epithelial cells. Treatment includes moisturizing the nipples with lanolin and gentle exfoliation. This can be exacerbated by a candidal infection as well and would require the same treatment stated previously. If these lesions do not heal, they may require surgical debridement.

Another controversial issue in breastfeeding is silicone implants. According to American Society of Plastic surgeons approximately 2 million women had breast implants from year 2000 to 2007. Although only little research has been done on effects of silicone implants on lactation, there are a few areas of concern including implants leaking material in breast milk, baby absorbing the silicone from the milk if it is spilled, and additional risk of the infant exposure to the silicone. Due to its presence in the environment it is difficult to distinguish between normal and abnormal maternal levels. It has been found that silicon is present in higher concentrations in cow milk and formula than in milk of humans with implants. An additional study directly assayed the silicone polymer and found that levels in the milk of women with implants were not significantly different from those in other human milk samples. The American Academy of Pediatrics in its recent policy statement on silicone breast implants and breastfeeding concluded that the “Committee on Drugs does not feel that the evidence currently justifies classifying silicone implants as a contraindication to breastfeeding. Safety of breastfeeding by women with silicone breast implants has not been adequately studied—a fact these women should be told. The potential health risks of artificial feeding have been shown and until there is better evidence, women with implants should be encouraged to breast-feed.

Other issues with breastfeeding include medications, nutrient supplementation, and mothers returning to work. These issues are broad in scope; in fact, whole books have been dedicated to these subjects. The most important issue to understand when considering medication use during pregnancy is that limited research has been done in this area and that there is insufficient information on most medicines to advocate their use. Health care providers should try to use the safest medications possible that will allow mothers to continue breastfeeding. If this is not possible mothers should be encouraged to pump the milk and discard it to maintain the milk supply.
Nutrient supplementation is another controversial issue. Vitamin D is recommended for supplementation in either dark-skinned women or women who do not receive much sunlight. The iron found in breast milk, although in low concentrations, is highly absorbable. Infants who are breast-fed do not need additional sources of iron until they are 4-6 months old. This is the time when most children are started on cereal. Choosing an iron-fortified cereal will satisfy the additional iron requirement.

Return to work is the major reason why women discontinue breastfeeding. Planning this return from birth and pumping milk for storage help women to continue breastfeeding. Employers who provide time and a comfortable place to pump milk at work will also improve breastfeeding rates. Although the goal is to increase the number of women who begin breastfeeding and continue it throughout the first year of the infant’s life, many women cannot or do not choose to breast-feed. Their decision must be supported and they must be educated on alternative methods of providing nutrition for their infant.

**Maternal Nutrition and Breastfeeding**

There are many studies that look at maternal nutrition and breastfeeding. It is well known that adequate fluid intake is necessary for milk production. Studies seem to suggest that the benefits of infant nutrition outweigh the risk of any maternal effects of breastfeeding.

Often some maternal foods that are strong in flavor, such as garlic, broccoli, and onions, can provide a flavor to breast milk that is displeasing to the infant or can create increased flatulence. These food types should be avoided if they interfere with feeding. There are also women that are concerned with creating allergies based on food that is consumed while breastfeeding. Currently there is lack of evidence that maternal dietary restrictions (like avoiding peanuts) during pregnancy or lactation play a significant role in prevention of atopic disease in infants. Antigen avoidance during lactation does not prevent atopic disease with possible exception of eczema although more data are needed to substantiate conclusion.

**Vegetarian Diet and Breastfeeding**

The number of Americans choosing a vegetarian diet has increased dramatically in the past decade. With these increasing numbers more research has been done in an effort to evaluate the feasibility of a vegetarian diet in infancy. A vegetarian diet is defined as a diet consisting of no meat. This definition does not encompass the variety of vegetarian diets that are consumed. A pure vegetarian or vegan consumes only plant food. In general most pure vegetarians also do not use products that result from animal cruelty such as wool, silk, and leather. Lacto-ovo vegetarians consume dairy products and eggs in addition to plants and lacto-ovo vegetarians consume only dairy products with their plant diet.

There is great variety in each of these diets and therefore great variety in the type and amount of food necessary for adequate nutrition. Milk from breastfeeding mothers who are vegetarians is adequate in all nutrients necessary for proper growth and development. Although all required nutrients can be found in any vegetarian diet, in infancy the amount necessary may be difficult to provide without supplementation. The American Dietetic Association stated that a lacto-ovo vegetarian diet is recommended in infancy. If this diet is not desired by parents or is not tolerated by children, then supplementation may be necessary. Vitamin B₁₂, iron, and vitamin D are nutrients that may need to be supplemented, depending on environmental factors.

**Contraindications to Breastfeeding**

Although considered the optimal method of providing infant nutrition during the first year of life, breastfeeding may be contraindicated in some mothers. Scenarios that may preclude breastfeeding include mothers who actively use illicit drugs such as heroin, cocaine, alcohol, and PCP; mothers with HIV infection or AIDS; and mothers receiving pharmacotherapy with agents transmitted in breast milk and contraindicated in children, particularly potent cancer agents. Some immunizations for foreign travelers and military personnel may also be contraindicated in breastfeeding mothers. Infants with galactosemia should also not breast-feed.

**Infant Formulas**

The historical record reveals that methods of replacing, fortifying, and delivering milk and milk substitutes date back to the Stone Age. Evidence suggests that the original infant “formulas” of the early and mid-twentieth century consisted of 1:1 concentrations of evaporated milk and water with supplemental cod liver oil, orange juice, and honey. As the number of working mothers steadily increased during this time, the use of infant formulas became more popular.

In the past three decades, more sophisticated neonatal medical practices have led to the development of countless infant formula preparations to meet a wide variety of clinical situations. Formulas exist as concentrates and powders that require dilution with water and as ready-to-feed preparations. Commonly, formula preparations provide 20 cal/oz with standard dilutions of 1 oz concentrate to 1 oz water and 1 scoop powder formula to 2 oz water for liquid concentrates and powders, respectively. Formulas exist as cow’s milk–based, soy-based, and casein-based preparations.

**A. Cow’s Milk-Based Formula Preparations**

This is the preferred, standard non–breast milk preparation for otherwise healthy term infants who do not breast-feed or for whom breastfeeding has been terminated prior to 1 year of age. Cow’s milk–based formula closely resembles human breast milk and is composed of 20% whey and 80% casein with 50% more protein/dL than breast milk as well as iron,
linoleic acid, carnitine, taurine, and nucleotides. Formulas containing docosahexaenoic acid and arachidonic acid have been recently marketed to promote eye and brain development. So far no randomized trials have shown any benefit although no harm has been established.

Approximately 32 oz will meet 100% of the recommended daily allowance (RDA) for calories, vitamins, and minerals. These formula preparations are diluted to a standard 20 cal/oz and are typically whey-dominant protein preparations with vegetable oils and lactose. There are also multiple lactose-free preparations. Most standard formula preparations do not meet the RDA for fluoride, and exclusively formula-fed infants may require 0.25 mg/d of supplemental fluoride.

### B. Soy-Based Formula Preparations

Indicated primarily for vegetarian mothers and lactose-intolerant, galactosemic, and cow’s milk–allergic infants, soy-based formulas provide a protein-rich formula that contains more protein per deciliter than both breast milk and cow’s milk formula preparations. Because the proteins are plant based, vitamin and mineral composition is increased to compensate for plant-based mineral antagonists while supplementing protein composition with the addition of methionine. Soy-based formulas tend to have a sweeter taste owing to a carbohydrate composition that includes sucrose and corn syrup. There is no proven benefit of soy-based formulas for milk protein allergy. Soy-based formulas should not be used for preterm infants because they cause less weight gain and increase the risk of osteopenia of prematurity. ProSobee, Isomil, and I-Soyalac are common soy-based preparations.

### C. Casein Hydrolysate–Based Formula Preparations

This poor-tasting, expensive formula preparation is indicated principally for infants with either milk and soy-protein allergies or intolerance. Other indications include complex gastrointestinal pathologies. This formula, which contains casein-based protein and glucose, is not recommended for prolonged use in preterm infants owing to inadequate vitamin and mineral composition and proteins that may be difficult to metabolize. Standard preparations provide 20-24 cal/oz.

### D. Premature Infant Formula Preparations

Indicated for use in preterm infants of less than 1800 g birth weight, and with three times the vitamin and mineral content of standard formula preparations, these formulations provide 20-24 cal/oz. Premature infant preparations are approximately 60% casein and 40% whey, with 1:1 concentrations of lactose and glucose as well as 1:1 concentrations of long- and medium-chain fatty acids. Commercially available preparations include Enfamil Premature with Iron, Similac Natural Care Breast Milk Fortifier, and Similac Special Care with Iron. Similac Neo-Care, designed for preterm infants weighing more than 1800 g at birth, provides 22 cal/oz in standard dilution.

#### Human Milk Fortifiers for Preterm Infants

Human milk fortifiers (HMFs) are indicated for preterm infants less than 34 weeks’ gestation or less than 1500 g birth weight once feeding has reached 75% full volume. HMFs are designed to supplement calories, protein, phosphorus, calcium, and other vitamins and minerals.

Enfamil-HMF is mixed to 24 cal/oz by adding one 3.8-g packet to 25 mL of breast milk, increasing the osmolality to greater than 350 mOsm/L. Increased osmolality may enhance gastrointestinal irritability and affect tolerance. Practitioners may recommend a lower osmolality for the first 48 hours, beginning with one packet of Enfamil-HMF in 50 mL of breast milk, producing 22 cal/oz. The maximum caloric density from this HMF is 24 cal/oz. Practitioners may add emulsified fat blends to increase caloric needs.

Similac Natural Care is a liquid milk fortifier that is typically mixed in a 1:1 ratio with breast milk. Other alternatives may include feedings with breast milk and fortifier. The osmolality of Similac Natural Care is lower than that of Enfamil—280 mOsm/L. This liquid fortifier may be preferable, particularly for infants whose mothers have low milk production.

Other specially formulated formulas are available including antireflux and hypoallergenic formulas. Reflux usually does not require treatment unless there is poor weight gain. Antireflux formulas decrease emesis and regurgitation, but long-term benefit in terms of growth and development has not been established. Hypoallergenic formulas have shown to promote slightly greater weight gain in the first year of life. They have also shown improvement in atopic symptoms.

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**Berlin CM: Silicone breast implants and breastfeeding. Pediatrics 1994;94:547-549.**

**Breastfeeding Report Card—United States, 2008.**


Web Sites

La Leche League: http://www.lalecheleague.org
Resources for breastfeeding products and information: http://www.breastfeedingbasics.org
http://www.breastfeeding.hypermart.net
http://www.medela.com
Infectious diseases are a major cause of disease in children. The widespread use of antibiotics has greatly reduced morbidity and mortality, but infections are still one of the most common types of problems encountered by physicians who care for children.

FEVER WITHOUT A SOURCE

General Considerations

Fever is the primary sign that indicates an infectious process in children of all ages. Other than fever, however, many children do not display signs or symptoms indicative of the underlying disease. Twenty percent of febrile children, after history and physical examination, have fever without a source of infection. The physician's dilemma is to separate children with a serious bacterial illness from those with a viral or nonserious bacterial illness. A serious bacterial illness is defined variably, but generally includes growth of a known bacterial pathogen from cerebrospinal fluid, blood, urine, or stool, as well as abscess or cellulitis and pneumonia with positive blood cultures. Children are generally divided into three groups for evaluation purposes: young children aged 3 months to 3 years, young infants aged 2-3 months, and neonates (≤1 month of age). There is no absolute demarcation between these ages. Rather, one age group fades into the next, and the physician is left to make a judgment about how to treat each child in the border ages.

Young children are much more likely to show outward signs of illness, and their evaluation is much easier than that of younger infants. Neonates are a separate diagnostic group, more likely to have infections with organisms seen in the newborn period and less likely to show overt clinical signs of infection.

No officially adopted, evidence-based guidelines have been written detailing suggested guidelines based on expert opinion, group consensus, and locally performed research studies. Baraff and colleagues published a set of useful practice guidelines that are summarized in Table 5-1.

The frequency and nature of serious bacterial illness is different in the three different age groups. Neonates younger than 1 month of age are the most difficult to diagnose. The rate of serious bacterial illness in nontoxic febrile neonates has been reported to be between 8.6% and 12.6%. However, existing screening protocols lack the sensitivity and negative predictive value to identify infants at low risk for these infections. For this reason, it is generally accepted that all febrile infants younger than 1 month of age be admitted to the hospital, given a complete sepsis workup, and treated with parenteral antibiotics pending the results of the workup. Of these infants, approximately 65% have a viral infection, 13% have a serious bacterial illness, and the rest have nonbacterial gastroenteritis, aseptic meningitis, or bronchiolitis. Of the infants with serious bacterial illnesses, roughly 7% have a urinary tract infection (UTI), with Escherichia coli being the most common pathogen. Three percent have bacteremia, with group B Streptococcus, Enterobacter, Listeria, Streptococcus pneumoniae, E coli, Enterococcus, and Klebsiella all being found. Fewer than 2% have meningitis, usually caused by Klebsiella, Listeria, and group B Streptococcus.

In evaluating infants older than 1 month of age, it is useful to first identify which infants are at low risk for a serious bacterial illness. The criteria for low risk are being previously healthy, having no focal source of infection found on physical examination, and having a negative laboratory evaluation, defined as a white blood cell (WBC) count of 5000-15,000/mm³, fewer than 1500 bands/mm³, normal urinalysis, and, if diarrhea is present, fewer than 5 WBCs per high-power field in the stool. Chest radiography is included in some, but not all, sets of criteria. Lumbar puncture may be performed at the physician's discretion but should always be done if empiric antibiotics are to be used. Additional low-risk criteria are appearing nontoxic and having a good social situation.
with reliable follow-up. Low-risk, nontoxic-appearing infants may be treated as outpatients, with close follow-up. Most recommendations are to use empiric antibiotics, but some authors feel that antibiotics may be withheld if the infant can be followed closely. All toxic-appearing or non–low-risk infants should be hospitalized and treated with parenteral antibiotics. The risk of serious bacterial illness in toxic-appearing infants in this age group is about 17%. The overall frequency of such infections in this age group is roughly 9% overall and 1%-2% in low-risk infants, with most of the infections being UTIs, bacteremia, and bacterial enteritis. Meningitis accounts for slightly more than 1% of febrile infants.

Similar criteria may be used to evaluate children aged 3 months to 3 years. The most common serious bacterial illnesses in this group are bacteremia and UTIs. UTIs are present in nearly 5% of febrile infants younger than 12 months of age. In this group, 6%-8% of girls and 2%-3% of boys have UTIs. The rates are higher in those with higher temperatures. After 12 months of age, the prevalence of UTI is lower.

In this age group, the rate of bacteremia has been reported to be 3%-11%, with a mean of 4.3% if the temperature is 39°C (102.2°F) or higher. The most common organisms isolated are *S. pneumoniae* (85%), *Haemophilus influenzae* type b (10%), and *Neisseria meningitidis* (3%). The rate of infection with *H. influenzae* has fallen dramatically since the use of the Hib vaccine has become widespread, and the rate of pneumococcal bacteremia is expected to do likewise in the near future.

Occult pneumonia is rare in febrile children who have a normal WBC count and who do not have signs of lower respiratory infection, such as cough, tachypnea, rales, or rhonchi.

As in younger infants, toxic-appearing or non–low-risk infants should be hospitalized and treated with parenteral antibiotics. The rate of serious bacterial infections

### Table 5-1. Evaluation and treatment of febrile children.

<table>
<thead>
<tr>
<th>Infant &lt;&lt;1 mo of age</th>
<th>Child 3 mo to 3 y of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admit for evaluation and treatment</td>
<td>Toxic: admit</td>
</tr>
<tr>
<td><strong>Infant 2-3 mo of age</strong></td>
<td>Nontoxic:</td>
</tr>
<tr>
<td>Toxic or non-low risk: admit</td>
<td>Temperature &lt;&lt;39.0°C (102.2°F):</td>
</tr>
<tr>
<td>Nontoxic, low risk:</td>
<td>No tests or antibiotics</td>
</tr>
<tr>
<td>Option 1</td>
<td>Symptomatic treatment for fever</td>
</tr>
<tr>
<td>• Blood culture</td>
<td>Return if fever persists &gt;&gt;48 h or if condition deteriorates</td>
</tr>
<tr>
<td>• Urine culture</td>
<td>Temperature &gt;&gt;39.0°C (103.1°F):</td>
</tr>
<tr>
<td>• Lumbar puncture</td>
<td>Urinalysis: if positive, perform culture, treat with oral third-generation cephalosporin</td>
</tr>
<tr>
<td>• Ceftriaxone, 50 mg/kg IM (1 g max)</td>
<td>If child has not received pneumococcal conjugate vaccine:</td>
</tr>
<tr>
<td>• Return for reevaluation within 24 h</td>
<td>• If temperature &gt;&gt;39.5°C, obtain WBC count</td>
</tr>
<tr>
<td></td>
<td>• If WBC count &gt;&gt;15,000/mm³, obtain blood culture, administer</td>
</tr>
<tr>
<td></td>
<td>ceftriaxone, 50 mg/kg</td>
</tr>
<tr>
<td>Option 2</td>
<td>If SaO₂ &lt;&lt;95%, respiratory distress, tachypnea, rales, or temperature</td>
</tr>
<tr>
<td>• Blood culture</td>
<td>&gt;&gt;39.5°C and WBC count &gt;&gt;20,000/mm³, obtain chest x-ray</td>
</tr>
<tr>
<td>• Urine culture</td>
<td>Symptomatic treatment for fever</td>
</tr>
<tr>
<td>• Careful observation</td>
<td>Return if fever persists &gt;&gt;48 h or if condition deteriorates</td>
</tr>
</tbody>
</table>

**Low-risk criteria:**

**Clinical**
- Previously healthy, term infant with uncomplicated nursery stay
- Nontoxic appearance
- No focal bacterial infection on examination (except otitis media)

**Laboratory**
- WBC count 5000-15,000/mm³, <<1500 bands/mm¹
- Negative Gram stain of unspun urine (preferred), or negative urine leukocyte esterase and nitrite, or <<5 WBCs/HPF
- CSF <<8 WBCs/mm³ and negative Gram stain

in toxic-appearing children in this age group has been reported to be 10%-90%, depending on the definition of toxic. Low-risk, non–toxic-appearing children in this age group may be treated as outpatients. The use of empiric antibiotics pending culture results is left to the physician’s discretion. There is general consensus that bacteremia is a risk factor for development of infectious complications, such as meningitis. However, pneumococcal bacteremia responds well to oral antibiotics, so these drugs can be used in children who appear well despite having positive blood cultures.

Clinical Findings

A. Symptoms and Signs

The most important clinical decision is to decide which infants appear toxic and therefore need more aggressive evaluation and treatment. “Toxic” is defined as a picture consistent with the sepsis syndrome—lethargy, signs of poor perfusion, marked hypoventilation or hyperventilation, or cyanosis. “Lethargy” is defined as an impaired level of consciousness as manifested by poor or absent eye contact or by failure of the child to recognize parents or to interact with people or objects in the environment.

Fever is defined as temperature of 38°C (100.4°F) or higher. Rectal measurement is the only accurate way to determine fever. A careful, complete physical examination is necessary to exclude focal signs of infection. The skin should be examined for exanthems, cellulitis, abscesses, or petechiae. Between 2% and 8% of children of all ages with fever and a petechial rash have a serious bacterial infection, most often caused by *N meningitidis*. Common childhood infections such as pharyngitis and otitis media should be sought, and a careful lung examination should be done looking for evidence of pneumonia. The abdomen should be examined for signs of peritonitis or tenderness. A musculoskeletal examination should be done looking for evidence of osteomyelitis or septic arthritis. The neurologic examination should be directed toward the level of consciousness and should look for focal neurologic deficits.

B. Laboratory Findings

The laboratory investigation includes WBC count and differential, urinalysis and urine culture, blood culture, lumbar puncture with routine analysis and culture, and chest x-ray. If the child has diarrhea, stool cultures should be evaluated.

Treatment

All infants younger than 1 month of age should be hospitalized. An appropriate antibiotic regimen includes ceftriaxone (50 mg/kg/d) with or without gentamicin. In the past, ampicillin has been used routinely to cover the possibility of *Listeria* infection. Although it appears that the frequency of infection with *Listeria* is decreasing, ampicillin may be added to this regimen if the physician chooses.

Ceftriaxone is likewise an appropriate antibiotic for hospitalized older infants and children and for infants and children treated as outpatients. In infants 2-3 months of age, a single intramuscular dose of ceftriaxone should be given. The child should be reevaluated in 18-24 hours and a second dose of ceftriaxone given. If blood cultures are found to be positive, the child should be admitted for further treatment. If the urine culture is positive and the child has a persistent fever, the child should be admitted for treatment. If the child is afebrile and well, outpatient antibiotics may be used.

Table 5-1 presents guidelines that may be useful for investigating and treating febrile children.


INFECTIONS OF THE UPPER RESPIRATORY TRACT

OTITIS MEDIA

ESSENTIALS OF DIAGNOSIS

- Preexisting upper respiratory infection (URI; 93%).
- Fever (25%).
- Ear pain (variable, depending on age).
- Bulging, immobile tympanic membrane that is dull gray, yellow, or red in color.
- Perforated tympanic membrane with purulent drainage (diagnostic).

General Considerations

Acute otitis media (AOM) is the most common reason that children see a physician, accounting for almost 30 million physician visits each year among children younger than 1 year of age. Almost all children have at least one episode of otitis media each year, and one-third have three or more episodes.

Pathogenesis

When cultures of middle ear fluid are done, *S pneumoniae* is found in about 35%, *H influenzae* in about 25%, and *Moraxella catarrhalis* in about 15%. Ten percent of effusions show more than one of these bacteria, and about 25% are sterile. Viruses are recovered in a large percentage of cases, with or without bacteria, but whether their role is causative or not remains unclear.
Prevention

There are several identified risk factors for otitis media, not all of which are easily modifiable for prevention of the disease. The chief risk factor is day care. Other risk factors include increased number of siblings in the house, exposure to tobacco smoke, pacifier use, formula feeding, and lower socioeconomic status. Children with abnormalities of the palatal architecture, such as those with cleft palate or Down syndrome, are at greatly increased risk. Widespread use of vaccines against *H influenzae* type b and *S pneumoniae* are not expected to have much impact on the disease, as the infection is generally caused by nontypeable *Haemophilus* and by strains of pneumococcus not covered by the pediatric 7-valent vaccine.

Clinical Findings

A. Symptoms and Signs

Despite the frequency with which physicians see children with otitis media, the diagnostic criteria are not standardized, and the diagnosis itself is often unclear. Otitis media most often begins with a URI, and as many as 93% of children with AOM have typical symptoms of URI. Symptoms of AOM may develop over only a few hours, or the onset may be more gradual. Ear pain is the most characteristic symptom. Younger children do not localize pain as obviously as older children. Fever is present only in about 25% and is more common in younger children. The tympanic membrane bulges and may be cloudy, yellow, or red in color. Erythema of the tympanic membrane may be caused by fever or by screaming, so this sign is of questionable reliability. The drum generally is immobile with pneumatic otoscopy or tympanometry. The infection is bilateral in half of affected children. The tympanic membrane ruptures in fewer than 5% of cases, but pus draining through a perforation is diagnostic.

Differential Diagnosis

As previously discussed, the primary illness that may be confused with AOM is acute URI. Many of the symptoms are identical, and findings in the tympanic membrane may be subtle and nondiagnostic.

Complications

Complications of otitis media fall into two main categories—suppurative and nonsuppurative. Suppurative complications may arise from direct extension of the infection into the surrounding bones or into the adjacent brain, such as mastoiditis, venous sinus thrombosis, and brain abscess. They may also arise from hematogenous spread of the bacteria from the middle ear, primarily sepsis and meningitis. The main suppurative complication is mastoiditis, which develops in about 1 in 1000 cases. Recent research shows that treatment of otitis media does not reduce the incidence of this complication. The bacteria responsible for hematogenous spread are principally *S pneumoniae* and *H influenzae*.

Nonsuppurative complications are primarily those that arise from middle ear effusion and inflammation and scarring of the structures of the middle ear. Antibiotic treatment does not influence the persistence of middle ear effusions after otitis media, nor does it have any effect on long-term hearing and language development. In summary, it appears that complications of otitis media may not be preventable by antibiotic treatment.

Treatment

Although antibiotic treatment has long been the standard of care for children with AOM, research has shown that the benefits of antibiotics are much less clear than was believed in the past. As many as 59% of children have resolution of symptoms within 24 hours without treatment, and between 80% and 85% recover in 1-7 days without antibiotics. Antibiotic treatment reduces the persistence of symptoms at 2-7 days to 7%, or about a 12% reduction.

The high spontaneous resolution rate makes comparisons of treatments difficult. Narrow-spectrum antibiotics have the same success rate as broad-spectrum antibiotics, although adverse effects, primarily gastrointestinal, are more common with the latter. All guidelines recommend oral amoxicillin as first-line therapy. The AAP/AAFP (American Academy of Pediatrics/American Academy of Family Physicians) guideline recommends high-dose amoxicillin (80-90 mg/kg/d), as this dose has been found to be more effective against penicillin-resistant *S pneumoniae* than standard-dose treatment. However, the studies supporting high-dose therapy are based on bacteriologic cure; evidence that high-dose therapy is clinically superior is lacking. All guidelines recommend high-dose amoxicillin-clavulanate (90/6.4 mg/kg/d) as second-line treatment. Some also recommend various cephalosporins, including ceftriaxone, cefdinir, cefprozil, or cefuroxime, as second-line therapy or as first-line treatment for children with “non–type I” penicillin allergy. No guidelines recommend azithromycin, trimethoprim-sulfamethoxazole, erythromycin, or cefaclor, except in cases of severe penicillin allergy, or when the organism is known to be sensitive to one of these drugs. Studies also document that a 5-day course of antibiotics is as effective as the standard 10-day course. Thus, based on numerous studies, a recommended approach is to treat children with AOM using a 5-day course of narrow-spectrum antibiotics.

Another acceptable option is withholding antibiotic treatment for 48-72 hours, treating pain as needed, and beginning antibiotic therapy if the symptoms do not resolve within this time period. This may be considered in children over the age of 2 years if the presenting illness is not severe (fever <39°C [102.2°F] and mild or no pain). This is also an option for children between the ages of 6 months and 2 years,
if the diagnosis of otitis media is uncertain and the symptoms are not severe.

It is important to note that studies have not adequately addressed the issues of treatment of children younger than 2 years of age and treatment of frequently recurrent or complicated otitis media. Physicians are left to their clinical judgment as to the best treatment for these children.

The best treatment for children with frequent recurrences of otitis media is another area of study. The best evidence is that children will only benefit from daily antibiotic prophylaxis if they have had more than three episodes in 6 to 18 months. The magnitude of benefit is small, with a reduction of about one episode per year. Antibiotics studied have primarily been narrow-spectrum drugs, such as erythromycin, amoxicillin, sulfisoxazole, and trimethoprim-sulfamethoxazole. Insertion of tympanostomy tubes as treatment for persistent otitis media with middle ear effusions has not been found to improve developmental outcomes.

Prognosis

In general, children with otitis media recover uneventfully. The half-life of the middle ear effusion is about 4 weeks, with 10% persistence at 4 months. Repeated courses of antibiotics have no effect on these effusions and should not be used.

1. Group A β-Hemolytic Streptococcal Infection

ESSENTIALS OF DIAGNOSIS

- Moderate to severe tonsillar swelling.
- Moderate to severe tender anterior cervical lymphadenopathy.
- Scarlatiniform rash (depending on the strain of bacteria).
- Absence of moderate to severe viral symptoms (cough, nasal congestion).

General Considerations

GABHS cause approximately 15% of cases of sore throat in children. The infection is uncommon in children younger than 3-5 years of age and in adolescents older than 11-15 years of age.

Clinical Findings

A. Symptoms and Signs

Clinical symptoms and signs overlap those of viral pharyngitis and URIs. The Centor criteria have been validated for adults but not for children. Attia and colleagues proposed a predictive model for GABHS after examining a large number of signs and symptoms. The findings most highly correlated with GABHS are moderate to severe tonsillar swelling, moderate to severe tender anterior cervical lymphadenopathy, scarlatiniform rash, and the absence of moderate to severe coryza. If all four of these are present, the likelihood of GABHS is 95%. Excluding scarlatiniform rash, the presence of the remaining three gives a probability of greater than 65%. In the absence of moderate to severe tonsillar enlargement, moderate to severe lymphadenopathy, and scarlatiniform rash and in the presence of moderate to severe coryza, the likelihood of GABHS is less than 15%.

PHARYNGITIS

Sore throat is a common problem in pediatrics, leading to millions of physician office each year. However, obtaining a clear diagnosis as to the cause of this problem is far from simple. The most important diagnosis to make is infection with group A β-hemolytic streptococci (GABHS), which is responsible for about 15% of cases of pharyngitis. Antibiotic treatment has only a modest effect on the course of the disease, but adequate treatment with antibiotics effectively prevents the important complication of rheumatic fever. Non-GABHS occasionally cause pharyngitis but do not lead to rheumatic fever. Viruses of many sorts cause the vast majority of cases, including some cases of exudative pharyngitis. Adenoviruses can cause pharyngoconjunctival fever, with exudative pharyngitis and conjunctivitis. Epstein-Barr virus causes infectious mononucleosis, which commonly produces other signs, such as generalized lymphadenopathy and splenomegaly, in addition to exudative pharyngitis. Herpesviruses and coxsackie viruses can cause ulcerative stomatitis and pharyngitis. Most viruses, however, cause signs and symptoms that overlap with those of GABHS. The literature contains numerous recommendations for diagnosis and treatment, but there is no clear consensus as to the most accurate or most cost-effective method for evaluation and treatment of the child with a sore throat.
B. Laboratory Findings

Rapid antigen detection tests are commonly used in practice. Although the sensitivities of these assays may be reported as very high in laboratories, in practice they may have a false-negative rate as high as 20%. The sensitivity and specificity of throat culture is dependent on technique and may also have a false-negative rate of 10%-20%. Another complicating factor is the inability of either rapid antigen testing or culture to distinguish between a true streptococcal infection and a viral infection in a child who is an otherwise asymptomatic carrier. Carrier rates among asymptomatic children may be as high as 17%, depending on the age of the child and the season of the year. Centers for Disease Control and Prevention (CDC) recommends treating only rapid-antigen or culture proven streptococcal disease to avoid promoting antibiotic resistance in other pharyngeal bacteria.

Complications

Complications of GABHS fall into two main categories: nonsuppurative and suppurative. The nonsuppurative complications are rheumatic fever and post-streptococcal glomerulonephritis. The main suppurative complications are peritonsillar and retropharyngeal abscess (see section Peritonsillar Abscess, later).

Acute rheumatic fever follows about 3% of cases of untreated GABHS. The cause is still not fully understood, but the prevailing theory is that there is some similarity between certain streptococcal antigens and certain myocardial proteins leading to antistreptococcal antibody recognition and interaction with the myocardial proteins. There is great geographic variability in the incidence of this disease. Rheumatic fever can be prevented by treatment of GABHS, even if treatment is delayed for up to 9 days, but a full 10 days of treatment is necessary for complete prevention. Post-streptococcal glomerulonephritis likewise seems to be caused by a poorly understood antigen-antibody reaction. Unlike rheumatic fever, glomerulonephritis is not prevented by treatment of GABHS.

Treatment

Treatment of GABHS may accomplish two things—quicker resolution of disease and prevention of some complications. Treatment of the acute infection may shorten the course of the disease by a small amount, although untreated disease will resolve within several days in most children. It is not clear whether immediate antibiotic treatment offers greater benefit than symptomatic treatment. It is generally believed that treatment reduces the rate of suppurative complications, but for many children who present with peritonsillar abscess, the initial streptococcal infection would not have been recognized in its earlier stages.

Currently, no GABHS are resistant to penicillin or cephalosporins. For reasons that are unclear, numerous studies show that cephalosporins have higher rates of clinical and bacteriologic success than penicillin. However, penicillin V is still considered the drug of choice for children who are not allergic to penicillin. There is no agreement as to the best alternative in penicillin-allergic children. Because of increasing resistance to erythromycin in some areas, clindamycin is often recommended. It is well established that 10 days of treatment is necessary to achieve the maximum possibility of bacterial eradication from the pharynx. However, for reasons that are unclear, streptococci persist in the pharynx in about 10% of treated children, regardless of which antibiotic is used. There is no consensus as to the best way to deal with this phenomenon.

Prognosis

Streptococcal pharyngitis is ordinarily a benign, self-limited disease. Morbidity and mortality are primarily related to the previously mentioned complications. Antibiotic treatment can eliminate many but not all of these.


CDC Academic Detailing Sheet, March 2006.


2. Peritonsillar Abscess

ESSENTIALS OF DIAGNOSIS

Severe sore throat.

Odynophagia.

High fever.

Unilateral pharyngeal swelling with deviation of the uvula.

General Considerations

Peritonsillar abscess is the most common deep space head and neck infection in children, accounting for almost half of these infections. It is most commonly caused by infection with GABHS. The exact cause is unknown, but it is thought that the infection usually spreads from the tonsil itself into the deep spaces behind the tonsil, where it produces a collection of pus. It can occur in children of all ages, as well as in adults, but it affects older children and adolescents more than younger children. It is almost always unilateral.
Clinical Findings

A. Symptoms and Signs

Most children with peritonsillar abscess have had symptoms of pharyngitis for 1-7 days before presenting with symptoms related to the abscess. Many of these children have been treated with antibiotics for pharyngitis before developing the abscess. The most common symptoms are severe throat or neck pain, painful swallowing, high fever, and poor oral intake, sometimes with dehydration. The most common physical signs are cervical adenopathy, uvular deviation, and muffled voice with trismus. Symptoms are less clear and the examination more difficult in younger children, and young children who cannot cooperate may have to be examined under sedation.

B. Laboratory Findings

The WBC count is usually elevated, with a left shift. Throat cultures for streptococci are positive in only about 16% of specimens.

C. Imaging Studies

Computed tomography and ultrasound studies of the neck often show the abscess, but the diagnosis is generally made by history and physical examination.

Differential Diagnosis

The chief disease in the differential diagnosis is epiglottitis. This infection is uncommon in an era of widespread immunization against H influenzae type B, but the clinical picture may be identical in young children. Examination in the operating room under sedation may be necessary to establish the diagnosis.

Complications

Prompt treatment is necessary, because untreated abscesses may spread into other deep spaces in the head and neck. The airway may be compromised by swelling, especially in younger children. If the abscess ruptures into the throat, aspiration of pus may cause pneumonia.

Treatment

The treatment is drainage of the abscess, either by incision or by needle aspiration. This is generally done by an otolaryngologist or a surgeon familiar with the anatomy of the neck. Tonsillectomy is often done at the discretion of the surgeon, either at the time of the acute infection or shortly thereafter. Antibiotics effective against streptococci and staphylococci, such as nafcillin or ceftriaxone, are indicated, initially intravenously. Once cultures of the pus indicate the causative organism, treatment may be focused according to its antibiotic sensitivities.

Prognosis

Children generally recover uneventfully once appropriate treatment is begun, but they may be at increased risk for a second infection.


INFLUENZA

Essentials of Diagnosis

Nonspecific respiratory infection in infants and young children.

In older children, respiratory symptoms—coryza, conjunctivitis, pharyngitis, dry cough.

In older children, pronounced high fever, myalgia, headache, malaise.

General Considerations

Influenza is a respiratory virus that causes a respiratory infection of variable severity in children. Although influenza itself is a benign, self-limited disease, its sequelae, primarily pneumonia, can cause serious illness and occasionally death.

Pathogenesis

Influenza is caused by a variety of influenza viruses. Types A and B cause epidemic illness, whereas type C produces sporadic cases of respiratory infections. Infection with influenza virus confers limited immunity that lasts several years, until the natural antigenic drift of the virus produces a pathogen that is genetically distinct enough to escape this protection. Because every virus is new for infants, the attack rate is highest in infants and young children, with between 30% and 50% showing serologic evidence of infection in a normal year.

Prevention

The most effective way to prevent influenza and its complications is to immunize people of all ages at highest risk for complications. Influenza vaccine protects against both types A and B. Recent studies show that complication rates are similar across all children, regardless of what are often considered to be risk factors, and that otherwise healthy children younger than 2 years of age, and possibly those between the ages of 2 and 4 years as well, have a higher rate of complications than older children. For this reason, routine annual immunization has been recommended for children between the ages of 6 and 59 months. In 2008, the ACIP recommended
routine immunization of all children between the ages of 5 and 18 years, as well.

Children younger than 9 years who have never been immunized against influenza should receive two doses of vaccine, 1 month apart. Children 9 years of age and older need only one dose. The unit dose for children 6-35 months of age is 0.25 mL. The unit dose for children 36 months of age and older is 0.5 mL. The vaccine must be repeated annually. The vaccine should be given in October or November, to protect children during the peak months of December through February. Peak antibody levels are achieved roughly 2 weeks after immunization (2 weeks after the second dose in vaccine-naive children).

Chemoprophylaxis with a variety of drugs is an alternative to immunization, although this option is much more expensive than the vaccine. Because strains of influenza virus most recently active in United States have been resistant to amantadine and rimantadine, these drugs are no longer recommended for this purpose. Oseltamivir is indicated for prophylaxis in children older than 1 year, and zanamivir can be used in children older than 5 years of age. The optimal duration of treatment is not known. The H1N1 influenza virus that emerged in 2008 is likewise resistant to amantadine and rimantadine. At this date this virus is almost always sensitive to oseltamivir and zanamivir.

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**Clinical Findings**

**A. Symptoms and Signs**

Influenza viruses types A and B cause nearly identical symptoms, except that the duration of symptoms in type A infection is usually several days, whereas symptoms usually last only 2 or 3 days in type B infection. Influenza in infants and young children causes a nonspecific respiratory infection. Occasionally the fever is high enough and the child toxic enough in appearance to prompt hospitalization and workup for sepsis. In older children and adolescents, the disease presents with the abrupt onset of respiratory symptoms, such as URI symptoms, conjunctivitis, pharyngitis, and dry cough. The features that distinguish influenza from the usual URI are high fever and pronounced myalgia, headache, and malaise. The acute symptoms typically last for 2-4 days, but the cough and malaise may persist for several days longer. Physical findings are nonspecific and include pharyngitis, conjunctivitis, cervical lymphadenopathy, and occasionally rales, wheezes, or rhonchi in the lungs.

During the 2007-2008 influenza season, the emergence of a new strain of influenza virus—H1N1—was identified in several countries. This virus spread rapidly around the world to become a pandemic. It appears to have less of a seasonal incidence than the usual influenza virus, but it is otherwise clinically similar to seasonal influenza. The case-fatality rate is about the same as seasonal influenza (<1%). However, children and young adults in the United States have no prior immunity to this strain of virus, so it has the potential to cause widespread infection in the United States and worldwide, with a correspondingly high number of deaths among children and adults. H1N1 was the predominant influenza strain in the United States during the 2009-2010 season. Children age 6 months to 18 years are considered to be at high risk for complications from this virus and should therefore be given high priority for immunization. In the fall of 2009, a vaccine against this strain was released. It is available as an inactivated injectable vaccine that can be given to any patient and as a live-attenuated virus nasal spray vaccine. The live-virus vaccine should not be given to children less than 2 years of age, to immunosuppressed children, or to children on chronic aspirin therapy. With either vaccine, children less than 10 years of age should be given two doses at least 28 days apart.

**B. Special Tests**

Influenza is generally diagnosed based on clinical criteria. If confirmation of infection is desired, the virus can be identified by nasopharyngeal swabs sent for polymerase chain reaction (PCR) identification of the influenza virus. In centers where the test can be done in house, the results can usually be known in about one day. Identification of the specific strain of influenza virus takes longer. While rapid identification kits are available for bedside testing, these are generally considered too poorly sensitive and specific to be of much clinical utility.

**Complications**

Otitis media and pneumonia are the most common complications from influenza. Up to 25% of children develop otitis media after a documented influenza infection. Influenza causes a primary viral pneumonia, but the more serious pneumonic complications are caused by bacterial superinfection.

**Treatment**

Treatment of established influenza infection within 2 days of the onset of symptoms can reduce the duration of symptoms by about 1 day compared with placebo. However, no drug has been shown to reduce the incidence of serious complications following the disease. Because of resistance in recent viral strains, amantadine and rimantadine are no longer recommended. Oseltamivir can be used in children older than 1 year of age, and zanamivir can be used for children age 7 years and older. Both are given as a 5-day course. Given the cost of these medications and their inability to prevent complications, immunization is clearly a superior alternative for controlling influenza and its sequelae.

**Prognosis**

Influenza is ordinarily a benign self-limited disease. Morbidity and mortality are related either to postinfluenza pneumonia or to exacerbation of underlying chronic illness caused by the virus.
CHAPTER 5


INFECTIONS OF THE LOWER RESPIRATORY TRACT

CROUP (ACUTE LARYNGEOTRACHEOBRONCHITIS)

ESSENTIALS OF DIAGNOSIS

- URI prodrome.
- Barking cough.
- Symptoms worst on first or second day, with gradual resolution.
- Lungs clear.
- Inspiratory stridor, respiratory distress, cyanosis in severe cases.

General Considerations

Croup is a relatively common infection in children, causing between 27,000 and 62,000 hospitalizations each year. Most cases occur in the autumn and early winter, with most hospitalizations in October and February. The peak age incidence of croup is 3 months to 5 years of age.

Pathogenesis

Croup is caused by an infection of the upper airways—the larynx, trachea, and the upper levels of the bronchial tree—and obstruction of these airways caused by edema produces most of the classic symptoms of the disease. Nearly all cases of croup are caused by viruses. Parainfluenza viruses cause 75% of cases. Adenovirus and respiratory syncytial virus (RSV) cause most of the remainder, and Mycoplasma pneumoniae accounts for 3%-4% of cases.

Clinical Findings

A. Symptoms and Signs

The symptoms of croup are usually typical, and diagnosis is not difficult. Most children present after several days of prodromal URI symptoms, which are followed by the gradual onset of a barking, “seal-like” cough. Stridor is generally mild and intermittent at first, primarily with inspiration and worse when the child is agitated. Typically, respiratory distress is only mild to moderate. In most children, this is the maximum extent of the disease. The symptoms are generally worst on the first or second day, are usually worse at night than during the day, and gradually resolve over several days. If the symptoms progress beyond this point, the child develops worsening respiratory distress, more pronounced and more constant stridor, and cyanosis.

The physical findings of croup are variable and depend on the severity of the illness. The lungs are usually clear. The degree of subcostal and intercostal retractions, the degree of stridor, and the presence of cyanosis are important clues to the severity of the illness. If the child is cyanotic and in respiratory distress, manipulation of the pharynx (eg, trying to examine the pharynx using a tongue depressor) may trigger respiratory arrest. This maneuver should therefore be avoided until the clinician is in a position to manage the child’s airway by endotracheal intubation.

B. Laboratory Findings

Laboratory findings are generally minimal. The WBC count is usually normal or slightly elevated; however, counts greater than 15,000/mm³ are seen in about 20% of children. The blood oxygen saturation may be normal or decreased, depending on the severity of the disease.

C. Imaging Studies

In a typical child with croup, the chest x-ray is normal. In 40%-50% of children, anteroposterior soft-tissue x-rays of the neck show subglottic narrowing, causing the classic “steeple” sign of croup.

Differential Diagnosis

Croup must be differentiated from other respiratory illness that cause cough as the main symptom. Normally, the time course and nature of the cough are diagnostic. Spasmodic croup lacks the URI prodrome and has a more abrupt onset than typical croup. Bacterial tracheitis presents as typical croup that worsens instead of improving after a few days. Children with epiglottitis and peritonsillar abscesses are acutely ill and often toxic appearing, and while they may have a cough, it is not the predominant feature of the disease. Children with bronchiolitis are usually younger than the children with croup, and their lungs show diffuse fine end-expiratory wheezes. Likewise, expiratory wheezing is a prominent feature of asthma but not of croup, which may produce prominent inspiratory stridor in children with severe disease. Children with pneumonia usually have a looser, more productive cough, they often have more focal pulmonary findings on examination, and chest x-ray often shows an infiltrate.

Complications

About 15% of children with croup experience complications of varying severity. These are usually related to extension of the infection to other parts of the respiratory tract, such as otitis media or viral pneumonia. Bacterial pneumonia is unusual, but bacterial tracheitis may occur. Children with...
severe croup may develop complications of hypoxemia, if this is not adequately treated. Death is unusual and generally due to laryngeal obstruction.

### Treatment

Perhaps the most critical decision to make when evaluating children with croup is which patients need to be treated in the hospital and which will do well at home. Between 1.5% and 15% of children with croup are hospitalized for treatment, and of these, 1%-5% require intubation and ventilation. The published croup scoring systems may be useful for research purposes, but they do not present validated criteria for determining the best course of treatment for an individual child. High fever, toxic appearance, worsening stridor, respiratory distress, cyanosis or pallor, hypoxia, and restless-ness or lethargy are all symptoms of more severe disease and should prompt the physician to admit the child for inpatient treatment.

Most children with croup may be treated at home. The mainstay of treatment has long been held to be cool, moist air, although research has not confirmed the effectiveness of this treatment. Although corticosteroids have long been an accepted part of inpatient treatment, their role in outpatient management of this disease has only more recently been addressed. A single intramuscular dose of dexamethasone, 0.6 mg/kg, may be effective in reducing the severity of moderate to severe croup in patients treated at home. Because the onset of action for dexamethasone is about 6 hours, a single dose is 0.6 mg/kg, intramuscularly, and it should be given as early as possible in the course of the disease. The drug can be given as a single dose, which remains effective for the remainder of the course of the disease. The dose is 0.6 mg/kg, intramuscularly, and it should be given as early as possible in the course of the disease. Nebulized steroids and oral dexamethasone are more effective than placebo but less effective than intramuscular dexametha-sone. Children hospitalized for treatment of croup should be observed carefully for any signs of respiratory distress. Intubation and mechanical ventilation are necessary in a small percentage of children with this disease.

### Prognosis

The natural history of croup is that recurrences are common. However, as children grow, the airways grow larger and are less affected by edema, and symptoms tend to become less severe over time.


### BRONCHIOLITIS

**ESSENTIALS OF DIAGNOSIS**

- URI symptoms.
- Paroxysmal wheezy cough.
- Dyspnea.
- Tachypnea.
- Diffuse fine rales.

### General Considerations

Bronchiolitis is a common disease of infants, affecting up to 7% of infants and leading to hospitalization in up to 1% during the first 2 years of life. It is an infection that causes edema and obstruction of the small airways. Bronchiolitis is seen most commonly in the first 2 years of life, with a peak age of about 6 months. Older children and adults contract the same infection, but because they have larger airways, they do not experience the same degree of airway obstruction. In fact, an older sibling or a parent is often the source of the infant’s infection.

### Pathogenesis

Bronchiolitis is almost always viral in etiology. RSV causes more than half of cases; others are caused by parainfluenza viruses, with a few cases caused by *M pneumonia*. Pathologically, edema and accumulated cellular debris cause obstruction of small airways. This obstruction causes a ventilation-perfusion mismatch with wasted perfusion, a right-to-left shunt, and hypoxemia early in the course of the disease.

### Prevention

Since 1999, palivizumab has been available in the United States for prevention of RSV disease in high-risk infants. The drug has been shown to decrease hospitalization rates among high-risk infants with and without chronic lung disease, although the death rates in the initial studies were not significantly different between the treatment and placebo groups. The decision to use this drug is based on the age of the child at the onset of RSV season and the child’s medical history. The AAP recommends prophylaxis with palivizumab for children younger
Clinical Findings

A. Symptoms and Signs

The typical course of bronchiolitis begins with the exposure of an infant to another person with a URI. The infant generally has URI symptoms for several days, with or without fever, then experiences the gradual onset of respiratory distress, with a paroxysmal wheezy cough and dyspnea. The infant may be irritable and feed poorly, but there are usually no other systemic symptoms. The temperature is often in the range of 38.5-39°C (101.3-102.2°F), although it may be subnormal to greatly elevated.

Physical examination shows the child to be tachypneic, with a respiratory rate as high as 60-80 per minute, and often in severe respiratory distress. Alar flaring, retractions, and use of accessory muscles of respiration may be evident. Examination of the lungs often shows a prolonged expiratory phase with diffuse wheezes. Diffuse fine rales at the end of expiration and the beginning of inspiration are typical findings. The lungs are often hyperinflated with shallow respirations, and breath sounds may be nearly inaudible if the obstruction is severe.

The most critical phase of bronchiolitis is the first 2-3 days of the illness. Most cases resolve in 1-3 days without much difficulty. However, in severe cases, symptoms may develop within hours and may be protracted.

B. Laboratory Findings

The laboratory finding of most utility is the oxygen saturation, which may be used to help determine the severity of respiratory distress and the need for hospitalization. If bronchiolitis is suspected, a nasopharyngeal swab may be done for RSV culture, but this has little, if any, effect on the outcome of the illness.

C. Imaging Studies

Radiography usually shows signs of hyperinflation. In about one-third of children, x-rays show scattered areas of consolidation. These may represent postobstructive atelectasis or inflammation of alveoli. It may not be possible to exclude early bacterial pneumonia solely on the basis of radiographic findings.

Differential Diagnosis

An important item in the differential diagnosis of bronchiolitis is acute asthma, as there may be many similarities in history and physical examination between these two conditions. Asthma is unusual in the first year of life, and the incidence of bronchiolitis peaks at 6 months of age. The presence of one or more of the following favors the diagnosis of asthma: family history of asthma, sudden onset without a preceding URI, repeated attacks, a markedly prolonged expiratory phase of respiration, and response to one dose of epinephrine.

Complications

Bronchiolitis is ordinarily a benign disease. Complications are related to hypoxemia and are more common and more severe in children with underlying cardiac or pulmonary disease. The mortality rate is 1%-2% for all infants, 3%-4% in children with underlying cardiac or pulmonary disease, and 20%-67% in immunocompromised children.

Treatment

Treatment of bronchiolitis is primarily supportive. The decision to hospitalize the child is clinical, based on the degree of respiratory distress. Placing the child in a tent with cool humidified oxygen both relieves hypoxemia and reduces water loss from tachypnea. Intravenous fluids may be necessary. Antibiotics and steroids are of no benefit in bronchiolitis, but antibiotics may be given if the x-ray suggests pneumonia. The role of bronchodilators is controversial. Some infants with what appears to be bronchiolitis respond to these medications, suggesting a possible link between bronchiolitis and reactive airways disease. Also, studies of bronchiolitis are often confounded by the possible inclusion of children with asthma. Nebulized epinephrine has been shown by consistent randomized controlled trials and systematic reviews to decrease oxygen requirements, respiratory rate, and wheezing. Beta-agonists are not beneficial but may be useful in children with preexisting asthma. Bronchodilators should be discontinued if patients do not respond quickly, to avoid complications associated with these drugs. Treatment with anti-inflammatory medications such as nebulized budesonide or cromolyn sodium after an episode of bronchiolitis can reduce wheezing episodes and hospital admissions for bronchospasm. Whether such treatment is useful for all children or should be reserved only for children with clinically apparent wheezing after bronchiolitis has not been established. Despite considerable initial interest, ribavirin has not been shown to be of benefit, and it is no longer recommended for use in children with bronchiolitis.
Prognosis

There appears to be a relationship between bronchiolitis and reactive airways disease, although the exact connection is unclear. Some studies have shown an increased incidence of airway hyperreactivity that may persist for years in children who have had bronchiolitis.

Pertussis

**ESSENTIALS OF DIAGNOSIS**

- URI symptoms.
- Paroxysms of coughing, often with “whoops” on inspiration.
- Coughing to the point of vomiting.
- Dyspnea.
- Seizures.

**General Considerations**

Pertussis is a bacterial infection that affects airways lined with ciliated epithelium. It is endemic in the general population, with epidemics occurring every 3-4 years. The disease is most common in unimmunized infants and in adults, because immunity wanes 5-10 years after the last immunization. Pertussis causes serious disease in children and mild or asymptomatic disease in adults. Infants younger than 6 months of age have greater morbidity than older children, and those younger than 2 months have the highest rates of pertussis-related hospitalization, pneumonia, seizures, encephalopathy, and death. Pertussis is highly contagious, with attack rates as high as 100% in susceptible individuals exposed at close range.

**Pathogenesis**

The most common cause of pertussis is *Bordetella pertussis*, but adenoviruses can cause a similar disease. Pathologically, the bacteria attack ciliated epithelium in the respiratory tree, where they produce toxins and other active factors. These cause inflammation and necrosis of the walls of small airways, which lead in turn to plugging of airways, bronchopneumonia, and hypoxemia.

**Prevention**

The key to prevention of pertussis is immunization. However, immunization does not confer complete protection, and immunized children may be asymptomatic reservoirs for infection. Of the 7288 cases reported in 1999, 27% occurred in children younger than 7 months of age (i.e., in children too young to have received the full initial course of three doses of pertussis vaccine), 11% occurred in children between the ages of 1 and 4 years, and 28% were in children between the ages of 10 and 19 years. In 2006, a vaccine combining acellular pertussis vaccine with tetanus and diphtheria toxoids (Tdap) was recommended for use in children aged 11-18 years as a substitute for the adolescent tetanus-diphtheria vaccine. Tdap is also recommended for adults 19-64 years of age to replace the next booster dose of Td vaccine and for adults who have close contact with infants less than 12 months of age. Td vaccine is still recommended for children 7-9 years of age.

**Clinical Findings**

**A. Symptoms and Signs**

Children younger than 2 years of age show the most typical symptoms of the disease. In these children, 100% have paroxysms of coughing, with 60%-70% manifesting the “whoops” that give the disease its nickname of “whooping cough”; 60%-80% have vomiting induced by coughing; 70%-80% have dyspnea lasting more than 1 month; and 20%-25% have seizures. Children older than 2 years have lower incidences of all these symptoms and a shorter duration of disease, whereas adults often have atypical symptoms. High fever is unusual in all ages.

Pertussis has an incubation period lasting 3-12 days. After that, the disease progresses through three stages, each lasting approximately 2 weeks:

1. The *catarrhal stage* is characterized by symptoms typical of a URI. The symptoms are nonspecific, and the diagnosis of pertussis is usually not considered.

2. The *paroxysmal stage* lasts 2-4 weeks, occasionally longer. During this stage, episodes of coughing increase in severity and number. The typical paroxysm is 5-10 hard coughs in a single expiration, followed by the classic “whoop” as the patient inspires. The paroxysms recur until the mucus plugs causing the cough are dislodged. Coughing to the point of vomiting is common, and the diagnosis of pertussis should be considered in any patient with this symptom. The paroxysms are exhausting; the child may appear apathetic and may lose weight because he or she is too weak to eat or drink. The paroxysms may be frequent enough to cause hypoxemia, which may be severe enough to cause anoxic encephalopathy. Between the paroxysms, however, the patient may not appear otherwise especially sick.
3. During the convalescent stage, the paroxysms gradually decrease in frequency and number. The patient may experience a cough for several months after the disease has otherwise resolved.

The diagnosis of pertussis can usually be made in the paroxysmal stage, but it requires a certain level of suspicion. A cough lasting more than 2 weeks and associated with posttussive vomiting should prompt the physician to consider the diagnosis. There are no specific physical findings.

B. Laboratory Findings

A high WBC count (20,000-50,000/mm³) with an absolute lymphocytosis is common but not specific to the disease. The organism can be obtained for culture or staining by a nasopharyngeal swab. The sensitivity of culture is related to the stage of the disease and is very high early in the disease, when pertussis is least suspected. Culture is about 80% sensitive during the first 2 weeks of infection, 14% after the fourth week of infection, and zero after 5 weeks. Direct fluorescent antibody staining can provide a rapid diagnosis, but it has variable sensitivity and specificity, and all suspected cases should be cultured for definitive identification. Serology is useful only for retrospective diagnosis.

Differential Diagnosis

Any illness that causes cough should be considered in the differential diagnosis. Older children and children who have been immunized against the disease may have milder, atypical symptoms, and the only clue to the disease may be the long duration of the symptoms.

Complications

Complications of pertussis are numerous and often severe. Pneumonia is the most frequent complication and is seen in almost all fatal cases. *S. pneumoniae, Staphylococcus aureus,* and oral flora are the most common organisms involved. A high fever or absolute neutrophilia in a patient with pertussis may be the only clues to a secondary bacterial infection. The cough may be severe enough to rupture alveoli and may cause interstitial and subcutaneous emphysema or pneumothorax. The cough may also cause epistaxis, melena, subconjunctival hemorrhage, spinal epidural hematoma, intracranial hemorrhage, rupture of the diaphragm, or umbilical or inguinal hernia. Inability to eat or drink may lead to dehydration or electrolyte imbalances. Seizures are usually caused by anoxia but may be caused by hyponatremia secondary to inappropriate antidiuretic hormone secretion. Finally, anoxia may be severe enough to lead to coma.

Prognosis

The prognosis of pertussis depends primarily on the age of the patient. Mortality is rare in adults and children. With proper supportive care, the mortality rate for children younger than 6 months of age—the group at highest risk—is approximately 1%. Most mortality is due to pneumonia and cerebral anoxia.

Patients younger than 3 months of age—the group at highest risk—is approximately 1%. Most mortality is due to pneumonia and cerebral anoxia.

Treatment

Treatment is primarily supportive, involving hydration, pulmonary toilet, and oxygen. The decision to hospitalize the patient depends on the child’s age and general condition. Essentially all children younger than 6 months of age are admitted to the hospital. Nearly all children who require ventilation are younger than 3 months of age. Older children may be admitted if they experience complications of the disease or if their families are unable to provide care at home. Infants born prematurely and those with underlying cardiac, pulmonary, or neuromuscular disorders are also at higher risk for complications.

The patient should be placed in respiratory isolation until antibiotics have been given for at least 5 days. Erythromycin given for 14 days will eliminate the bacteria from the respiratory tract within 3-4 days. Trimethoprim-sulfamethoxazole, azithromycin, and clarithromycin are effective alternatives. If antibiotics are given within 14 days of the onset of the disease, they may abort or shorten the course of the disease, but the diagnosis of pertussis is rarely made in this stage of the illness. Once the paroxysmal stage begins, erythromycin will not affect the course of the disease, although it will shorten the period of infectivity and reduce communicability. Other appropriate antibiotics should be given if pneumonia or another secondary bacterial infection is suspected. Bronchodilators and steroids are probably of no benefit, and cough suppressants are likewise not helpful.

During a pertussis epidemic, newborns should receive their first immunization at 4 weeks of age, with repeat doses given at 6, 10, and 14 weeks of age. Partially immunized children younger than 7 years of age should complete the immunization series at the minimum intervals, and completely immunized children younger than 7 years should receive one booster dose, unless they have received one in the preceding 3 years. Children older than 7 years do not need further immunizations. Children who have had documented pertussis at any age are exempt from further pertussis immunizations. All contacts of patients with pertussis should be given erythromycin for 14 days after the date of their last contact with the patient. Continuous contacts of the patient (eg, parents) should be given erythromycin until the patient’s cough has stopped, or until the patient has received erythromycin for 7 days.
PNEUMONIA

ESSENTIALS OF DIAGNOSIS

► Fever.
► Acute respiratory symptoms.
► Radiographic evidence of parenchymal infiltrates.

General Considerations

Pneumonia occurs more often in young children than in any other age group, with an incidence of 34-40 cases per 1000 in children younger than 5 years of age. Many definitions of pneumonia have been proposed, based on several different criteria. The criteria used in this chapter are the presence of fever, respiratory findings, and evidence of parenchymal infiltrates on chest radiography. Although accurate diagnosis of an infection as potentially serious as pneumonia is obviously desirable, there are significant obstacles to diagnostic certainty.

Pathogenesis

Viruses are a leading cause of pneumonia in children of all ages. Bacterial infections are more common in developing countries and in children with complicated infections.

Age is an important consideration in determining the potential etiology of pneumonia. Neonates younger than 20 days of age are most likely to have infections with pathogens that cause other neonatal infection syndromes, including group B streptococci, gram-negative enteric bacteria, cytomegalovirus, and Listeria monocytogenes.

Children between the ages of 3 weeks and 3 months may have infections caused by Chlamydia trachomatis, normally acquired from exposure at the time of birth, to infection in the mother’s genital tract. RSV pneumonia peaks at 2-7 months of age and is difficult to distinguish from bronchiolitis. S pneumoniae is probably the most common cause of bacterial pneumonia in this age group. S aureus is an uncommon cause of pneumonia but is associated with severe disease.

Respiratory viruses of many types are the most common cause of pneumonia in children between the ages of 4 months and 4 years. S pneumoniae and nontypeable H influenzae are common bacterial causes. M pneumoniae mainly affects older children in this age group. Tuberculosis should be considered in children who live in areas of high tuberculosis prevalence.

M pneumoniae is the most common cause of pneumonia in children aged 5-15 years. Chlamydia pneumoniae has long been thought to be an important cause of pneumonia in these children, but its role is open to question, given a high rate of recovery of this organism from asymptomatic children.

Pneumococcus is the most likely cause of lobar pneumonia. As in younger children, tuberculosis should be considered in areas of high prevalence.

Prevention

The only significantly effective form of prevention is immunization. With widespread immunization in the United States, pneumonia caused by H influenzae type b has become uncommon, and infections caused by S pneumoniae are likewise becoming much less common.

Clinical Findings

A. Symptoms and Signs

Perhaps that most confounding problem in diagnosis of pneumonia is that the symptoms and signs of pneumonia overlap significantly, and indeed are often identical to, those of other cough-producing illnesses, such as those discussed previously. Young infants are particularly likely to have nonspecific signs and symptoms. Assessing the sensitivity and specificity of signs is complicated by the lack of a true gold standard for diagnosis. Tachypnea is an important finding. This is defined by a respiratory rate greater than 60 per minute in infants younger than 2 months, greater than 50 in infants aged 2-12 months, and greater than 40 in children older than 12 months of age. Evidence of increased work of breathing, such as subcostal or intercostal retractions, nasal flaring, and grunting, may indicate more severe disease. Auscultatory findings are variable and include decreased breath sounds, wheezes, rhonchi, and crackles. The absence of these various pulmonary findings is helpful in predicting that a child will not have pneumonia, but the presence of these is only moderately predictive of the presence of pneumonia.

B. Laboratory Findings

Laboratory findings are generally not helpful in the diagnosis of pneumonia. A WBC count greater than 17,000/mm³ indicates a higher likelihood of bacteremia, although blood cultures are rarely positive except in complicated infections, and oxygen desaturation indicates more severe disease. Sputum culture is the most accurate way to ascertain the cause of the infection, although obtaining a sputum sample from a child is obviously problematic.

C. Imaging Studies

A positive chest radiograph is generally considered to be diagnostic evidence of pneumonia. In children, however, radiographic patterns of respiratory infections are highly variable and may not be helpful in differentiating pneumonia from bronchiolitis, or bacterial disease from infection with viruses or atypical organisms. In infants especially, bacterial pneumonia may produce infiltrates that range from lobar consolidation to interstitial infiltrates.
Differential Diagnosis

The differential diagnosis of pneumonia includes all the previously discussed illness in which dyspnea and cough are prominent features of the disease.

Treatment

The appropriate treatment of childhood pneumonia depends on the age of the child and on the physician's clinical judgment as to how sick the child is. Neonates should all be treated as inpatients. Infants aged 3 weeks to 3 months may be treated as outpatients if they are not febrile or hypoxemic and do not appear toxic or have an alveolar infiltrate or a large pleural effusion. Older infants and children may be treated as outpatients if they do not appear seriously ill.

The choice of antibiotics depends on the age of the child and the most likely cause of infection. Neonates should be treated with ampicillin and gentamicin, with or without cefotaxime, as appropriate for a neonatal sepsis syndrome. Some studies show that amoxicillin is a highly effective treatment in children between 2 months and 5 years of age. Macrolides are also appropriate first choices for children 3 weeks to 3 months and 5-15 years of age. All macrolides are equally effective. Doxycycline may be used in children older than 8 years. Children who are ill enough to require inpatient treatment should be treated with erythromycin, either orally or intravenously, plus either cefotaxime or cefuroxime.

In children between 4 months and 4 years of age, treatment may be withheld if a viral infection is considered to be the most likely cause. Otherwise, high-dose amoxicillin is the appropriate first-line treatment. For children sick enough to require hospitalization, intravenous ampicillin is appropriate. For children who appear septic or who have alveolar infiltrates or large pleural effusions, cefotaxime or cefuroxime should be used.

An important caveat in choosing an antibiotic is the consideration of the likelihood that the child has an infection with S. pneumoniae. If this is thought to be likely, knowledge of local antibiotic resistance patterns is important. A growing rise in macrolide resistance is paralleling the rise in penicillin resistance in some parts of the United States, with important implications for antibiotic selection.

Prognosis

Worldwide, pneumonia is an important cause of death in children. In developed countries, however, the death rate for childhood pneumonia has dropped dramatically with the development of antibiotics.


Infectious mononucleosis is a clinical syndrome usually caused by Epstein-Barr virus (EBV). Although ordinarily a benign illness, it has several important, if unusual complications.

Pathogenesis

Although EBV is by far the most common cause of mononucleosis, 5%-10% of mononucleosis-like illnesses are caused by cytomegalovirus, Toxoplasma gondii, or a variety of other viruses. EBV infects 95% of the world’s population. It is transmitted in oral secretions by kissing and saliva-to-saliva transmission, as is common in children. The virus is shed for up to 6 months after the acute infection and then intermittently for the life of the person. Most infants and young children have inapparent infections or infections that are indistinguishable from other childhood respiratory infections. In developed countries, about one-third of infections occur in adolescence or early adulthood, and of those infected, about one-half develop clinically apparent disease.

The infection begins in the cells of the oral cavity, then spreads to adjacent salivary glands and lymphoid tissue. Eventually the virus infects the entire reticuloendothelial system, including the liver and spleen.

Prevention

Because the virus is ubiquitous and is shed intermittently by nearly every adult, there is no effective prevention for this illness.

Clinical Findings

A. Symptoms and Signs

In adolescents, the incubation period is 30-50 days, but it may be shorter in younger children. There is often a 1-2 week prodromal period of nonspecific respiratory symptoms, including fever and sore throat. Typical symptoms include fever, sore throat, myalgia, headache, nausea, and abdominal pain.

Physical findings include pharyngitis, often with exudative tonsillitis and palatal petechiae similar to streptococcal pharyngitis. Lymphadenopathy is seen in 90% of cases, most
often in the anterior and posterior cervical chains and less often in the axillary and inguinal chains. Epitrochlear adenopathy is a highly suggestive finding. Splenomegalgy is found in about 50% of cases and hepatomegaly in 10%-25%. Symptomatic hepatitis, with or without jaundice, may occur but is unusual. Various rashes, most often maculopapular, are seen in less than half of patients, but nearly all patients develop a rash if they are given ampicillin or amoxicillin.

**B. Laboratory Findings**

At the onset of the illness, the WBC count is usually elevated to 12,000-25,000/mm$^3$; 50%-70% of these cells are lymphocytes and 20%-40% are atypical lymphocytes. Fifty to 80% of patients have elevated hepatic transaminases, but jaundice occurs in only about 5%.

The most commonly performed diagnostic test is the Monospot test. The diagnosis may be confused by the fact that this test is often negative during the first week of symptoms. It should only be used in adolescents, as it has a sensitivity of less than 50% in children younger than 14 years of age. In the early days of the infection, looking for atypical lymphocytes in a CBC may be a reasonable approach.

**C. Imaging Studies**

No imaging studies are routinely useful in this illness. Ultrasound shows splenomegaly more accurately than physical examination but is usually performed only to assess the risk of splenic rupture in patients who are active in sports.

**Differential Diagnosis**

Streptococcal pharyngitis is the chief illness in the differential diagnosis. This may coexist with mononucleosis, or the child with mononucleosis may be a carrier of *Streptococcus*, so a positive throat culture does not definitively rule out mononucleosis. Likewise, a negative Monospot test in the first several days of the illness does not rule out mononucleosis. Lymphadenopathy associated with mononucleosis is usually more generalized than that associated with streptococcal infections.

**Complications**

Mononucleosis is normally a benign illness. The most serious complication is spontaneous splenic rupture. This occurs in 0.1%-0.2% of patients, almost always during the first 3 weeks of the illness. The risk of splenic rupture is elevated with trauma, and all patients with this illness should avoid contact sports for 1 month. Those with documented splenomegaly should not return to sports until resolution has been confirmed by ultrasound.

Other complications are unusual and include rare cases of airway obstruction (<5%), symptomatic hepatitis (rare), and a variety of neurologic complications (1%-5%), including meningitis, encephalitis, and cranial, autonomic, or peripheral neuritides. Hemolytic anemia may occur in about 3% of cases. Aplastic anemia is rare. Mild neutropenia and thrombocytopenia are common early in the disease, but severe cytopenias are rare.

**Treatment**

Treatment is generally symptomatic. Steroids speed recovery, but because most patients recover uneventfully, these should be used only for severe or complicated cases. Accepted indications for the use of steroids include impending airway obstruction, severe hemolytic anemia, severe thrombocytopenia, and persistent severe disease.

**Prognosis**

Symptoms typically last 2-4 weeks. Relapses may occur for 6 months to 1 year.


**GASTROENTERITIS**

**ESSENTIALS OF DIAGNOSIS**

- Diarrhea.
- Vomiting may be present or absent.

**General Considerations**

Diarrheal diseases are among the most common illnesses and perhaps the leading cause of death among children worldwide. It is estimated that there are 1 billion illnesses and 3-5 million deaths from these illnesses each year. In the United States, there are an estimated 20-35 million cases of diarrhea annually, with 2-4 million visits to physicians and over 200,000 hospitalizations but only 400-500 deaths. Gastroenteritis may be caused by any of a large number of viruses, bacteria, or parasites. Most infections are caused by ingestion of contaminated food or water.

**Pathogenesis**

Four families of viruses can cause gastroenteritis. All are spread easily through fecal-oral contact, and many are associated with localized outbreaks in hospitals, day-care centers, and schools. Rotavirus is a common cause of gastroenteritis during winter months. It primarily affects children between 3 months and 2 years of age, and by age 4 or 5 years, nearly all
children have serologic evidence of infection. Norwalk virus is the most common cause of gastroenteritis among older children and, along with astroviruses and enteric adenoviruses, causes year-round, often localized outbreaks of disease.

Bacteria may cause either inflammatory or noninflammatory diarrhea. Common causes of inflammatory diarrhea are *Campylobacter jejuni*, enteroinvasive or enterohemorrhagic *E. coli*, *Salmonella* species, *Shigella* species, and *Versinia enterocolitica*. Noninflammatory diarrhea may be caused by enteropathogenic or enterotoxigenic *E. coli* or by *Vibrio cholerae*.

The most common parasitic cause of diarrhea in the United States is *Giardia lamblia*. Numerous other parasites, including protozoa and various types of roundworms and flatworms, may cause diarrhea. Most parasitic infections cause chronic diarrhea and are beyond the scope of this chapter.

**Prevention**

The most effective prevention measure is for children to have access to uncontaminated food and water. Careful hand washing and good sanitation practices also help prevent the spread of infection among children. An increased rate of breast-feeding has been shown to decrease the incidence of gastroenteritis among all children in small communities.

In 2006, the Advisory Committee on Immunization Practices recommended that the new oral rotavirus vaccine (Rotarix®) be given to all children at 2, 4, and 6 months of age. This immunization schedule has been shown to be effective for two seasons after administration, but no studies have been done to establish whether it is effective for longer. It should be noted that, unlike the initial rotavirus vaccine, which was withdrawn from the market, the new vaccine has not been shown to be associated with an increased rate of intussusception. In 2008, a second oral vaccine (RotaTeq®) was licensed as a two-dose series, given at 2 and 4 months of age. The ACIP does not express a preference for one vaccine over the other.

**Clinical Findings**

**A. Symptoms and Signs**

The cardinal sign of gastroenteritis is diarrhea, with or without vomiting. Systemic symptoms and signs may include fever and malaise. Fever and severe abdominal pain are more common with inflammatory diarrhea. The estimated degree of dehydration should be established before beginning treatment.

In most children with viral gastroenteritis, fever and vomiting last less than 2-3 days, although diarrhea may persist up to 5-7 days. Most cases of diarrhea caused by foodborne toxins last 1-2 days. Many, but not all bacterial infections persist for longer periods of time.

**B. Laboratory Findings**

Most children with gastroenteritis from any cause have a short-lived illness, and the cause of the infection is rarely ascertained. Stool cultures for bacteria and examination for parasites should be done if the stool is positive for blood or leukocytes, if diarrhea persists for more than 1 week, or if the patient is immunocompromised. The presence of fecal leukocytes indicates an inflammatory infection, although not all such infections produce a positive test. Blood indicates a hemorrhagic or inflammatory infection. In a child who appears significantly dehydrated, serum electrolytes should be tested, especially if the child is hospitalized for fluid therapy.

**Complications**

Diarrheal diseases are for the most part benign, self-limited infections. Mortality is primarily caused by dehydration, shock, and circulatory collapse. Bacterial pathogens may spread to remote sites and cause meningitis, pneumonia, and other infections. *E. coli* O157:H7 may cause hemolytic-uremic syndrome.

**Treatment**

The keys to treatment of gastroenteritis are rehydration, or avoidance of dehydration, and early refeeding. Children who are severely (>>10%) dehydrated or who appear toxic or seriously ill should be admitted to the hospital for rehydration and treatment. Otherwise, children may be managed at home. Vomiting is the chief obstacle to rehydration or maintenance of hydration. Children who are vomiting should be given frequent (every 1-2 minutes) very small amounts (5 mL) of rehydration solution to avoid provoking further attacks of emesis. The idea that the gastrointestinal tract should be rested for a time by avoiding oral intake has been disproved (Table 5-2).

Children who have diarrhea but who are not dehydrated should continue on whatever age-appropriate foods they were taking before the illness. In those who are dehydrated but not severely so, oral rehydration has been shown to be effective.

**Table 5-2. Evaluation of dehydration in children.**

<table>
<thead>
<tr>
<th>Stage of Dehydration</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild dehydration</strong></td>
<td>Slightly dry mucous membranes</td>
</tr>
<tr>
<td></td>
<td>Any one sign from the moderate category</td>
</tr>
<tr>
<td><strong>Moderate dehydration</strong></td>
<td>Loss of skin turgor</td>
</tr>
<tr>
<td></td>
<td>Sunken eyes</td>
</tr>
<tr>
<td></td>
<td>Very dry mucous membranes</td>
</tr>
<tr>
<td></td>
<td>Depressed anterior fontanelle (infants)</td>
</tr>
<tr>
<td><strong>Severe dehydration</strong></td>
<td>Signs consistent with moderate dehydration, plus one or more of the following:</td>
</tr>
<tr>
<td></td>
<td>Thready/absent radial pulse</td>
</tr>
<tr>
<td></td>
<td>Cold extremities</td>
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<tr>
<td></td>
<td>Coma</td>
</tr>
</tbody>
</table>

the preferred method of rehydration. Juices, water flavored with drink mix, and sports drinks do not have the recommended concentrations of carbohydrates and electrolytes and should be avoided. The World Health Organization’s or UNICEF’s reduced-osmolarity rehydration solution is the preferred therapy. Children who are mildly (3%-5%) dehydrated should be given 50 mL/kg of solution, plus replacement of ongoing losses from stool or emesis, over each 4-hour period. Children who are moderately (6%-9%) dehydrated should be given 100 mL/kg, plus losses, over each 4-hour period. Refeeding with age-appropriate foods should begin as soon as the child is interested in eating. The classic BRAT (bananas, rice cereal, applesauce, toast) diet is lacking in calories, protein, and fat and is no longer recommended.

Therapy with antiarrheal and antiemetic medications has been shown to have minimal effect on the volume of diarrhea. Additionally, these drugs have an unacceptably high rate of side effects, and their use is not recommended.

Even when diagnosed, many bacterial infections do not require treatment. All Campylobacter (erythromycin) and Shigella (trimethoprim-sulfamethoxazole or cefalexin) infections should be treated. Infections with Salmonella should not be treated with antibiotics unless the child is younger than 3 months of age or has evidence of bacteremia or disseminated infection. Ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, and cefotaxime are appropriate choices. Treatment of E coli O157:H7 infection does not reduce the severity of the illness and may increase the likelihood of hemolytic-uremic syndrome. Other E coli infections should be treated only if they are severe or prolonged. Giardia infections should be treated with metronidazole or quinacrine.

**Prognosis**

With proper rehydration and refeeding, morbidity and mortality from viral gastroenteritis is minimal. Morbidity and mortality from bacterial infections is dependent on the virulence of the organism and complications from distant spread or remote effects, such as hemolytic-uremic syndrome.


**URINARY TRACT INFECTIONS**

**ESSENTIALS OF DIAGNOSIS**

- Common bacterial cause of febrile illness in young children.
- Symptoms often lacking or nonspecific in young children.
- Urinalysis not always reliable, need culture for accurate diagnosis.

**General Considerations**

UTIs are the most common serious bacterial infection in children younger than 2 years of age. Among febrile young children, between 3% and 5% have a UTI, and among infants younger than 8 weeks of age, UTIs account for approximately 7.5% of febrile illnesses. UTI may be a marker for urinary tract anomalies in young children. It is generally believed that UTIs may lead to renal scarring, which may cause hypertension and renal insufficiency later in life.

**Pathogenesis**

In the first 8-12 weeks of life, some UTIs may be caused by hematogenous spread of bacteria from a remote source. Otherwise, the infections are caused by bacteria ascending the urethra into the bladder. From the bladder, bacteria may ascend the ureters to cause pyelonephritis.

The most common pathogens responsible for UTIs are enteric bacteria. E coli is found in 70%-90% of infections. Pseudomonas aeruginosa is the most common nonenteric gram-negative pathogen, and Enterococcus species are the most common gram-positive organisms seen. Group B Streptococcus is occasionally found in neonates. S aureus is rarely seen in children who do not have indwelling catheters and suggests seeding from a distant focus, such as renal abscess, osteomyelitis, or endocarditis. The most important factors in prevalence of UTI are the patient’s age and gender. In newborns, preterm infants are several times more likely to have a UTI than full-term infants. Until the age of 3 months, boys are more likely to be infected than girls, but thereafter infections in girls predominate for the rest of childhood. Uncircumcised boys younger than 3 months of age and girls younger than 12 months of age have the highest rates of UTI. The usual age at which children experience a first symptomatic infection is 1-5 years. In this age group girls are 10-20 times more likely to have a UTI than boys. Two-thirds of young children with a febrile UTI have acute pyelonephritis.

**Clinical Findings**

**A. Symptoms and Signs**

Among children younger than 2 years of age, symptoms are often lacking or nonspecific. Parents may become suspicious if the child appears to be in pain while urinating, but otherwise fever may be the only presenting complaint. Among children who have developed language skills, typical UTI symptoms, such as dysuria, urgency, and urinary frequency, may be seen. Fever is the only reliable clinical sign distinguishing upper tract infection (pyelonephritis) from lower tract infection (cystitis).
CHAPTER 5

B. Laboratory Findings
To be reliable, urine for analysis must be collected by catheterization or by suprapubic aspiration. Urine collected in an adhesive collection bag is too often contaminated by skin flora to be useful.

Positive findings on urinalysis are positive dipstick tests for leukocyte esterase or nitrite or the microscopic finding of pyuria (>>5 WBCs per high-power field). However, urinalysis in young children is not sensitive enough to stand alone as a diagnostic test, and urine culture is needed for accurate diagnosis. The bacterial colony count that defines a UTI varies by collection method and by gender. In a specimen collected by suprapubic aspiration, the finding of any gram-negative organisms or of more than 10^3 gram-positive organisms indicates a 99% probability of UTI. In catheter-obtained specimens, more than 10^4 bacteria indicates a 95% probability of UTI and 10^9-10^10 is considered suspicious. The numbers are similar for clean-voided urine specimens, although in boys, more than 10^4 bacteria indicates a probable UTI.

Blood cultures should be done as part of the workup of a young infant with fever without an apparent source. Blood cultures are unlikely to be positive in children older than 2 months. Even when blood cultures are positive, they will show the same organism as the urine culture, and they contribute little if anything to the diagnosis.

C. Imaging Studies
The goal of imaging is to diagnose the presence of vesicoureteral reflux (VUR) and other urinary tract anomalies that are associated with a high rate of recurrent infections. Shortly after finishing treatment for a first febrile UTI, children should have a voiding cystourethrogram (VCUG), either with x-ray contrast dye or with a radionuclide tracer. Renal ultrasonography will show other structural abnormalities and may be considered in addition to the VCUG. Although children with VUR have a higher risk of UTI, VUR is found in only about one-third of children with pyelonephritis. Other anomalies, such as a posterior urethral valves (in boys) or duplication of the collecting system, are found in a small number of children.

In recent years, the recommended strategy for imaging has become controversial. The AAP recommends ultrasonography and either VCUG or nuclide scanning with DMSA (dimercaptosuccinic acid) for all children with UTI between the ages of 2 months and 2 years. Recent guidelines from the United Kingdom recommend ultrasound only for children with “atypical” or recurrent UTI. DMSA scanning is recommended for children younger than 3 years of age with atypical UTI, and VCUG is not recommended.

Although all boys with a first UTI should receive a full diagnostic workup, as girls grow from toddlers to school age, the likelihood of significant findings decreases. There is no clear guidance from the literature as to the age after which a girl with a first UTI should be subjected to an expensive, uncomfortable, and potentially traumatic investigation.

Differential Diagnosis
UTI should be considered in any child who presents with a febrile illness in whom the cause of the fever cannot be readily ascertained by physical examination.

Complications
Acute complications of UTI include sepsis, renal abscess, and disseminated infection, including meningitis. Recurrent pyelonephritis can cause renal scarring, which can lead to hypertension or renal insufficiency later in life.

Treatment
A. Acute Infection
Infants younger than 2 months with UTI should be hospitalized and treated with intravenous antibiotics as indicated for sepsis until cultures identify the causative organism and the best antibiotic for treatment. Infants 2 months to 2 years of age may be treated as outpatients with oral antibiotics unless they appear toxic, are dehydrated, or are unable to retain oral intake. Older children can usually be treated as outpatients unless they appear seriously ill. The initial choice of antibiotic may be a sulfonamide, trimethoprim-sulfamethoxazole, or a cephalosporin. Resistance of E. coli to ampicillin is widespread enough in the United States to make ampicillin or amoxicillin a poor choice for initial therapy. Nitrofurantoin, which is excreted in the urine but does not reach therapeutic blood levels, should not be used to treat febrile children with a UTI. In general, the duration of treatment should be 7-10 days. Some authorities recommend 14 days of treatment, but there are no data comparing 10 days to 14 days of treatment.

If the child responds clinically to treatment within 2 days, no further immediate follow-up is needed (eg, reculture of the urine or immediate imaging studies). If the child is not improving after 2 days of treatment, the urine should be recultured and renal ultrasonography should be performed immediately.

Once treatment of a first infection has been completed, the child should be continued on either full or prophylactic doses of antibiotics until imaging studies have been completed. Appropriate prophylactic antibiotics include trimethoprim-sulfamethoxazole, sulfisoxazole, and nitrofurantoin.

B. Prevention of Recurrent Infection
Prevention of long-term sequelae focuses on prevention of recurrent infection. This, in turn, involves correction, if possible, of associated urinary tract abnormalities. Widespread use of prenatal ultrasonography has led to the identification of infants with intrauterine hydronephrosis. In many boys with VUR, renal scarring is thought to be congenital, whereas in girls it is more highly associated with recurrent infection. The degree of VUR is important in determining appropriate treatment. Mild VUR generally improves over time as the bladder enlarges and the length of the submucosal tunnel through which the ureter passes increases. More severe
degrees of reflux are unlikely to improve and more often require surgical correction. Posterior urethral valves and ureterovesical obstruction also require surgical intervention. The AAP guidelines recommend antibiotic prophylaxis for all children with UTI. The UK guidelines do not recommend prophylaxis after the first UTI, whether or not VUR is present.

In children with structurally normal urinary tracts, treatment of chronic constipation has been shown to decrease the recurrence of UTI, as has behavioral correction of voiding dysfunction associated with incomplete emptying of the bladder. Improving hygiene, especially in girls, has not been shown to decrease UTI rates. Based on retrospective studies, circumcision of boys has been claimed to be associated with decreased UTI rates, but there are no randomized controlled trials investigating this idea.

For some children with recurrent UTIs, long-term prophylactic antibiotic treatment may be effective in reducing the frequency of infections. However, there are no clear guidelines as to when this treatment should be considered.

INFECTIONS OF THE SKIN

IMPETIGO

ESSENTIALS OF DIAGNOSIS

- Nonbullous: yellowish crusted plaques.
- Bullous: bullae, with minimal surrounding erythema, rupture to leave a shallow ulcer.

General Considerations
Impetigo is a bacterial infection of the skin. More than 70% of cases are of the nonbullous variety.

Pathogenesis
Most cases of nonbullous impetigo are caused by *Staphylococcus aureus*. Group A β-hemolytic streptococci are found in some cases. Coagulase-positive *S aureus* is the cause of bullous impetigo. Methicillin-resistant *S aureus* (MRSA) has been isolated from patients with bullous impetigo. MRSA should be considered when selecting antibiotics for treatment of this infection. Impetigo can develop in traumatized skin, or the bacteria can spread to intact skin from its reservoir in the nose.

Clinical Findings
Nonbullous impetigo usually starts as a small vesicle or pustule, followed by the classic small (<2 cm) honey-colored crusted plaque. The infection may be spread to other parts of the body by fingers or clothing. There is usually little surrounding erythema, itching occurs occasionally, and pain is usually absent. Regionally lymphadenopathy is seen in most patients. Without treatment, the lesions resolve without scarring in 2 weeks.

Bullous impetigo is usually seen in infants and young children. Lesions begin on intact skin on almost any part of the body. Flaccid, thin-roofed vesicles develop, which rupture to form shallow ulcers.

Differential Diagnosis
Nonbullous impetigo is unique in appearance. Bullous impetigo is similar in appearance to pemphigus and bullous pemphigoid. Growth of staphylococci from fluid in a bulla confirms the diagnosis.

Complications
Cellulitis follows about 10% of cases of nonbullous impetigo but rarely follows bullous impetigo. Either type may rarely lead to septicemia, septic arthritis, or osteomyelitis. Scarlet fever and post-streptococcal glomerulonephritis, but not rheumatic fever, may follow streptococcal impetigo.

Treatment
Localized disease may be treated with mupirocin ointment. Patients with widespread lesions or evidence of cellulitis should be treated with systemic antibiotics effective against staphylococci and streptococci. If infection with MRSA is a possibility, intravenous vancomycin is the preferred drug for hospitalized patients. Trimethoprim-sulfamethoxazole is almost always effective against community-acquired MRSA and may be considered a preferred agent where *S aureus* is a likely causative agent.

FUNGAL INFECTIONS

General Considerations
Fungal infections of the skin and skin structures may be generally grouped into three categories: dermatophyte infections, other tinea infections, and candidal infections.
Pathogenesis

Dermatophytoses are caused by a group of related fungal species—primarily *Microsporum*, *Trichophyton*, and *Epidermophyton* species—that require keratin for growth and can invade hair, nails, and the stratum corneum of the skin. Some of these organisms are spread from person to person, some from animals to people, and some infect people from the soil. Other fungi can also cause skin disease, such as *Malassezia furfur* in tinea versicolor. Finally, *Candida albicans*, a common resident of the gastrointestinal tract, can cause diaper dermatitis and thrush.

Clinical Findings

A. Symptoms and Signs

1. Dermatophytoses

   a. Tinea corporis—Infection of the skin produces one or more characteristic gradually spreading lesions with an erythematous raised border and central areas that are generally scaly but relatively clearer and less indurated than the margins of the lesions. The central clearing helps to differentiate these lesions from those of psoriasis. Small lesions may resemble those of nummular eczema. The lesions may have a somewhat serpiginous border, but they are usually more or less round in shape, hence the common name of “ringworm.” They can range in size from one to several centimeters.

   b. Tinea capitis—Fungal infection of the scalp and hair is the most common dermatophytosis in children. This presents as areas of alopecia with more or less regular borders. Typically, the hair shafts break off a few millimeters from the skin surface, distinguishing this from alopecia areata. The infection may also produce a sterile inflammatory mass in the scalp, called a kerion, which may be confused with a bacterial infection.

2. Nondermatophyte infections

   a. Tinea versicolor—Tinea versicolor is normally seen in adolescents and adults. The causative organism, *M furfur*, is part of the normal skin flora. The infection most often becomes evident during warm weather, when new lesions develop. A warm, humid environment, excessive sweating, and genetic susceptibility are important factors for developing this infection. Because treatment does not eradicate the fungus from the skin, it often recurs annually, during the summer months, in susceptible individuals. The lesions are characteristically scaly macules, usually reddish brown in light-skinned people but often hyper- or hypopigmented in people of color. They can be found almost anywhere on the body but are seen most commonly on the torso. The lesions are rarely pruritic. The individual lesions may enlarge and coalesce to form larger lesions with irregular borders.

   b. Thrush—Thrush is a common oral infection in infants. Isolated incidents of this disease are common in immunocompetent infants, but recurrent infections in infants or infections in children and adolescents may indicate an underlying immune deficiency. The infection presents as thick white plaques on the tongue and buccal mucosa. These can be scraped off only with difficulty, revealing an erythematous base.

   c. Candidal diaper dermatitis—This infection is most common in infants from 2 to 4 months of age. *Candida* is a common colonist of the gastrointestinal tract, and infants with diaper dermatitis should be examined for signs of thrush. The fungus does not ordinarily invade the skin, but the warm, humid environment of the diaper area provides an ideal medium for growth. The infection is characterized by an intensely erythematous plaque with a sharply demarcated border. Advancing from the border are numerous satellite papules, which enlarge and coalesce to enlarge the affected area.

B. Special Tests

Dermatophyte and other tinea infections are usually diagnosed clinically. Examination of potassium hydroxide preparations of scrapings from the affected area, which show hyphae, confirms the diagnosis. Fungal cultures may be helpful when the diagnosis is suspected but cannot otherwise be confirmed. Diagnosis of candidal infections is generally made by clinical findings.

Treatment

Tinea corporis is treated with topical antifungal medications. Nystatin, miconazole, clotrimazole, ketoconazole, and terbinafine creams are all effective. Rarely, widespread infection requires systemic therapy.

Topical therapy is ineffective in tinea capitis. The gold standard for treatment has long been griseofulvin, but because of the 6-week duration of therapy required, other treatments of shorter duration are becoming more popular. Fluconazole, itraconazole, and terbinafine can be given for 2 weeks, with an additional week of treatment if the response is incomplete. Ketoconazole is not recommended due to rare incidents of hepatotoxicity.

Tinea versicolor can be treated with topical selenium sulfide lotion or any of the previously listed topical creams. In older children, systemic treatment can also be given, either with ketoconazole or itraconazole for 5 days.

Candidal infections are most often treated with nystatin. Diaper dermatitis responds well to topical nystatin cream. If intense inflammation is present, topical steroids for a few days may be helpful. Thrush is usually treated with nystatin suspension. Up to 2 weeks may be needed for complete resolution of the infection. In resistant cases, the mouth may be painted with gentian violet.
Prognosis

All these infections in immunocompetent children respond well to treatment. However, left untreated, they can cause widespread and significant skin disease.

PARASITIC INFESTATIONS

SCABIES

ESSENTIALS OF DIAGNOSIS

- Intense pruritus.
- Small erythematous papules.
- Burrows are pathognomonic but may not be seen.

Pathogenesis

Scabies is a common infestation caused by the mite Sarcoptes scabei. The disease is acquired by physical contact with an infected person. Transmission of the disease by contact with infested linens or clothing is less common, because the mites can only live off the body for 2-3 days. The female mite burrows between the superficial and deeper layers of the epidermis, laying eggs and depositing feces as she goes along. After 4-5 weeks, her egg laying is complete, and she dies in the burrow. The eggs hatch, releasing larvae which move to the skin surface, molt into nymphs, mature to adults, mate, and begin the cycle again. Pruritus is caused by an allergic reaction to mite antigens.

Clinical Findings

A. Symptoms and Signs

Diagnosis is based primarily on clinical suspicion, as physical findings are highly variable and the disease can mimic a wide variety of skin conditions. The classic early symptom is intense pruritus. The usual finding is 1- to 2-mm erythematous papules, often in a linear pattern. The finding of burrows connecting the papules is diagnostic but is not always seen. In infants, the disease may involve the entire body—including the face, scalp, palms, and soles—and pustules and vesicles are common. In older children and adolescents, the lesions are most often seen in the interdigital spaces, wrist flexors, umbilicus, groin, and genitalia. Severe infestation may produce widespread crusted lesions.

B. Special Tests

Potassium hydroxide preparations of skin scrapings may show entire mites, eggs, or fecal pellets. However, success in finding these is limited and a negative examination does not rule out the disease.

Treatment

Permethrin cream, applied to the entire body (excluding the face in older children) is the preferred treatment. Treatment will kill mites and eliminate the risk of contagion within 24 hours. However, pruritus may continue for several days to 2 weeks after treatment. The entire family should be treated at the same time, and all clothing and bedding should be washed. Many reports also demonstrate the effectiveness of oral ivermectin (200 mcg/kg, given once, then repeated in 1-2 weeks), although it is not approved by the FDA for this indication. When used to treat scabies, it has not been conclusively shown to have any serious adverse effects. Although no definite toxicity has been shown, data on safety and effectiveness are lacking in children less than 5 years of age or less than 15 kg and in pregnant women. It is recommended that ivermectin not be given to these patients.


LICE (PEDICULOSIS)

ESSENTIALS OF DIAGNOSIS

- Pruritus.
- Visualization of lice on the body or nits in hair.

Pathogenesis

Three varieties of lice cause human disease. Pediculus humanus corporis causes infestations on the body, and Pediculus humanus capitis causes infestation on the head. Phthirus pubis, or crab lice, infests the pubic area. All are spread by physical contact, either with an infested person or with clothing, towels, or hairbrushes that have been in recent contact with an infested person. Symptoms are caused by an allergic reaction to louse antigens that develop after a period of sensitization. Body lice can be a vector for other disease, such as typhus, trench fever, and relapsing fever. Infestation with pubic lice is highly correlated with infection by other sexually transmitted diseases. Nits are the eggs of the louse. They are cemented to hairs, are usually less than 1 mm in length, and are translucent. Body lice lay their nits in the seams of clothing. The nits can remain viable for up to 1 month and will hatch when exposed to body heat when the clothing is worn again.

Prevention

Body lice are associated primarily with poor hygiene and can be prevented by regular bathing and washing of clothing and bedding. There are no specific measures for prevention of infestation by other types of lice.
Clinical Findings

The cardinal symptom of louse infestation is pruritus, which develops as the person becomes sensitized. Excoriations in the infested area are common. The lice themselves can usually be seen easily. Head and pubic lice are easily seen, but body lice are only present on the body when feeding.

Treatment

Permethrin cream, applied for 8-12 hours, is the treatment of choice for body lice. Clothing and bedding should be washed, because exposure to hot water will kill the nits. Permethrin cream rinse is used to treat head and pubic lice. Thorough combing with a fine-toothed nit comb after treatment for head lice is useful in removing nits and reducing the probability of reinfection.

INFECTIOUS DISEASES WITH SKIN MANIFESTATIONS

BACTERIAL INFECTIONS

Scarlet Fever (Scarlatina)

ESSENTIALS OF DIAGNOSIS

- Symptoms of streptococcal pharyngitis.
- “Sandpaper” rash.
- Circumoral pallor.
- “Strawberry” tongue (red or white).

General Considerations

Scarlet fever is an infection caused by certain strains of group A streptococci. The infection most commonly begins as a typical streptococcal pharyngitis, but it can also follow streptococcal cellulitis or infection of wounds or burns.

Clinical Findings

The classic feature of scarlet fever is the rash. It develops 12-48 hours after the onset of pharyngitis symptoms, usually beginning in the neck, axillae, and groin and becoming generalized within 24 hours. The rash is a fine, faintly erythematous exanthem that is often more easily felt than seen, giving it the name of “sandpaper” rash. The rash itself is usually not present on the face, but there is often flushing of the face except for the area around the mouth (circumoral pallor). The tongue is often erythematous and swollen. In the early stages of the disease, the tongue may have swollen papillae protruding through a white coating (white “strawberry” tongue). Later in the illness, the coating desquamates, leaving the tongue red and the papillae swollen (red “strawberry” tongue). After about 1 week, desquamation begins on the face and progresses downward over the body, finally involving the hands and feet.

Differential Diagnosis

Kawasaki disease and any of the viral exanthems may be confused with scarlet fever.

Complications

Scarlet fever is generally a benign disease. In severe cases, bacteremia and sepsis may occur, and rheumatic fever may follow an untreated infection. Glomerulonephritis may also be a sequel.

Treatment

Treatment of scarlet fever is no different from treatment of the primary streptococcal infection.

VIRAL INFECTIONS

1. Roseola (Exanthem Subitum)

ESSENTIALS OF DIAGNOSIS

- Sudden onset of high fever.
- No diagnostic signs.
- Development of rash as fever breaks after 3-4 days.

Pathogenesis

Human herpesvirus 6 (HHV 6) causes the vast majority of cases of clinical roseola, although other viruses cause some cases as well. It is rare in infants younger than 3 months and in children older than 2 years of age; most cases occur in infants between the ages of 6 and 12 months. Infections occur year round.

Clinical Findings

A. Symptoms and Signs

The hallmark of roseola is the abrupt onset of high fever, often 39.4-41.1°C (103-106°F). Febrile seizures occur in up to one-third of patients. Despite the high fever, children usually look relatively well. Mild signs of upper respiratory infection may be seen, but there are no diagnostic signs. After 3-4 days, the fever breaks suddenly, followed by the appearance of a rash. This is usually a macular or maculopapular rash that starts on the trunk and spreads to the arms and neck and
then often to the face and legs. The rash resolves within 3 days, but it may be more transient.

**B. Laboratory Findings**

Laboratory findings are usually normal.

**Differential Diagnosis**

In the early stages of the disease, many children with high fever and seizures are admitted to the hospital for workup of suspected meningitis or sepsis. After the rash appears, the diagnosis is obvious in retrospect.

**Complications**

Rare cases of encephalitis or fulminant hepatitis have been reported.

**Treatment & Prognosis**

Treatment is entirely symptomatic. Unless the patient develops one of the rare complications listed earlier, roseola is a benign, self-limited infection.

2. Varicella (Chickenpox)

**ESSENTIALS OF DIAGNOSIS**

- Prodrome of upper respiratory–like symptoms.
- Rash consists of small vesicles on erythematous base.
- Vesicles rupture with crusting.

**General Considerations**

Approximately 90% of adults in the United States have serologic evidence of varicella infection, whether they have had clinically apparent disease or not.

**Pathogenesis**

The varicella-zoster virus is a herpesvirus. After resolution of the initial infection, the virus produces a latent infection in the dorsal root ganglia. Reactivation produces herpes zoster (shingles).

**Prevention**

Childhood immunization should prevent most disease. The vaccine is given in two doses—the first between 12 and 18 months of age, and the second between 4 and 6 years of age. Varicella-zoster immune globulin can help prevent infection in immunocompromised children, nonimmune pregnant women who are exposed to the virus, and newborns exposed to maternal varicella.

**MMWR Jan 02, 2009**

**Clinical Findings**

The usual incubation period of varicella is about 14 days. Most children experience a prodromal phase of upper respiratory–like symptoms for 1–2 days before the onset of the rash. Fever is usually moderate. Almost all infected children will develop a rash. The extent of the rash is highly variable. Lesions usually begin on the trunk or head but eventually can involve the entire body. The classic lesion is a pruritic erythematous macule that develops a clear central vesicle. After 1–2 days, the vesicle ruptures, forming a crust. New lesions develop daily for 3–7 days, and typically lesions are scattered over the body in various states of evolution at the same time. Ulcerative lesions on the buccal mucosa are common. The infection is contagious from the onset of the prodrome until the last of the lesions has crusted over.

**Differential Diagnosis**

Varicella usually presents as an unmistakable clinical picture, but the rash may be missed in children with mild disease.

**Complications**

In immunocompetent children, the most common complication is bacterial superinfection of the lesions, causing cellulitis or impetigo. Other, more serious complications are most common in children younger than 5 years or adults older than 20 years of age. Meningoencephalitis and cerebellar ataxia can occur. These normally resolve within 1–3 days without sequelae. Viral hepatitis is common but normally subclinical. Varicella pneumonia is uncommon in healthy children; it usually resolves after 1–3 days but may progress to respiratory failure in rare cases.

**Treatment**

Treatment is ordinarily symptomatic, including antipruritic medications if needed. Aspirin should be avoided to prevent development of Reye syndrome. Patients with signs of disseminated varicella, such as encephalitis and pneumonia, should be treated with intravenous acyclovir.

**Prognosis**

Varicella is normally a benign, self-limited disease. Complications in immunocompetent children are rare.
3. Erythema Infectiosum (Fifth Disease)

**ESSENTIALS OF DIAGNOSIS**

- Prodrome of mild upper respiratory–like symptoms.
- Rash begins as erythema of cheeks, then becomes more generalized—macular at first, then reticular.
- Rash lasts 1-3 weeks.

**General Considerations**

Erythema infectiosum (fifth disease) is a common childhood infection that rarely causes clinically significant disease.

**Pathogenesis**

The disease is caused by parvovirus B19. It appears sporadically but often in epidemics in communities. Children are infectious during the prodromal stage, which is inapparent or mild and usually indistinguishable from an upper respiratory infection. The rash is an immune-mediated phenomenon that occurs after the infection, so children with the rash are not infectious and should not be restricted from school or other activities.

**Clinical Findings**

Erythema infectiosum begins with a prodromal stage of upper respiratory symptoms, headache, and low-grade fever. This stage may be clinically inapparent.

The rash occurs in three phases, often transient enough to go unnoticed. The first stage is facial flushing, described as a “slapped cheek” appearance. Shortly afterward, the rash becomes generalized over the body, initially as a faint erythematous, often confluent, macular rash. In the third stage, the central regions of the macules clear, leaving a distinctive faint reticular rash. The rash comes and goes evanescently over the body and can last from 1 to 3 weeks. There are rarely any other associated findings.

**Differential Diagnosis**

Erythema infectiosum is usually clinically recognizable, but it may be confused with other viral exanthems.

**Complications**

Arthritis is rare in children but may occur in adolescents. Thrombocytopenic purpura and aseptic meningitis are rare complications.

Fetal hydrops and fetal demise may be seen in fetuses whose mothers contract the infection. It is estimated that 5% or fewer of infected fetuses will be affected by the virus.

**Treatment & Prognosis**

There is no known treatment for this disease. Except for rare complications in children, this is a benign infection. Fetal complications are unusual.

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**INFLAMMATORY DISORDERS OF THE SKIN**

**ATOPIC DERMATITIS**

**ESSENTIALS OF DIAGNOSIS**

- Pruritus is the cardinal symptom.
- Lesions are excoriated, scaly, and may become lichenified.

**General Considerations**

Atopic dermatitis is a common skin disorder in children, affecting 10%-15% of the population. It appears during the first year of life in 60% of cases and during the first 5 years in 85%.

**Pathogenesis**

The cause of atopic dermatitis is unclear. It has a strong association, both in the individual and in families, with allergic rhinitis and asthma, and is classified as an atopic disorder. Food allergies, primarily to cow’s milk, wheat, eggs, soy, fish, and peanuts, have been implicated in 20%-30% of cases.

**Clinical Findings**

The diagnosis is based on the presence of three of the following major criteria: pruritus, lesions with typical morphology and distribution, facial and extensor involvement in infants and children, chronic or chronically relapsing dermatitis, and personal or family history of atopic disease.

Pruritus is the hallmark of the disease, usually preceding the skin lesions, which usually develop as a reaction to scratching. The skin becomes excoriated, develops weeping and crust ing, and later may become scaly or lichenified. Secondary bacterial infection is common. In infants, the lesions usually involve the face but may appear in a generalized pattern over much of the body. In young children, the extensor surfaces of the extremities are often involved. In older children and adults, the disease often moves to involve the flexion areas of the extremities instead. The disease typically is chronic, although remissions and relapses are common.

**Differential Diagnosis**

Atopic dermatitis may be confused with seborrheic dermatitis, especially in infants, in whom facial lesions are common.
Atopic dermatitis does not usually follow the distribution of oil glands, as is typical with seborrheic dermatitis. It may also be confused with psoriasis, contact dermatitis, scabies, and cutaneous fungal infections.

**Complications**

The most common complication is secondary bacterial infection. Low-grade bacterial infection should be considered as a factor in lesions that do not respond well to usual therapies.

**Treatment**

Nonpharmacologic measures are important in the treatment of this disease. Long baths and bathing in hot water exacerbate dryness of the skin and should be avoided. Use of soaps that do not contain fragrances may be helpful, or it may be necessary to use nonsoap cleansers instead. Moisturizers that contain fragrances and other irritants will aggravate the problem. If secondary infection is suspected, systemic antibiotics effective against streptococci and staphylococci should be given.

Topical corticosteroids are the mainstay of treatment. The lowest potency preparation that is effective should be used, especially on the face and the diaper area, which are more sensitive to the skin atrophy associated with the prolonged use of higher-potency steroids. Systemic steroids are useful for severe acute flares. Antipruritic medications may be useful, but these all have significant sedative side effects. Doxepin, a tricyclic antidepressant with strong antihistaminic effects, is often useful in patients with severe manifestations.

Tacrolimus and pimecrolimus, topical immune modulators, are less effective than high-potency topical steroids. Whether they are as effective or less effective than medium-potency steroids is unclear. Because these drugs do not cause skin atrophy, they may be useful for prolonged treatment of facial lesions. In February 2005, the Food and Drug Administration issued a “black box” warning for these drugs based on concerns of cancer related to lymphoproliferative changes seen in some post-transplantation patients. A joint task force of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology reviewed the data the same year and concluded that the evidence did not support a causal link between these drugs and lymphoma.

**SEBORRHEIC DERMATITIS**

**ESSENTIALS OF DIAGNOSIS**

- Inflamed lesions with yellowish or brownish crusting.
- Lesions may be localized or generalized.

**General Considerations**

Seborrheic dermatitis is a common inflammatory disorder of the skin. It is most common in infancy and adolescence, when the sebaceous glands are more active. It generally resolves or lessens in severity after infancy, but localized lesions or mild, generalized scalp disease may be seen throughout adulthood.

**Pathogenesis**

The exact cause of seborrheic dermatitis is unknown. Infection with Malassezia yeasts has been implicated, and the disease may be caused by an abnormal inflammatory or immune response to the fungus.

**Clinical Findings**

The typical lesions of seborrheic dermatitis are inflammatory macular lesions, usually with brownish or yellowish scaling. Inflammation may begin during the first month of life, and it usually becomes evident within the first year. In infants, the lesions may be generalized, but in older children, lesions are most common in areas where sebaceous glands are concentrated, such as the scalp, face, and axillae. Marginal blepharitis may be seen. Cradle cap is a common variant seen in infants, either by itself or in association with other lesions. This is seen as scaling and crusting of the scalp, often with extremely heavy buildup of scale in untreated infants.

**Differential Diagnosis**

Atopic dermatitis is the main element in the differential diagnosis. The disease may also be confused with psoriasis and other cutaneous fungal infections.

**Complications**

Secondary infection, either bacterial or fungal, is a common complication.

**Treatment**

Topical treatment with antifungal creams or shampoo is the mainstay of treatment. Topical steroids may be used for intense inflammation. Short courses of treatment with oral antifungal drugs, such as fluconazole, may be useful for control of severe of widespread disease. Scalp lesions usually respond to antiseborrheic shampoos, such as selenium.
sulfide. Cradle cap is treated by soaking the scales with mineral oil and then gently debriding them with a toothbrush or washcloth. Following debridement, cleansing with baby shampoo is normally adequate for control; antiseborrheic or antifungal shampoos usually are not necessary.


**Prognosis**

Seborrheic dermatitis generally resolves or lessens in severity after infancy, but localized lesions or mild, generalized scalp disease may be seen throughout adulthood.

**ACNE VULGARIS**

**Essentials of Diagnosis**

- Comedones, open or closed.
- Papules, pustules, or nodules.

**General Considerations**

Acne vulgaris is an extremely common skin disease in older children and adolescents. The prevalence of this disorder increases with age: 30%-60% of 10- to 12-year-olds and 80%-95% of 16- to 18-year-olds are affected.

**Pathogenesis**

Acne is caused by the interaction of several factors in the pilosebaceous unit of the skin. The basic abnormality is excessive sebum production caused by sebaceous gland hyperplasia and generally related to androgenic influences. Hyperkeratinization of the hair follicle results in obstruction of the follicle and the formation of a microcomedone. Sebum and cellular debris accumulate, forming an environment that can become colonized by *Propionibacterium acnes*. The presence of the bacteria provokes an immune response that includes the production of inflammatory mediators. Lesions are most commonly seen in areas of the body that have the highest concentration of sebaceous glands. The face is the most common site for lesions to develop, but the chest, back, neck, and upper arms may be affected as well.

Although the androgenic influences that cause the increase in sebum production are generally related to puberty, a number of factors can cause or aggravate acne. Mechanical obstruction or irritation (eg, by shirt collars) can be a factor. Cosmetics can occlude follicles and trigger eruptions. Medications, most commonly anabolic steroids, corticosteroids, lithium, and phenytoin, can cause or aggravate acne. Hyperandrogenic states, such as polycystic ovary syndrome, are often associated with acne. Emotional stress has been shown to exacerbate the problem. Finally, the role of diet has long been controversial. No specific foods have been found to aggravate acne, despite common assumptions. However, acne is almost uniformly a disease of Western cultures, and some authorities are studying the role of the high-glycemic-index Western diet in its development. This diet leads to higher levels of insulin-like growth factor, which has androgenic effects.

**Clinical Findings**

Several types of lesions characterize this disease, and they can occur in varying combinations and degrees of severity. Microcomedones can evolve into visible comedones, either open (“blackheads”) or closed (“whiteheads”). Inflammatory papules and pustules may develop. Nodules are pustules larger than 5 mm in size. Hyperpigmentation and scarring may develop at the sites of more severe lesions.

Multiple classification systems have been devised to characterize this disorder. The disease may be classed as comedonal, papulopustular (inflammatory), and nodulocystic (also inflammatory, but more severe). The American Academy of Dermatology defines three levels of severity. In mild acne, there are a few to several papules and pustules, but no nodules. In moderate acne, there are several to many papules and pustules and a few nodules. In severe disease, there are extensive papules and pustules, along with many nodules.

**Differential Diagnosis**

The diagnosis is usually straightforward. The physician should consider drug-induced acne if the patient is taking any medications. Severe acne in athletes raises the possibility of anabolic steroid use. In women, severe acne, hirsutism, and other signs of virilization suggest an underlying hyperandrogenic condition.

**Complications**

The primary morbidity of acne is psychological. This can be a serious problem for the adolescent patient. Hyperpigmentation and scarring may result from more severe disease, especially from nodulocystic acne.

**Treatment**

The various treatments for acne are aimed at reducing infection and inflammation, normalizing the rate of desquamation of follicular epithelium, or correcting hormone excesses or other systemic factors. Treatments work better in combination than singly.

A. **Topical Antibiotics**

Antibiotics are directed at the infectious component of acne. By reducing infection, they also have a beneficial effect on the...
inflammatory component of the disease. *P. acnes* has been developing antibiotic resistance worldwide, and this may be responsible for some treatment failures.

Available topical antibiotic preparations include erythromycin, clindamycin, benzoyl peroxide, and azelaic acid. Available evidence shows that erythromycin and clindamycin work better in combination with benzoyl peroxide than either agent alone. The different strengths of benzoyl peroxide appear to be about equally effective.

**B. Oral Antibiotics**

It is generally believed that oral antibiotics are more effective than topical agents and therefore more useful in severe disease. However, because few, if any, good-quality comparisons of the two modalities exist, it is impossible to be certain of this. Tetracycline is the mainstay of oral antibiotic treatment. Side effects are minimal—primarily gastrointestinal upset. Doxycycline may be taken with food to minimize gastric upset, but this agent is more photosensitizing than tetracycline. Minocycline is a more effective agent against *P. acnes* than the other tetracyclines, but it is more expensive and has a higher incidence of serious side effects, such as vertigo and lupus-like syndrome. It is generally best reserved for disease that does not respond to first-line agents. All tetracyclines bond to calcium in bone and teeth and can cause staining of dental enamel. They should not be given to children younger than 10 years of age. Erythromycin is an alternative when tetracyclines cannot be used.

**C. Topical Retinoids**

Retinoids are derivatives of vitamin A. They prevent the formation of comedones by normalizing the desquamation of the follicular epithelium. Tretinoin has been in use much longer than the other agents, adapalene and tazarotene. All agents have the main adverse effect of excessive drying, burning, and inflammation of the skin. This can be ameliorated by changing to a lower concentration of the agent or by periodically skipping a day of application. Although tretinoin has been rated pregnancy category C, and there are no clear indications of teratogenicity, the role of topical retinoids in pregnancy is a matter of debate. Tazarotene has been designated pregnancy category X.

All agents are available in various strengths and vehicles. The choice of vehicle is determined by the patient’s skin type.

**D. Isotretinoin**

Isotretinoin is a metabolite of vitamin A that reduces sebaceous gland size, decreases sebum production, and normalizes desquamation of follicular epithelium. It is effective for severe nodular acne and for acne unresponsive to other treatments. Adverse effects are common, including dry eyes, dry skin, headache, and mild elevation in liver enzymes and serum lipids. Benign intracranial hypertension is less common but must be considered if the patient develops headaches. Despite commonly held beliefs, evidence does not support the idea that depression is a side effect of this drug. Isotretinoin is extremely teratogenic, with major malformations occurring in 40% of infants exposed during the first trimester, so it must be used only after a negative pregnancy test—preferably after two negative tests—and with strict attention to contraception.

**E. Hormonal Therapy**

Because of the antiandrogenic effect of the progestin component, combined oral contraceptives are effective in reducing the severity of acne in women. Although some newer brands have been explicitly marketed for this indication, they have not been proved superior to older, less-expensive brands.

**F. Combination Therapy**

Agents for the treatment of acne work best in combination. The choice of agents can be tailored to the severity of the disease. Because of the time required for complete turnover of the epithelium, at least 6-8 weeks of treatment should be given before assessing the effectiveness of the regimen. If the disease is not adequately controlled, the regimen may be intensified (eg, by increasing the concentration of a retinoid, changing from a topical to an oral antibiotic, or adding another agent). Patients should be advised that total suppression of lesions may not be possible, but otherwise, the patient’s assessment can be used as a guide to decide whether more intensive treatment is necessary.

For patients with comedones only, retinoids are the first line of therapy. These are applied once a day to the entire area involved.

For those with mild to moderate inflammatory acne, topical antibiotics are the treatment of choice. As mentioned previously, erythromycin and clindamycin are more effective in combination with benzoyl peroxide than alone. These are applied twice daily. Retinoids can be added if comedones are present.

For moderate to severe inflammatory acne, oral antibiotics can be substituted for topical agents.

For severe nodulocystic acne or for disease unresponsive to other regimens, isotretinoin is the treatment of choice.

For women with acne, oral contraceptives are a reasonable first-line treatment.

**Prognosis**

Although in general, acne diminishes at the end of adolescence, it may persist into adult life.
Routine vaccination of children is one of the most important medical advances of the twentieth century. Important concerns about vaccination include the child’s age and underlying medical conditions, disease burden, vaccine efficacy, adverse reactions, and official recommendations.

**HEPATITIS B VACCINE**

In the United States the estimated number of persons chronically infected with hepatitis B virus (HBV) is 1.25 million, 36% of whom acquired HBV during childhood. HBV infection becomes chronic in 90% of those infected as infants, 30%-60% of those infected before the age of 4 years, and only 5%-10% of those infected as adults. Each year, HBV infects about 78,000 persons de novo and kills about 6000. Up to 25% of individuals infected with HBV as infants will die of HBV-related chronic liver disease as adults.

HBV transmission occurs primarily by blood exchange or by sexual contact with persons who are either acutely or chronically infected. In 30%-40% of cases, the source of infection is not identified. Some cases may result from inapparent contamination of skin lesions or mucosal surfaces: hepatitis B surface antigen (HBsAg) has been found in impetigo, in saliva, and on toothbrush holders of persons chronically infected with HBV. HBV can be transmitted between young children.

**Rationale for Routine Hepatitis B Vaccination**

Although anti-HBV antibody levels diminish following vaccination, most persons remain protected through the immunologic memory in recruited lymphocytes. Immunologic memory and the long incubation period of HBV infection allow most immunized persons with low titers to mount a protective anamnestic immune response. The number of vaccine doses administered, intervals between doses, genetics, prematurity, and underlying medical conditions affect immunogenicity. After the third dose of hepatitis B (HepB) vaccine, more than 95% of children seroconvert. Titers improve with longer intervals between the second and third doses so the vaccine series does not need to be restarted regardless of dose delay. Efficacy for HepB vaccine is high. Prematurity with low birth weight and immunosuppression are associated with lower rates of seroconversion. HepB vaccination should be delayed in preterm infants weighing less than 2 kg until 1 month of age or hospital discharge, whichever first, unless the mother is HBsAg-positive or has unknown HBsAg status, in which case the vaccine should be given within 12 hours of birth.

**Adverse Reactions**

After administration of HepB vaccine, 3%-9% of children have pain at the injection site; 8%-18% have mild, transient systemic adverse events such as fatigue and headache; and 1%-6% have temperature higher than 37.7°C (99.8°F).

**Recommendations**

The comprehensive US hepatitis B vaccination policy includes: (1) prevention of perinatal HBV infection, (2) routine vaccination of infants (Figure 7-1), (3) catch-up immunization of adolescents not previously vaccinated, and (4) catch-up immunization of young children at high risk for infection (http://www.cdc.gov/vaccines/vpd-vac/hepB/default.htm#recs).

Postvaccination testing is not indicated after routine vaccination of infants, children, or adolescents. Postvaccination testing for anti-HBs is recommended at 9-15 months of age for infants born to HBsAg-positive mothers. An adequate antibody response is a titer of 10 mIU/mL or greater.

**PERTUSSIS VACCINE**

More than 10,000 cases of pertussis were reported in the United States in 2008, probably representing hundreds of thousands of infections. Waning immunity after childhood pertussis vaccination is the apparent reason for disease perpetuation. In older persons, pertussis ranges from mild
**Figure 7-1.** Recommended childhood immunization schedule, 2010, United States. (See the Age 7-18 and Catch-UP schedules at http://www.cdc.gov/vaccines/recs/schedules/default.htm.)

<table>
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<th>Birth</th>
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<th>2 months</th>
<th>4 months</th>
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<th>18 months</th>
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1. Hepatitis B vaccine (HepB). (Minimum age: birth)
   - At birth:
     - Administer monoclonal HepB to all newborns before hospital discharge.
     - If mother is hepatitis B surface antigen (HBsAg)-positive, administer HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth.
     - If mother's HBsAg status is unknown, administer HepB within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if HBsAg-positive, administer HBIG (no later than age 1 week).
   - After the birth dose:
     - The HepB series should be completed with either monovalent HepB or a combination vaccine containing HepB. The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks. The final dose should be administered no earlier than age 24 weeks.
     - Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg 1 to 2 months after completion of at least 3 doses of the HepB series, at age 9 through 18 months (generally at the next well-child visit).
     - Administration of 4 doses of HepB to infants is permissible when a combination vaccine containing HepB is administered after the birth dose. The fourth dose should be administered no earlier than age 24 weeks.

2. Rotavirus vaccine (RV). (Minimum age: 6 weeks)
   - Administer the first dose at age 6 through 14 weeks (maximum age: 14 weeks 6 days). Vaccination should not be initiated for infants aged 15 weeks 0 days or older.
   - The maximum age for the final dose in the series is 8 months 0 days.
   - If Rotarix is administered at ages 2 and 4 months, a dose at 6 months is not indicated.

3. Diphtheria and tetanus toxoid and acellular pertussis vaccine (DTaP).
   - Minimum age: 6 weeks.
   - The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.

4. Haemophilus influenzae type b conjugate vaccine ( Hib).
   - Minimum age: 6 weeks.
   - If PRP-OMP (PedvaxHIB or Comvax [HepB-Hib]) is administered at ages 2 and 4 months, a dose at 6 months is not indicated.
   - HibIT (DTaP-Hib) and HibVax (PRP-T) should not be used for doses at ages 2, 4, or 6 months for the primary series but can be used as the final dose in children aged 12 months through 4 years.

5. Pneumococcal vaccine. (Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPSV]).
   - PCV is recommended for children aged younger than 5 years. Administer 1 dose of PCV to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
   - Administer PCV 1.5 years or more after last dose of PCV to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant. See MMWR 1997;46(no. RR-8).

6. Inactivated poliovirus vaccine (IPV). (Minimum age: 6 weeks)
   - The final dose in the series should be administered on or after the 4th birthday and at least 6 months following the previous dose.
   - If 4 doses are administered prior to age 4 years a fifth dose should be administered at age 4 through 6 years. See MMWR 2009;58(03):292-30.

7. Influenza vaccine (seasonal). (Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV]; 2 years for live, attenuated influenza vacc (LAIV)).
   - Administer annually to children aged 6 months through 18 years.
   - For healthy children aged 2 through 6 years (i.e., those who do not have underlying medical conditions that predispose them to influenza complications), either LAIV or TIV may be used, except LAIV should not be given to children aged 2 through 4 years who have had wheezing in the past 12 months.
   - Children receiving TIV should receive 0.25 mL if aged 6 through 35 mcg or 0.5 mL if aged 3 years or older.
   - Administer 2 doses (separated by at least 4 weeks) to children aged 6 months through 8 years who are receiving influenza vaccine for the first time or who were vaccinated for the first time during the previous influenza season but received a dose.

8. Measles, mumps, and rubella vaccine (MMR). (Minimum age: 12 months)
   - Administer the second dose routinely at age 4 through 6 years. However, second dose may be administered before age 4, provided at least 28 days have elapsed since the first dose.

9. Varicella vaccine. (Minimum age: 12 months)
   - Administer the second dose routinely at age 4 through 6 years. However, second dose may be administered before age 4, provided at least 3 months have elapsed since the first dose.
   - If children aged 12 months through 12 years the minimum interval between doses is 3 months. However, if the second dose was administered at 28 days after the first dose, it can be accepted as valid.

10. Hepatitis A vaccine (HepA). (Minimum age: 12 months)
    - Administer to all children aged 1 year (i.e., aged 12 through 23 months).
    - Administer 2 doses at least 6 months apart.
    - Children not fully vaccinated by age 2 years can be vaccinated at subsequent visits.
    - HepA also is recommended for older children who live in areas where vaccination programs target older children, who are at increased risk for infection or for whom immunity against hepatitis A is desired.

11. Meningococcal vaccine. (Minimum age: 2 years for meningococcal conjunctival vaccine [MCV4] and for meningococcal polysaccharide vaccine [MCPSV]).
    - Administer MCV4 to children aged 2 through 10 years with persistent complement deficiency, anatomic or functional asplenia, and certain conditions placing them at high risk.
    - Administer MCV4 to children previously vaccinated with MCV4 or MIP at least last day if first dose administered at age 2 through 6 years. See MMWR 2009;58:1042-3.

The Recommended Immunization Schedules for Persons Aged 0 through 18 Years are approved by the Advisory Committee on Immunization Practices.
cough to classic infection: paroxysms of cough truncated by inspiratory whoop, cyanosis, apnea, or post-tussive vomiting. Cough can last for months, with significant disruption of daily activities.

The majority of pertussis-related hospitalizations and serious complications occur in infants. One-fifth of reported cases are in infants under 6 months of age, too young to be fully vaccinated. Most reported cases of pertussis in infants younger than 12 months, who suffer a case-fatality rate of 0.6%, require hospitalization.

Complications of pertussis include pneumonia, the leading cause of death, and seizures. Encephalopathy, due to hypoxia or minute cerebral hemorrhages, occurs in about 1% of cases, is fatal in approximately one-third of those afflicted, and causes permanent brain damage in another one-third.

Pertussis is highly contagious: 70%-100% of susceptible household contacts and 50%-80% of susceptible school contacts become infected following exposure. The incubation period is typically 7-10 days long. Contagion lasts from 1 week after exposure to 3 weeks after onset of symptoms. Transmission is by respiratory droplets or occasionally by contact with freshly contaminated objects. Adults and adolescents are the primary source of pertussis infection for young infants. The reported incidence rate among adults and adolescents has risen.

➤ Rationale for Vaccination

Before routine pertussis vaccination, peaks in whooping cough incidence occurred approximately every 3-4 years, and virtually all children eventually were infected. Between 1925 and 1930, in the Unites States, 36,013 persons died as a result of pertussis-related complications. After pertussis vaccination became widespread in the mid-1940s, the incidence of pertussis dropped by more than 95%, although it has been increasing in recent years, partly as a result of the use of polymerase chain reaction diagnosis.

➤ Vaccine Efficacy

Diphtheria, tetanus, acellular pertussis (DTaP) vaccines have efficacy rates ranging from 80% to 89%. Although the duration of protection is not known, cohorts from earlier trials show no loss of protection in 2- to 6-year follow-up periods.

➤ Adverse Reactions

Minor adverse reactions associated with DTaP vaccination include localized edema at the injection site, fever, and fussiness.

Uncommon adverse reactions after DTaP vaccination are persistent coughing for 3 or more hours, an unusually high-pitched cry, seizures (usually febrile seizures without any permanent sequelae), and hypotonic-hyperorresponsive episodes. On rare occasions a child might have an anaphylactic reaction to DTaP, contraindicating further doses of DTaP. Rarely, temporary swelling of the entire limb has occurred after the fourth or fifth DTaP dose.

➤ Recommendations

Five doses of DTaP vaccine are recommended for all children prior to school entry. Premature infants should be vaccinated with full doses at the appropriate chronological age, according to the recommended childhood immunization schedule, because fractional doses are not as immunogenic and might not reduce adverse reactions. Completing the recommended series is important for optimal efficacy.

To reduce the incidence of adolescent pertussis and, as a secondary goal, infection of infant siblings, the Advisory Committee on Immunization Practices (ACIP) recommends tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis (Tdap) vaccine for adolescents aged 11-18 years.

PNEUMOCOCCAL CONJUGATE VACCINE

Prior to the introduction of pneumococcal conjugate vaccine (PCV), Streptococcus pneumoniae, a gram-positive diplococcus with over 90 different types of polysaccharide capsule, caused about 17,000 cases of invasive disease, including 200 deaths annually among children younger than 5 years. Respiratory tract droplets spread infection. Invasive disease consists of bacteremia, meningitis, or infection in a normally sterile site. S. pneumoniae is a common cause of community-acquired pneumonia, sinusitis, and otitis media and a leading cause of bacterial meningitis in young children.

➤ Rationale for Vaccination

Risk factors for invasive pneumococcal disease include age, race, recent use of antibiotics, day-care attendance, and chronic medical conditions; breast-feeding protects against the disease. The incidence is highest among infants. Rates are two- to threefold higher among African Americans and three- to sevenfold higher among Alaska Natives and Native Americans, compared with Caucasians. Children with sickle cell disease have high rates of pneumococcal disease; penicillin prophylaxis reduces the risk for pneumococcal disease, but the rates are still elevated.

The two vaccines that protect against pneumococcus are the 23-valent polysaccharide vaccine (PPV) and the 13-valent conjugate vaccine (PCV13), which replaced the 7-valent conjugate vaccine in 2010 in the United States. PCV is T cell–independent, so it does not produce an anamnestic response. Immunity may not be long-lasting. It is not effective in children younger than age 2 years. PCV elicits a T cell–dependent response leading to an anamnestic response and is effective in infants. The vaccine reduces nasopharyngeal carriage rates of S. pneumoniae, which leads to herd immunity. Based on data of the PCV7 formulation, vaccine efficacy against invasive disease is 94% for serotypes included in the vaccine. Efficacy is 11% against clinical pneumonia, 33% against clinical pneumonia with radiographic infiltrate, and 73% against pneumonia with radiographic consolidation of 2.5 cm or greater (most typical of S. pneumoniae).
No serious adverse reactions are associated with PCV13: 10%-14% develop redness and 15%-23% develop tenderness at the injection site. Fever of 38°C (100.4°F) or less occurs in 15%-24% of vaccinees.

The ACIP recommends four doses of PCV13 for routine infant immunization. All children of age 2 to 5 years who have not received PCV13, should receive one dose of PCV13. Children aged 2 years and older with chronic disorders of the pulmonary system, cardiovascular diseases, diabetes mellitus, chronic liver diseases, chronic renal failure or nephrotic syndrome, functional or anatomic asplenia (eg, sickle cell disease or splenectomy), immunosuppressive conditions (eg, congenital immunodeficiency), or receiving chemotherapy with alkylating agents, antimetabolites, or long-term systemic corticosteroids should receive PPV in addition to PCV13 (see ACIP recommendations for details). One-time PPV revaccination after 5 years is recommended for these same children.

Poliovirus spreads to 73%-96% of susceptible household contacts, primarily via the fecal-oral route (oral-oral possible). The incubation period ranges from 3 to 35 days. Up to 95% of cases of poliovirus infection are subclinical, approximately 5% are nonparalytic, viral illness with complete recovery, 1%-2% nonparalytic aseptic meningitis, and less than 2% paralytic poliomyelitis. The case-fatality rate is 2%-5% in children and 15%-30% in adults.

The last case of wild poliomyelitis contracted in the United States was reported in 1979 and the last case in the Americas in 1991. In 1994, the Americas were declared free of indigenous poliomyelitis, but poliovirus was isolated from a few Amish children in the United States in 2005. Poliovirus vaccination is still recommended because of outbreaks in other countries, importation of wild poliovirus, and its highly contagious nature.

Prior to school entry, four doses of all-inactivated poliovirus vaccine (IPV) (oral poliovirus vaccine doses count) are recommended for all children.

During the influenza season, hospitalizations increase because of pneumonia and other complications. Preschoolers, especially infants younger than age 1 year are at high risk. Complications include bacterial pneumonia, worsening of chronic respiratory and cardiac diseases, sinusitis, otitis media, primary viral pneumonia (uncommon), and rarely Reye syndrome, associated with concomitant salicylate use in children, who also have an increased risk of encephalopathy and death.

Transmitted from person to person, usually via the airborne route, influenza is extremely contagious; consequently, persons in crowded environments, such as students, are at high risk. The incubation period is 2 days (range, 1-5 days). Young children can shed virus for up to 6 days before onset of symptoms, have the highest attack rate (14%-40% yearly, especially high in preschoolers), and frequently infect their family members.

Two influenza vaccines are currently licensed: trivalent inactivated influenza vaccine (TIV) and live attenuated influenza vaccine (LAIV). The LAIV contains three, cold-adapted viruses that replicate at 25°C (77°F), a temperature at which wild strains do not grow well. The LAIV replicates somewhat in the nasopharynx, where the temperatures are cooler, but inefficiently in lower airways where temperatures are warmer.

The effectiveness of influenza vaccine depends primarily on the degree of similarity between the vaccine virus strains and wild circulating virus during the influenza season and on the immunocompetence of the vaccine recipient. TIV has moderate efficacy of 44%-57% defined in children aged 1-5 years and good efficacy of ≥77% in older children and adolescents. Immunity from TIV may not persist beyond a year. Hence, annual vaccination just prior to the influenza season is recommended. Protection develops within 2 weeks after vaccination. In healthy children, LAIV was 94% efficacious against culture-confirmed influenza for two doses and 89% for one dose.

A. Trivalent Inactivated Influenza Vaccine

Local reactions to TIV are soreness at the injection site that lasts less than 2 days. In persons previously exposed to influenza disease or vaccination, split-virus vaccine and placebo have similar rates of systemic reactions such as fever. In young children not previously exposed to influenza vaccine, fever, malaise, and myalgia can occur after TIV. A study from the Vaccine Safety Datalink found no serious reactions from TIV among 251,600 children younger than 18 years.

B. Live Attenuated Influenza Vaccine

Persons vaccinated with LAIV shed vaccine virus. In one day-care study, 80% of vaccinees aged 8-36 months shed vaccine
MEASLES, MUMPS, & RUBELLA (MMR) VACCINE

In 2008 in the United States, the number of indigenous cases reported for measles was 132, for mumps 396, and for rubella 17. Mini outbreaks continue to occur periodically.

Measles can cause severe morbidity, but acutely fatal, or cause a delayed fatal encephalopathy (subacute sclerosing panencephalitis) in adolescence. Worldwide measles kills about 280,000 people per year. Mumps produces excruciating bilateral parotitis and sometimes pancreatitis, orchitis, cerebellar ataxia, or death. Usually rubella causes only posterior cervical adenopathy, arthralgia, and minimal rash, but it can also produce devastating congenital rubella syndrome.

Outbreaks start with an imported measles case that spreads among persons unvaccinated due to philosophic or religious exemptions: the attack rate among unvaccinated household contacts is 90% or higher. Infected persons can transmit measles from 4 days prior to 4 days after rash onset.

Rationale for Vaccination

The first dose of MMR protects only 95% of children, necessitating a second dose for all. After two doses, more than 99% of persons are immune. Mothers with a history of wild viral disease confer higher initial levels of antibody to their infants, who then have protective antibody levels until about 11 months of age. The duration of immunity transferred to infants from vaccinated mothers is about 9 months. Currently MMR vaccination at 12 months of age is ideal. Immunity is probably lifelong in almost all persons who initially seroconvert. The rate of waning immunity is less than 0.2% per year.

Adverse Reactions

Pain, irritation, and redness at the injection site are common but mild. Reactions to measles vaccine include fever (usually <38.8°C [102°F]) between days 7 and 12, transient rash between days 5 and 20, or transient thrombocytopenia (1 in 25,000 to 2 million doses). Adverse reactions to rubella vaccine include generalized lymphadenopathy in children and transient arthralgia in young women, and to mumps vaccine include transient orchitis in young men. MMR does not cause autism.

Recommendations

The MMR vaccine is given routinely to all healthy children at age 12-15 months with a second dose at age 4-6 years. A second dose is especially important for college students.

VARICELLA VACCINE

Varicella-zoster virus (VZV) causes chickenpox, a generally self-limited and benign illness. However, the hospitalization rate is 5 cases per 1000 population. Because transmission rates are as high as 90% and communicability via aerosol droplets begins 1-2 days prior to rash onset, prevention of spread requires universal vaccination. Complications include secondary skin infection (impetigo and invasive group A streptococcal disease), pneumonia, and other severe disorders. The lifetime risk for herpes zoster is at least 10%.

Rationale for Vaccination

Before universal VZV vaccination the majority of individuals hospitalized each year for VZV-related complications were in the 1 to 4-year-old group because VZV was so common at those ages. Routine VZV vaccination in the United States produced a substantial reduction in hospitalization due to significant reduction in cases of varicella among all age groups. Routine vaccination is cost-effective: each dollar spent on universal immunization avoids approximately $5 in costs.

Varicella vaccine contains live attenuated virus and is effective against moderately severe and severe disease. Breakthrough disease is usually mild, producing fewer than 30 pox lesions. A two-dose vaccination strategy was adopted to reduce breakthrough cases.
Adverse Reactions

Following subcutaneous injection, local pain and erythema occur in 2%-20% after the first dose and up to 47% after the second dose. From 4% to 10% develop a median of 5 varicella-like, short-lived (2-8 days) lesions 5-41 days after administration. A brief, low-grade fever develops in 12%-30% of vaccinees. Vaccine virus can rarely be transmitted to healthy immunocompetent persons. A rare severe reaction following vaccination is hypersensitivity to gelatin or neomycin. Persons with previously unrecognized prior immunization or VZV infection are not at increased risk from vaccine. Zoster is less common among vaccinees.

Recommendations

The ACIP recommends the first dose for ages of 12-18 months and the second dose for ages 4-6 years with catch-up vaccination through 18 years of age for previously uninfected or unvaccinated children. At least 80% of those without a history of chickenpox are actually immune. Serologic tests are not required. Immunocompromised persons require no special precautions except avoidance of direct contact with a vaccine-induced rash.

Postexposure Prophylaxis

VZV vaccine is effective in modifying varicella if given within 3-5 days of exposure to wild varicella. Artificial varicella-zoster immune globulin (VariZIG) is recommended for exposed immunosuppressed patients and for infants of mothers who develop varicella 5 days before to 2 days after delivery at 125 units/10 kg (maximum of 625 units; minimum of 125 units).

MENINGOCOCCAL CONJUGATE VACCINE

Neisseria meningitidis, the most common cause of bacterial meningitis in children and young adults in the United States, causes approximately 2200-3000 cases of invasive disease annually, at an incidence of 0.8-1.5 cases per 100,000 persons. Death occurs in about 10% of cases, and sequelae such as limb loss, neurologic disabilities, and hearing loss occur in 11%-19%.

N meningitidis is transmitted via respiratory tract droplets and occurs sporadically most often in children younger than 5 years of age. Serogroup B accounts for more than 30% of meningococcal disease and tends to occur in children younger than age 2 years. Serogroup Y also accounts for about 30% of sporadic cases, while serogroups A and C cause most outbreaks.

In the pre-vaccine era, a nationwide survey found that the incidence of meningococcal disease for freshmen college students living in dormitories was 5.1 per 100,000, compared with 0.7 per 100,000 other undergraduates and 1.4 per 100,000 18- to 23-year-olds in the general population.

Vaccine Types

The meningococcal (groups A, C, Y, and W-135) conjugate vaccine (MCV-4) is recommended for all adolescents at age 11-12 years with catch up vaccination for ages 13-18 years and for persons age 2-55 years with high-risk medical indications including anatomic or functional asplenia, deficiencies in terminal complement components, and travelers to, or residents of, hyperendemic areas such as sub-Saharan Africa. It provides long-term immunity. A study in 2 to 10-year-old children found that serum bactericidal antibody titers were significantly higher for all serogroups in MCV-4 recipients compared with nonconjugated quadrivalent meningococcal polysaccharide vaccine (MPSV-4) recipients at 28 days and 6 months after vaccination. College freshman living in dormitories or wishing protection against meningococcus should be vaccinated with MCV-4. Two MCV4 brands exist for somewhat different age ranges; see package inserts, the software Shots (www.immunizationed.org), or CDC information for details.

Following intramuscular injection, the most common adverse events are mild local pain, headache, and fatigue. Mild to moderate systemic reactions such as fever, fussiness, and drowsiness are infrequent.

ROTA VIRUS VACCINE

Each year in the United States rotavirus caused 2-3 million cases of gastroenteritis, 60,000 hospitalizations, and a reported 20 to 60 deaths.

The ACIP recommends that all infants receive either 3 doses of pentavalent or 2 doses of monovalent rotavirus vaccine. Doses are given 2 months apart. Both vaccines are oral, live virus given in the first 6 months of life and reduce the risk of severe gastroenteritis by 98%. Side effects include irritability and gaseousness. Intussusception rates are not increased.

References:


We expect our children to be active and energetic, but when they exceed the norms for their age in their displays of activity, their lack of impulse control, or their inability to focus attention, they are likely to experience problems in social, familial, academic, and emotional interactions. Self-esteem is adversely affected, and these individuals are at greater risk of developing antisocial disorders, substance abuse disorders, academic failure, employment failure, and secondary mood and anxiety disorders. These behavioral variants, therefore, cause a significant social burden and are often brought to the attention of primary care physicians. This chapter addresses three Axis I childhood behavioral problems likely to be encountered in the primary care setting: attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD).

The controversies surrounding behavioral problems and their treatments have generated several comprehensive reviews that have improved understanding of these conditions. In 1998, the American Medical Association Council on Scientific Affairs concluded that there was little evidence of overtreatment with neurostimulants in the United States. That same year, the National Institutes of Health (NIH) conducted a Consensus Conference on the Diagnosis and Treatment of ADHD that concluded “there is validity in the diagnosis of ADHD as a disorder with broadly accepted symptoms and behavioral characteristics that define the disorder.” Details are available at http://odp.od.nih.gov/consensus/cons/110/110_statement.htm. An International Consensus Letter from prominent leaders in the field in 2002 concluded decisively that “All the major medical associations and government health agencies recognize ADHD as a genuine disorder because of the scientific evidence indicating it is so overwhelming.”

### ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

#### ESSENTIALS OF DIAGNOSIS

- A persistent pattern of inattention, hyperactivity, or both; more frequent and severe displays of impulsivity.
- Academic underachievement and behavioral problems.

#### General Considerations

Up to 20% of school-aged children in the United States have behavioral problems and at least half of these involve attention of hyperactivity difficulties. ADHD is the most common and well-studied of the childhood behavioral disorders. All family physicians have encountered the classically hyperactive child and his or her beleaguered parents and teachers in practice and in social interactions, but, likewise, may have overlooked the quiet but inattentive “daydreamer.” The seeming dichotomy between the hyperactive and the inattentive types of ADHD can be confusing to both clinicians and the public. Primary care physicians should be familiar with the features of this disorder and are ideally positioned to evaluate and treat the majority of children and families dealing with this condition.

#### Pathogenesis

Neurophysiologic data suggest that there is no single cognitive or behavioral deficit common to all individuals with ADHD. Emerging data suggest that individuals with ADHD have abnormalities in the frontal-striatal circuits but the exact problem has not been isolated.
Individuals diagnosed with ADHD are likely to experience significant difficulties with executive functioning which impairs academic performance, social relationships, self-control, and memory. Thomas Brown, Ph. D. outlines six executive functions observed in individuals diagnosed with ADHD. These include (1) organizing and prioritizing (difficulty getting started on tasks); (2) focusing and sustaining attention (easily distracted); (3) regulating alertness, sustaining effort (drowsiness); (4) managing frustration (low frustration tolerance or disproportionate emotional reactions); (5) working memory (difficulty retrieving information); and (6) self-regulation (difficulty inhibiting verbal and behavior responses).

There is good evidence that ADHD is not caused by too much television (although patients may be attracted and distracted by it); by food allergies (although the rare child may display inattention secondary to such allergies); by excess sugar, artificial flavorings, colorings, or preservatives in food; by poor home life or parenting skills (although the behaviors of ADHD do upset the classic parent-child confrontation seen in ODD and account for some of that common comorbidity); or by poor schools or teachers. Some data suggest that maternal smoking, cocaine use, and alcohol use in pregnancy could play a role in some children with ADHD. Fetal alcohol syndrome results in similar problems with hyperactivity, inattention, and impulsivity.

Evidence now favors ADHD as a lifelong process. Preschoolers are being identified with great predictability for developing ADHD symptoms once in school. Up to 80% of ADHD children have features into adolescence and 65% into adulthood. The family physician is ideally placed to assist patients across the life span.


### Epidemiology & Cultural Demographics

Analysis by the Centers for Disease Control and Prevention (CDC) of data from the 2003 National Survey of Children’s Health places the national prevalence of ADHD in the United States among children aged 4-17 years at 7.8% (11% of males and 4.4% of females) and shows that 4.3% of children are currently being treated with medications (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5434r2.htm). The ratio of male to female children is estimated at 4:1 for the hyperactive type of ADHD and 2:1 for the inattentive type. For ADHD alone, without comorbid factors such as CD, there are no differences along socioeconomic classes. Among races in the United States, the CDC reports the following prevalences: 8.6% of white children, 7.7% of black children, 9.7% of multiracial children, and 4.5% of others. It would seem that ADHD arises across ethnic groups and, although cultural and ethnic factors may contribute to variations in diagnosis, there is no cultural or ethnic component to the etiology and true prevalence of ADHD.

Studies support a substantial genetic contribution to ADHD. Sibling studies show a risk of ADHD among siblings of a child with the diagnosis that is two to three times that in normal controls. The parents of children with ADHD have a higher incidence of the condition than societal norms and have a higher incidence of other psychiatric problems, and relatives have a higher incidence of mood problems, anxiety disorders, learning disabilities, CD, antisocial personality disorder, substance abuse problems, depression, and marital dysfunction.

#### Clinical Findings

##### A. Diagnostic Criteria

There is no single diagnostic test or tool for ADHD. The diagnostic criteria included in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, (DSM-IV-TR) are the current basis for the identification of individuals with ADHD. Meeting these criteria (Table 8-1) does not exclude the possibility of other conditions, and the full differential diagnosis must be considered by the evaluating physician (see Table 8-2). There is rarely a need for extensive laboratory analysis, but screening for iron deficiency and thyroid dysfunction is reasonable.

The American Academy of Child and Adolescent Psychiatry and the American Academy of Pediatrics (AAP), with input from members of the American Academy of Family Physicians, have formulated evidence-based practice guidelines to aid in the improvement of current diagnostic and treatment practices. These guidelines can be accessed at the AAP’s Web site (http://aappolicy.aappublications.org/cgi/content/full/pediatrics;105/5/1158). The diagnosis is made by parent interview, direct observation, and use of standardized and scored behavioral checklists such as the Connors Parent and Teacher Rating Scales, Child Behavior Checklist (CBCL), Vanderbilt ADHD Diagnostic Parent and Teacher Scales, Achenbach, along with computerized tests (Gordon Diagnostic Testing, Connors Continuous Performance Task, TOUA) measuring impulsivity and inattention that are specific for ADHD and should include input from both parents and teachers. The criterion for diagnosis on the checklist is two standard deviations above the mean in the number of ADHD symptoms displayed.

Three subtypes of ADHD are recognized (see Table 8-1): predominantly inattentive (accounting for 20%-30% of ADHD individuals), predominantly hyperactive-impulsive (accounting for <15%), and the combined subtype (the most common, accounting for 50%-75% of cases). Individuals with the inattentive subtype have fewer behavioral problems but are subject to mood fluctuations. Those with an inattentive component have more academic problems than those with a purely hyperactive component. Individuals with the combined subtype have the highest incidence of comorbid psychiatric problems and problems with substance abuse, and are the most impaired.

Some children may not fully meet DSM-IV-TR criteria. A useful reference for these children has been supplied by the AAP in its Diagnostic and Statistical Manual for Primary Care.
Table 8-1. DSM-IV-TR diagnostic criteria for attention-deficit/hyperactivity disorder.

A. Either (1) or (2):
(1) Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention
(a) Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
(b) Often has difficulty sustaining attention in tasks or play activities
(c) Often does not seem to listen when spoken to directly
(d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
(e) Often has difficulty organizing tasks and activities
(f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
(g) Often loses things necessary for tasks or activities (eg, toys, school assignments, pencils, books, or tools)
(h) Is often forgetful in daily activities

(2) Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity
(a) Often fidgets with hands or feet and squirms in seat
(b) Leaves seat in classroom or in other situation in which remaining seated is expected
(c) Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
(d) Often has difficulty playing or engaging in leisure activities quietly
(e) Is often “on the go” or often acts as if “driven by a motor”
(f) Often talks excessively

Impulsivity
(g) Often blurts our answers before questions have been completed
(h) Often has difficulty awaiting turn
(i) Often interrupts or intrudes on others (eg, butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.
C. Some impairment from the symptoms is present in two or more setting (eg, at school [or work] and at home).
D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
E. The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder and are not better accounted for by another mental disorder (eg, mood disorder, anxiety disorder, dissociative disorder, or a personality disorder).

Code Based on Type:
314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type: if both criterion A1 and A2 are met for the past 6 months.
314.00 Attention-Deficit/Hyperactivity Disorder, Predominately Inattentive Type: if criterion A1 is met but criterion A2 is not met for the past 6 months.
314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type: if criterion A2 is met but criterion A1 is not met for the past 6 months.

Coding Note: For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, “In Partial Remission” should be specified.

314.9 Attention-Deficit/Hyperactivity Disorder: Not Otherwise Specified: this category is for disorders with prominent symptoms of inattention or hyperactivity/impulsivity that do not meet criteria for attention-deficit/hyperactivity disorder. Examples include
1. Individuals whose symptoms and impairment meet the criteria for attention-deficit/hyperactivity disorder, predominantly inattentive type but whose age at onset is 7 years or older.
2. Individuals with clinically significant impairment who present with inattention and whose symptom pattern does not meet the full criteria for the disorder but have a behavioral pattern marked by sluggishness, daydreaming, and hypoactivity.

(DSM-PC), Child and Adolescent Version. The DSM-PC considers environmental and developmental influences on the more common variations in behavior to help in the diagnosis and management of children with attention, hyperactivity, and impulsivity.

**B. Comorbidities**

ADHD is often associated with other Axis I diagnoses, especially in patients referred to psychiatrists. From 35% to 60% of referred ADHD children have ODD, and 25%-50% will develop CD. Of these, 15%-25% progress to antisocial personality disorder in adulthood. Indeed, ADHD can be used as a reliable early predictor of disruptive behavior disorders. A family history of conduct problem aids this prediction. Among children with ADHD, those who are most hyperactive-impulsive are at greatest risk for development of ODD; however, it is possible to distinguish between the two disorders. ODD behaviors, such as “loses temper,” “actively defies,” and “swears,” are less characteristic of children with ADHD.

Anxiety disorders are more common in the predominantly inattentive type of ADHD; for example, 25%-40% of referred children have a concurrent anxiety disorder. As many as 50% of referred children with ADHD eventually develop a mood disorder—most commonly depression, diagnosed in adolescence. The diagnosis of bipolar disease in childhood increased the risk of concurrent label of ADHD because of the overlap of behaviors. About half the children with Tourette syndrome have ADHD, and the symptoms of ADHD usually precede the other symptoms of that syndrome. The medical treatment of Tourette syndrome and ADHD is complicated by the effects of stimulant medications on tics. Determination of the coexistence of ADHD and Tourette syndrome is vital to ensure that appropriate social and educational services are obtained for these children. (Tourette syndrome is discussed in detail in Chapter 43.)

There appears to be a strong correlation between sleep disorders and ADHD. Children who snore are almost twice as likely as their nonsnoring counterparts to meet diagnostic criteria for ADHD. This is particularly true for younger (<8 years) boys, for whom the risk is three times higher in snorers. Whether this is a cause-and-effect phenomenon needs further study, but this link should be kept in mind when taking a history.

There is a definite association among ADHD, academic problems, and learning disabilities. Between 20% and 50% of children with ADHD have at least one type of learning disorder. In any child with ADHD in whom academic achievement seems to lag behind intelligence, testing for learning disabilities should be performed. The documentation of a learning disability makes it easier to obtain academic accommodations and modifications through individual educational plans as protected by the Individuals with Disabilities Education Act (IDEA). Individuals with ADHD have a higher risk of reading problems, as well as arithmetic and writing difficulties. They are often poor spellers and have poor penmanship. These problems are associated with difficulties in the executive functions of integration of working memory and motor coordination and fluency, all mediated by the lack of intact inhibitory processes.

There does not seem to be an association between intelligence and ADHD, although the verbal scores, mental arithmetic scores, and digital span scores in many intelligence quotient (IQ) tests can be lower in children with ADHD due to problems with working memory. These differences appear when hyperactive behavior is factored out of the testing and are thought to be due to the methodology rather than true differences in intelligence. The true impact of ADHD is on the application of intelligence in everyday functioning and academic work.

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**Differential Diagnosis**

Table 8-2 lists the differential diagnosis for ADHD.

**Treatment**

**A. Pharmacotherapy**

Medications commonly used in the treatment of ADHD are listed in Tables 8-3 and 8-4.

1. **Stimulants**—The efficacy of this class has been proven in controlling some of the manifestations of ADHD but they are not a “cure.” The fact that stimulants are controlled substances (Schedule II) with an abuse potential justifies the close scrutiny of their use. About 65% of children with ADHD show improvement in the core symptoms of hyperactivity, inattention, and impulsivity with their first trial of a stimulant and up to 95% will respond when given appropriate trials of various stimulants. The management of these medications can be complex, and treatment failures may more often be the result of improper treatment strategies than effective medication.

The pharmacokinetics of stimulants are characterized by rapid absorption, low plasma protein binding, and rapid extracellular metabolism. Up to 80% may be excreted in the urine unchanged or de-esterized. Therefore half-lives are short and frequent dosing or sustained release preparations are necessary. Response does not seem to be weight dependent so weight dependent dosing strategies are not as helpful as with other medications. Plasma levels of these agents have not been shown to be useful in determining optimal dosing.

Successful management of the stimulants used in ADHD treatment requires a systematic approach such as that outlined in the following model. It comprises four phases: (1) counseling, (2) titration, (3) maintenance, and (4) potential termination.
A. Counseling phase—The goals of this phase are to explain the rationale for the trial of the medication with both the expected positive effects and potential negative effects. Children must understand why they are being treated. They should know that the physician and not their parents or teachers is responsible for their treatment. The details of the treatment should also be discussed, including the choice of medication, dosage, and expected frequency of follow-up. Parents should be told which behaviors to monitor, what side effects to expect, and how they will be dealt with. Physicians should also explain the expected changes in dosing and timing of the medications, and the anticipated eventual shift from short-acting to sustained-release preparations.

An important step is to determine the targeted symptoms, which will be unique for each child and family. This requires that the physician and parents review the child’s symptoms and prioritize them based on their effect on the child’s performance. Responders have shown specific effects, as outlined below.

Motor Effects
- Reduced hyperactivity
- Decreased excessive talking and disruption
- Improved handwriting
- Improved fine motor control

Social Effects
- Reduction in off-task behaviors
- Improved ability to play and work independently
- Decreased intensity of behavior
- Reduced anger
- Improved (but not normalized) peer social interaction
- Improved parent-child interactions
- Reduced verbal and physical aggression

Cognitive Effects
- Greater sustained attention
- Reduced distractibility
- Improved short-term memory
- Increased accuracy of academic work

Perhaps the most important step at this phase is the choice of medications. Stimulants most commonly used include methylphenidate (Ritalin), dexmethylphenidate (Focalin), dextroamphetamine (Dexedrine), and mixed amphetamine salts (Adderall). Pemoline (Cylert), used in the past was discontinued in the United States in October 2005 because of liver toxicity. It requires biweekly monitoring of liver enzymes and the signing of an informed consent. In recent years, novel drug delivery systems have been developed for stimulants and these formulations have become routine in clinical practice. These agents range from short-acting immediate release formulations to extended release formulations in the form of pills, pellets, a prodrug, a patch or transdermal system and an osmotic release pump system. The benefits of a medication may be apparent for as short as 2-4 hours or as long as 15 hours depending on the formulation employed. Concerta is a form of methylphenidate that uses an osmotic mechanism to provide effective extended treatment approximating the three times daily dosing of methylphenidate immediate release. Daytrana is a methylphenidate transdermal delivery system (MTS). Patches are applied once daily and deliver a consistent amount of methylphenidate during the time the patch is worn. The MTS system may be a useful

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Table 8-2. Differential diagnosis of ADHD.

<table>
<thead>
<tr>
<th>General Medical Conditions</th>
<th>Neurologic Conditions</th>
<th>Psychiatric Conditions</th>
<th>Environmental Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing impairment</td>
<td>Learning disability&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Conduct disorder&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Improper learning environment (eg, unsafe, disruptive)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>Tic disorders (eg, Tourette syndrome)</td>
<td>Oppositional defiant disorder</td>
<td>Mismatch of school curriculum with child’s ability (eg, gifted, learning disabled)</td>
</tr>
<tr>
<td>Medication effects, (eg, antihistamine decongestants, β-agonists, anticonvulsants)</td>
<td>Seizure disorders</td>
<td>Substance abuse</td>
<td>Family dysfunction or stressful home environment&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Asthma</td>
<td>Mental retardation (eg, fetal alcohol syndrome, fragile X syndrome, phenylketonuria)</td>
<td>Anxiety&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Poor parenting (eg, inappropriate, inconsistent, punitive)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>Developmental delays</td>
<td>Post-traumatic stress disorder</td>
<td>Child neglect or abuse&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Eczema</td>
<td>Brain injury</td>
<td>Depression</td>
<td>Parental psychopathology</td>
</tr>
<tr>
<td>Enuresis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Sleep disorders</td>
<td></td>
<td></td>
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<tr>
<td>Nephrotic syndrome</td>
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<tr>
<td>Malnutrition</td>
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<tr>
<td>Hypothyroidism</td>
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<td></td>
<td></td>
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<tr>
<td>Lead toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Common comorbid and associated conditions.

### Table 8-3. Medications Approved by the FDA for ADHD (alphabetical by class).

<table>
<thead>
<tr>
<th>Generic Class/Brand Name</th>
<th>Dose Form</th>
<th>Typical Starting Dose</th>
<th>FDA Max/Day</th>
<th>Off-Label Max/Day</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amphetamine preparations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adderall</td>
<td>5, 7, 10, 12, 15, 20, 30 mg tab cap</td>
<td>3-5 y: 2.5 mg qd</td>
<td>40 mg</td>
<td>&gt;50 kg: 60 mg</td>
<td>Short-acting stimulants often used as initial treatment in small children (&lt;16 kg), but have disadvantage of bid-tid dosing to control symptoms throughout day.</td>
</tr>
<tr>
<td>Dextrostat</td>
<td>5, 10 mg cap</td>
<td>3-5 y: 2.5 mg qd, 6 y: 5 mg qd-bid</td>
<td>40 mg</td>
<td>&gt;50 kg: 60 mg</td>
<td>Longer-acting stimulants offer greater convenience, confidentiality, and compliance with single daily dosing, but may have greater problematic effects on evening appetite and sleep.</td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextrostat spansule</td>
<td>5, 10, 15 mg cap</td>
<td>6 y: 5-10 mg qd-bid</td>
<td>40 mg</td>
<td>&gt;50 kg: 60 mg</td>
<td></td>
</tr>
<tr>
<td>Adderall XR</td>
<td>5, 10, 15, 20, 35, 30 mg cap</td>
<td>6 y: 10 mg qd</td>
<td>30 mg</td>
<td>&gt;50 kg: 60 mg</td>
<td></td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>30, 50, 70 mg cap</td>
<td>30 mg qd</td>
<td>70 mg</td>
<td>Not yet known</td>
<td></td>
</tr>
<tr>
<td><strong>Methylphenidate preparations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focalin</td>
<td>2.5, 5, 10 mg cap</td>
<td>2.5 mg bid</td>
<td>20 mg</td>
<td>50 mg</td>
<td>Short-acting stimulants often used as initial treatment in small children (&lt;16 kg), but have disadvantage of bid-tid dosing to control symptoms throughout day.</td>
</tr>
<tr>
<td>Methylin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5, 10, 20 mg tab</td>
<td>5 mg bid</td>
<td>60 mg</td>
<td>&gt;50 kg: 100 mg</td>
<td>Longer-acting stimulants offer greater convenience, confidentiality, and compliance with single daily dosing, but may have greater problematic effects on evening appetite and sleep. Metadate CD and Ritalin LA caps may be opened and sprinkled on soft food.</td>
</tr>
<tr>
<td>Ritalin&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metadate ER</td>
<td>10, 20 mg cap</td>
<td>10 mg qAM</td>
<td>60 mg</td>
<td>&gt;50 kg: 100 mg</td>
<td>Longer-acting stimulants offer greater convenience, confidentiality, and compliance with single daily dosing, but may have greater problematic effects on evening appetite and sleep. Metadate CD and Ritalin LA caps may be opened and sprinkled on soft food.</td>
</tr>
<tr>
<td>Methylin ER</td>
<td>10, 20 mg cap</td>
<td>10 mg qAM</td>
<td>60 mg</td>
<td>&gt;50 kg: 100 mg</td>
<td></td>
</tr>
<tr>
<td>Ritalin SR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20 mg</td>
<td>10 mg qAM</td>
<td>60 mg</td>
<td>&gt;50 kg: 100 mg</td>
<td></td>
</tr>
<tr>
<td>Metadate CD</td>
<td>10, 20, 30, 40, 60 mg</td>
<td>20 mg qAM</td>
<td>60 mg</td>
<td>&gt;50 kg: 100 mg</td>
<td></td>
</tr>
<tr>
<td>Ritalin LA</td>
<td>10, 20, 30, 40 mg</td>
<td>20 mg qAM</td>
<td>60 mg</td>
<td>&gt;50 kg: 100 mg</td>
<td></td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concerta</td>
<td>18, 27, 36, 54 mg cap</td>
<td>18 mg qAM, Begin with 10 mg patch qd, then titrate up by patch strength</td>
<td>72 mg</td>
<td>108 mg Not yet known</td>
<td>Swallow whole with liquids. Nonabsorbable tablet shell may be seen in stool.</td>
</tr>
<tr>
<td>Daytrana patch</td>
<td>10, 15, 20, 30 mg patches</td>
<td>5 mg qAM</td>
<td>30 mg</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td>Focalin XR</td>
<td>5, 10, 15, 20 mg cap</td>
<td>5 mg qAM</td>
<td>30 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Selective norepinephrine reuptake inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>10, 18, 25, 40, 60, 80, 100 mg cap</td>
<td>Children and adolescents &lt;70 kg: 0.5 mg/kg/d for 4 d; then 1 mg/kg/d for 4 d; then 1.2 mg/kg/d</td>
<td>Lesser of 1.4 mg/kg or 100 mg</td>
<td>Lesser of 1.8 mg/kg or 100 mg</td>
<td>Not a Schedule II medication. Consider if active substance abuse or severe side effects of stimulants (ie, mood lability, tics); give qAM or divided doses bid (effects on late evening behavior); do not open capsule; monitor closely for suicidal thinking and behavior, clinical worsening, or unusual changes in behavior.</td>
</tr>
<tr>
<td>Straterra</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FDA, Food and Drug Administration; ADHD, attention-deficit/hyperactivity disorder.**

<sup>a</sup>Generic formulation available.

Vyvanse (lisdexamfetamine dimesylate) is an innovative dextroamphetamine prodrug. This system may be associated with diminished abuse potential and toxicity potential. There appears to be little overall difference in the available agents as to the number of children who respond initially, and the side effect profiles appear to be very similar. Each child will react differently to the various stimulants, and finding the optimal agent and dose is a matter of trial and error. The patient and parents must be aware of this and active in the decisions that will follow. Many times a combination of short- and long-acting medications is necessary to ensure the best coverage for the periods of peak target symptoms. A useful analogy is to insulin therapy in diabetes mellitus.

Absolute contraindications to the use of stimulants include concomitant use of monoamine oxidase (MAO) inhibitors, psychosis, glaucoma, underlying cardiac conditions, existing liver disorders, and a history of stimulant drug dependence. Adverse cardiovascular effects of stimulant have consistently documented mild increases in pulse and blood pressure of unclear clinical significance. In March 2006 the Pediatric Advisory Committee of the Food and Drug Administration (FDA) addressed the risk of sudden death occurring with agents used for the treatment of ADHD. The Pediatric Advisory Committee did not support a recommendation for a black box warning. Nevertheless, physicians should be aware of rare but serious cardiovascular risks. Caution should be used in treating patients who have a family history of early cardiac death of arrhythmias or a personal history of structural abnormalities, palpitations, chest pain, and shortness of breath or syncope of unclear origin either before or during treatment with stimulants.
b. Titration phase—Medication management requires close monitoring of behaviors and frequent dosing modifications in timing and strength to achieve optimal results. Titration usually lasts several months and entails weekly monitoring by the physician, much of which can be done by phone. Neither drug levels nor laboratory tests will determine appropriate dosing, and there is wide variation in response and side effects. Patients and families should be counseled that the initial dose may be ineffective and that the process of identifying the optimal dose will take time to do properly.

The most common side effects of stimulants are appetite suppression, which may be accompanied by nausea or stomach pain (but usually not); difficulty falling asleep; irritability; sadness; or rebound in hyperactive behaviors as the medication wears off. Side effects are the most common reason for discontinuation of these medications. Table 8-5 lists common side effects of stimulants and strategies to manage those side effects.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Management Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite Suppression</td>
<td>Will decrease with time (why stimulants eventually fail as “diet pills”) Try to time meals when medication effect is minimal or worn off Make breakfast a major meal, prior to dosing Make favorite foods for lunch Offer substantial meal at bedtime</td>
</tr>
<tr>
<td>Delayed Sleep Onset</td>
<td>Determine if problem was preexisting, in which case an afternoon dose may actually help If real, consider decreasing afternoon dosing Usual sleep hygiene maintenance (same bedtime routine, bed just for sleep, etc) Rarely consider second agent such as clonidine or trazodone (usually with consultation)</td>
</tr>
<tr>
<td>Rebound or “Wearing-Off” Phenomenon</td>
<td>Check dosing, consider a 4 pm dosing of a short-acting agent Switch to longer-acting agents (pharmacokinetics decrease withdrawal)</td>
</tr>
<tr>
<td>Tics</td>
<td>Check child for emergence of Tourette syndrome Simple tics are common and not necessarily associated with stimulants, they can be observed If troublesome or irretractable, stop stimulant and consider adding or substituting another agent (such as a centrally acting α-agonist) with consultation</td>
</tr>
<tr>
<td>Depression</td>
<td>Check timing of symptoms; if they concur with medication timing, consider a different agent Make sure that attention problems were not really a mood problem consider consultation</td>
</tr>
<tr>
<td>Social Withdrawal</td>
<td>Uncommon effect of “zombie-like” behavior due to excessive dosing Check timing of symptoms and dosing; decrease dose or increase intervals</td>
</tr>
</tbody>
</table>

Most of the short-acting agents have their effect on symptoms for about 3-4 hours. The mixed amphetamine salts (Adderall) have an intermediate length of action of 4-6 hours. Methylphenidate has extended release forms including Ritalin LA and Metadate CD which also may be opened and sprinkled on food. Similarly, dexmethylphenidate (Focalin) has an extended version that can be opened and sprinkled on food. The MTS patch (Daytrana) is designed to be worn for 9 hours and to have similar action to the release mechanics seen in the long-acting methylphenidate (Concerta). Long-acting medications are preferable to shorter-acting agents because they have less rebound phenomenon and they do not require a noontime dose in school. The effects of the longer-acting agents on the target symptoms must be compared with the effects established by the shorter agents. The longer-acting agents have a delayed onset of action (usually about 1 hour compared with 20 minutes for the shorter-acting agents.) In addition, the longer-acting agents may be less potent milligram for milligram, therefore, conversion is not always straightforward.

The final step of the titration phase is an attempt to convert from the shorter-acting agents to longer-acting agents or even combining them to obtain the maximum benefit. It is possible to use a lower dose of the long-acting agent as a baseline and give shorter-acting agents for periods where control is needed the most. Dosage modification is always an individual process and requires a great deal of communication among the patient, parents, teacher, and prescribing physician.

c. Maintenance phase—Once the dosage of a long-acting agent is established and target symptoms are controlled, the frequency of visits between the physician and the patient can decrease. Because stimulants are Schedule II controlled substances, prescriptions with no refills are usually written monthly; however, several states allow 3-month prescriptions. In the large MTA cooperative study in 1999, the children with the best outcomes had monthly 30-minute medication visits. Growth and vital signs should be checked and documented, and it is vital to monitor the medication effects and the child’s progress. Issues to address include (1) adequacy and timing of the dosage, (2) compliance with the regimen, (3) changes in school or out-of-school activities that may affect medical therapy, and (4) maintenance of appropriate growth. An initial drop-off in weight gain usually occurs during titration phase, but over 2 years this reverses, resulting in no long-term sustained growth suppression from stimulant use. Drug holidays are no longer standard procedure, but parents may opt for their children to have periods off the medications to minimize potential unknown drug effects or to assess the continuing need for the medication.

d. Termination of stimulant medication—The decision to stop stimulant therapy is based on a clinical trial off of the medication and close monitoring of target symptoms. If there is an immediate return of targeted behaviors when
medication is accidentally forgotten, the child is not yet ready for a trial off medication. In planning a trial off medication, the physician should choose a less-stressful period such as school vacations. Completion of a 2-week period without return of symptoms warrants an extended trial. The child’s behavior should be monitored for about 1 year before deciding to permanently discontinue stimulant therapy.

**Preschoolers**

Diagnosing ADHD in preschoolers is especially difficult because many non-ADHD children at this age often display episodes of high energy and inattentiveness, yet the vast majority of these concerns remit within 3-6 months. However, there are some “red flag behaviors” which may help differentiate normal, age-appropriate behaviors from possible early indicators of ADHD. These are chronic problematic behaviors identified before the age of 3 and continue to persist at age 4 and after. Specific parental complaints include chronic motor restlessness, high energy level which is often described by parents as living with the “Energizer Bunny” or a “tornado.” Additional parental complaints include intense and prolonged temper tantrums, impatience, and extreme aggressiveness. To be considered “atypical” these behaviors must be evaluated with regard to their intensity, or severity, duration, and pervasiveness.

Intervention should include a thorough evaluation by a clinician knowledgeable in early childhood development, to rule out possible coexisting problems such as pervasive developmental delays, sensory issues, and environmental factors. Utilization of Parent-Teacher Behavioral Rating Scales, consultation with the preschool teacher, and classroom observation are recommended.

Treatment is multimodal focusing upon the utilization of behavior modifications techniques, parent training, and the possible adjunct of medication if behavior strategies prove to be ineffective.

Placement in a day care program should be carefully and cautiously evaluated because the stimulating environment has the potential of exacerbating problematic behaviors in the child, adding stress to caregivers, and frustration and disappointment for parents.

**Treatment of Preschoolers with Stimulant Medication**

ADHD has been described as a neurobehavioral disorder with onset of symptoms often in preschool years. Stimulant medications have been widely prescribed for this age group. The practitioner must balance the potential benefits of early identification and intervention with the risks of over-identification and potential treatment of preschool-aged children who do not have ADHD.

Methylphenidate is frequently prescribed off label for the treatment of ADHD symptoms in preschoolers despite FDA warnings against use in children younger than 6 years of age. Off label use increased from 15% in family practitioners to 49% between 2000 and 2003 for ADHD in children younger than 5 years of age.

Children with developmental delays are prone to higher rates of side effects including social withdrawal, irritability and lability, decreased appetite and weight loss, initial insomnia, and repetitive behaviors. A decrease in growth rate may be observed in the first year of methylphenidate treatment. Preschoolers have been noted to metabolize methylphenidate more slowly than school-age children. Therefore, cautious titration is recommended.


2. **Nonstimulants**—Many nonstimulant medications are being used for ADHD, alone and in combination with neurostimulants. Nonstimulant agents are less well-studied and are summarized here to inform the physician about their use. These medications usually are used when comorbidities are involved, and they may best be managed in partnership with a pediatric psychiatrist through close follow-up. They vary from established effective treatments such as the tricyclic antidepressants to potentially effective ones such as the highly selective catecholamine reuptake inhibitors (eg, atomoxetine [Strattera]) discussed below. Nonstimulants are often used to treat both ADHD and comorbid states, and their effectiveness alone is generally less than that of the neurostimulants. Fear and misunderstanding about the effects of neurostimulants make these non-stimulant agents attractive to parents. An excellent review of these alternative medications appears in *Child and Adolescent Psychiatric Clinics of North America.*
FDA approval in 2003 of atomoxetine HCl for the treatment of ADHD in children older than 6 years of age and adults added a noncontrolled medication to the treatment arsenal for this disorder. Initially developed as a selective serotonin reuptake inhibitor (SSRI), this agent was found to have more selective norepinephrine reuptake inhibition and subsequently shown to have some effect in patients with ADHD. As with SSRIs, there appears to be an increase in suicidal thoughts in children who take atomoxetine (an increase of ~0.5% over placebo). The FDA has placed a black box warning on atomoxetine, and parents should be made aware of this risk. Atomoxetine has also been associated with rare but serious liver failure.

Atomoxetine has been found to be effective in both children and adults with both predominantly inattentive and predominantly hyperactive forms of ADHD for up to 10 weeks. Similar compounds have been shown to be less effective for the core problems of distractibility and hyperactivity than the 95% response rate seen with the neurostimulants, but the lack of addictive and abuse potential makes this class of agents attractive to many parents and physicians. Adverse effects include abdominal pain, decreased appetite, nausea, vomiting, and somnolence. As with stimulants, this medication class interacts with MAO inhibitors. Cardiovascular side effects include increases in blood pressure and heart rate, and atomoxetine has caused urinary retention problems in adults. The drug has also been shown to potentiate the cardiovascular effects of albuterol, and its use should be avoided in patients with asthma. In adults, it appears to have similar sexual side effects as SSRIs.

Dosing of atomoxetine is by weight at an initial dose of 0.5 mg/kg/d, increasing every 3 days to a target dosage of 1.2 mg/kg/d. It is dosed once daily and is believed to have effects for 16 hours. The total daily dose should not exceed 1.4 mg/kg/d or 100 mg total, whichever is less. As with other neurotransmitter inhibitors, the full effects may not be seen for several weeks. For now, this agent could be considered when patients fail to respond to properly titrated stimulants, cannot tolerate stimulants, or refuse to try stimulants.

Atomoxetine (Strattera) for ADHD. Med Lett Drugs Ther 2003;45:11. [PMID: 12571539]


B. Psychotherapeutic Interventions

1. Behavioral modification—Behavioral modifications are designed to improve specific behaviors, social skills, and performance in specific settings. Behavioral approaches require detailed assessment of the child’s responses and the conditions that elicited them. Strategies are then developed to change the environment and the behaviors while maintaining and generalizing the behavioral changes. The most prudent approach to the treatment of ADHD is multimodal, and combination therapy with psychosocial interventions and medications produces the best results.

Behavioral therapy alone is less effective than protocol-based medication alone and has shown little additional benefits when added to medications for inattention, impulsivity, and hyperactivity. The efficacy of behavioral modification comes from enhanced academic and social successes, which are hard to measure and generalize. Intensive behavioral therapy alone was shown to have equal efficacy to the usual care in the community even if medications were given to the community care group. This confirms the viability of specialized behavioral treatment in parents who prefer nonpharmacologic therapy of ADHD.

2. Educational interventions—Teachers and schools play a huge role in the identification and subsequent management of ADHD. The education of children with ADHD is covered by three federal statutes: the Individuals with Disabilities Education Act (IDEA), Section 504 of the Rehabilitation Act of 1973, and the Americans with Disabilities Act (ADA) of 1990. The diagnosis of ADHD alone is not enough to qualify for special education services. The ADHD must impair the child’s ability to learn. A 1991 Department of Education Policy Clarification Memorandum specifies three categories by which ADHD children may be eligible for special education. They are (1) health impaired (other documented condition such as Tourette syndrome), (2) specific learning disability (could be ADHD alone if there is a significant discrepancy between a child’s cognitive ability or intelligence and his or her academic performance), and (3) seriously emotionally disturbed. It is therefore vital to document all comorbid conditions in these children. For children who qualify, the accommodation strategies and specific goals should be outlined in the student’s Individualized Education Plan (IEP) which is mandated under IDEA and is usually put together by teachers and parents along with school psychologists and administrators. Occasionally parents will ask for physician input into this process as they advocate for their children. Physician documentation of the diagnosis and management of ADHD is necessary to obtain accommodations for college entry examinations and other testing.

3. Parent education and training—Parental understanding of ADHD is vital to successful treatment. Parents must know the difference between nonadherence and inability to perform. They need to understand that ADHD is not a choice but a result of nature. Parent education can be frustrating at times because parents of children with ADHD often have features of the disorder themselves. Many parents respond well to referral to local and national support groups such as Children and Adults with Attention Deficit/Hyperactivity Disorder (CHADD) or the Attention Deficit Disorder Association (ADDAA).

Parent training programs such as developed by Russell Barkley and others provide confused and overwhelmed parents with specific management strategies shown to be effective in reducing noncompliance. In these group training
sessions, parents are taught skills in how to more effectively communicate with their child, learn how to consequate noncompliance, and enhance school performance.

Some families require formal family therapy to treat the dysfunction that is caused or aggravated by raising a child with ADHD. The basic strategies focus on helping the family solve problems together. Table 8-6 outlines some of the strategies parents and families can use to manage ADHD behaviors.

4. Other behavioral approaches—Many other behavioral strategies have been used in the treatment of children with ADHD. These include social skills training, academic skills training, cognitive behavior modifications, therapeutic recreation, and individual psychotherapy. These approaches must be individualized for each situation and require the involvement of a trained therapist who works with a physician. They require time and, in many cases, financial commitment.

C. Alternative and Complementary Therapies

Because ADHD does not have an easily understood etiology and no pharmacologic “magic bullet” exists to cure the disorder, and because of the stigma associated with the use of stimulant medications, there exists an eager market for alternative therapies. Caution should be used whenever a remedy claims to work for everyone with ADHD, uses only testimonials as evidence, cites only one study for support, fails to list the active ingredients, or is based on a “secret formula” and describes itself as harmless because it is “natural.” Likewise, one should be careful not to alienate patients who find that a certain remedy is working for them, allowing for social and academic success. The physician’s role is to advocate, educate, and protect patients in making decisions about alternative therapies.

Although some of these therapies have received good reviews from prestigious backers, they have shown little or no evidence of efficacy. Some therapies, such as elimination diets, have shown promise with a very small subset of patients (enough to allow for some outstanding testimonials) but have never been proven better than placebo in controlled studies. Sugar has often been labeled as the cause of all behavioral problems in children, but the studies have either been inconclusive or shown no correlation between sugar intake and attention and learning. Vitamin therapy has shown efficacy only in proven deficiency states, and mega doses can be potentially dangerous. There is also no evidence that caffeine is effective for ADHD in adolescents or adults. Although many “cures” for ADHD claim to have been tested in clinical trials, the NIH’s National Center for Complementary and Alternative Medicine (NCCAM) has found no studies that prove efficacy. An excellent review of alternative treatments can be found at http://psychservices.psychiatryonline.org/cgi/content/full/53/9/1096.

<table>
<thead>
<tr>
<th>Table 8-6. Advice for parents and families of children with ADHD.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accept Your Child’s Limitations</strong></td>
</tr>
<tr>
<td><strong>Avoid Large, Formal Gatherings</strong></td>
</tr>
<tr>
<td><strong>Provide Outlets for the Excessive Energy</strong></td>
</tr>
<tr>
<td><strong>Use Incentives Before Punishment</strong></td>
</tr>
<tr>
<td><strong>Utilize Behavior Modification Techniques at Home, School, and Public</strong></td>
</tr>
<tr>
<td><strong>Short-Term Punishment Is More Effective than Long-Term Consequences</strong></td>
</tr>
<tr>
<td><strong>Make a Schedule</strong></td>
</tr>
<tr>
<td><strong>Make Simple House Rules</strong></td>
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<tr>
<td><strong>Make Sure Your Directions Are Understood</strong></td>
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<tr>
<td><strong>Reward Good Behavior</strong></td>
</tr>
<tr>
<td><strong>Make Sure the Child Is Supervised at All Times</strong></td>
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<tr>
<td><strong>Watch the Child around His or Her Friends</strong></td>
</tr>
<tr>
<td><strong>Set Homework Routine</strong></td>
</tr>
<tr>
<td><strong>Focus on Effort, Not Grades</strong></td>
</tr>
<tr>
<td><strong>Talk with the Child’s Teachers</strong></td>
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</tbody>
</table>

**Prognosis**

Follow-up studies of children with ADHD show that adult outcomes vary greatly. There are three general outcome
groups. The largest group is the 50%-60% of affected children who continue to have concentration, impulsivity, and social problems in adulthood. These problems lead to workplace difficulties, troubled relationships, poor self-esteem, and emotional lability; however, success is possible if these individuals are matched to the right spouse and job. About 30% of affected children function well in adulthood and have no more difficulty than controlled normal children. The final group comprises about 10%-15% who, in adulthood, have significant psychiatric or antisocial problems. Predictors for bad outcomes include comorbid CD, low IQ, and concurrent parental pathology. Treatment for all groups has been shown to be effective for the core symptoms over the short term, and the continuation of treatment may be necessary to maintain gains and improve the quality of life for patients and their families. Long-term treatment and outcome studies have yet to be performed.

The consequences of ADHD are significant. Up to 40% of children with ADHD require some form of special education by adolescence, 25%-35% never finish high school. Individuals with ADHD are at increased risk of serious injuries, accidental poisoning, cigarette smoking, traffic citations, automobile accidents, substance use, and early death, especially if untreated.

The exact financial impact of ADHD is unknown, but one study placed the national costs at $31.6 billion. Studies have shown that ADHD children incur twice the annual per capita health care costs of children without ADHD. They have 10 times the number of mental health visits, 3 times the number of prescriptions, and 1.6 times the number of primary care visits above and beyond their mental health visits.

**Resources Web Sites**

- ADD Warehouse: www.addwarehouse.com
- American Academy of Child and Adolescent Psychiatry: www.aacap.org
- American Academy of Family Physicians (AAFP): www.aafp.org
- Children and Adults with Attention Deficit Hyperactivity Disorder (CHADD): www.chadd.org
- National Institute of Health: www.nih.gov

**Professional References**


**Assessment**

- Conners Continuous Performance Test II Version 5 for Windows, Keith Conners, Ph. D.
- Conners K-CPT Kiddie Continuous Performance Task Computer Program for Windows V.S., Keith Conners, Ph.D.
- Conners Rating Scales revised (CRS-R), Keith Conners, Ph. D.
- Children’s Depression Inventory, Maria Kovacs, Ph. D.
- Gordon Diagnostic System, Michael Gordon, Ph. D.
- T.O.V.A Tests of Variables of Attention

**OPPOSITIONAL DEFICIENT DISORDER**

**General Considerations**

ODD is defined by the age-inappropriate display of angry, irritable, and oppositional behaviors that have occurred for at least 6 months. Although many parents would categorize their teenagers as fitting this description, the object in applying this diagnosis is to define and help individuals whose behavior clearly impairs their functioning. The diagnosis is not made if an individual’s behaviors are part of a psychotic or mood disorder, nor can it be made if the criteria for CD are met.

The experts who created this category hoped to provide a means of diagnosing the aggressive and antisocial behaviors exhibited in early and middle childhood that do not attain the severity seen in CD. Children with ODD do not usually have significant problems with the law and are not typically physically aggressive. Most do not progress to CD, but if no action were taken until the destructive behaviors of CD were manifested, valuable time could be lost. There is much overlap and comorbidity with ODD and ADHD but also clear evidence of divergence from attention deficit syndromes. In children with ODD, the problem is more an inability to inhibit moody outbursts and less an issue of executive functioning, as in ADHD. Owing to its relatively new emergence as a separate diagnostic entity, ODD has not been extensively studied and is usually linked to CD.

**Psychopathology**

ODD is seen as a behavioral disorder and is not associated with any known physical or biochemical abnormality. There is some evidence that children with ODD have higher androgen levels than normal controls, but this finding is not conclusive. The cause is generally related to social, parental, and child factors.

**A. Social Factors**

A correlation exists between ODD and living in crowded conditions such as high-rise buildings with inadequate play space. There is a correlation between social class and ODD, but no correlation to paternal employment or maternal employment. Finally, there appears to be some correlation to the quality of the day care if the mother is employed.
B. Parental Factors

It is difficult to tell whether parental behavior causes ODD or vice versa, but there are strong correlations between the way parents act and oppositional behavior. Parents of ODD children (not all, but certainly in pattern) tend to be critical, rejecting, lacking in warmth, passive, and unstimulating. Mothers, especially, demonstrate high levels of anxiety and depression. Family relationships, especially the marital relationship, tend to be strained. This sets up a vicious cycle as the child becomes more insecure and more difficult to handle, to which the parents react with more rejection.

C. Child Factors

It has been impossible to determine if the adverse temperamental factors that contribute to ODD are present from birth. ODD children are more likely to have language delay and have a higher incidence of enuresis beyond age-controlled peers.

The presentation of oppositional behaviors is highly variable. During the preschool years, transient oppositional behavior is normal. However, when these behaviors are of a persistent nature and last beyond the preschool years, the development of more disruptive behaviors is likely. On the basis of research data, two possible developmental trajectories have been suggested. In most oppositional children, especially those who are not physically aggressive, oppositional behaviors peak around age 8 years and decrease beyond that. In a second group of children, delinquent behaviors follow the onset of oppositional behaviors. Early physical aggression is a key element of this group, with physically aggressive children being more likely to progress to the violation of other property that categorize CD.

Prevalence & Demographics

The reported prevalence of ODD varies from 2% to 16% of the school-aged population. Studies show an increasing rate of diagnosis from grade school to middle school to high school and then a decrease in college-aged individuals. Unlike CD and ADHD, gender differences are minimal in ODD, and boys are only slightly more likely to receive a diagnosis of ODD than girls. Conclusive date on racial or cultural differences do not exist, but worldwide ODD and CD are more prevalent among families of low socioeconomic status who tend to live in close quarters. Early onset of disruptive behaviors in which the rights of others are violated (as in CD), which has a worse prognosis and the highest social burden, seems to be concentrated in cities in the United States.

Certain familial situations are associated with the diagnosis of ODD. ODD is more common when at least one parent has a history of a mood disorder, CD, antisocial personality disorder or a substance-related disorder, and 18% of children with ODD have alcoholic fathers. Family adversity scores in children with ODD are usually intermediate between those of children with CD and normal children. Whether this is a cause or effect is unknown, but the family physician is ideally suited to help address and untangle these complex issues.

Clinical Findings

A. Symptoms and Signs

Common manifestations of ODD include persistent stubbornness, resistance to directions, and unwillingness to negotiate and compromise with others. Defiant behaviors include persistent testing of limits, arguing, ignoring orders, and denying blame for most misdeeds. Hostility usually takes the form of verbal abuse and aggression. The most common setting is the home and behavioral problems may not be evident to teachers or others in the community. Because the symptoms of the disorder are most likely to be manifested toward individuals that the patient knows well, they are rarely apparent during clinical examination. Children with ODD do not see themselves as the problem but instead view their behavior as a reasonable response to unreasonable demands. They have problems with low self-esteem, lability of mood, and low tolerance of frustration and are more likely to be involved with substance abuse. These are difficult children to live with and difficult homes to live in, and families frequently turn to their physicians for help.

B. Diagnostic Criteria

DSM-IV-TR has specific diagnostic criteria for ODD (Table 8-7). The clinical features that bring children to family physicians’ offices are based on control issues, aggression, and hostilities.

Table 8-7. DSM-IV-TR diagnostic criteria for oppositional defiant disorder.

<table>
<thead>
<tr>
<th>A. A pattern of negativistic, hostile, and defiant behavior lasting at least 6 months, during which four (or more) of the following are present:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Often loses temper, (2) often argues with adults, (3) often actively defies or refuses to comply with adult’s requests or rules, (4) often deliberately annoys people, (5) often blames others for his or her mistakes or misbehavior, (6) is often touchy or easily annoyed by others, (7) is often angry and resentful, (8) is often spiteful or vindictive.</td>
</tr>
</tbody>
</table>

**Note:** Consider a criterion met only if the behavior occurs more frequently than is typically observed in individuals of comparable age and developmental level.

B. The disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning.

C. The behaviors do not occur exclusively during the course of a psychotic or mood disorder.

D. Criteria are met for conduct disorder, and, if the individual is age 18 years or older, criteria are not met for antisocial personality disorder.

Source: Reproduced, with permission, from American Psychiatric Association: Diagnostic and Statistical manual of Mental Disorders. 4th ed, text revision. APA, 2000.
and activity. Control issues start early, with battles over bedtime and mealtime starting at age 3 or 4 years. Children with ODD demonstrate verbal aggression toward their parents almost as soon as they can talk. This may progress to physical aggression that is usually directed at parents or caretakers and rarely at strangers. Activity levels are variable and may depend on the common comorbid condition of ADHD. Other features include anxiety and an increased incidence of temper tantrums and breath-holding attacks.

*DSM-IV-TR* does not establish an age of onset for the diagnosis other than “younger than 18.” The average onset of ODD behaviors is 6 years, and behaviors tend to peak at age 8. Diagnosis is made by parents, patient, or teacher history and direct observation.

Some behavioral checklists are available that can identify the pattern of ODD. They include the Child Behavioral Checklist, the BACS-2, (*American Guidance Service, Inc.*), and the Rochester Adaptive Behavior Inventory. A structured interview such as the diagnostic Interview for Children and Adolescents or the Child and Adolescent Psychiatric Assessment may be helpful. It is rare that any medical testing or neuropsychiatric testing is necessary, unless comorbid states are present.

**C. Comorbidities**

ODD is common among children with ADHD. The disruptive behaviors of ADHD tend to bring out the parental behaviors associated with ODD. The combination of ADHD, ODD, family adversity, and low verbal IQ are predictors of progression to more serious conduct disorders and antisocial behaviors as adults. However, although up to 50% of ADHD children have ODD behaviors, only about 15% of those diagnosed with ODD have ADHD.

About 15% of ODD children have anxiety disorders and approximately 10% have depression of mood disorders. Addressing these problems can often help with the oppositional behaviors.

**Differential Diagnosis**

All the behaviors of ODD are present in CD; thus, ODD is not diagnosed in the presence of CD. Although comorbidity is seen with mood disorders, the diagnosis of ODD should not be made if a major mood disorder or a psychotic disorder is present. ODD should be distinguished from ADHD although both may be present in many children, in which case both diagnoses should be given. Physical causes for oppositional behavior must be considered, especially if hearing or auditory comprehension is impaired. The diagnosis of ODD in mentally retarded individuals is difficult and can only be made if the behaviors exceed those usually seen in individuals with corresponding cognitive impairment and age. Bipolar disease can be confused with ODD. Any of the social or medical conditions listed earlier in Table 8-2 could also be confused with ODD.

**Treatment**

Management of ODD depends on the extent of behavioral problems. Children with ODD demonstrate lower degrees of impairment and are more socially competent than children with CD. Furthermore, children with CD come from less advantaged families and, by definition, have greater conflict with school and judicial systems compared with children with ODD. These differences can be used to predict which children may need more aggressive intervention.

**A. Behavioral Therapy**

The vast majority of these patient and their families can be managed with behavioral therapies, especially parental training and family therapy.

Parental-controlled behavioral modification is based on social learning theory and uses naturally occurring consequences to teach social skills and self-evaluation. *Parents are taught* problem-solving skills, techniques to avoid power struggles, how to minimize emotional reactions to oppositional behaviors, to give clear instructions and consistent limits, to positively reinforce good behaviors and to utilize punishment selectively. Parent training is usually conducted by psychologists or trained social workers and can be conducted in groups. Advice to parents includes the importance of communicating with each other to avoid situations in which the child plays one against the other. Communication with teachers and principals is also important.

Studies have shown that children who watch 4-6 hours of television a day are more violent, more likely to use drugs, and more preoccupied with sex, and the AAP recommends that television viewing should be limited to 1-2 hours per day. Likewise, video games can be addictive and children who play violent video games are more physically aggressive and not as intelligent as controls.

Many families of children with ODD are characterized by low socioeconomic status, parental psychopathology, and marital conflict. These issues also need to be addressed by counseling or medication if behavioral modification techniques are to be successful with the child. Family therapy may be indicated to address family dysfunction from the oppositional behavior or from primary parental or marital problems. Behavioral intervention can be performed in which the family learns how to negotiate together. One technique for adolescents is parent-child contracting, which involves written agreements for behavioral changes in both parties based on specific contingencies.

**B. Medications for Oppositional Defiant Disorder**

Medication for youth with ODD should not be the sole intervention and are primarily adjunctive, palliative, and noncurative. Medications may be beneficial in the context of other diagnoses and as such may be helpful adjuncts to a treatment package for symptomatic treatment and to treat comorbid conditions. For example, stimulants and atomoxetine may be...
useful in treating ODD in the context of another principal diagnosis such as ADHD. ODD behaviors in the context of an anxiety disorder or a depressive disorder may be successfully treated with an SSRI. Aggressive and oppositional behaviors complicate a wide range of other diagnoses in this age range. Therefore medications should target specific syndromes as much as possible.

C. Pharmacotherapy for Comorbid Conditions

There is no accepted pharmacologic treatment for oppositional behaviors, but comorbid conditions such as ADHD or depression must be properly addressed and appropriately treated. For children who do not respond to nonmedical interventions or are extremely impaired, it is best to consult a pediatric psychiatrist. Medications used for ODD include clonidine, lithium, carbamazepine, valproic acid, and risperidone; all have significant risks and their use should be monitored carefully.

Prognosis

The most serious consequence of ODD is the development of more dangerous conduct problems. Although the majority of children with ODD will not develop CD, in some cases ODD appears to represent a developmental precursors of CD. This seems to hold true for boys more than for girls. In cases in which ODD preceded CD, the onset of CD is typically before age 10 years (childhood-onset CD). For children in whom such symptoms subsequently decrease with maturity, the prognosis is good. If oppositional behaviors progress and begin to involve the violation of others’ rights, then the child will probably progress to CD.

Psychopathology

The etiology is CD is unknown but seems to involve an integration of genetic or constitutional factors with familial and environmental factors.

A. Constitutional Factors

The risk of CD is higher in children whose biological or adoptive parents have antisocial personality disorder, and siblings of children with CD have a higher risk for developing the condition as well. CD is also more common in children whose biological parents have ADHD, CD, alcohol dependence, mood disorders, and schizophrenia. Studies examining physiologic factors that might explain CD have centered around a decreased autonomic response to various stimuli in these individuals. Essentially, it seems to take a lot of stimulation to generate an autonomic and visceral response in individuals with CD, especially those with the early-onset form of the disorder. Hormonal factors have been studied, in particular, the influence of testosterone on aggression and cortisol on anxiety. Trends but no distinct cause-and-effect relationships have been noted. Neurotransmitters also play a role in aggression, and current research points to serotonin as an important mediator.

General Considerations

The most serious disruptive behavioral problem of childhood seen in primary care is CD. Although many normal children have lapses in judgment and break rules or hurt others, CD represents a persistent or repetitive pattern of such behaviors. These behaviors represent a significant problem for patients, their families, and society in general, and often physicians are consulted to help. Social norms tend to be culturally specific, and significant differences may exist among cultures or societal groups in determining when (and what) behavior is deemed antisocial. Physicians and professionals must be aware that their judgments of abnormality will be affected by the values of their particular society.

CD is a condition in which the expertise of physicians has implications for society in general as well as for individual patients and their families. It is also a condition that is a referral diagnosis for most primary care physician and may be best addressed by working in conjunction with specialized pediatric and adolescent psychiatrists and therapists. Family physicians may be called on for brief behavioral counseling and sometimes psychotherapy; however, their biggest role may be the determination and treatment of the many comorbid conditions found in these individuals. CD also comprises a public health concern by contributing to school and gang violence, weapon use, substance abuse, and high drop-out rates. It is therefore important to identify these behaviors and intervene as early as possible.

CONDUCT DISORDER

A repetitive and persistent pattern of behavior in which the basic rights of others and major age-appropriate societal norms are violated.

Behavior characterized by aggression toward people and animals, destruction of property, deceitfulness or theft, and serious violation of rules.
B. Environmental Factors

Exposure to antisocial behavior in a caregiver increases the risk of CD. Child abuse also increases risk, especially sexual abuse in girls. Although once thought to play a role, divorce does not seem to be a contributor once one controls for parental psychopathology. There is no doubt that the caregiver-child interaction contributes to disruptive behavior. The influence is bidirectional, with parents’ behavior influencing the child’s and vice versa. Factors in these relationships include (1) low levels of parental involvement in the child’s activities, (2) poor supervisions, and (3) harsh and inconsistent disciplinary practices. The child views behavioral problems as strategies to secure attention and become closer to the caregiver or parent. Neighborhood and peer factors also contribute to the incidence of CD. Being poor, living in crowded conditions in a high-crime neighborhood, and having a “deviant” peer group all increase the risk of CD.

Prevalence & Demographics

The prevalence of CD varies from 1% to 10% overall, depending on the studied population, with ranges of 6%-16% in boys and 2%-9% in girls younger than 18 years of age. CD tends to increase from middle childhood to adolescence. Although certain behaviors (e.g., physical fighting) decrease with age, the most serious aggressive behaviors (e.g., robbery, rape, and murder) increase during adolescence. The differing incidence of CD in boys and girls does not occur until after age 6 years, and boys and girls with CD manifest differing behaviors. Boys exhibit more fighting, stealing, vandalism, and school discipline problems, whereas girls are more likely to lie, be truant, run away, and abuse substances.

The incidence of CD does not seem to have racial or ethnic correlations if one controls for socioeconomic group and for high-crime neighborhoods. Although some observers contend that the incidence of CD is on the rise, many authorities would argue that differences between generations in the perception of youth crime are influenced by recall bias in the older population.

Clinical Findings

The key to the diagnosis of CD is the disregard for the rights of others and the rules of society as shown by affected individuals. The *DSM-IV-TR* allows for a broad range of behaviors and makes a clear distinction between early-onset and later-onset CD. This distinction is useful because the prognosis is much better if onset of these behaviors is after age 10.

A. Symptoms and Signs

Children with CD are referred to physicians by either parents or authorities. Younger children may present with behaviors that include outright refusal to cooperate with examinations or immunizations and a history of frequently running away from parents. Older children may be referred by teachers or school administrators, who request a medical evaluation prior to allowing a suspended student back into school. Adolescents may present after they have been arrested for violent or destructive behaviors. These behaviors are not only disruptive but involve blatant breaking of societal rules and violation of the rights of others.

B. Diagnostic Criteria

Because of some significant differences in CD that occurs before or after age 10, the disorder is subtyped into two groups: early-onset and late-onset. There are four main groupings of behaviors in CD: (1) aggression to people or animals, (2) destruction of property, (3) deceitfulness or theft, and (4) serious violation of rules. Due to the diversity of disruptive behaviors, *DSM-IV-TR* includes “specifiers” that classify behaviors into mild, moderate, and severe. These are useful in trying to predict the nature of the presenting problems, the developmental course, and the outcomes.

Behavioral disorders must be differentiated from normal reactions to abnormal circumstances. The *DSM-IV-TR* states that the diagnosis of CD should not be made when behaviors are in response to the social context. Screening questions might include asking about troubles with police, involvement in physical fights, suspensions from school, running away from home, sexual activity, and the use of tobacco, alcohol, and drugs.

Physicians must distinguish normal adolescent risk-taking and antisocial behaviors from CD. Normal experimentation usually does not harm others and does not recur persistently. According to the *DSM-IV-TR*, three specific CD behaviors should be present for at least 6 months to make the diagnosis. The full *DSM-IV-TR* criteria are listed in Table 8-8.

It has become more common to utilize standardized interviews in making the diagnosis of CD. These include the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule for Affective Disorders and Schizophrenia for School-Age Children, and the Diagnostic Interview for Children and Adolescents. These interviews are time consuming and expensive but yield more information than behavioral checklists. Pictorial instruments are available for very young children. Because parents and authorities usually do not know the full extent of the child’s behaviors, it is useful to interview them as well.

Most primary care physicians refer cases of CD to pediatric psychiatrists but may be involved in the initial workup. Rarely are any special tests necessary.

C. Comorbidities

A clear majority (75%) of children with CD have at least one other psychiatric diagnosis. The relationship between ADHD and CD has been studied the most. Thirty percent to 50% of children with CD also have ADHD. ADHD can be conceptualized as a cognitive-developmental disorder, with an earlier age at onset than CD. Children with ADHD more frequently show deficits on measures of attention and cognitive function, have hyperactivity, and have greater neurodevelopmental
The number of conduct problems and effect on others
diagnostic criteria for conduct
absence of any
Reproduced, with permission, from the American Psychiatric
few if any conduct problems in excess of those required to make
by Ross Green is an excellent reference for
DSM-IV-TR
Association:
Source:
Table 8-8.
Severe:
Moderate:
Mild:
312.82 Conduct Disorder, Adolescent-Onset Type:
312.81 Conduct Disorder, Childhood-Onset Type:
Code based on age at onset:
312.81 Conduct Disorder, Childhood-Onset Type: onset of at least one
criterion characteristic of conduct disorder prior to age 10 years
312.82 Conduct Disorder, Adolescent-Onset Type: absence of any
criteria characteristic of conduct disorder prior to age 10 years
312.89 Conduct Disorder, Unspecified Onset: age at onset is not known
Specify Severity:
Mild: few if any conduct problems in excess of those required to make
the diagnosis and conduct problems cause only minor harm to others
Moderate: number of conduct problems and effect on others
intermediate between “mild” and “severe.”
Severe: many conduct problems in excess of those required to make
the diagnosis or conduct problems cause considerable harm to others
A. A repetitive and persistent pattern of behavior in which the basic
rights of others or major age-appropriate societal norms or rules are
violates, as manifested by the presence of three (or more) of the
following criteria in the past 12 months, with at least one criterion
present in the past 6 months:
Aggression to people and animals
(1) Often bullies, threatens, or intimidates others
(2) Often initiates physical fights
(3) Has used a weapon that can cause serious physical injury to others
(e.g., a bat, brick, broken bottle, knife, gun)
(4) Has been physically cruel to people
(5) Has been physically cruel to animals
(6) Has stolen while confronting a victim
(7) Has forced someone into sexual activity
Destruction of property
(8) Has deliberately engaged in fire-setting with the intention of
causing serious damage
(9) Has deliberately destroyed other’s property (other than by
fire-setting)
Deceitfulness or theft
(10) Has broken into someone else’s house, building or car
(11) Often lies to obtain goods or favors to avoid obligations (i.e., “cons”
others)
(12) Has stolen items of nontrivial value without confronting a victim
(e.g., shoplifting, but without breaking and entering; forgery)
Serious violations of rules
(13) Often stays out at night despite parental prohibitions, beginning
before age 13 years
(14) Has run away from home overnight at least twice while living in
parental or parental surrogate home (or once without returning for
a lengthy period)
(15) Is often truant from school, beginning before age 13 years
B. The disturbance in behavior causes clinically significant impairment
in social, academic, or occupational functioning.
C. If the individual is aged 18 years or older, criteria are not met for
antisocial personality disorder.

Differential Diagnosis
All of the social or medical conditions listed earlier in Table 8-2
may cause behaviors that could minimize being crossed when
others’ rights or societal rules are broken. If a child meets the cri-
teria for both disorders, the diagnosis of CD takes precedence.
Children with ADHD have disruptive and impulsive behav-
ior but their behavior does not violate age-appropriate societal
norms and rarely hurts others. If the diagnostic criteria for
both disorders are met, the child is given both diagnoses.

Late onset of CD may be associated with substance abuse
dependence, especially in the previously normal child.
There may be a large overlap of such abuse with CD. Repeated
use of alcohol at an early age (10-13 years) is a marker for
development of CD.
Treatment

The family physician is usually the first health professional consulted by parents of children with CD. A key element in the initial treatment of these children is to obtain parental involvement. Although many parents of children with CD have problems themselves, they do not want their children to follow their path. All parties need to be aware of the possibility of a poor prognosis without the interventions of the caregiver.

Behavioral interventions are similar to those for ODD. Parents need to establish monitoring of their child’s activities and friends. They need to structure those activities and set consistent behavioral guidelines with consistent and clear consequences. Referral to family counseling can help with communication problems. For children with mild CD, this may be all that is needed, but for those with moderate to severe CD, collaborative resources such as school counselors, residential care, juvenile court designated workers, and the Department of Social Services can provide wrap-around services for children and adolescents who are generally unmotivated and resistive to any type of intervention that may be necessary.

Pharmacotherapy should be considered an adjunct to behavioral therapies or can be directed at specific comorbid states. Medications target specific symptoms as there is no approved medication for CD. Table 8-9 summarizes some of the medications that are used in the treatment of CD. These should be prescribed in collaboration with a specialist unless the primary physician is very familiar and comfortable with the medication and the condition.

A. Psychopharmacology in Conduct Disorder

Psychopharmacological interventions alone are insufficient to treat youth with CD. Medications are best seen as adjunctive treatments. Very often, youths with CD have other diagnoses. Because aggression, mood lability, and impulsivity may be seen in a wide range of comorbid diagnoses, these symptoms may be targets for pharmacological interventions. Antidepressants, anticonvulsants, lithium carbonate, alpha agonists, and antipsychotics have been used clinically. The potential side effects of various classes of medications may potentially outweigh their benefits. Comorbid ADHD symptoms may be best managed with stimulant medication; however, caution must be used in view of the fact that many youths with conduct disorder engage in the practice of substance abuse.

Prognosis

The social burden and public health concerns associated with CD make diagnosis and treatment of this condition very important. About 40% of children with early-onset CD are diagnosed in adulthood with antisocial personality disorder or psychopathology. Overall about 30% of children with CD continue to demonstrate a repetitive display of illegal behaviors. Antisocial behavior rarely begins in adulthood, and the family cycle of such behaviors is difficult to break. It is therefore critical that early onset of CD be diagnosed and appropriate interventions implemented to avoid a lifetime of criminal activity or prison and a continuation of such behaviors in subsequent generations. As with all the disruptive behaviors of childhood, family physicians can have a significant impact through screening, recognition, treatment, and referral.

Table 8-9. Drug classes used in the treatment of conduct disorder.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Target Symptoms</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurostimulants</td>
<td>Depression and aggression</td>
<td>Abuse potential, cardiac effects</td>
</tr>
<tr>
<td>Antidepressants (eg, bupropion)</td>
<td>Depression and aggression</td>
<td>Agitation, GI side effects</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Depression, obsessive behaviors</td>
<td>Agitation, serotonin syndrome</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Aggression</td>
<td>LFTs and CBC abnormalities</td>
</tr>
<tr>
<td>Lithium</td>
<td>Mania, aggression</td>
<td>Weight gain, cholinergic effects</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Aggression</td>
<td>Weight gain, cholinergic effects</td>
</tr>
<tr>
<td>α-Blockers (eg, clonidine)</td>
<td>Aggression, sleep problems</td>
<td>Cardiac effects, dry mouth</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; LFTs, liver function tests; CBC, complete blood count.
Seizures

Donald B. Middleton, MD

ESSENTIALS OF DIAGNOSIS

- Occurrence of an aura.
- Alteration in or impaired consciousness or behavior.
- Abnormal movement.
- Interictal trauma or incontinence.
- Eyewitness account.
- Presence of fever.
- Postictal confusion, lethargy, or sleepiness.
- Diagnostic electroencephalogram.
- Abnormality on neuroimaging.

General Considerations

Despite an alarming appearance, a single seizure rarely causes injury or permanent sequelae or signals the onset of epilepsy. The lifetime risk for seizure is 10% but only 2% of the population develops epilepsy, defined as usually unprovoked, recurrent seizures. The annual number of new seizures in children and adolescents is 50,000-150,000, only 10,000-30,000 of which constitute epileptic seizures. Epilepsy has an annual incidence of 50 and a prevalence of 500-1000 per 100,000 population. The incidence is high in childhood, decreases in midlife, and then peaks in the elderly. Generally, epilepsy presents as repetitive seizures, but even a single seizure coupled with a significant abnormality on neuroimaging or a diagnostic electroencephalogram (EEG) can signify epilepsy. During childhood the incidence of partial seizures is 20 per 100,000; generalized tonic-clonic seizures, 15 per 100,000; and absence seizures, 11 per 100,000.

Only about 30% of children get a medical evaluation after a single seizure. In contradistinction, more than 80% of children with a second seizure obtain medical assistance. Recognizable, treatable seizure etiologies; negative family histories; normal physical examinations; lack of head trauma; normal EEG findings; and normal neuroimaging results indicate low risk for seizure recurrence. Each year about 3% of 6-month-old to 6-year-old children have a febrile seizure, the most common seizure entity. The likelihood of these children developing epilepsy is extremely low.


Pathogenesis

A seizure results from an abnormal, transient outburst of involuntary neuronal activity. Anoxic degeneration, focal neuron loss, hippocampal sclerosis (common in temporal lobe epilepsy), and neoplasia are examples of pathologic central nervous system (CNS) changes that can produce seizures. Why a seizure spontaneously erupts is unclear, but abnormal ion flow in damaged neurons initiates the event.

Seizures are either generalized (a simultaneous discharge from the entire cortex) or partial (focal, a discharge from a focal point within the brain). Generalized seizures impair consciousness and, with the exception of some petite mal (absence) spells, cause abnormal movement, usually intense muscle contractions termed convulsions. Because generalized convulsions occur most commonly in the absence of a focal defect, the initiating mechanism of a generalized seizure is less well understood than that of a partial seizure from a focal CNS lesion. Partial seizures may either impair consciousness (complex) or not (simple) and can start with almost any neurologic complaint, the aura, including abnormal smells, visions, movements, feelings, or behaviors. Partial seizures can progress to and thus mimic generalized seizures, a fact that sometimes obscures the true nature of the problem because the commotion of the convulsion dominates recall of events. The etiology of epilepsy in childhood is 68% idiopathic, 20% congenital, 5% traumatic, and 4% postinfectious, but
only 1% each vascular, neoplastic, and degenerative. The latter three are much more common in adulthood: 16% vascular, 11% neoplastic, and 3% degenerative. Complex partial seizures, the most difficult type to control, afflict 21% of children; generalized tonic-clonic seizures, the easiest to control, 19%; absence seizures, rare in adults, 12%; simple partial seizures 11%; other generalized seizures 11%; simultaneous multiple types, often syndrome associated, 7%; myoclonic seizures, often difficult to recognize because of limited motor activity, 14%; and other types 5%. In adults, 39% of epilepsy cases are complex partial seizures, 25% generalized, 21% simple partial, and 15% other types.

The majority of convulsions are due to an inciting event such as head trauma, CNS infection, drug ingestion, or metabolic abnormalities such as hypoglycemia, hyponatremia, or alcohol withdrawal, but the cause of many reactive seizures remains unknown. Nonspecific etiologies such as stress or sleep deprivation are often blamed for lowering the seizure threshold. Impact seizures are common after head trauma, but the 5-year risk for epilepsy is only 2%. On the other hand, 15%-30% of children with depressed skull fractures develop epilepsy. Syncopal episodes with diminished CNS perfusion often result in minor twitching or even major tonic-clonic seizures that do not portend epilepsy.

Unprovoked seizures are more likely to be epilepsy. The majority of epileptic seizures have no known cause so are termed cryptogenic. Those with identifiable causes like prior head trauma are called symptomatic. If genetic inheritance is at fault, the epilepsy is idiopathic. Genetic predisposition to epilepsy has been clearly defined for many entities, including tuberous sclerosis and juvenile myoclonic epilepsy which affects 1-3 per 1000 persons and is linked to chromosome 6. A genetic predisposition to seize is probably distributed throughout the population.

Table 9-1 presents a scheme of seizure description to guide treatment and predict outcome. Some forms of epilepsy are specially categorized as epilepsy syndromes (eg, infantile spasms [West syndrome] or benign childhood epilepsy with centrotemporal spikes [rolandic epilepsy or BECTS]). Table 9-2 lists a general classification of epilepsy syndromes.

### Table 9-1. Classification of seizures.

<table>
<thead>
<tr>
<th>I. Generalized</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Convulsive: tonic, clonic, tonic-clonic</td>
<td></td>
</tr>
<tr>
<td>B. Nonconvulsive: absence (petit mal), atypical absence, myoclonic, atonic</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Partial (focal or localization related)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Simple (consciousness preserved): motor, somato-sensory, special sensory, autonomic, psychic</td>
</tr>
<tr>
<td>B. Complex (consciousness impaired): at onset, progressing to loss of consciousness</td>
</tr>
<tr>
<td>C. Evolving to secondary generalized</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III. Unclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Syndrome: West syndrome (infantile spasms), Lennox-Gastaut syndrome, neonatal seizures, others</td>
</tr>
<tr>
<td>B. Other</td>
</tr>
</tbody>
</table>

### Table 9-2. Abbreviated classification of epilepsies and epileptic syndromes.

<table>
<thead>
<tr>
<th>I. Localization-related (focal, local, partial) epilepsies and syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Idiopathic (genetic) with age-related onset</td>
</tr>
<tr>
<td>1. Benign childhood epilepsy with centrotemporal spikes (rolandic or BECTS)</td>
</tr>
<tr>
<td>2. Childhood epilepsy with occipital paroxysms</td>
</tr>
<tr>
<td>3. Primary reading epilepsy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Symptomatic (remote or preexisting cause)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Febrile convulsions</td>
</tr>
<tr>
<td>2. Related to other identifiable situations: stress, hormonal changes, drugs, alcohol, sleep deprivation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Cryptogenic (unknown etiology)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. With both types</td>
</tr>
<tr>
<td>1. Neonatal seizures</td>
</tr>
<tr>
<td>2. Severe myoclonic epilepsy in infancy</td>
</tr>
<tr>
<td>B. Without unequivocal generalized or focal features</td>
</tr>
<tr>
<td>1. Sleep-induced grand mal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Generalized epilepsies and syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Idiopathic with age-related onset in order of age at onset</td>
</tr>
<tr>
<td>1. Benign neonatal familial convulsions</td>
</tr>
<tr>
<td>2. Benign neonatal convulsions</td>
</tr>
<tr>
<td>3. Benign myoclonic epilepsy in infancy</td>
</tr>
<tr>
<td>4. Childhood absence epilepsy (pyknolepsy)</td>
</tr>
<tr>
<td>5. Epilepsy with grand mal seizures on awakening</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Nonspecific etiology</td>
</tr>
<tr>
<td>B. Specific syndromes</td>
</tr>
<tr>
<td>1. Diseases presenting with or predominantly evidenced by seizures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III. Epilepsies and syndromes undetermined as to whether they are focal or generalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. With both types</td>
</tr>
<tr>
<td>1. Neonatal seizures</td>
</tr>
<tr>
<td>2. Severe myoclonic epilepsy in infancy</td>
</tr>
<tr>
<td>3. Acquired epileptic aphasia (Landau-Kleffner syndrome)</td>
</tr>
</tbody>
</table>

| B. Without unequivocal generalized or focal features |
| 1. Sleep-induced grand mal |

<table>
<thead>
<tr>
<th>IV. Special syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Situation-related seizures</td>
</tr>
<tr>
<td>1. Febrile convulsions</td>
</tr>
<tr>
<td>2. Related to other identifiable situations: stress, hormonal changes, drugs, alcohol, sleep deprivation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Isolated, apparently unprovoked epileptic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. Epilepsies characterized by specific modes of seizure precipitation</td>
</tr>
<tr>
<td>D. Chronic progressive epilepsy partialis continua of childhood</td>
</tr>
</tbody>
</table>

Prevention

Primary prevention includes advice to pregnant mothers to avoid addictive drug use (alcohol, cocaine, benzodiazepines), trauma (automobile safety), and infection (young kittens with toxoplasmosis). Obstetric techniques minimize birth trauma and cerebral anoxia, the leading cause of cerebral palsy, an unfortunately persistent disorder despite efforts to reduce its incidence. Family history may reveal significant errors of metabolism (Gaucher disease) or chromosomes, some of which are amenable to treatment. Strict attention to childhood immunization to prevent especially pneumococcal or Haemophilus influenzae type b infection; and to safety during childhood activities (using car seats, wearing bicycle helmets, supervision when swimming or in the bathtub) and for adolescents (wearing seatbelts); and avoidance of addictive drugs (alcohol, cocaine, phencyclidine) are examples of appropriate, primary seizure prevention strategies. Annual influenza vaccination decreases the potential for febrile illness and secondary seizures. A full night’s sleep, regular exercise, and a well-rounded diet are extremely important in the primary prevention of seizures.

Secondary prevention requires attention to the triggers, such as drugs that lower seizure threshold or cause seizures de novo (Table 9-3). Some children seize after prolonged fasting, possibly from hypoglycemia: for example, the unfed infant who seizes on Sunday morning when the parents oversleep, the “Saturday night seizure.” Stimulation from light or noise, startle responses, faints, metabolic derangements, or certain video games, television shows, or computer programs can cause repetitive seizures. Avoidance of any known precipitant is required to reduce future likelihood of another event. Individuals with epilepsy should not drive until seizure free for 6 months, swim or take baths alone, or engage in potentially dangerous activities. Patient education and referral to sources such as the Epilepsy Foundation play important roles in keeping patients healthy and active.

Table 9-3. Drugs linked to seizures.

<table>
<thead>
<tr>
<th>A. Over-the-counter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Antihistamines: cold remedies</td>
</tr>
<tr>
<td>2. Ephedra: common in diet supplements</td>
</tr>
<tr>
<td>3. Insect repellents and insecticides: benzene hexachloride</td>
</tr>
<tr>
<td>4. “Health” and “diet” drugs: ginkgo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Antibiotics: penicillins, imipenem, fluoroquinolones; acyclovir, ganciclovir; metronidazole; mefloquine; isoniazid</td>
</tr>
<tr>
<td>2. Asthma treatments: aminophylline, theophylline, high-dose steroids</td>
</tr>
<tr>
<td>3. Chemotherapeutic agents: methotrexate, tacrolimus, cyclosporine</td>
</tr>
<tr>
<td>4. Mental illness agents: tricyclics, selective serotonin re-uptake inhibitors, methylphenidate, lithium, antipsychotics, bupropion</td>
</tr>
<tr>
<td>5. Anesthetics and pain relievers: meperidine, propoxyphene, tramadol; local (lidocaine) or general anesthesia</td>
</tr>
<tr>
<td>6. Antiabetic medications: insulin and oral agents</td>
</tr>
<tr>
<td>7. Miscellaneous: some β-blockers, immunizations, radiocontrast</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Drugs of abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Alcohol</td>
</tr>
<tr>
<td>2. Cocaine</td>
</tr>
<tr>
<td>3. Phencyclidine</td>
</tr>
<tr>
<td>4. Amphetamine</td>
</tr>
<tr>
<td>5. LSD</td>
</tr>
<tr>
<td>6. Marijuana overdose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D. Drug withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Benzodiazepines: diazepam, alprazolam, clorazapoxide; flumazenil in benzodiazepine-dependent patients</td>
</tr>
<tr>
<td>2. Barbiturates</td>
</tr>
<tr>
<td>3. Meprobamate</td>
</tr>
<tr>
<td>4. Pentazocine may precipitate withdrawal from other agents</td>
</tr>
<tr>
<td>5. Alcohol</td>
</tr>
<tr>
<td>6. Narcotics</td>
</tr>
<tr>
<td>7. Antiepileptic drugs: rapid drop in levels</td>
</tr>
</tbody>
</table>


Clinical Findings

A. Symptoms and Signs

The clinician must decide whether a neurologic event could be a seizure, and if so, what evaluations are necessary (Table 9-4), and whether treatment is required to prevent recurrence. The consequences of diagnosing a seizure including the effects on the family, school, driving, and work must be considered as well as special circumstances such as risks during pregnancy. The primary tool for seizure assessment is the history including (1) age at onset; (2) family history; (3) developmental status; (4) behavior profile; (5) intercurrent distress including fever, vomiting, diarrhea, or illness exposure; (6) precipitating events, including exposure to flashing lights, toxins, or trauma; (7) sleep pattern; (8) dietary pattern; and (9) drug use. Whether an aura occurred is a critical feature pointing to a partial seizure, although a brief aura can also accompany a generalized seizure. Any symptom can constitute an aura. An aura usually requires more extensive evaluation for a focal CNS lesion. Because 20% of childhood seizures occur only at night, a description of early morning behavior, including transient neurologic dysfunction or disorientation, is especially important. Reports of preictal, ictal, and postictal events from both the patient and witnesses help to clarify the seizure type and therapy.
Mental retardation and cerebral palsy are among the most common conditions associated with epilepsy. Other cognitive disorders linked to epilepsy include attention deficit hyperactivity disorder, learning disorders, and dementia. Associated psychological difficulties such as depression, psychoses, anxiety disorders including panic attacks, eating disorders like anorexia nervosa, or personality disorders are common in epilepsy and often make recognition or control of seizures difficult. In adults sleep apnea can cause recurrent seizures. The myriad causes of seizures (Table 9-5) require diligence to elucidate.

1. **Generalized seizures**—Tonic-clonic (grand mal) seizures are both the most common and the most readily recognized. A short cry just before the seizure, apnea, and cyanosis are usual. The majority of these seizures are reactive, do not recur, last less than 3 minutes (usual maximum 15 minutes), and have no major sequelae. Following a convolution, Todd postictal paralysis can persist for up to 24 hours even without an underlying structural lesion. When myoclonic or tonic-clonic epilepsy begins between ages 8 and 18 years, prospects for permanent remission are poor: about 90% relapse when antiepileptic drug (AED) treatment is stopped.

More difficult to identify, typical absence spells (petit mal) are 10-30 second losses of consciousness, unresponsive stare, and occasional chewing or lip smacking without collapse.

Common from ages 3 to 20 years, these spells, often precipitated by photic stimulation or hyperventilation, interrupt normal activity only briefly. Up to 50% of petit mal seizures evolve into tonic-clonic seizures, especially if the onset was during adolescence. About 10% of epileptic children have atypical absence spells with some motor activity of the extremities, duration greater than 30 seconds, and postictal confusion. Many of these children are mentally handicapped.

**Table 9-5.** Some causes of seizures.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflex</td>
<td>Photic stimulation, colors, television, video games</td>
</tr>
<tr>
<td>Visual</td>
<td>Music, loud noise, specific voice or sound</td>
</tr>
<tr>
<td>Auditory</td>
<td>Smells</td>
</tr>
<tr>
<td>Olfactory</td>
<td>Tap, touch, immersion in water, tooth brushing</td>
</tr>
<tr>
<td>Somatosensory</td>
<td>Hemisensory (eg, purposeless picking at clothes or lip smacking)</td>
</tr>
<tr>
<td>Cognitive</td>
<td>Math, card games, drawing, reading</td>
</tr>
<tr>
<td>Motor</td>
<td>Movement, swallowing, exercise, eye convergence, eyelid blinking</td>
</tr>
<tr>
<td>Other</td>
<td>Startle, eating, sudden position change, sleep deprivation</td>
</tr>
<tr>
<td>Genetic</td>
<td>Neurofibromatosis, Klinefelter syndrome, Sturge-Weber syndrome, tuberous sclerosis</td>
</tr>
<tr>
<td>Structural</td>
<td>Hippocampal sclerosis, neoplasia, cerebral atrophy (dementia)</td>
</tr>
<tr>
<td>Congenital</td>
<td>Hamartoma, porencephalic cyst</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>Arteriovenous malformation, stroke</td>
</tr>
<tr>
<td>Infectious</td>
<td>Syphilis, tuberculosis, toxoplasmosis, HIV infection, meningitis, encephalitis</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Porphyrin, phenylketonuria, electrolyte disorder (eg, hypoglycemia, hypocalcemia, hypomagnesemia), hyperosmolality, hyperventilation, drugs</td>
</tr>
<tr>
<td>Trauma</td>
<td>Depressed skull fracture, concussion</td>
</tr>
<tr>
<td>Other</td>
<td>Collagen vascular disease (systemic lupus erythematosus), eclampsia, demyelinating disease (multiple sclerosis), blood dyscrasias (sickle cell disease, idiopathic thrombocytopenia), mental disease (autism)</td>
</tr>
</tbody>
</table>

the early morning. An aura of numbness or tingling in the mouth often precedes motor arrest of speech and excessive salivation in a conscious child. Although not in itself dangerous, nocturnal BECTS may generalize into grand mal convulsions. About 20% of these children have only one episode; 25% develop repetitive seizures unless treated. By age 16 years almost all are seizure free.

The classic, albeit rare, simple partial seizure is the Jack- sonian march, an orderly progression of clonic motor activity, distal to proximal, indicating a focal motor cortex defect. The arm on the side to which the head turns may be extended while the opposite arm flexes, creating the classic fencer's posture. Many of these seizures generalize into clonic-tonic convulsions.

Myoclonic jerks consist of single or repetitive contractions of a muscle or muscle group and account for 7% of seizures in the first 3 years of life. Benign occipital epilepsy has an onset between ages 1 and 14 years with a peak incidence between ages 4 and 8 years and consists of migraine-like headaches with vomiting, loss of vision, visual hallucinations, or illusions. Episodes usually stop during adolescence.

Complex partial seizures usually begin after age 10 years and last 1-2 minutes each. Consciousness may be lost at onset or gradually; postictal confusion occurs in 50%-75%. Behavior alteration including hissing, random wandering, sleepwalking, irrelevant speech, affective change such as fearfulness or anger, and autonomic dysfunction such as vomiting, pallor, flushing, enuresis, falling, and drooling demonstrate the variety of manifestations. Especially common are changes in body or limb position, ictal confusion, and a dazed expression. The child always exhibits amnesia for these events.

 Syndromes usually present with several different types of seizures closely linked in time. Myoclonic jerks, grand mal seizures, and absence spells in a mentally deficient individual suggest Lennox-Gastaut syndrome.

### C. Laboratory Findings

The decision to perform tests is based on (1) the patient's age (younger than 6 months requires action); (2) history of preceding illness, especially gastroenteritis and dehydration; (3) history of substance abuse or drug exposure; (4) type of seizure (eg, complex partial seizures); (5) failure to return to normality following a seizure; and (6) interictal abnormal neurologic examination. Table 9-6 lists the usual evaluations. The majority of evidence fails to support routine testing, especially for first-time, tonic-clonic seizures.

Routine blood tests are more often abnormal in patients with isolated seizures than in those with epilepsy. Persons taking carbamazepine, diuretics, or other medications can develop hyponatremia. Glucose, magnesium, and calcium levels, and complete blood counts (CBC) usually are normal. A high creatine phosphokinase or prolactin level (done within 10-30 minutes of the seizure) may indicate prior seizure activity. Other helpful evaluations include toxicology screens, pregnancy tests, and psychometric studies. Lumbar puncture is required for suspected meningitis, unusual in a fully immunized person. Meningococcal meningitis is most likely to affect young infants, first-year college students residing in a dormitory room, or travelers returning from the Middle East.

An EEG is diagnostic in 30%-50% of first-time seizures; accuracy improves to 90% with repetitive testing. A routine EREG is not necessary for a single febrile seizure. A focally abnormal EEG suggests the need for neuroimaging. Up to a one-third of seizure victims with normal EEGs eventually are proven to have epilepsy. Awake, asleep, hyperventilation, and photic-stimulated EEG tracings are best at uncovering an abnormality. Because tracings within 48 hours of a seizure may be falsely abnormal, the optimal timing for an EEG is in debate. EEG patterns are particularly diagnostic in absence spells, BECTS, and juvenile myoclonic epilepsy. Video-EEG recording can verify a seizure diagnosis or detect psychogenic
seizures. Twenty-four-hour EEG monitoring often reveals an unexpectedly high seizure frequency.

Many experts advise that an EEG is indicated for all patients with first nonfebrile seizures or repetitive febrile seizures, about 5% of whom develop epilepsy. However, obtaining an EEG after the first seizure may not be worthwhile, especially as treatment with an AED often causes new dilemmas. About 2% of normal children have abnormal EEGs. Seizure reoccurrence is 50% with an abnormal EEG and 25% with a normal EEG. Similar criticism can be leveled at neuroimaging. In the absence of other abnormalities, an underlying brain tumor in children and adolescents is extremely rare, but seizures are not. In an international review of 3291 children with brain tumors, only 35 otherwise normal children (1%) had a seizure as the initial difficulty. The key is to perform a complete physical examination and provide follow-up. Parental or patient acquiescence with a decision to delay evaluation until a second seizure occurs is advisable.

Magnetic resonance imaging (MRI) is preferred over a computed tomography (CT) scan. Although abnormalities are detected in up to one-third of MRIs, only 1%-2% of these findings influence either treatment or prognosis, especially in otherwise normal children. Table 9-7 lists recommended evaluations for neuroimaging for each seizure type.

### Table 9-6. Recommendations for evaluation of a first seizure.

<table>
<thead>
<tr>
<th>Study</th>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electroencephalogram</td>
<td>All patients&lt;sup&gt;b&lt;/sup&gt;</td>
<td>A&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Blood tests (electrolytes, glucose, blood urea nitrogen [BUN], creatinine, calcium, magnesium)</td>
<td>Individual basis: especially indicated for age 6 mo or younger; continued illness; history of vomiting, diarrhea, dehydration, or diuretic use</td>
<td>A&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Toxicology screening</td>
<td>Possible drug or substance of abuse exposure</td>
<td>C&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>Possible meningitis or central nervous system (CNS) infection; continued CNS dysfunction</td>
<td>B&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>CNS imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Computed tomography (CT)</td>
<td>Value limited largely to head trauma</td>
<td>A&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Magnetic resonance imaging (MRI)</td>
<td>Best performed for:</td>
<td>A&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Prolonged postictal paralysis or failure to return to baseline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persistent significant cognitive, motor, or other unexplained neurologic abnormality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age younger than 12 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perhaps with partial seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>An EEG indicative of nonbenign seizure disorder</td>
<td></td>
</tr>
<tr>
<td>Prolactin level</td>
<td>Variable benefit; 10-30 min after a seizure</td>
<td>B&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Creatine kinase level</td>
<td>Variable benefit</td>
<td>C&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>A, supported by clinical studies and expert opinion; B, expert opinion; limited evidence for support; C, limited to specific situations; insufficient evidence for or against this evaluation.

<sup>b</sup>Somewhat in debate.


Table 9-7. Imaging recommendations for childhood seizures.

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>Imaging Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal</td>
<td>Cranial ultrasound preferred</td>
</tr>
<tr>
<td></td>
<td>CT acceptable</td>
</tr>
<tr>
<td>Partial</td>
<td>MRI preferred</td>
</tr>
<tr>
<td></td>
<td>CT acceptable</td>
</tr>
<tr>
<td>Generalized</td>
<td>MRI or CT but low yield</td>
</tr>
<tr>
<td>Neurologically normal</td>
<td>MRI preferred</td>
</tr>
<tr>
<td>Neurologically abnormal</td>
<td>CT acceptable</td>
</tr>
<tr>
<td>Intractable or refractory</td>
<td>MRI preferred</td>
</tr>
<tr>
<td></td>
<td>SPECT acceptable</td>
</tr>
<tr>
<td></td>
<td>PET acceptable</td>
</tr>
<tr>
<td>Febrile</td>
<td>“No study” recommended</td>
</tr>
<tr>
<td>Post-traumatic (seizures within 1 wk of trauma)</td>
<td>CT preferred</td>
</tr>
<tr>
<td></td>
<td>MRI acceptable</td>
</tr>
</tbody>
</table>

SPECT, single photon emission computed tomography.


Differential Diagnosis

Seizures mimics in infants include gastroesophageal reflux, brief shuddering, benign non-epileptic myoclonus, or the Moro reflex; in toddlers, breath-holding spells, night terrors, and benign paroxysmal vertigo; and in older persons, tics, behavior problems, hysteria, panic attacks, transient global amnesia, and hyperventilation. Persons with psychogenic seizures (pseudo-seizures) must be evaluated for psychiatric disturbances, especially depression or suicidal ideation. Psychogenic seizures account for 20% of referrals to epilepsy centers and often coexist with true seizures. Malingering to avoid stressful situations such as school or true conversion reactions can occur in adolescents or adults. Malingering patients may use soap to simulate frothing at the mouth, bite their tongues, or urinate or defecate voluntarily to simulate seizures.

The differential diagnosis includes drugs of abuse, narcolepsy, migraine, Tourette syndrome, shuddering attacks, hereditary tremors, and cough-induced or vasovagal syncopal convulsions. Syncope seizures, uncovered through tilt table testing, are best treated with control of syncope, not seizures. Cardiac entities such as prolonged QT interval (electrocardiogram) or aortic stenosis or hypertrophic cardiomyopathy (echocardiogram) should be considered in those with a family history of fainting or suggestive physical findings. Specialist consultation, video-EEG recording, 24-hour EEG recording, and watchful waiting almost always provide the correct diagnosis eventually.

A. First Aid and Initial Care

Acute assistance for a seizure requires placing the patient prone, removing eyeglasses, loosening clothing and jewelry, clearing the area of harmful objects, and not putting any object into the patient's mouth or attempting to apply any restraint. After the seizure, the patient should be placed on one side and observed until awake. Families should call for medical assistance if a seizure lasts longer than 3 minutes, the patient requests assistance or is injured, or a second seizure occurs. After a tonic-clonic seizure, vigorous stimulation may reduce postictal apnea and perhaps sudden death. To reduce the risk of sudden death, patients with epilepsy should be encouraged to sleep in the supine position. Hospitalization is necessary only if the patient is at high risk, lives alone without appropriate supervision, or remains ill. Postictal confusion, sleepiness, headache, muscle soreness, and lethargy are common. Patients and families appreciate an explanation of what transpired, information as to how to avoid further difficulties, and definite follow-up arrangements. Avoidance of seizure-provoking activities and provocative drugs or behaviors is appropriate treatment for reactive seizures.

B. Pharmacotherapy

Correctable reactive seizures or unprovoked seizures that are benign or infrequent do not require AEDs. Many experts do not use AEDs for a single seizure: medication side effects include worsening seizure severity or frequency, organ damage, or even death. AEDs do not positively affect long-term prognosis or always provide seizure control: 20%-30% of those on AEDs still have significant seizure activity.

All primary care physicians should have a command of basic AED use and side effect profiles. Table 9-8 provides
Information on selected AEDs. Three newer important drugs are (1) lamotrigine approved for those older than 2 years of age for generalized tonic-clonic epilepsy and partial epilepsy and started at 0.15 mg/kg/d, divided into two doses, increased by 0.15 mg/kg every 2 weeks to a maintenance dose of 1-5 mg/kg/d (maximum of 400 mg/d); (2) levetiracetam for partial epilepsy in those older than 4 years of age and for myoclonic epilepsy in those older than 12 years; and (3) topiramate approved for persons older than 2 years. Some drugs (adrenocorticotropic hormone [ACTH], nitrazepam, pyridoxine [vitamin B$_6$], vigabatrin, acetazolamide, felbamate rufinamide, tiagabine, oxcarbazepine, lacosamide, pregabalin and zonisamide) usually require specialist help.

The selection of AED is based on the seizure type, inaccurately identified at least 25% of the time. The least toxic AED, usually carbamazepine, lamotrigine, valproic acid, or levetiracetam, is initiated. Primary generalized seizures respond best to monotherapy with valproic acid, which controls seizures in 80%. Divalproex has fewer side effects,
of the gastrointestinal tract. Lamotrigine, carbamazepine, and levetiracetam are also good choices to control tonic-clonic or partial convulsions. Ethosuximide is ideal for absence spells, with lamotrigine and valproic acid as alternatives. Sometimes difficult to control, juvenile myoclonic epilepsy responds best to valproic acid. Gabapentin or pregabalin can be added when control of partial seizures is inadequate. Any new symptom or sign in a patient on an AED must trigger a search in a standard reference for AED side effects (Table 9-9). These are sometimes serious and often unfamiliar to primary care physicians. Many of the newer agents are also expensive. Due to side effects, phenytoin has fallen from favor but is still frequently prescribed because it is the cheapest effective AED. For a patient on phenytoin, whenever any drug is added to or withdrawn from the medical regimen, a serum phenytoin level should be obtained, usually 5–7 days later. Phenobarbital should not be used. For home treatment of acute repetitive seizures, rectal diazepam gel (0.2–0.5 mg/kg) or buccal or intranasal midazolam liquid (0.25–1 mg/kg) both appear to be safe and effective.

Use of one drug to control seizures—increased to its maximum or to just below toxicity—is best. If one drug proves ineffective, another AED is started while the current AED is withdrawn slowly over at least 1 to several weeks. Polytherapy is fraught with drug side effects and often loss of seizure control, but to achieve satisfactory control requires two drugs in 25% of patients. Neurologic consultation is often a superior choice to random new drug use.

Serum AED levels to guide dosage should be obtained (1) as a check on compliance; (2) to detect toxicity, especially with multiple agent regimens or in the young or mentally handicapped; (3) when the drug regimen is changed; (4) for poor seizure control; and (5) when a problem develops that can affect drug levels. Table 9-10 provides a scheme for monitoring the effects of three common AEDs: valproic acid, phenytoin, and carbamazepine. Valproic acid levels often fail to predict toxicity or seizure control. Whether seizure-free patients require periodic drug level monitoring is unclear. Growing children may need levels more often, but after informing patients and parents about the plan, allowing a seizure-free child to “grow out” the AED like a slow taper off medication seems reasonable. In some circumstances like pregnancy or salicylate use, free-AED serum levels may be a better guide to dosing, especially for phenytoin and valproic acid.

Whether routine checks of hematologic or liver functions require periodic drug level monitoring is unclear. Growing children may need levels more often, but after informing patients and parents about the plan, allowing a seizure-free child to “grow out” the AED like a slow taper off medication seems reasonable. In some circumstances like pregnancy or salicylate use, free-AED serum levels may be a better guide to dosing, especially for phenytoin and valproic acid.

### Table 9-9. Side effects of selected antiepileptic drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Hirsutism, coarse facial appearance, gum hyperplasia, nystagmus</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Hyponatremia (up to 10% of patients)</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Hair loss, weight gain, edema, pancreatitis, thrombocytopenia</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Life-threatening rash (~1 out of 50 children)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Personality change</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Renal stones, weight loss</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Renal stones</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Abdominal pain, abnormal behavior</td>
</tr>
</tbody>
</table>

### Table 9-10. Recommended monitoring parameters for antiepileptic drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Complete blood count (CBC) with platelets at baseline, then twice monthly for first 2 mo, and annually or as clinically indicated</td>
</tr>
<tr>
<td></td>
<td>Blood chemistries with emphasis on hepatic and renal function and electrolytes at baseline, then at 1 mo, and annually or as clinically indicated</td>
</tr>
<tr>
<td></td>
<td>Electrocardiogram (ECG) at baseline for patients &gt;40 y and as clinically indicated</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>CBC at baseline and as clinically indicated</td>
</tr>
<tr>
<td></td>
<td>Blood chemistries with emphasis on hepatic and renal functions at baseline, annually, and as clinically indicated</td>
</tr>
<tr>
<td></td>
<td>ECG at baseline for patients &gt;40 y and as clinically indicated</td>
</tr>
<tr>
<td></td>
<td>Phenytoin level in 1 wk, then in 1 mo, and annually or as clinically indicated in older patients</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>CBC with platelets at baseline, then twice monthly for first 2 mo, and annually or as clinically indicated</td>
</tr>
<tr>
<td></td>
<td>Blood chemistries with emphasis on hepatic function at baseline, then at 1 mo, and annually or as clinically indicated</td>
</tr>
<tr>
<td></td>
<td>Protime, international normalized ratio (INR), partial prothrombin time (PPT) at baseline and annually</td>
</tr>
<tr>
<td></td>
<td>Valproic acid level weekly for 2 wk, then annually or as clinically indicated in older patients</td>
</tr>
</tbody>
</table>

parents should be warned to be alert for fever, jaundice, itching, bruising, and bleeding, as signs of toxicity. Many physicians follow CBCs, liver and renal tests, and serum AED levels periodically, once or twice a year. Some AEDs, especially carbamazepine, phenytoin, primidone, and topiramate, may interfere with oral contraceptives. Midcycle bleeding indicates possible oral contraceptive failure. Management includes alternative contraceptive methods, a higher estrogen content product, or a noninteracting AED such as gabapentin or lamotrigine.

No specific seizure-free time interval predicts resolution of epilepsy. A single seizure type, normal neurologic examination, normal IQ, and normal EEG all predict good outcomes if the AED is stopped. Of 1013 patients free of seizures for 2 years, 40% had a recurrence following drug withdrawal compared with 12% of those who maintained AED treatments. Freedom from drug side effects and daily medication must be weighed against this 28% difference with potential loss of job or driving ability or possible injury. A recent abnormal EEG would make a decision to stop therapy more difficult. Phenytoin, carbamazepine, and valproic acid should be slowly withdrawn over at least 6-10 weeks. Once children grow into young adulthood, assuming a 2- to 5-year period without seizures, attempts to stop AED treatment ought to be strongly considered.

**Pregnancy**—Since all AEDs can cause fetal malformations, the AED that controls seizures the best, except possibly valproic acid, should be continued. A fetal sonogram can identify malformations. Folic acid, 4 mg daily, and vitamins D and K during the last 4 weeks minimize fetal problems. It is helpful to follow serum AED levels during pregnancy. Women who take AEDs can safely breast-feed.

**C. Referral or Hospitalization**

Poorly controlled or complicated seizures or progressive developmental delay should prompt neurologic consultation. Hospitalization is necessary for prolonged or complicated seizures, status epilepticus, inadequate family resources, or parental or physician anxiety. In general, seizures are not dangerous, but persons with repetitive seizures must be guarded from injury and other complications.

**D. Surgery and Other Treatments**

At least 20% of patients with epilepsy are inadequately controlled with AEDs alone. Surgery for epilepsy, including temporal lobe lesion resection, results in 80% seizure-free outcomes for specific epilepsy types. Candidates for surgery have recurrent uncontrolled seizures, focal EEGs, and consistent focal abnormalities on neuroimaging. PET or single photon emission computed tomography imaging often reveals unsuspected abnormalities.

Vagal nerve stimulation is less invasive and controls or reduces seizures in about 40% of patients with previously refractory epilepsy. The ketogenic diet reduces episodes by about 50% but compliance is difficult. These treatments all require referral and extensive evaluation prior to institution.

**F. Alternative Therapies**

Few alternative therapies have evidence-based support. Pyridoxine (vitamin B6) and magnesium have scientific
Seizures

Febrile Convulsions

The most common seizure disorder, febrile convulsions affect 3% of children between ages 6 months and 6 years. After age 14 years febrile seizures are rare. Despite a recurrence rate of 30%, only 3% of these individuals develop epilepsy. Those with a family history of epilepsy, abnormal neurologic or developmental status prior to the seizure, or a prolonged (>15 minute) focal seizure have at least a 15% chance of epilepsy. Commonly, a toddler with an upper respiratory infection, enterovirus, or roseola suddenly seizes during an afternoon nap. Usually short tonic-clonic convulsions, such seizures are multiple in one-third of cases. Postictal sleepiness can last several hours. Laboratory tests are unnecessary unless the child is younger than age 6 months or meningitis is suggested by failure to arouse, continued focal seizures, or physical findings (stiff neck, bulging fontanel, rash). Seizures that occur in the office or emergency department can be indicative of serious infection.

Treatment consists of reassurance to worried parents that the worst has passed and that these seizures leave no permanent brain damage. Controlling fever with warm baths, acetaminophen (10-15 mg/kg every 4 hours), or ibuprofen (5-10 mg/kg every 6 hours) may reduce immediate risk of recurrence. If begun at the onset of fever, buccal or intranasal midazolam, 0.25-1 mg/kg; oral or rectal valproic acid, 20 mg/kg every 8 hours for 1-3 days; or diazepam, 0.5 mg/kg every 8 hours for 1-3 days can reduce recurrence. Intravenous lorazepam is the drug of choice for prolonged febrile seizures. Hospitalization is best if seizures are prolonged beyond 30 minutes or are recurrent or complicated, if follow-up is inadequate, or if parents or the physician want observation. Chronic treatment is advised only for the child with multiple recurrences, persistent neurologic abnormality, or worrisome EEG findings.


Status Epilepticus

Any recurrent or prolonged seizure uninterrupted by consciousness for more than 30 minutes is termed status epilepticus (SE), which carries a low risk of permanent residual brain damage that can be minimized through rapid treatment. About 5% of children with febrile convulsions and 20% of all persons with epilepsy have SE at least once. Newly diagnosed epileptic patients often develop SE. Although all seizure types—including myoclonic or simple partial seizures—can present in SE, most commonly consciousness is severely impaired. A persistent grand mal seizure is readily identified as SE, but diagnosing SE in a comatose patient with no abnormal motor movement can be difficult without an EEG. Confused but moving persons may be in absence or complex partial epilepsy SE. Diagnosis is based on EEG findings. Death is usually related to a serious underlying etiology rather than SE itself.

Management requires stabilization of vital signs. Adolescents and adults should be given 100 mg of thiamine with 50 mL of 50% glucose (children: 2-4 mL/kg of 25% glucose) and naloxone (0.1 mg/kg up to 2 mg; children 0.01 mg/kg) repeated as necessary. Lorazepam, 0.1 mg/kg (maximum of 4 mg) intravenous push at 2 mg/min, is successful in stopping 80% of SE episodes in 2-3 minutes. A second dose in 10 minutes is frequently successful in the remaining 20%. Poorly controlled SE responds to phenytoin, 20 mg/kg intravenous push at 50 mg/min, while monitoring the electrocardiogram and blood pressure, or its safer produg, fosphenytoin, given at 30 mg/kg intravenous push at 150 mg/min. Other alternatives are midazolam and propofol. Some SE in children younger than 18 months of age responds to pyridoxine, 50 mg intravenously. For other information, the clinician is referred to the Cochrane Database. Once the SE is controlled, a search for the underlying cause should be conducted.


Neonatal Seizures

Neonatal seizures are difficult to recognize. In the first month of life, clonic-tonic seizure activity is uncommon. Focal rhythmic twitches, recurrent vomiting, high-pitched crying, posturing, chewing, apnea, cyanosis, and excessive salivation should raise alarm. Diligent inquiry into family history, prenatal history, and maternal habits is warranted. Neurologic
consultation is advisable. Often difficult to control, these seizures may have a dismal outcome. Treatment for maternal drug addiction with resultant neonatal drug withdrawal seizures, which usually leave no residual defects, includes paregoric, methadone, and phenobarbital. Table 9-11 lists suggested evaluations.


**Table 9-11. Evaluation of neonatal seizures.**

| I. History |  
| --- | --- |
| A. Pregnancy related |  
| 1. Infection: toxoplasmosis, rubella, cytomegalovirus, herpes, syphilis (TORCHS); immunoglobulin M level |  
| 2. Maternal addiction: smoking, alcohol, cocaine, heroin, barbiturates |  
| 3. Maternal behavior: inadequate prenatal care, lack of folic acid |  
| B. Delivery related |  
| 1. Anoxia |  
| 2. Trauma |  
| C. Family history: chromosomal disorders, errors of metabolism |  
| II. Physical findings |  
| A. Recognizable patterns of malformation: eyes, ears, hands, facies, head shape |  
| B. Delivery related |  
| 1. Anoxia |  
| 2. Trauma |  
| C. Family history: chromosomal disorders, errors of metabolism |  
| III. Laboratory evaluation |  
| A. Neuroimaging: cranial ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) scan |  
| B. Chest radiograph |  
| C. Cerebral spinal fluid: culture, cell count, Gram stain, India ink, VDRL, glycine, glucose, protein, xanthochromia |  
| D. Blood test: cultures, complete blood count, electrolytes, renal function, glucose, magnesium, calcium, karyotype, glycine, lactate, ammonia, long-chain fatty acid levels |  
| E. Urine: culture, glucose, protein, cells |  

VDRL, Venereal Disease Research Laboratory.

Clinical practice guidelines for management of patients with seizure disorders are presented in Table 9-12. Overall about one-third of patients have a second seizure, and about 75% of these experience a third seizure. No adverse outcomes are likely even with up to 10 untreated seizures. A study of 220 children indicated that 92% of those treated for idiopathic seizures remained seizure free for as long as 5 years. Eventually 70% of epileptic children and 60% of adults become seizure free off of treatment.

**Table 9-12. Clinical practice guidelines for management of patients with seizure disorders.**

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile seizure</td>
<td>Children with febrile seizures, even if recurrent, should rarely be treated with antiepileptic drugs (AEDs).</td>
</tr>
<tr>
<td>Provoked seizure</td>
<td>Long-term prophylactic AED treatment for children with head injuries or correctable causes of seizure is not indicated.</td>
</tr>
<tr>
<td>Unprovoked, tonic-clonic epileptic seizure</td>
<td>AED treatment should generally not be commenced routinely after a first, unprovoked tonic-clonic seizure.</td>
</tr>
<tr>
<td>Generalized epilepsy</td>
<td>The choice of first AED should be determined, where possible, by the syndromic diagnosis and potential adverse effects.</td>
</tr>
<tr>
<td>Focal seizure</td>
<td>When appropriate monotherapy fails to reduce seizure frequency, combination therapy should be considered.</td>
</tr>
<tr>
<td>Monitoring for adverse effects of AEDs</td>
<td>Routine AED level monitoring is generally not required.</td>
</tr>
<tr>
<td>Withdrawal of AEDs</td>
<td>Withdrawal of AED treatment should be considered for individuals who have been seizure free for 2 or more years.</td>
</tr>
<tr>
<td>Prolonged or serial seizure</td>
<td>Prolonged or serial seizures can be treated with intravenous lorazepam or intranasal or buccal midazolam or rectal diazepam.</td>
</tr>
</tbody>
</table>

**Prognosis**

Clinical practice guidelines for management of patients with seizure disorders are presented in Table 9-12. Overall about one-third of patients have a second seizure, and about 75% of these experience a third seizure. No adverse outcomes are likely even with up to 10 untreated seizures. A study of 220 children indicated that 92% of those treated for idiopathic seizures remained seizure free for as long as 5 years. Eventually 70% of epileptic children and 60% of adults become seizure free off of treatment.

“Do it, move it, make it happen. No one ever sat their way to success.”
—Unknown

The United States continues to battle an epidemic of physical inactivity and obesity. Over the past three decades, declines in physical inactivity have mirrored the rise in obesity among children and adolescents. Longitudinal data from the National Health and Examination Surveys show that over the past 30 years the percentage of overweight and obese adolescents in the United States has increased from 5% to over 17%. Obese youth are less likely to engage in physical activity and are much more likely to report chronic health problems compared with peers of normal weight. Obese adolescents are also more likely to be obese as adults.

During adolescence, levels of spontaneous physical activity drop significantly from childhood levels. The number of US adolescents meeting recommended activity levels is low, and this figure has not changed significantly over the past 10 years (Figure 10-1). Adolescents spend much of their time engaged in sedentary activities. Most adolescents engage in at least 1 hour of technology-related behavior (television viewing, Internet surfing, gaming device) per day. In contrast, adolescents currently average a mere 12 min/d of vigorous physical activity. One-third of US high-school students are not regularly active; one-half of high school seniors are not enrolled in physical education classes, and 70% of all high school students watch at least 1 hour of television every day of the week. For those students enrolled in physical education, the actual amount of class time devoted to physical activity has dropped significantly over the past decade. Students spend a majority of time in physical education class standing around, waiting for instructions, or socializing. Teens who are active in school sporting activities are more likely to be active as adults. The bottom line is that behaviors that are initiated in childhood tend to consolidate during adolescence. Therefore, health-related behaviors, such as dietary habits and physical activity patterns, solidify during adolescence and persist into adulthood. Recognition of individuals who are insufficiently active, overweight, or obese during adolescence is important.

DEFINITIONS

The following definitions apply to the discussion of physical activity and obesity (Table 10-1). Physical fitness refers to a general state of well-being that allows an individual to perform activities of daily living in a vigorous manner. Physical fitness is further described in terms of health-related characteristics and skill-related characteristics. Health-related components of physical fitness include cardiorespiratory endurance, muscular strength, muscular endurance, flexibility, and body composition. Skill-related components of physical fitness include power, speed, agility, and balance. Historically, physical education programs have focused on skill-related activities and athletic ability. From a public health perspective, however, the health-related components of physical fitness are more important.
in terms of overall morbidity and mortality from chronic diseases related to physical inactivity.

Physical activity refers to any bodily movement resulting in the expenditure of energy. Physical activity occurs in a broad range of settings. Leisure-time activities, occupational activities, routine activities of daily living, and dedicated exercise sessions are all valid forms of physical activity. Physical activity varies along a continuum of intensity from light (eg, housework) to moderate (eg, jogging) to more vigorous (eg, strenuous bicycling). Exercise is a structured routine of physical activity specifically designed to improve or maintain one of the components of health-related physical fitness. Historically, society has placed more emphasis on formal exercise programs as the primary means of achieving physical fitness rather than promoting physical activity in a more general sense.

Body mass index (BMI) is the anthropometric measurement of choice for assessing body composition in children, adolescents, and adults. BMI is calculated by dividing an individual’s weight (in kilograms) by the square of the individual’s height (in meters). Charts and digital tools for the office (http://www.cdc.gov/nccdphp/dnpa/bmi/calc-bmi.htm) and for handheld computers (http://hin.nhlbi.nih.gov/bmi_palm.htm) are available for rapid calculation of BMI. Normative values for underweight, normal weight, overweight, and obesity for adolescents have been established, and are presented in Table 10-2. BMI-for-age charts have replaced standard weight-for-height charts as the preferred mechanism for tracking weight in children and adolescents (Figures 10-2 and 10-3). Overweight adolescents are those who fall between the 85th and 95th percentile of BMI-for-age. Obese adolescents are above the 95th percentile of weight-for-age.


### Risks Associated with Physical Inactivity

Physical inactivity is a primary risk factor for cardiovascular disease and all-cause mortality. A sedentary lifestyle also contributes to increased rates of diabetes, hypertension, hyperlipidemia, osteoporosis, cerebrovascular disease, and other chronic conditions.

### Table 10-1. Definitions of physical activity, physical fitness, and exercise.

<table>
<thead>
<tr>
<th>Physical activity</th>
<th>Any bodily movement that results in the expenditure of energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical fitness</td>
<td>A general state of overall well-being that allows individuals to conduct the majority of their activities of daily living in a vigorous manner</td>
</tr>
<tr>
<td>Health-related physical fitness</td>
<td>Aerobic capacity (cardiorespiratory endurance) Body composition Muscular strength Muscular endurance Flexibility</td>
</tr>
<tr>
<td>Skill-related physical fitness</td>
<td>Power Agility Speed Balance Coordination Reaction time</td>
</tr>
<tr>
<td>Exercise</td>
<td>A structured routine of physical activity specifically designed to improve or maintain one of the components of health-related physical fitness</td>
</tr>
</tbody>
</table>

### Table 10-2. Definitions of overweight and obesity for adolescents and adults.

<table>
<thead>
<tr>
<th>Definition</th>
<th>Clinical Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (adults)</td>
<td>BMI &gt;30</td>
</tr>
<tr>
<td>Overweight (adults)</td>
<td>BMI 25.1-29.9</td>
</tr>
<tr>
<td>Obesity (adolescents)</td>
<td>BMI &gt;95th percentile for age</td>
</tr>
<tr>
<td>Overweight (adolescents)</td>
<td>95th &lt; BMI &gt;85th percentile for age</td>
</tr>
<tr>
<td>Underweight (adolescents)</td>
<td>BMI &lt;5th percentile for age</td>
</tr>
</tbody>
</table>

**Source:** Centers for Disease Control and Prevention (http://www.cdc.gov/nccdphp/dnpa/bmi/bmi-for-age.htm).
Body mass index-for-age percentiles: Males, 2-20 years

![Graph showing body mass index (BMI) percentiles for males aged 2-20 years.](http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/set1/chart15.pdf)

Published May 30, 2000.

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

> Figure 10-2. Body mass index for age: males. (From Centers for Disease Control and Prevention, Atlanta, Georgia. Available at: http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/set1/chart15.pdf.)
Figure 10-3. Body mass index for age: females. (From Centers for Disease Control and Prevention, Atlanta, Georgia. Available at: http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/set1/chart16.pdf.)
colons. Adolescents who are less physically active are more likely to smoke cigarettes, less likely to consume appropriate amounts of fruits and vegetables, less likely to routinely wear a seat belt, and more likely to spend increased time engaged in sedentary technology-related behaviors.

Physical activity serves numerous preventive functions. In addition to preventing chronic diseases such as hypertension, diabetes, and cardiovascular disease, sufficient levels of physical activity on a regular basis are associated with lower rates of mental illness. Teens who spend more time engaged in sedentary technology-related behaviors have higher rates of depression. Physically active adolescents have lower levels of stress and anxiety and have higher self-esteem than sedentary peers. Active adolescents also have fewer somatic complaints, and are more confident about their own future health. They have improved relationships with parents and authority figures, and also have a better body image.


FACTORS INFLUENCING PHYSICAL ACTIVITY

Despite the overwhelming evidence supporting the health-related benefits of physical activity, young Americans are increasingly sedentary. A complex interaction of social, cultural, gender-based, environmental, and familial factors associated with “modern living” has contributed to decreased rates of physical activity.

Social Factors

Socioeconomic status is one of the strongest predictors of physical activity in both adolescents and adults. Lower socioeconomic status is associated with lower levels of spontaneous physical activity. Youth of higher socioeconomic status engage in more spontaneous physical activity, are more frequently enrolled in physical education classes, and are more active during physical education classes compared with peers of lower socioeconomic status. This relationship persists when controlling for age, gender, and ethnicity. The Task Force on Community Preventive Services (www.thecommunityguide.org), found strong evidence of the effectiveness of implementing programs which increase the length or activity levels of school-based physical education classes, improving both physical activity levels and physical fitness in school-aged children and adolescents.

Social mobility also plays an important role in shaping levels of physical activity. Specifically, achieved levels of social positioning are more strongly associated with positive health behaviors and increased levels of physical activity than the social class of origin. Youth with active friends are more likely to be active. Youth with sedentary friends are more likely to be sedentary. There are also significant differences in patterns of spontaneous physical activity when youth attending public schools are compared with youth attending private secondary schools. In the public school system, individuals are more likely to enroll in physical education classes. In private schools, adolescents are more likely to participate in organized team sports. Participation in organized sports is associated with higher levels of physical activity in adulthood.

Unfortunately, all Americans have become increasingly reliant on automated transportation. This has had a negative impact on the simplest form of physical activity: walking. Historically, most youth walked to school. This is no longer the case. Despite the fact that one-third of American schoolchildren live less than 1 mile from their school, fewer than 25% of these children walk or bike to school. The number of children walking to school in the United States has decreased by 66% since 1977.

Cultural & Ethnic Factors

Cohort studies consistently suggest that there are inherent cultural differences in levels of spontaneous physical activity. Data from the Youth Risk Behavior Survey and the National Longitudinal Study of Adolescent Health show that minority adolescents engage in the lowest levels of physical activity. These findings are consistent for both leisure-time physical activity and activity during physical education class.

Currently, 25% of adolescents consider themselves to be “too fat.” Hispanic youth are more likely to view themselves as overweight when compared with African Americans and non-Hispanic whites. Those adolescents who view themselves as overweight are significantly less physically active than their normal-weight peers and are less likely to engage in healthy behaviors. Compared with non-Hispanic whites, African American and Hispanic youth are at significantly higher risk for being overweight and obese.

There are important cultural differences in perceptions about the inherent value of exercise. Not all cultures encourage using leisure time for fitness activities. In fact, dedicating time for exercise as an isolated activity can be viewed as either selfish or a waste of time. Cultural and ethnic differences also exist in television viewing habits. Hispanic and African American adolescents spend significantly more time watching television than do non-Hispanic whites.

Gender-Specific Factors

There are significant differences in levels of spontaneous physical activity between male and female adolescents. Boys are more active than girls from childhood through adolescence. Levels of physical activity decline for both boys and girls during adolescence, but there is a disproportionate decline for
girls. The reasons for this are unclear. Factors that are positively associated with an increased likelihood of physical activity among female adolescents include perceived competence at a particular activity, perceived value of the activity, favorable physical appearance during and after the activity, and positive social support for the activity.

**Environmental Factors**

Many of the barriers to physical activity are environmental. Of these, television, Internet surfing, and video gaming (“screen-time” activities) may be the most important for adolescents. It is estimated that between the ages of 8 and 18, youth spend an average of 4.5 h/d engaged in technology-related sedentary behaviors. This translates to over 25% of waking hours being spent in front of a video monitor. By contrast, adolescents spend less than 1% of their time (an estimated 12-14 min/d) engaged in vigorous physical activity. The impact of television, video, personal computers, and handheld gaming devices on the activity levels of youth is so significant that the American Academy of Pediatrics has released a position statement recommending that youth watch a maximum 2 hours of quality screen time per day.

Television is not the only environmental issue contributing to adolescent inactivity and obesity. Adolescents are more reliant than ever on labor-saving devices. Elevators and escalators take precedence over staircases, and other technology-related sedentary behaviors such as video gaming and Internet surfing have further reduced the incentive to get up and get moving. Acquisition of a driver’s license is an important milestone of adolescence. Unfortunately, it provides an additional excuse to enable sedentary behavior. Poor community planning has resulted in a paucity of safe gymnasiums or playing fields for adolescents to access or use during their leisure time. Lack of proper community planning, evidenced by the absence of, or poorly maintained sidewalks as well as poorly controlled crossings (i.e. lack of traffic lights; it crosswalks) also contribute to decreased physical activity in children. Increased crime rates, higher measures of social deprivation, and roaming dogs are other environmental factors which have been linked to lower rates of physical activity in children and adolescents. The Community Guide found that both community-scale and street-scale urban design efforts are meaningful ways to improve physical activity. Creation of, or enhanced access to places for physical activity combined with informational outreach activities was likewise effective. In addition, there is an abundance of readily available, inexpensive, calorically dense foodstuffs. The rate of processed food consumption parallels the rise in overweight and obesity in adolescents.

**Familial Factors**

Finally, there are factors inherent within individual families that shape how active young individuals will be. Children and adolescents with overweight parents are more likely to be overweight themselves. Interestingly, parental levels of physical activity do not accurately predict their children’s levels of physical activity. Children and youth from larger families are more active than children from small families. Children whose parents watch a great deal of television are more likely to spend time watching television themselves. Children whose parents are available to provide transportation to organized sporting activities are more likely to be physically active. Individuals who are forced to exercise as children are less likely to be physically active as adults. Thus, although it is important for parents to model physical activity, clearly there are external forces at work in an adolescent’s life shaping individual patterns of health-related behaviors.

**ASSESSMENT**

There are three ways to assess physical activity levels in adolescents: (1) direct observation, (2) activity or heart rate monitors, and (3) self-report questionnaires. Of these, direct observation and assessment via electronic measuring devices like

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**References**

accelerometers provide the most accurate and objective measurements. Direct observation, however, is quite labor intensive and higher technology solutions like accelerometers and electronic heart rate monitoring devices may still be expensive enough to be prohibitive for many adolescents. There are, however, accurate, and rapid clinical tools for assessing physical activity levels in adolescents worth considering.

The Patient-Centered Assessment and Counseling for Exercise Plus (PACE+) Nutrition program has been developed to assist clinicians in assessing physical activity levels and to counsel patients regarding appropriate levels of physical activity and proper nutrition. As part of this program, a rapid self-report screening tool has been developed specifically to assess levels of adolescent physical activity (Table 10-3). This simple two-question survey provides clinicians with a validated assessment of whether adolescents are achieving recommended levels of physical activity on a regular basis. The combination of BMI and the PACE+ activity measure allows for a rapid clinical assessment of adolescents’ physical activity status, weight status, and potential health risk. Two other simple screening tools, the World Health Organization Health Behavior in Schoolchildren (WHO HBSC) and International Physical Activity Questionnaire (IPAQ short version) have also been validated for use when assessing adolescent physical activity levels. Additionally, electronic monitoring devices including heart-rate monitors, accelerometers, and pedometers can provide even more objective assessments of physical activity levels in adolescents. While heart-rate monitors and accelerometers may still be a bit expensive for routine clinical use, pedometers are clearly within reach as an affordable, cost-effective, and valid assessment method for assessing adolescents’ levels of physical activity.

### Table 10-3. Sixty-minute screening measure for moderate-to-vigorous physical activity in adolescents: PACE+ (patient-centered assessment and counseling for exercise plus nutrition).

**Physical activity** is any activity that increases your heart rate and makes you get out of breath some of the time.

**Physical activity** can be done in sports, playing with friends, or walking to school.

Some examples of physical activity include running, brisk walking, rollerblading, biking, dancing, skateboarding, swimming, soccer, basketball, football, and surfing.

Add up all the time you spend in physical activity each day (don’t include your physical education or gym class).

1. Over the past 7 days, on how many days were you physically active for a total of at least 60 minutes per day?
   
   
   _1_2_3_4_5_6_7

2. Over a typical or usual week, on how many days are you physically active for a total of at least 60 minutes per day?

   _1_2_3_4_5_6_7

**Scoring:** Add the value from question 1 and question 2 and divide by 2 (Q1 + Q2/2). If this score is less than 5, the individual is not meeting current physical activity guidelines.


### GUIDELINES & CLINICAL INTERVENTIONS

It is known that risk factors for chronic disease track from childhood into adolescence and from adolescence into adulthood. Overweight adolescents are more likely to become overweight adults. Because levels of obesity are rising sharply among adolescents and levels of physical activity are declining, there is an acute need for interventions to promote physical activity in children and adolescents. Through the years, multiple guidelines have been proposed to assist clinicians in providing activity counseling for their adolescent patients (Table 10-4).

### American College of Sports Medicine/American Heart Association Guidelines

The most recent American College of Sports Medicine (ACSM)/American Heart Association (AHA) guidelines for physical activity in individuals elder than 18 years of age recommend a minimum of 30 minutes of moderate-intensity activity 5 days a week or 20 minutes of vigorous activity 3 days a week. Moderate-intensity aerobic activity is equivalent to a brisk walk while vigorous-intensity activity is exemplified by jogging. Individuals can further improve their health in a dose-response relationship by exceeding these minimum recommendations for physical activity.


### International Consensus Conference on Physical Activity Guidelines for Adolescents

Convened in 1993, this expert panel recommends that adolescents be physically active on most if not all days of the week. Adolescents should strive for activity 3-5 days per week for
20 minutes or more at levels requiring moderate-to-vigorous exertion. Activity should routinely occur as part of play, games, sporting activities, work, recreation, physical education, or planned exercise sessions. These guidelines also emphasize the importance of considering family, school, and community factors when counseling adolescents about physical activity. The American Academy of Pediatrics extends builds on this recommendation to promote that adolescents accumulate 60 minutes of physical activity during the course of a day. Activity should be moderate in intensity and should be varied in type to include recreation, sports, or home-based, community-based, and school-based activities. Activities that are unstructured and enjoyable have the best rates of compliance.

<table>
<thead>
<tr>
<th>Guideline Source</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Consensus Conference on Physical Activity Guidelines for Adolescents/American Academy of Pediatrics Statement</td>
<td>Physical activity 3-5 d/wk Activity sessions of 20 min or more requiring moderate-to-vigorous physical exertion Emphasis on consideration of familial, social, and community factors when promoting activity</td>
</tr>
<tr>
<td>ACSM/AHA Consensus Statement</td>
<td>All Americans should strive to be physically active on most, preferably all days of the week according to individual abilities Goal of accumulating 30 min of moderate-to-vigorous physical activity each day Sedentary individuals benefit from even modest levels of physical activity Sufficient levels of activity can be accumulated through independent bouts of activity throughout the day</td>
</tr>
<tr>
<td>Healthy People 2010</td>
<td>Increase the proportion of adolescents who engage in moderate physical activity for at least 30 min on 5 or more d/wk Increase the proportion of adolescents who engage in vigorous activity 3 or more d/wk for 20 min or more per occasion Increase the proportion of adolescents participating in daily physical education Increase the proportion of adolescents who spend at least 50% of class time during physical education engaged in physical activity Increase the proportion of adolescents who walk to school (&lt;1 mile) Increase the proportion of adolescents who bicycle to school (&lt;2 miles)</td>
</tr>
<tr>
<td>Physical Activity Guidelines for Americans</td>
<td>Accumulate 60 min of moderate-to-vigorous activity every day Children and adolescents should perform cardiovascular activities on 3 d of the week and muscle-strengthening or bone-strengthening activities on 3 d of the week All activities should be age and developmentally appropriate to avoid the risk for overtraining.</td>
</tr>
</tbody>
</table>

Healthy People 2010 contains national health objectives published by the Department of Health and Human Services. Healthy People 2010 builds on previous initiatives and serves as a bridge to the soon to be released Healthy People 2020 (www.healthy-people.gov). The number one Leading Health Indicator is Physical Activity. Of the 13 adolescent health objectives outlined in Healthy People 2010, 6 are specifically targeted to promote physical activity. Objectives relating specifically to physical activity in adolescents are presented in Table 10-4.

Dietary Guidelines for Americans

Now in its sixth edition, these guidelines are the cornerstone for providing clinical nutritional advice. Emphasizing the inherent relationship between physical activity, dietary choices, and resultant weight issues, the current edition of the Guidelines is the first to specifically recommend physical activity as a part of routine dietary practice. Adolescents should aim to accumulate 60 minutes or more of moderate physical activity on a daily basis.

Physical Activity Guidelines for Americans

In 2008, the US Department of Health and Human Services released the Physical Activity Guidelines for Americans. Recognizing that children and adolescents who are more active have improved health and a lower burden of disease,
there are several key recommendations from the new guidelines: (1) All adolescents should perform 60 minutes or more of moderate-to-vigorous physical activity every day. (2) As part of the daily physical activity, children and adolescents should perform cardiovascular activities on 3 days of the week and muscle-strengthening or bone-strengthening activities on 3 days of the week. In addition, all activities should be age and developmentally appropriate to avoid the risk for overtraining.


**PROMOTING PHYSICAL ACTIVITY: HOW CAN FAMILY PHYSICIANS HELP?**

Health care professionals play a central role in promoting physical activity among adolescents. Adolescents have the lowest utilization of health care services of any segment of the population. They do, however, rely on their physician as a reliable source of health care information. Clinicians should therefore consider the opportunity to provide preventive advice at each adolescent visit. Using a modification of the 5A approach to tobacco cessation, physicians should ask adolescents about their current levels of physical activity and advise adolescents about appropriate levels of physical activity. Adolescents should strive for 60 minutes of moderate-to-vigorous physical activity or 10,000 and 11,700 steps per day if using a pedometer.

When reviewing guidelines or recommending life-style changes with adolescent patients, it is important to promote the concept of physical activity as opposed to physical fitness. Adolescents should be aware that cumulative bouts of physical activity are just as effective as sustained periods of exercise in attaining health-related benefits. For changes to be effective in adolescence and likely to persist, physical activity should be enjoyable and social support for the activity from family, peers, and or the local community is the key. Using established guidelines within the context of social, cultural, familial, and environmental factors, clinicians must improve preventive counseling services to adolescents.

Adams et al: Translating physical activity recommendations for overweight adolescents to steps per day. AJPM 2009; 37(2):137-40. [PMID: 19524391]


**SPECIAL CONSIDERATIONS**

**Performance-Enhancing Supplements**

Over the past decade, the use of performance-enhancing supplements has increased significantly. One-half of the US population consumes some form of nutritional supplement on a regular basis, resulting in over $44 billion in annual sales. Reasons cited for the use of dietary nutritional supplements include ensuring good nutrition, preventing illness, improving performance, warding off fatigue, and enhancing personal appearance.

Estimates suggest that roughly 5% of all adolescents have used some form of performance-enhancing nutritional supplements. Adolescents, in particular, are vulnerable to the allure of performance-enhancing products.

Creatine is the most commonly used performance-enhancing supplement. Creatine is reported to increase energy during short-term intense exercise, increase muscle mass, increase strength, increase lean body mass, and decrease lactate accumulation during intense exercise. Although it is clear that supplementation with exogenous creatine can raise intramuscular creatine stores, it is not clear how effective creatine is as a performance aid. In general, creatine supplementation may be useful for activities requiring short, repetitive bouts of high-intensity exercise. There is conflicting evidence, however, as to whether it is effective in increasing muscle strength or muscle mass. There are no scientific data regarding the safety or effectiveness of long-term use of creatine in adolescents.

Anabolic-androgenic steroids (AAS) are another important category of performance-enhancing substances used by adolescents. Testosterone is the prototypical androgenic steroid hormone. Many synthetic modifications have been made to the basic molecular structure of testosterone in an attempt to promote the anabolic, muscle-building effects of testosterone while minimizing androgenic side effects. Androstenedione is one of several oral performance-enhancing supplements that are precursors to testosterone. The effectiveness of androstenedione as a performance-enhancing supplement is debatable. To date, the largest controlled trial examining its effectiveness showed no significant gains in muscular strength compared with a standard program of resistance training. The Anabolic Steroid Control Act of 2004 expanded the definition of anabolic steroids to include androstenedione and tetrahydrogestrinone (THG)—a designer steroid whose use was implicated in accusations of steroid use by several famous US athletes—as controlled substances, making their use as performance-enhancing drugs illegal.

Despite this ban, it is estimated that 3%-10% of adolescents have used anabolic steroids. Importantly, adolescents who use anabolic steroids have been shown to be more likely to engage in high-risk personal health behaviors such as tobacco use and excessive alcohol consumption. Users of other nutritional performance-enhancing supplement have also been shown to engage in similar predictable high-risk...
behaviors. The American Academy of Pediatrics has recently published a position statement strongly discouraging the use of performance-enhancing substances.

Clinicians should be aware of the prevalence of performance-enhancing supplement use in the adolescent population. They should also be aware of health-related behaviors that often accompany the use of these products and provide preventive counseling accordingly. The preparticipation physical examination represents an excellent opportunity for clinicians to provide information about performance-enhancing products to young athletes. When counseling adolescents about the use of performance-enhancing products it is helpful to ask the following questions: (1) Is the product safe to use? (2) Why does the adolescent want to use a particular product? (3) Is the product effective in helping to meet the desired goal? (4) Is the product legal? Many adolescents will either try or continue to use performance-enhancing products regardless of the information or advice they receive. Nevertheless, they should be aware of potential health risks or bans from competition that accompany use of performance-enhancing products. The use of performance-enhancing supplements in adolescents should be discouraged.

**Female Athlete Triad**

Although many adolescents engage in too little physical activity, there is a segment of the population for whom too much exercise leads to specific physiologic side effects. The female athlete triad refers to the combination of disordered eating, amenorrhea, and osteoporosis that can accompany excessive physical training in young female athletes. Athletes particularly at risk include those who participate in gymnastics, ballet, figure skating, distance running, or any other sport that emphasizes a particularly lean physique.

The preparticipation physical examination represents an excellent opportunity for clinicians to screen for and to prevent the female athlete triad. During this examination, screening questions for female athletes should include careful menstrual, dietary (including a history of disordered eating practices), and exercise histories. When elicited, a history of amenorrhea (particularly in a previously menstruating woman) should be taken seriously. The American College of Sports Medicine recommends that these women be considered at risk for the female athlete triad and that a formal medical evaluation should be undertaken within 3 months.


**Exercise & Sudden Death**

Another small segment of the adolescent population is at risk during exercise. These individuals are predisposed to sudden cardiac death during physical activity. Highly publicized events among well-known athletes have further focused attention on this issue. Although the incidence of sudden cardiac death in young athletes is fortunately quite low, proper screening is still important. Here again, the preparticipation physical examination represents an excellent clinical opportunity for prevention.

When screening for sudden death in young athletes, the medical history should include questions about exercise-related syncope or near-syncope, shortness of breath, chest pain, or palpitations. The clinician should ask about a family history of premature death or premature cardiovascular disease. Any prior history of a cardiac murmur or specific knowledge of an underlying cardiac abnormality (either structural, valvular, or arrhythmic) in the athlete should be elicited as well. If the examining clinician has any suspicion that the athlete might have a symptomatic arrhythmia, that individual should be withheld from physical activity pending consultation with a cardiologist.

On physical examination, blood pressure should be recorded. The precordial fields should be auscultated in the supine, squatting, and standing positions. Murmurs that increase with moving from the squatting to standing position or that increase with the Valsalva maneuver are of potential concern and merit further evaluation. The equality of the femoral pulses should be noted. While routine use of modalities like EKGs, stress testing, and/or echocardiograms as screening efforts are not routinely recommended, if any abnormalities are noted on the initial preparticipation history or physical examination, a more detailed evaluation including them and/or cardiology consultation may be warranted.


**General Considerations**

More than eight million Americans suffer from eating disorders. Approximately 90% of them are young women; however, middle-aged women, children, and men are also affected. The prevalence of eating disorders appears to vary by the population being studied. Recently, the recognition of binge eating disorder (BED), a putative diagnosis currently a form of “Eating Disorder Not Otherwise Specified,” has changed the face of eating disorders. While anorexia (AN) and bulimia nervosa (BN) appear to primarily affect women, the ratio of women to men with BED is approximately 3:2. There are also significant cross-cultural differences in the prevalence and presentation of AN, BN, and BED.

Eating disorders are more prevalent in industrialized societies (where food is abundant and thinness is valued as attractive) than in developing countries. Women in western countries traditionally have exhibited greater concern for body habitus than those in developing countries, who appear to be more accepting of and comfortable with a fuller body shape. In many of the latter societies, a fuller figure has been considered the cultural stereotype of attractiveness, although this ideal appears to change when individuals from these societies integrate into western culture.

Westernization has affected many countries, and individuals from other cultures should not be excluded from consideration of an eating disorder diagnosis. Immigration from non-Western to Western cultures appears to place individuals at greater risk for eating disorders. Indeed, degree of acculturation into American society is associated with eating disorder risk, likely due to the adoption of Western body-image ideals. As individuals (particularly girls and women) from cultures in which AN is unknown or extremely rare immigrate to westernized societies with higher rates of AN, they tend to develop disorders as they attempt to acculturate.

Two core features are common across all eating disorders; namely, severe disturbance in eating habits, and excessive concern and/or dissatisfaction with body shape and weight. However, on the surface, individuals with AN and BED present quite differently. Further, AN, BN, and BED differ in terms of prevalence, demographic correlates, and medical ramifications. Classification of both overeating and under-eating disorders into a single category poses difficulties for the conceptualization and treatment of these conditions.


**Normative versus Abnormal Eating**

Before detailing the clinical characteristics of various eating disorders, it is necessary to identify what is meant by “normative eating.” In so doing, it becomes apparent that a great deal of dieting occurs in Western culture as part of normal eating. In fact, estimates suggest that anywhere from 15% to 80% of the population may be dieting at a given time. Despite these statistics, over 65% of the adult population, and about 16% of children and adolescents aged 2-19 years, are considered overweight or obese. High prevalence of obesity appears to disproportionately affect those of racial and ethnic minorities. About 70% of African American and Mexican American adults, compared to about 62% of non-Hispanic white adults, are considered overweight or obese. Similarly, 21% of African American and Mexican American children, compared with 14.6% of non-Hispanic white children, are overweight.

The term “dieting” in lay culture has been used to describe a wide variety of behaviors ranging from healthful (eg, eating more vegetables, increasing exercise) to extreme (eg, prolonged fasting, self-induced vomiting). Appropriateness of dieting should be considered in light of the specific behaviors that comprise dieting. Further, consideration of dieting in the context of an individual’s weight status is an important factor in evaluating whether dieting is pathological (in underweight or non-overweight individuals) versus appropriate (in overweight
individuals). It has been suggested that dieting typically precedes eating disorder onset in cases of BN, while for BED, binge eating has been reported as preceding the onset of dieting in approximately half of cases.

Women are most likely to restrict their food intake to control their weight or lose weight, but increasingly men are also engaging in dieting behavior. Perhaps most worrisome is the prevalence of dieting among adolescents and even children. Data suggest that that 40% of 9-year-old girls have dieted, and even 5-year-olds voice concern about their diet that appear to be linked to cultural standards for body image. Although most individuals who diet do not develop an eating disorder, dieting, in combination with other factors, may be an important precipitant to the development of eating disorders. The acceptance of dieting as “normative” may prohibit recognition of problem eating.

### Prevalence of Eating Disorders

The prevalence and incidence rates for eating disorders vary significantly, depending on the disorder and the population. Generally speaking, of patients with classic signs and symptoms of AN or BN, 90% are female, 95% are white, and 75% are adolescent when they develop the disorder. These data are substantiated by several cross-cultural studies that have reported few, if any, cases in rural areas of Africa, the Middle East, or Asia with the exception of Japan, the only non-Western country that has seen a substantial and persistent increase in eating disorders. AN has been implicated as a “culture-bound syndrome” because certain cultural mores are reflected in the signs and symptoms of the disorder. In adults, recent studies of racial and ethnic differences in eating disorder prevalence within a nationally-representative sample suggest that AN is less common in African American and Latino populations compared to non-Hispanic whites. However, several studies have shown that other abnormal eating behaviors may be as common more so among African American women (eg, purging by laxatives vs vomiting, binge eating). African American women are also more likely to develop BN or BED than AN, and a recent study found a strong association between BED and obesity in this population. Given the high rates of obesity in ethnic minority populations, experts have postulated that BED is a significant problem among these groups. The predominance of non-Hispanic whites among cases of AN may contribute to cultural bias in diagnosis, with less recognition of eating disorders among ethnic minorities.

Compared to adults, the prevalence of eating disorders among adolescents is characterized by a differential racial and ethnic pattern. Indeed, among high school students, Hispanic and non-Hispanic white girls tend to report similar levels of eating disordered attitudes and cognitions, such as excessive shape and weight concern and extreme dieting, which may be risk factors for full-syndrome disorders. African American girls, however, report lower body weight concerns and behaviors than girls of other ethnicities. Among adolescent boys, nearly all ethnic minorities report more eating disorder symptoms and weight concerns compared to Caucasian boys. How subthreshold disturbances and risk factors manifest into differential prevalence of full-syndrome disorders across cultures is not well understood.

It is traditionally thought that AN and BN tend to affect adolescent girls of middle to upper socioeconomic status. Age- and sex-specific estimates suggest that about 0.5%-1% of adolescent girls develop AN, whereas 5% of older adolescent and young adult women develop BN. This population also exhibits a high frequency of coexistence between AN and BN. It has been reported that as many as 50% of AN patients may exhibit bulimic behaviors while 30%-80% of patients with BN have a history of AN. Although constituting a small segment of patients with eating disorders, male adolescents must not be forgotten. Most, however, tend to have a diagnosis of BN or BED.

Data suggest that approximately 3%-5% of people surveyed in a general population have BED. Although being overweight is not a criterion for the diagnosis of BED, it has been estimated that slightly over 11% of individuals who join Weight Watchers and 30% of individuals who present to hospital-based weight control programs meet the diagnosis of BED. In contrast to AN and BN, BED appears to afflict adults of all socioeconomic strata and education level equally. Furthermore, BED is often diagnosed in middle-aged adults.

Finally, it should be noted that despite the emphasis on AN, BN, and BED in both the literature and the media, the diagnostic category of “eating disorder not otherwise specified” (EDNOS)—excluding BED—is the most prevalent eating disorder in the United States, affecting 6%-10% of young women. Recent research suggests that individuals diagnosed with EDNOS did not differ significantly from AN and BED in terms of eating or general pathology. However, individuals with BN exhibited greater eating and general psychopathology compared to EDNOS. Girls meeting all criteria for AN except amenorrhea did not differ from full-syndrome AN. Further, nearly 40% of individuals diagnosed with EDNOS went on to develop either AN or BN with 1-2 years. Thus, EDNOS seems to represent a heterogenous category whose symptoms overlap substantially with traditional eating disorders. Clinicians should monitor possible progression of EDNOS to full syndrome AN, BN, or BED, especially given the paucity of treatment recommendations for EDNOS.

EATING DISORDERS


Pathogenesis

The origins of eating disorders are extremely complex and poorly understood. However, biological, psychological, cultural, and societal factors are likely contributors to the predisposition, precipitation, and perpetuation of these disorders. Typically, individuals with eating disorders are thought to have a biological or genetic predisposition that is activated by environmental (ie, sociocultural, psychosocial) factors.

Risk factors for developing an eating disorder include participation in activities that promote thinness (eg, ballet dancing, modeling, and athletics) and certain personality traits, such as low self-esteem, difficulty expressing negative emotions, difficulty resolving conflict, being perfectionistic, and neuroticism/anxiety. Mounting data also support substantial biological predispositions to AN and BN. Mothers and sisters of probands who had AN were found to have eight times the risk of developing an eating disorder compared with the general population. Genetic studies also lend strong support to the underlying biological supposition regarding eating disorders. Twin studies have shown heritability estimates in the 50%-90% range for AN and 35%-50% for BN, with monozygotic twins having higher concordance than dizygotic twins. A strong association between AN and BN in families has also been found in the Virginia Twin Registry.

Eating disorders may also be precipitated by psychosocial factors in vulnerable individuals. These precipitating factors often relate to developmental tasks of adolescence and include maturation fears, particularly those related to sexual development, peer group involvement, independence and autonomy struggles, family conflicts, sexual abuse, and identity conflicts. Two other psychological factors that figure prominently in the pathogenesis of BN or BED are sexual trauma and depression. Patients with either of these disorders are predisposed to have a family and personal history of depression. Therefore, it is important to note the presence of depression or history of sexual trauma during the initial patient assessment.

In the past two decades, the number of men who openly report dissatisfaction with their physical appearance has tripled. Today nearly as many men as women say they are unhappy with how they look. Fifty percent more men reportedly seek evaluation and treatment for eating disorders than they did in the 1990s. This trend may be rooted in an obsession with “six-pack abs” and bulging biceps that seems especially common among athletes and fitness enthusiasts. Pursuit of masculinity to the exclusion of healthy habits may be a precursor to eating disorder development in males. Additionally, exercise status and sexual orientation are two risk factors for eating disorders in men. Often men who develop eating disorders have a history of being overweight when they were younger. Men considered to be at increased risk of developing eating disorders include:

- Athletes, especially those participating in sports that work against gravity, such as gymnastics.
- Men with body issues.
- Men with personality traits such as perfectionism and impulsive behaviors, and those who have anxiety.
- Obese boys who face teasing and have low self-esteem.

Increasingly, research on the risk-factors for eating disorders has indicated that ED symptoms may emerge as early as middle childhood. Dieting, concerns about shape and weight, and body dissatisfaction are present in children as young as 5 years of age, and common among children aged 8-12 years. Early factors shown to be associated with later development of AN include feeding and gastrointestinal difficulties during infancy and early childhood, maternal body dissatisfaction, and dieting and shape concerns during early and middle childhood. Similarly, early concerns with eating and weight are potential red-flags for future development of BN. Overweight status during childhood has been shown to be related to future development of both BN and BED.

Loss of control eating, defined as the feeling of being unable to control what or how much one is eating regardless of the amount of food consumed, has been reported in young children. Loss of control eating is fairly common among children, especially among those who are overweight (prevalence estimates among overweight youth range from 4% to 45%). LOC eating in youth is analogous to binge eating in adults, and may be a precursor for future development of BED. Children who have loss of control eating are at risk for gaining excess weight as they grow, and they have more disturbed eating patterns, symptoms of depression and anxiety, and behavior problems compared to children without such behaviors. Children who are at risk for becoming overweight adults, including those who are overweight and who have overweight parents, should be queried about loss of control eating to monitor potential progression to BN or BED.

Bulik CM: Prevalence, heritability, and prospective risk factors for anorexia nervosa. Arch Gen Psychiatry 2006;63. [PMID: 16520436]

CHAPTER 11

Eating disorders are serious and complex problems, and the earlier an eating disorder is identified, the better the patient’s chance of recovery. This makes a compelling argument for targeted screening of at-risk groups, including gymnasts, runners, body builders, wrestlers, dancers, rowers, and swimmers. These groups warrant close monitoring because their sports or livelihood dictate weight restriction. The populations at highest risk for AN and BN are female adolescents and young adults, and screening should occur throughout adolescence, especially at ages 14 and 18 years. This correlates with the transition to high school and college and the associated stressors.

In contrast to AN and BN, which typically emerge during adolescence, BED is most frequently detected during middle adulthood, even though many individuals report an onset of the disorder in their mid-twenties and initial binge eating behaviors can begin even earlier. Because of the relatively high prevalence of BED in community samples (3%-5%), routine screening for binge eating among overweight adults may be warranted. Almost all individuals seeking treatment for weight control should be screened for BED because of the high incidence of this disorder in this group (about 30%-50%). Although these individuals may fall short of meeting the full criteria for BED, the problematic attitudes associated with the disorder will likely be uncovered. The tools used for screening can be very sophisticated and vary with the population being assessed. However, there are some that are easily incorporated into the routine primary care office visit (Table 11-1). These questions are very helpful for the early detection of BN and BED; some individuals with these disorders can be uncovered using self-report alone. Those with AN, on the other hand, are more often resistant to self-reporting and usually require reporting by others (ie, parents, friends). Therefore, it is imperative that parents, friends, teachers, family, dentists, and physicians become educated about the possible signs and symptoms associated with these difficult-to-manage disorders to facilitate prevention or early management of these individuals. Some cases of BN may be similarly difficult to detect, because many patients with BN are of a healthy weight status, and maintain secrecy surrounding bulimic behaviors.

### Prevention & Screening

#### Clinical Findings

##### A. Symptoms and Signs

The multiple symptoms experienced by the patient and signs noted by the physician are related to the numerous methods used to manipulate weight. When initially screening a patient, a symptom checklist can facilitate taking a history (Table 11-2). Although treatment-seeking individuals will often answer questions honestly, patients with AN are usually reticent to be seen or report any problem with weight.

If the review of systems contains primarily positive results, this may be indicative of a significant problem for the patient. Most commonly, female patients with AN complain of amenorrhea, depression, fatigue, weakness, hair loss, and bone pain (which may be indicative of pathologic fracture secondary to osteopenia). Constipation or abdominal pain, or both, occur frequently but may be commonly

#### Table 11-2. Evaluation of eating disorders: the history.

<table>
<thead>
<tr>
<th>History should include questions on the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (minimum/maximum, as well as ideal)</td>
</tr>
<tr>
<td>Menstrual history and pattern (if applicable: age of menarche, date of last period)</td>
</tr>
<tr>
<td>Body image (thin, normal, heavy; satisfaction/dissatisfaction with current weight)</td>
</tr>
<tr>
<td>Exercise regimen (amount, intensity, response to inability to exercise)</td>
</tr>
<tr>
<td>Eating habits</td>
</tr>
<tr>
<td>Sexual history (if applicable, a history of current sexual activity, number of partners, review of health habits and sexual practices that might place the patient at risk for sexually transmitted diseases [STD])</td>
</tr>
<tr>
<td>Current and past medication</td>
</tr>
<tr>
<td>Laxative/diuretic/diet pill use, ipecac, cigarettes, alcohol, drugs</td>
</tr>
<tr>
<td>Substance abuse (eg, cigarettes, alcohol, drugs)</td>
</tr>
<tr>
<td>Binge-eating and purging behavior (identify a binge: feeling of “loss of control,” how much, what kinds of food; presence of triggers: foods, time of day, feelings; frequency of binge eating; identify vomiting methods: finger, toothbrush)</td>
</tr>
<tr>
<td>Psychiatric history (substance abuse, mood/anxiety/ personality disorders)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
</tr>
</tbody>
</table>
mistaken as symptoms of endometriosis or pelvic inflammatory disease, which are disorders common to both anorexia and bulimia. Unlike AN, BN may be missed initially by the inexperienced clinician because these patients may present with normal or near-normal body weight or be slightly underweight. In addition to constipation and gastrointestinal pain, patients with BN may present with menstrual irregularity, food and fluid restrictions, abuse of diuretics and laxatives (causing dizziness and bloody diarrhea), misuse of diet pills (leading to palpitations and anxiety), frequent vomiting (resulting in throat irritation and pharyngeal trauma), sexually transmitted diseases (which appears to be related to impulsive, risk-taking behaviors associated with this disorder), and bone pain. Mouth sores, weaknesses, dental caries, heartburn, muscle cramps and fainting, hair loss, easy bruising, and cold intolerance are some of the more obvious presenting complaints.

B. Diagnostic Criteria

The hallmark of AN is the refusal to eat anything but minimal amounts of food, resulting in low body weight. The hallmark of BN is the attempt to restrict food intake that eventually leads to out-of-control eating episodes followed by inappropriate compensatory behaviors (eg, vomiting). The commonalities among the eating disorders include disturbance in body image (both body shape and body weight over-concern) and an excessive drive for thinness.

Currently, there is an increased focus on BED and the overlap among obesity, eating disorders, and other mental disorders. As previously noted, the most prevalent eating disorder listed in Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, (DSM-IV-TR) is EDNOS; it is important that clinicians consider this possibility in the differential diagnosis of patients with eating disorders.

1. Anorexia nervosa—The diagnostic criteria for AN are defined and listed in the DSM-IV-TR (Table 11-3). The hallmark of AN is the refusal to maintain minimum body weight, defined as maintenance of 85% of expected weight or BMI greater than 17.5 kg/m² or failure to make appropriate weight gains with growth. Patients with AN exhibit an intense fear of weight gain and body image disturbance, which may include any or all of its three components: emotional (eg, self-disgust), perceptual (eg, “my thighs are too fat”), and cognitive (eg, “people will hate me if I’m fat”). The onset of AN is typically between ages 14 and 18 years, although middle childhood cases have been reported. Amenorrhea (albeit controversial) is also a defining element. In prepubertal girls menarche is delayed, and in postmenarchal women, at least three consecutive menstrual cycles are absent. The amenorrhea is attributed to low levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and may eventually precede weight loss in up to 20% of patients.

Two subtypes of AN are identified: a binge eating–purging type and a restricting type. The former subtype includes patients who engage in diuretic laxative abuse, vomiting, and overuse of enemas to eliminate calories. Patients who do not engage in either binge eating or purging behaviors are categorized as having the restrictive subtype. AN binge eating–purging subtype differs from BN in weight criteria, size of the binge (usually smaller), and consistency of purging (less frequent).

2. Bulimia nervosa—BN is slightly more common than AN and largely seen in collegiate women, although the disorder usually starts in the late teenage years. Dieting often precedes and is associated with BN. This results in out-of-control eating and is followed by inappropriate compensatory behaviors. Patients with BN may be slightly more difficult to initially identify than those with AN, because most are within normal weight range for age and height. However, some may be overweight or slightly underweight.

The DSM-IV-TR defined criteria for BN (Table 11-4) include frequent episodes of binge eating in which more food than normal is consumed in a discrete period of time. The patient must also engage in recurrent inappropriate compensatory behaviors. Both criteria occur on average of two times per week for 3 months. BN is also divided into two subtypes: a purging type and a nonpurging type. The purging subtype requires regular engagement in self-induced vomiting and abuse of laxatives, diuretics, or enemas. The nonpurging subtype highlights

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Table 11-3. DSM-IV-TR criteria for anorexia nervosa.

<table>
<thead>
<tr>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Refusal to maintain body weight at or above a minimally normal weight for age and height (eg, weight loss leading to maintenance of body weight &lt;85% of that expected, or failure to make expected weight gain during period of growth, leading to body weight &lt;85% of that expected).</td>
</tr>
<tr>
<td>B. Intense fear of gaining weight or becoming fat, even though underweight.</td>
</tr>
<tr>
<td>C. Disturbance in the way in which one’s body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.</td>
</tr>
<tr>
<td>D. In postmenarcheal females, amenorrhea, ie, the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, eg, estrogen administration.)</td>
</tr>
</tbody>
</table>

Restricting Type: During the current episode of anorexia nervosa, the person has not regularly engaged in binge eating or purging behavior (ie, self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Binge Eating/Purging Type: During the current episode of anorexia nervosa, the person has regularly engaged in binge eating or purging behavior (ie, self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

other inappropriate behaviors, such as fasting and excessive exercise, but does not include vomiting or the abuse of laxatives, enemas, or diuretics. About two-thirds of patients with BN are of the purging subtype, and this subgroup has been found to exhibit more severe pathology, including more frequent binge eating and more psychiatric comorbidities, than individuals with nonpurging BN.

3. **Binge eating disorder**—The most recent of the eating disorder diagnostic categories is BED. BED is not fully recognized by the DSM-IV-TR. It is listed as a disorder meriting further study and patients currently are considered to meet the diagnostic criteria for EDNOS. (Research criteria for BED are found in an appendix to the DSM-IV-TR.)

Evidence suggests that BED affects women and men (3:2) more evenly, impacts a broader age range of individuals (aged 20-50 years), and likely affects African Americans and Hispanics as often as non-Hispanic whites. Most people with BED are obese and have a history of “yo-yo” dieting. The hallmark of BED is binge eating in the absence of compensatory behaviors. Patients report feeling a sense of “loss of control” while consuming larger amounts of food than is typical for most people in a discrete period of time. The episodes are associated with rapid eating, eating until uncomfortable, eating large amounts when they are not hungry, and eating alone. The patient typically experiences intense feelings of guilt and shame surrounding these eating episodes. Episodes occur for at least 2 days per week for a duration of 6 months. BED is characterized by a comparable elevated level of disordered eating attitudes (e.g., over-valuation of shape and weight) as the classic eating disorders of AN and BN.

### Table 11-4. DSM-IV-TR criteria for bulimia nervosa.

<table>
<thead>
<tr>
<th>A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Eating, in a discrete period of time (e.g., within any 2-h period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances.</td>
</tr>
<tr>
<td>(2) A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control how much one is eating).</td>
</tr>
<tr>
<td>B. Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, enemas, or other medications; fasting, or excessive exercise.</td>
</tr>
<tr>
<td>C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 mo.</td>
</tr>
<tr>
<td>D. Self-evaluation is unduly influenced by body shape and weight.</td>
</tr>
<tr>
<td>E. The disturbance does not occur exclusively during episodes of anorexia nervosa.</td>
</tr>
</tbody>
</table>


### Table 11-5. DSM-IV-TR criteria for eating disorder not otherwise specified.

The eating disorder not otherwise specified category is for disorders of eating that do not meet the criteria for any specific eating disorder. Examples include:

1. For females, all of the criteria for anorexia nervosa are met except that the individual has regular menses. |
2. All of the criteria for anorexia nervosa are met except that, despite significant weight loss, the individual’s current weight is in the normal range. |
3. All of the criteria for bulimia nervosa are met except that the binge eating and inappropriate compensatory mechanisms occur at a frequency of less than twice a week or for a duration of <3 mo. |
4. The regular use of inappropriate compensatory behaviors by an individual of normal body weight after eating small amounts of food (e.g., self-induced vomiting after the consumption of two cookies). |
5. Repeatedly chewing and spitting out, but not swallowing, large amounts of food. |


4. **Eating disorder not otherwise specified**—Persons with EDNOS include those who meet all the criteria for AN but have regular menses, normal-range weight, and less-frequent binges (Table 11-5). With this in mind, it is easy to understand the importance of identifying and treating these individuals. Nonetheless, many are frequently not treated by clinicians because they fail to meet the full diagnostic criteria for AN. Other individuals who fit into the category of EDNOS may meet subthreshold, but not full-syndrome criteria for BN. Often, this is because episodes occur at a lower frequency than that required to meet full syndrome criteria. Some EDNOS patients engage in other behaviors to control weight or shape, such as chewing food and spitting it out. The heterogeneity of EDNOS patients can make treatment recommendations difficult; however, following treatment guidelines for whichever disorder most closely matches the clinical presentation is recommended.

### C. Physical Examination

Whenever suspicion of an eating disorder is raised, a detailed physical and dental examination should be conducted (Table 11-6). Complications of AN and BN can affect most organ systems; however, early in the diagnosis the “good-looking” or “normal-weight” patient may elude diagnosis by even the most astute physician. Multi-layered, baggy clothing worn by adolescents may be representative of the latest fads in fashion or a significant eating disturbance. Just as baggy
Reproduced, with permission, from Fisher M et al: Eating

Table 11-6. Key components of the physical examination in patients with eating disorders.

<table>
<thead>
<tr>
<th>Physical examination, including</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of vital signs</td>
</tr>
<tr>
<td>Body temperature (hypothermia: &lt;35.5°C [96°F])</td>
</tr>
<tr>
<td>Heart rate (bradycardia: &lt;50)</td>
</tr>
<tr>
<td>Blood pressure (hypotension: 90/50 mm Hg)</td>
</tr>
<tr>
<td>Weight (taken with the patient dressed in a hospital gown) and height assessment should take into account previous height and weight percentiles, anticipated growth, and average weights of healthy adolescents of the same sex, height, and sexual maturation (prepared from National Center for Health Statistics [NCHS] data)</td>
</tr>
<tr>
<td>Evaluation of body mass index (BMI):</td>
</tr>
<tr>
<td>Quetelet BMI (weight-to-height relationship: defined as weight in kilograms divided by height in meters squared; this BMI is then compared with reference data; percentile tables for BMI for age and sex based on NCHS data have been developed for children and adolescents)</td>
</tr>
<tr>
<td>Gynecologic examination (if applicable):</td>
</tr>
<tr>
<td>Pelvic evaluation (atrophic vaginitis)</td>
</tr>
<tr>
<td>Breast evaluation (atrophy)</td>
</tr>
<tr>
<td>Pregnancy testing (where appropriate)</td>
</tr>
<tr>
<td>Sexually transmitted disease testing (where appropriate)</td>
</tr>
</tbody>
</table>


Table 11-6. Key components of the physical examination in patients with eating disorders.

Height, weight, and BMI should also be recorded regularly and at each visit. This is helpful in establishing the patient's weight trends, because few individuals with AN are overweight prior to the onset of their disease. These weight trends also help to identify the patient's failure to gain weight during normal adolescent growth spurts. It is vitally important to obtain accurate readings. Therefore, patients should be weighed in a hospital gown, not in personal clothing, because of the various strategies they employ to disguise their weight loss.

Careful examination of the patient's body should also be performed. Signs of AN such as brittle hair and nails, dry scaly skin, loss of subcutaneous fat, fine facial and body hair (lanugo hair), carotene pigmentation, breast atrophy, and atrophic vaginitis may be readily observable. Physical examination findings more representative of bulimic patients include the callused finger (Russell sign) used to induce vomiting, dry skin, and dull hair. Periodontal diseases are well-recognized sequelae of BN and may present as erosion of tooth enamel, mouth sores, dental caries, gum inflammation, chipped teeth, and sialadenosis (swelling of the parotid glands). BED patients are typically (but not always) overweight or obese and may present with common obesity-related health comorbidities.

D. Laboratory Findings

There are no confirmatory laboratory tests specific to the diagnosis of eating disorders, and reported findings may be normal. Nonetheless, screening or baseline evaluations are recommended and should include a complete blood count with differential, urinalysis, blood chemistries (electrolytes, calcium, magnesium, and phosphorus), thyroid function tests, an amenorrhea evaluation, and baseline electrocardiogram, as indicated. Generally speaking, laboratory abnormalities are due to the weight-control habits or methods used by the patient, or the resulting complications.

In the early stages of AN, laboratory findings may show elevated BUN, which may be secondary to dehydration; leukopenia due to increased margination of neutrophils; and pancytopenia. In addition, low circulatory levels of LH and FSH, osteopenia and osteoporosis, deficiency of gonadotropin-releasing hormone, low estradiol, elevated cortisol, low triiodothyronine (T<sub>3</sub>) and free thyroxine (T<sub>4</sub>), an increase in reverse T<sub>3</sub>, and hypoglycemia with diminished circulating insulin levels may be observed.

Laboratory testing in BN patients is also usually normal. However, when an abnormality is present (ie, metabolic alkalosis), it is usually due to the effects of binge eating and purging. Significant hypokalemia due to purging places the patient at high risk for cardiac arrhythmias, the most common cause of death in BN. Hypophosphatemia, metabolic acidosis (secondary to laxative abuse), and osteopenia and osteoporosis (in BN patients with a past history of AN) are also possible findings.

Laboratory findings in male patients with AN are characterized by low testosterone, diminished LH and FSH, and decreased testicular volume. Likewise, libido and sexual
functioning are diminished in these patients during the starved state. Also of note is the presence of osteopenia in male adolescents and young men with eating disorders. Although relatively common, this is usually an unrecognized clinical problem in these patients.


Differential Diagnosis

In patients presenting with weight loss, other differential diagnoses, both medical and psychiatric, must be considered. Eating disorder symptoms may be caused by numerous medical disorders, including brain tumors, malignancy, connective tissue disease, malabsorption syndrome, hyperthyroidism and infection, gastrointestinal disease (inflammatory bowel disease [IBD], Crohn disease, ulcerative colitis), menstrual irregularities, cystic fibrosis, and substance abuse (e.g., cocaine, amphetamines).

The psychiatric differential diagnosis includes affective and major depressive disorders, schizophrenia, obsessive-compulsive disorder, and somatization disorder. However, the diagnosis of an eating disorder is made by confirming, by history and mental state examination, the core psychopathology of a morbid fear for fatness, and not by ruling out all conceivable medical causes of weight loss or binge-purge behavior. Because eating disorders and affective disorders have both been shown to have an increased incidence in first-degree relatives of anorexics, a thorough family history should also be performed.


Complications

Complications of eating disorders are listed in Table 11-7.

Treatment

Overall, eating disorders present an unusual challenge for clinicians. Much of the denial, resistance, and anger of the patient and occasionally the family may now be directed at the physician. However, awareness that patients with these disorders are frequently ambivalent, desiring but often afraid of recovery and making the physician the target of their emotions and of the inner conflict, serves to facilitate the building of a trusting relationship, the foundation of effective therapy.

Table 11-7. Complications of eating disorders.

| Cardiovascular | bradycardia, congestive heart failure, dysrhythmias, electrophysiologic abnormalities, ipecac-induced cardiomyopathy, mitral valve prolapse, pericardial effusion, orthostatic hypotension |
| Dermatologic | acrocyanosis, brittle hair and nails, carotene pigmentation, edema, hair loss, lanugo hair, Russell sign |
| Endocrine | amenorrhea, diabetes insipidus, growth retardation, hypercortisolism, hypothermia, low T, syndrome, pubertal delay |
| Gastrointestinal | acute pancreatitis, Barrett esophagus, bloody diarrhea, constipation, delayed gastric emptying, esophageal or gastric rupture, esophagitis, fatty infiltration and focal necrosis of liver, gallstones, intestinal atony, Mallory-Weiss tears, parotid hypertrophy, perforation/rupture of the stomach, perimolysis and increased incidence of dental caries, superior mesenteric artery syndrome |
| Hematologic | bone marrow suppression, impaired cell-mediated immunity, low sedimentation rate |
| Neurologic | cortical atrophy, myopathy, peripheral neuropathy, seizures |
| Skeletal | osteopenia, osteoporosis, osteoporotic fracture |

A. Early-Stage Eating Disorders

A developmental perspective cannot be overemphasized for the early detection, and possible prevention, of eating disorders. The only factor consistently associated with more promising treatment outcomes for AN and other eating disorders is early detection and shorter duration of illness. Although many cases of early eating disturbance do not progress to full-syndrome eating disorders, the number of girls and boys in elementary, middle, and high schools engaging in extreme dieting (e.g., fasting, excessive exercise) and disordered eating behaviors (e.g., binge eating, purging behaviors) is alarmingly high. In fact, many of these individuals fall into the DSM-IV-TR category of EDNOS. Such behaviors should be monitored. Many cases of eating disorders are characterized by a prodromal period of dieting and excessive weight and eating concern that place vulnerable individuals at risk for full-syndrome eating disorders.

Management of the early or mild stages of an eating disorder diagnosis begins with the assessment of weight loss or weight control and establishment of a working relationship and rapport with the patient and family. Next, the physician focuses on the patient’s methods of weight loss or weight control. This opens the door to educating the patient on the importance of maintaining good health—including a discussion of normal eating, nutrition, and exercise—and assisting the patient in establishing a goal weight that will serve as a boundary for excessive weight loss.

In addition to the institution of an appropriate diet and weight goal, patients may also be instructed on beginning and maintaining a food diary. This assists the physician in identifying patterns and triggers for dysfunctional habits and gives patients a way of exerting some control over their eating behavior.

Another important component of treatment is to acknowledge the possibility of relapse and have a plan in
place. Discussing some of the potential triggers of relapse—relationship problems, family issues (eg, divorce, separation), academic and peer pressure—and the strategies to cope with them can help patients avoid feelings of hopelessness when they are experienced. The patient who relapses should be reevaluated within 3-6 weeks. Information obtained on the follow-up visit is helpful in determining if weight is changing precipitously, if there are changes in physical examination findings, or, most importantly, if the dysfunctional eating habits are more entrenched. These markers help to determine if the patient will require referral.

## B. Established Eating Disorders

Patients who clearly meet the criteria for an established eating disorder typically require management by a multidisciplinary team that includes a physician (family physician, pediatrician, or internist), nutritionist or dietician, nurse, mental health professional, and other support staff.

If the family physician is not an integral part of an established eating disorder treatment team, then his or her role is to coordinate and facilitate transfer. This role is critical because the trust in the primary care physician may not be readily transferred to the team of specialists. It is essential that the family physician remain involved in the patient’s treatment by providing regular medical assessments, supporting the patient and family, clarifying the tasks performed by each of the team members, reinforcing the importance of the referral, and preventing premature discontinuation of treatment.

Among the various approaches to the management of eating disorders are family therapy, short-term psychotherapies such as cognitive-behavioral therapy (CBT), and interpersonal psychotherapy (IPT), behavior modification, and psychoactive medications. Based on the condition of the patient (Table 11–6), they may be applied in the inpatient or outpatient setting.

### 1. Anorexia nervosa

Few empirically validated treatments have shown substantial efficacy for AN. Some patients, through medical management and nutritional change, along with psychotherapy, are able to maintain a requisite weight for medical stability; however, many patients retain subthreshold eating pathology and underweight status.

The primary treatment goals for AN are medical stability and weight stabilization. In the female patient, this means a weight at which ovulation and menses can occur; in the male patient, it entails return to normal hormone levels and sexual drive; and in adolescents and children, return to normal physical and sexual maturation. Other goals include treating medical and physical complications; motivating patients to cooperate and participate in treatment education regarding healthy nutrition and eating patterns; treating underlying eating disordered psychopathology and fear of weight gain that accompanies AN, as well as comorbid psychiatric conditions; encouraging and supporting family participation; and, ultimately, preventing relapse. Because of the variation and severity of symptoms presented, a comprehensive approach to available services and their clinical dimensions must be considered by the multidisciplinary team. Treatment approach will also vary based on the age of the patient. Younger patients are often more successfully treated by utilizing family therapy that involves the parent in re-feeding and using of the family for balancing food intake, exercise, bed-rest, and privileges.

The cornerstone of the multidisciplinary approach to treatment is inpatient or outpatient psychiatric management. While physicians manage the medical comorbidities and nutritionists help reestablish normal eating patterns, mental health professionals target treatment of the underlying psychological causes and symptoms of eating disorders, including distorted cognitions, body image issues, self-image and ego strength problems, and comorbid conditions (ie, mood and anxiety disorders).

They employ various behavioral or psychological therapies. The chronic and complex characteristics of AN are also inherent problems in the use of psychosocial modalities for treatment. Although behavior modification and family therapy are often effective during the acute refeeding program, psychodynamic therapies and short-term therapies are not. However, psychotherapy is thought to be very helpful once malnutrition is corrected. Clinicians use the CBT approach to restructure or modify distorted beliefs and attitudes regarding strict food rituals and dichotomous thinking (viewing the world as “black” or “white,” “all” or “none”). Individual psychodynamic and group therapy are also used by many therapists to address underlying personality disturbances after the acute phase of weight restoration has occurred.

The treatment services available range from intensive inpatient settings, through partial hospital and residential programs, to varying levels of outpatient care. The pretreatment patient evaluation (weight, cardiac, and metabolic status) is essential in determining where treatment will occur. For example, patients who are significantly malnourished, weighing less than 75% of their individually estimated ideal body weight, are likely to require a 24-hour hospital program. For these patients, hospitalization should occur before the onset of medical instability (ie, marked orthostatic hypotension, bradycardia of >40 beats/min, tachycardia >110 beats/min, hypothermia, seizures, cardiac dysrhythmia, or failure), which could otherwise result in greater risks when refeeding and a more problematic prognosis overall. In such patients, hospitalization is based on psychiatric and behavioral grounds such as acute food refusal, uncontrollable binge eating and purging, failure of outpatient management, and comorbid psychiatric diagnosis (Table 11–8).

For milder cases of AN, successful alternatives to intensive inpatient programs have been partial hospitalization and day treatment programs. These programs typically involve a high level of parental participation and are indicative of the patient’s motivation to participate in treatment. Initially, these programs require the patient’s presence and participation for 14 hours a day. However, as patients approach their target weight, they can be seen in outpatient sessions three
CHAPTER 11

Criteria for hospitalization.

Most patients with uncomplicated anorexia nervosa experience a slow but steady weight gain over a prolonged period of time. In some patients who have restricted their eating for a prolonged period, the weight gain is not sufficient to restore normal body weight. In these patients, the incremental weight increase prevents the gastric dilation, edema, and congestive heart failure experienced by patients with severe malnutrition. Thus, in patients with anorexia nervosa, it may still be necessary to limit caloric intake and induce weight gain in order to prevent physical sequelae.

It should be noted that mealtimes are planned. Although this results in a gradual increase in caloric intake, it may still be necessary to limit caloric intake and induce weight gain in order to prevent physical sequelae. Therefore, nutritional counseling serves as an adjuvant to other treatment modalities and has been noted to enhance the effectiveness of the overall treatment program.

Exceptions to the general rule of outpatient management include patients with severe medical complications or those who are uncooperative or noncompliant. For these patients, hospitalization may be considered. Indications for hospitalization include severe medical complications, family dysfunction, and comorbid conditions (ie, depression). If hospitalization is warranted, the treatment focus is on metabolic restoration, nutritional rehabilitation, and mood stabilization.

Patients selected for outpatient treatment are highly motivated; have brief symptom duration; cooperative, supportive families; no serious medical complications; and BMI greater than 17.5. Their management should also be orchestrated by a multidisciplinary team that includes a primary care physician (family practitioner, pediatrician), nutritionist, psychotherapist, family therapist, and support staff, because success is highly dependent on careful monitoring of weight obtained in a hospital gown and after voiding, orthostatic vital signs, temperature, urine specific gravity, and the patients' eating disorder symptoms and behaviors. As an initial step, a clearly written behavioral contract with the patient and family (if appropriate) can be established. The contract serves as an agreement to maintain an acceptable minimum weight and vital signs or be hospitalized. Criteria for treatment failure and hospitalization are also included. However, it should be noted that although behavioral contracts are encouraged, they may not be as effective in the outpatient setting because they are more difficult to monitor. Nonetheless, they are helpful in achieving the goal of outpatient management, which is to get the patient to self-monitor and assume responsibility for appropriate eating.

For the patient with anorexia nervosa, daily structure is key and should include three meals and several snacks each day. Parents should ensure that healthy foods are readily available and that mealtimes are planned. Although this results in a gradual increase in caloric intake, it may still be necessary to limit physical activity to facilitate weight gain of up to a pound per week. This incremental weight increase prevents the gastric dilation, edema, and congestive heart failure experienced by patients who have restricted their eating for a prolonged period of time.

Psychotropic medications are not useful in treatment of anorexia nervosa when patients are in a malnourished state. However, they are frequently used after sufficient weight restoration has occurred for maintenance and the treatment of other associated psychiatric symptoms. Psychotropic medications other than selective serotonin reuptake inhibitors (SSRIs) are most often used. They include neuroleptics for obsessive-compulsive symptoms and anxiety disorders, and acute anxiety agents to reduce anticipatory anxiety associated with eating.

### Table 11-8. Criteria for hospitalization.

<table>
<thead>
<tr>
<th>Any one or more of the following would justify hospitalization:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe malnutrition (weight, 75% ideal body weight)</td>
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<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Electrolyte disturbance</td>
</tr>
<tr>
<td>Cardiac dysrhythmia</td>
</tr>
<tr>
<td>Physiologic instability (eg, severe bradycardia, hypotension, hypothermia, orthostatic changes)</td>
</tr>
<tr>
<td>Arrested growth and development</td>
</tr>
<tr>
<td>Failure of outpatient treatment</td>
</tr>
<tr>
<td>Acute food refusal</td>
</tr>
<tr>
<td>Uncontrollable binge eating and purging</td>
</tr>
<tr>
<td>Acute medical complications of malnutrition, such as syncope, seizures, cardiac failure</td>
</tr>
<tr>
<td>Acute psychiatric emergencies, such as suicidal ideation or acute psychosis, and any comorbid diagnosis that interferes with treatment, such as severe depression, obsessive-compulsive disorder, or severe family dysfunction</td>
</tr>
</tbody>
</table>


2. **Bulimia nervosa**—Most patients with uncomplicated bulimia nervosa do not require hospitalization. Indications for the few patients (<5%) who require inpatient care include severe disabling symptoms that have not responded to outpatient management, binge-purge behavior causing severe physiologic or cardiac disturbances (ie, dysrhythmias, dehydration, metabolic abnormalities), and psychiatric disturbances (ie, suicidal ideation or attempts, substance abuse, major depression). If hospitalization is warranted, the treatment focus is on metabolic restoration, nutritional rehabilitation, and mood stabilization. These patients may also require assistance with laxative, diuretic, and illicit drug withdrawal.

Hospitalization is usually brief and management then transfers to partial hospitalization programs or outpatient treatment facilities. Partial hospitalization programs usually require the patient to be present 10 hours per day, 5 days a week. Support is usually provided in a group format and family participation is often required. Many of the treatment modalities for bulimia nervosa are similar to those for anorexia nervosa. However, the primary focus differs significantly. Although some bulimia nervosa patients may be slightly underweight, most are of normal weight; hence nutritional rehabilitation targets the patient's pattern of binging and purging in weight restoration. Therefore, nutritional counseling serves as an adjuvant to other treatment modalities and has been noted to enhance the effectiveness of the overall treatment program.

Interventions targeting the psychosocial aspects surrounding bulimia nervosa address the issues of binging and purging, food restriction, attitudes related to eating patterns, body image and developmental concerns, self-esteem and sexual difficulties, family dysfunction, and comorbid conditions (ie, depression). The most efficacious psychosocial approach is cognitive behavioral therapy (CBT), a relatively short-term approach specifically focused on the eating disorder symptoms and underlying cognitions (ie, low self-esteem, body image concerns) of patients. Patients managed with CBT demonstrate profound decrements in three very characteristic behaviors: binge eating, vomiting, and laxative abuse. However, the percentage of patients who can achieve total abstinence from binge-purge behavior is invariably small. Intensive psychodynamic therapy (IPT), also a short-term treatment, is considered a second line of treatment.

Other types of individual psychotherapy that are used in clinical practice include psychodynamic, approaches that may be helpful in treating some of the underlying causes of bulimia nervosa. Group psychotherapy is moderately successful. The efficacy of this approach is increased when it is combined with
nutritional counseling and frequent clinic visits. Family or marital therapy should also be considered in conjunction with other treatment modalities for adolescents living at home, older patients from dysfunctional homes, and patients experiencing marital discord.

Another important aspect of eating disorder management is pharmacotherapy with antidepressants (ie, SSRIs). These agents were first used in the acute phase of treatment for BN because of its well-established comorbid association with clinical depression. It was later reported that nondepressed patients also responded to these medications. Multiple clinical studies have shown the SSRIs to have an antibulimic (reduction in binge eating and vomiting rates) effect independent of their antidepressant effect. Therapists have also noted improvement in mood and anxiety symptoms. Other antidepressant medications used in the treatment of BN include the tricyclic antidepressants (imipramine/desipramine), the monoamine oxidase inhibitors (MAOIs; phenelzine and isocarboxazid). The MAOIs should be used with great caution and only in patients with severe BN. At this time, fluoxetine is the only SSRI approved by the Food and Drug Administration for the treatment of BN. A 20-mg/d dose is used to initiate treatment, with doses of 40-60 mg/d required for maintenance.

3. Binge eating disorder—Although most individuals with BED are obese, normal-weight people are also affected. Therefore, treatment usually focuses on the distress experienced by individuals rather than on their weight problem. CBT, IPT, and group approaches are effective. CBT, which teaches techniques to monitor eating habits and alternative responses to difficult situations, appears to be the most efficacious. For patients with greater eating-related and psychosocial distress, IPT appears to be a particularly potent treatment. The great majority of those affected can be treated as outpatients and hospitalization is rarely needed.

Similar to BN, pharmacotherapy has demonstrated effectiveness for the treatment of BED. SSRIs appear to foster reductions in binge eating, psychiatric symptoms, and the severity of the illness. Medications aiming to reduce weight among overweight and obese BED patients, including sibutramine and topiramate, have also shown promising results for weight reduction. There is mixed support for whether combining psychotherapy (CBT) with pharmacologic interventions enhances remission rates. However, specific medications (orlistat, topiramate) have been shown to enhance weight loss achieved with CBT and behavioral weight loss.

**Prognosis**

The prognosis for full recovery of patients with AN is modest. Many individuals demonstrate symptomatic improvement over time, but a substantial number have persistent problems with body image, disordered eating, and psychological challenges. A review of multiple carefully conducted follow-up studies of hospitalized populations (at least 4 years after onset of illness) showed that the outcomes for 44% could be rated as good (weight restored to within 15% of recommended weight for height; regular menses established), 24% were poor (weight never reached 15% of recommended weight for height; menses absent or sporadic), about 28% fell between the good and poor groups, and about 5% had died (early mortality). About two-thirds of patients continued to have morbid food and weight preoccupation and psychiatric symptoms, and about 40% continued to have bulimic symptoms. Longer duration of illness, lower initial weight, previous treatment failure, vomiting, family dysfunction, and being married have all been associated with a worse prognosis. Adolescents have better outcomes than adults, and younger adolescents have better outcomes than older adolescents.

The outcomes for patients with BN are more promising. Generally speaking, the short-term success rate for patients treated with psychosocial modalities and medication is reported to be 50%-70%, with relapse rates between 30% and 50% after 6 months to 6 years of follow-up. Data also suggest that slow, steady progress continues when the follow-up period is extended to 10-15 years. BN is associated with lower mortality and higher rates of recovery compared to AN.

Characteristically, patients with BN who have onset at an early age, milder symptoms at start of treatment, a good support system, and those more likely to be treated as outpatients, often have a better prognosis. Typically, individuals with BN have one or more relapses during recovery whereas those with AN generally have a more protracted and arduous course, requiring long-term, intensive therapy. Outcomes for BED are less certain. Without treatment, BED is often characterized by a chronic, fluctuating course, but many patients are able to decrease the frequency of binge eating with proper treatment.
Adolescent Sexuality

Peter J. Katsufrakis, MD, MBA
Margaret R. H. Nusbaum, DO, MPH

Although nearly 90% of parents want their children to have sex education, and over 90 national organizations believe that all children should have it, only 5% of children in the United States receive sex education. Adolescence is a time of tremendous physical and emotional turmoil. Family and cultural values, as well as personal experiences, including fears, lead to different sex education needs, such as understanding their bodies and body functions, exploring personal values, and setting sexual limits with partners. Unfortunately, not only parents but many clinicians are ill prepared to discuss health issues related to sex with adolescents. Additionally, teens may be uncomfortable discussing sexual issues with their peers and adults. This leaves adults with the responsibility for facilitating the discussion.

Lack of comprehensive sex education programs as well as differences in cognitive and physical maturity put adolescents at increased risk for unwanted or unhealthy consequences of sexual activity. This includes increased susceptibility for contracting sexually transmitted diseases and increased risk for morbidity associated with sexual activity.

SCOPE OF THE PROBLEM

Unintended Pregnancy

Nearly 50% of all pregnancies in the United States are not planned, with the highest rates of unintended pregnancies occurring among adolescents, lower income women, and black women. About 10% of 15- to 19-year-olds become pregnant every year and more than 40% become pregnant before age 20. Despite similar rates of adolescent sexual activity, the United States has the highest rate of adolescent pregnancy among developed nations.

Unintended pregnancy is socially and economically costly. Medical costs include lost opportunity for preconception care and counseling, increased likelihood of late or no prenatal care, increased risk for a low-birth-weight infant, and increased risk for infant mortality. The social costs include reduced educational attainment and employment
opportunity, increased welfare dependency, and increased risk of child abuse and neglect. In addition to being confronted with adult problems prematurely, adolescent parents’ ability to lead productive and healthy lives and to achieve academic and economic success is compromised.

Although abortion rates are higher for women in their twenties, accounting for 80% of total induced abortions, a greater proportion of adolescent pregnancies end in abortion (29%) than do pregnancies for women over 20 years of age (21%). Adolescents who terminate pregnancies are less likely to become pregnant over the next 2 years, more likely to graduate from high school, and more likely to show lower anxiety, higher self-esteem, and more internal control than adolescents who do not terminate pregnancies. For an adolescent, postponement of childbearing appears to improve social, psychological, academic, and economic outcomes of life (see Chapter 16).

Sexually Transmitted Diseases

Adolescents (10-19 years old) and young adults (20-24 years old) have the highest rate of sexually transmitted diseases, and rates of chlamydial and gonorrhea infection are highest among women aged 15-19 years. Additionally, one in five cases of AIDS in the United States is diagnosed in men and women aged 20–29 years, with the likelihood that HIV infection was acquired up to 10 years earlier. Education is key to preventing sexually transmitted diseases, and vaccination for hepatitis B and human papillomavirus—if not already done prior to adolescence—can reduce disease risk in this population (see Chapter 14).

Sexual Abuse

More than 100,000 children are victims of sexual abuse each year. Sexual abuse contributes to sexual and mental health dysfunction as well as public health problems such as substance abuse. Victims of sexual abuse may have greater difficulty with identity formation as well as problems establishing and maintaining healthy relationships with others. Additionally, they may engage in premature sexual behavior, frequently seeking immediate release of sexual tension, and have poor sexual decision-making skills, attempting to create intimacy through sex.

Although only a relatively small proportion of rapes are reported, a major national study found that 22% of women and approximately 2% of men had been victims of a forced sexual act. Unfortunately, adolescent boys are more likely to believe that sexual coercion is justifiable.

Delinquency and homelessness are associated with a history of physical, emotional, and sexual abuse, as well as negative parental reactions to sexual orientation. Homelessness is associated with exchanging sex for money, food, or drugs. Additionally, homeless adolescents are at high risk for repeated episodes of sexual assault.

Physical Changes

Adolescents often feel uncomfortable, clumsy, and self-conscious because of the rapid changes in their bodies. Disproportionate physical development among girls and boys contributes additionally to the awkwardness of adolescence. Adolescents must adapt to a new physical identity, which includes hormonal changes, menstruation (often irregular or unpredictable for the first 18-24 months), unpredictable spontaneous erections, nocturnal ejaculations (“wet dreams”), growth of pubic and axillary hair, and even the odors from maturing apocrine glands, necessitating deodorant use.

As adolescents are learning to adjust and grow comfortable with their changing bodies, questions concerning body image are common (eg, penis size, breast size and development, distribution of pubic hair, and changing physique in general). In addition to adapting to a new body, adolescents must develop social skills and learn to interact with peers and adults.

Psychosocial Changes

Adolescent psychosocial development necessitates that the adolescent develop a realistic and positive self-image and
identity. Adolescent identity includes the development of physical, cognitive, and social skills; emotional and spiritual maturity; and sexual identity, including sexual orientation. Adolescents must develop the ability not only to view themselves realistically but also to relate to others. This necessitates successfully achieving independence from the family. Successful acquisition of a stable sense of self allows the adolescent to move on to face the task of the young adult: achieving intimacy by developing openness, mutual trust, sharing, self-abandon, and commitment to another. Core developmental tasks of adolescence include the following:

1. Becoming emotionally and behaviorally independent rather than dependent; in particular, developing independence from the family.
2. Acquiring educational and other experiences needed for adult work roles and developing a realistic vocational goal.
3. Learning to deal with emerging sexuality and to achieve a mature level of sexuality.
4. Resolving issues of identity (essentially being reborn) and achieving a realistic and positive self-image.
5. Developing interpersonal skills, including the capacity for intimacy, and preparing for intimate partnering with others.

This development includes both internal (introspective) and external forces. Peers, parents or guardians, teachers, and coaches have an important influence on adolescent expectations, evaluations, values, feedback, and social comparison. Failure to accomplish the developmental tasks necessary for adulthood results in identity or role diffusion: an uncertain self-concept, indecisiveness, and clinging to the more secure dependencies of childhood. With physical, cognitive, and social changes, it is natural for adolescents to explore sexual relationships and sexual roles in their social interactions, which contributes to self-identity. The adolescent's task is to successfully manage the conflict between sexual drives and the recognition of the emotional, interpersonal, and biological results of sexual behavior.

### Sexual Changes

Gender identity forms a foundation for sexual identity. Gender identity, the sense of maleness or femaleness, is established by age 2 years, solidifying as adolescents experience and integrate sexuality into their identity.

Sexual identity is the erotic expression of self as male or female and the awareness of self as a sexual being who can be in a sexual relationship with others. The task of adolescence is to integrate sexual orientation into sexual identity. Heterosexual orientation is taken for granted by society. For lesbian and gay individuals, this creates a clash between outside cultural expectations and their inner sense of self. Currently in US society, the primary developmental task of the gay adolescent is to adapt to a socially stigmatized sexual role. Same-sex orientation emerges during adolescence but is far more subtle and complex; it includes behavior, sexual attraction, erotic fantasy, emotional preference, social preference, and self-identification—felt to be a continuum from completely heterosexual to completely homosexual (see Chapter 62).

Sexual orientation is typically determined by adolescence, or earlier, and there is no valid scientific evidence that sexual orientation can be changed. Nonetheless, society often stigmatizes homosexual behavior, identity, and relationships. These antihomosexual attitudes are associated with significant psychological distress for gay, lesbian, and bisexual (GLB) persons and have a negative impact on mental health, including a greater incidence of depression and suicide (as many as one-third have attempted suicide at least once), lower self-acceptance, and a greater likelihood of hiding sexual orientation. When GLB adolescents disclose their orientation to their families, they often experience overt rejection at home as well as social isolation. GLB adolescents often lack role models and access to support systems. They frequently run away and become homeless, which places them at higher risk for unsafe sex, drug and alcohol use, and exchanging sex for money or drugs. Although the research is limited, transgendered persons are reported to experience similar problems. Negative attitudes within society toward gay, lesbian, bisexual, and transgendered (GLBT) individuals lead to anti-gay violence. Media coverage of the Matthew Shepard case brought such violence to greater public awareness. Data from over two dozen studies indicate that 80% of gay men and lesbian women have experienced verbal or physical harassment on the basis of their orientation, 45% have been threatened with violence, and 17% have experienced a physical attack.

Adolescents with questions or concerns about sexual orientation need the opportunity to talk about their feelings, their experiences, and their fears of exposure to family and friends. GLBT adolescents need reassurance about their value as a person, support regarding parental and societal reactions, and access to role models. Parents, Families, and Friends of Lesbians and Gays (PFLAG) is a nationwide organization whose purpose is to assist parents with information and support (see Chapter 62).

Problems with sexual identity may manifest in extremes—sexually acting out or repression of sexuality. Frequent sexual activity and a variety of sexual partners, negative risk factors for physical or psychological health, suggest poor integration of sexual identity in adolescents. Sexual behavior might be used to gain a sense of security in terms of gender and sexual identity or to gain acceptance or status in a peer group.

### Cognitive Changes

Cognitively, the shift from concrete thinking to abstract thinking (the cognitive development of formal operations) begins in early adolescence (11-12 years) and usually reaches full development by 15-16 years—so 10- to 14-year-olds should not be expected to function with full capacity for abstract thinking. In contrast to younger children, adolescents:
• Show an increased ability to generate and hold in mind more than one complex mental representation.
• Show an appreciation of the relativity and uncertainty of knowledge.
• Tend to think in terms of abstract rather than only concrete representations; they think of consequences and the future (abstract) versus a sense of being omnipotent, invincible, infallible, and immune to mishaps (concrete).
• Show a far greater use of strategies for obtaining knowledge, such as active planning and evaluation of alternatives.
• Are self-aware in their thinking, being able to reflect on their own thought processes and evaluate the credibility of the knowledge source.
• Understand that fantasies are not acted out.
• Have the capacity to develop intimate, meaningful relationships.

Adolescents have the task of figuring out what should and should not be done sexually. In concrete thinking risks of sexual behavior are not completely understood or thought out. Abstract thinking allows the capacity for responsible sexual decision making. The concept of relationship is abstract. Sexual intimacy includes not only eroticism but also a sense of commitment: emotional closeness, mutual caring, vulnerability, and trust. The level of intimacy and cognitive development influences sexual decision making. It is estimated that one-third of the adult population may never have fully achieved operational thinking.

Adolescents often learn about sexuality from a wide range of sources outside of school (family, friends, television, movies, advertising, magazines, the Internet, partners, church, and youth organizations). In addition to physical changes, early- to middle-stage adolescents begin to experience sexual urges that may be satisfied by masturbation. Masturbation is the exploration of the sexual self and provides a sense of control over one’s body and sexual needs. Masturbation starts in infancy, providing children with enjoyment of their bodies. Parents are typically uncomfortable observing this behavior. In contrast to this activity in younger children, masturbation in adolescents is accompanied by fantasies. In early adolescence, masturbation is an important developmental task, allowing the adolescent to learn what forms of self-stimulation are pleasurable and integrating this with fantasies of interacting with another. Sexual curiosity intensifies. Typical reasons for sexual activity in early to mid-adolescence are curiosity, peer pressure, seeking approval, physical urges, and rebellion. Sexual activity can be misinterpreted by the adolescent as evidence of independence from the family or individualization. With older adolescents, the autoeroticism of masturbation develops into experimentation with others, including intercourse.

Adolescent girls may misinterpret sexual activity as a measure of a meaningful relationship. When sexual activity is used to meet needs such as self-esteem, popularity, and dependency, it delays or prevents developing a capacity for intimacy and is associated with casual and less responsible sexual activity. The adolescent must emerge from the transitional stage of sexual development into relational sexual intimacy by participating in sexual activities in a mature and responsible manner. Sexual activity then becomes an expression of the depth and meaningfulness of the relationship. Mature and responsible sexual activity is not used to satisfy social or personal needs, is neither coercive nor exploitive, and occurs in an atmosphere of trust and respect in which each individual feels free to engage or refuse to engage. Sexual intimacy typically includes identity as a “couple.”

Appropriate education, parental support, and a positive sexual self-concept are associated with a later age of first intercourse, a higher consistent use of contraceptives, and a lower pregnancy rate. Sexual self-concept seems to improve with age.

Parental supervision and limit setting, living with both parents in a stable environment, high self-esteem, higher family income, and orientation toward achievement are associated with delayed initiation of sexual activity.

Commitment to a religion or affiliation with certain religious denominations appears to have an effect on sexual behavior. For example, an adolescent’s frequent attendance at religious services is associated with a greater likelihood of abstinence. On the other hand, for adolescents who are sexually active, frequency of attendance is associated with decreased contraceptive use by girls and increased use by boys.

Evidence suggests that school attendance reduces adolescent sexual risk-taking behavior. Worldwide, as the percentage of girls completing elementary school has increased, adolescent birth rates have decreased. In the United States, adolescents who have dropped out of school are more likely to initiate sexual activity earlier, fail to use contraception, become pregnant, and give birth. Among those who remain in school, greater involvement with school, including athletics for girls, is related to less sexual risk taking, including later age of initiation of sex and lower frequency of sex, pregnancy, and childbirth.

Schools structure students’ time, creating an environment that discourages unhealthy risk taking, particularly by increasing interactions between children and adults. They also affect selection of friends and larger peer groups. Schools can increase belief in the future and help adolescents
plan for higher education and careers, and they can increase students’ sense of competence, as well as their communication and refusal skills. Parents vary widely in their own knowledge about sexuality, as well as their emotional capacity to explain essential health issues related to sex to their children. Schools often have access to training and communications technology and also provide an opportunity for the kind of positive peer learning that can influence social norms.

Evaluation of school-based sex education programs that typically emphasize abstinence, but also discuss condoms and other methods of contraception, indicates that the programs either have no effect on, or, in some cases, result in a delay in the initiation of sexual activity. There is strong evidence that providing information about contraception does not increase adolescent sexual activity by hastening the onset of sexual intercourse, increasing the frequency of sexual intercourse, or increasing the number of sexual partners. More importantly, providing this information results in increased use of condoms or contraceptives among adolescents who were already sexually active.

Early age of first intercourse and lack of contraceptive use are associated with early pubertal development, a history of sexual abuse, lower socioeconomic status, poverty, lack of attentive and nurturing parents, single-parent homes, cultural and familial patterns of early sexual experience, lack of school or career goals, and dropping out of school. Additional factors include low self-esteem, concern for physical appearance, peer group pressure, and pressure to please partners.

Compared with those not sexually active, sexually active male adolescents used more alcohol, engaged in more fights, and were more likely to know about HIV and AIDS. Similarly, sexually active female adolescents used more alcohol and cigarettes. Both sexually active male and female adolescents had higher levels of stress. Alcohol and drug use is associated with greater risk taking, including unprotected sexual activity.


**SOURCES OF INFORMATION**

**The Family**

Although not the most important source of information about sexuality, parents exert more influence on sexual attitudes. Furthermore, parent-adolescent communication mediates the strength of peer influence on sexual activity. Adolescents need stable environments, parenting that promotes healthy social and emotional development, and protection from abuse. They also need education, the development of skills, experiences that promote self-esteem, and access to sex health information and services, along with positive expectations and sound preparation for their future roles as partners in committed relationships and as parents.

Several family factors are known to be associated with increased adolescent sexual behavior and the risk of pregnancy. These include living with a single parent; having older siblings who have had sexual intercourse, have become pregnant, or have given birth; and, for girls, the experience of sexual abuse in the family. Family factors associated with decreased sexual activity and increased use of contraception include parents with higher education and income; close, warm parent-child relationships; and parental supervision and monitoring of children. However, parental control can be associated with negative effects if it is excessive or coercive.

The developmental tasks of adolescence include the transition from dependence on family to establishing an independent identity. The stresses of families tend to peak during adolescence, which is attributed to the desire among adolescents for an independent identity, the parents’ own unresolved parent-child conflicts, and possible changing gender role identities. Additionally, adolescent sexuality can be very threatening to adults, who may not have resolved their own issues concerning sexuality. With escalating stresses, the self-esteem of parents may decline, making them either highly impulsive or overly controlling or rigid. Heightening levels of anxiety contribute to blocked communication.

Both parental lack of rules and discipline as well as very strict discipline have been strongly associated with adolescent sexual activity, whereas parents who supervised their children’s dating and insisted on reasonable curfews were least likely to have adolescents who exhibited irresponsible sexual behaviors.

Because many parents are uncomfortable discussing sexuality with their children, family physicians must be proactive in initiating and facilitating conversations about the topic.

**The Family Physician**

Adolescents, in a developmental phase between childhood and adulthood, are often uncomfortable with body changes. Encouraging open communication at home is crucial. Making a handout (Table 12-1) available to parents might help facilitate discussions about sexuality. The quality of discussions at home about sexual matters is the most important factor of family life affecting the risk of teenage pregnancy. If information is not available at home, the family physician, uniquely positioned to serve as a resource, should take a proactive approach by creating the proper environment for discussion, initiating the topic of sexuality, and providing anticipatory guidance for both adolescents and their families (Table 12-2).

**A. Creating the Environment**

The physician should provide a confidential place that fosters open and nonjudgmental communication, which augments
Table 12-1. How to talk to your child about sex.

1. **Be available.** Watch for clues that show they want to talk. Remember that your comfort with the subject is important. They need to get a feeling of trust from you. If your child doesn’t ask, look for ways to bring up the subject. For example, you may know a pregnant woman, watch the birth of a pet, or see a baby getting a bath. Use a TV program or film to start a discussion. Libraries and schools have good books about sex for all ages.

2. **Answer their questions** honestly and without showing embarrassment, even if the time and place do not seem appropriate. A short answer may be best for the moment. Then return to the subject later. It’s OK to say, “I don’t know.” Not being able to answer a question can be an opportunity to learn with your child. Tell your child that you’ll get the information and continue the discussion later, or do the research together. Be sure to do this soon. Answer the question that is asked. Respect your child’s desire for information. But don’t overload the child with too much information at once. Try to give enough information to answer the question clearly, yet encourage further discussion.

3. **Use correct names** for body parts and their functions to show that they are normal and OK to talk about.

4. **Practice talking about sex** with your partner, another family member, or a friend. This will help you feel more comfortable when you do talk with your child.

5. **Talk about sex more than once.** Children need to hear things again and again over the years to really understand, because their level of understanding changes as they grow older. Make certain that you talk about feelings and not just actions. It is important not to think of sex only in terms of intercourse, pregnancy, and birth. Talk about feeling oneself as man or woman, relating to others’ feelings, thoughts, and attitudes, and feelings of self-esteem.

6. **Respect their privacy.** Privacy is important, for both you and your child. If your child doesn’t want to talk, say, “OK, let’s talk about it later,” and do. Don’t forget about it. Never search a child’s room, drawers, or purse for “evidence.” Never listen in on a telephone or private conversation.

7. **Listen to your children.** They want to know that their questions and concerns are important. The world they’re growing up in is different from what yours was. Laughing at or ignoring a child’s question may stop them from asking again. They will get information, accurate or inaccurate, from other sources. When the problem belongs to your child, listen, watch their body language to know when they are ready for you to talk, repeat back to them what you think you heard, listen, respond, and guide them through solving their problem. Talk to your children, trust them, have confidence in them, and respect their feelings.

8. **Share your values.** If your jokes, behaviors, or attitudes don’t show respect for sexuality, then you cannot expect your child to be sexually healthy. They learn attitudes about love, caring, and responsibility from you, whether you talk about it or not. Tell your child what your values are about sex and about life. Find out what they value in their lives. Talk about your concern for their health and their future.

9. **Make it easier for your children to talk with you.** Choose words wisely to keep communication open. Use “I” statements because “you” statements can sound accusatory or like a put-down. Instead of telling them what to do, share your values but don’t try to control your children. If you act in a controlling manner by telling them what to do, your reaction is likely to lead to their being resentful, insecure, or even rebellious. But you don’t want to give them freedom without responsibility for their actions as they are likely to become self-centered, demanding, or even anxious. Teach your child how to make decisions: (a) have your child identify the problem, (b) analyze the situation, (c) search for options or solutions, (d) think about possible consequences to these options, (e) choose the best option, (f) take action, and then (g) watch for the results.


Table 12-2. Office approach to adolescent health care.

1. **Establish comfortable, friendly relationships that permit discussion in an atmosphere of mutual trust well before sensitive issues arise.** Ensure confidentiality before the need arises. Establish separate discussions with parents and adolescents as a matter of routine.

2. **Take a firm, proactive role to initiate developmentally appropriate discussions of sexuality.** Recognize and use teachable moments regarding sexuality.

3. **Provide anticipatory guidance and resources to facilitate family discussions about sexuality and cue families and preteens about upcoming physical and psychosocial developmental changes.**

4. **Enhance communication skills.** Use reflective listening. With a nonjudgmental manner, accept what adolescents have to say without agreeing or disagreeing.

5. **Use a positive approach when discussing developmental changes and needed interventions, complimenting pubertal changes.**

6. **Increase knowledge of family systems and the impact physicians can have on the family.**

7. **Discuss topics about sexuality incrementally over time to improve assimilation and decrease embarrassment.** Avoid scientific terms. Keep answers to questions thorough yet simple. Be cautious about questions that might erode trust.

8. **Know your limitations.** Use other professional staff and referrals when necessary.

or fulfills the parental role. The individuation of the adolescent should be supported by having a separate discussion with parents or guardians and adolescent. Ensuring confidentiality for the preadolescent or adolescent helps create a trusting environment. An office letter to the parent can outline policies regarding confidentiality and clearly communicate the desire to work with parents in making the office accessible to adolescents as possible. Many states have particular laws regarding the ability of adolescents to seek health care for specific issues—such as contraception, mental health, substance abuse, and pregnancy—without parental presence or approval. Family physicians need to be familiar with the nuances of these laws in their practicing state.

B. Proactive Approach

Physicians should recognize opportunities to provide anticipatory guidance, such as to adults who are seeing them for their health needs and mention having a preteen or teen at home. They should cue the preteen positively about upcoming physical changes and cue the parent or family by recommending that issues concerning sex be discussed with the adolescent at home. In the office and at home, sexuality should be discussed incrementally over time. Parents are more influential in early adolescence whereas peer groups are more influential in later adolescence; the extent to which adolescents can balance these two factors influences their risk-taking behavior.

C. Asking the Question

Family physicians should initiate the topic of sexuality with adolescents during health maintenance or perhaps even acute care visits. Questions might include the following: Are you dating? Whom are you attracted to? Conversations about sexuality should be tailored to the adolescent’s stage of physical, social, and emotional development (Table 12-3). Because abstract thinking is still undergoing development, adolescents need explicit examples to understand ideas. History taking must be specific and directive. Instructions should be concrete. Answers to questions should be simple and thorough.

Concerns in early adolescence typically relate to body image and what is “normal,” both physically and socially. Information and reassurance about pubertal changes are critical parts of physical examinations. Conversations may include addressing concerns about obesity, acne, and body image that affect self-perception of acceptability and attractiveness. Discussions about how to handle peer pressure may always be helpful. The adolescent’s understanding of safer sexual practices as well as the ability to negotiate the behavior in which they are willing or not willing to participate should be explored. Giving the adolescent the opportunity to role-play the discussion regarding these issues may contribute to confidence in successfully negotiating with a current or future partner.

Although it is important not to make assumptions about sexual orientation, an adolescent who presents with depression and suicidal ideation should be questioned about this. Hiding one’s orientation increases stress. It is important to be aware of community resources for GLBT adolescents such as psychologists and counselors, GLBT community support groups, and organizations such as PFLAG.

Caring for adolescents can be exciting and challenging. Physicians should recognize that their own projections of unfinished sexual issues from their adolescence may surface in caring for adolescent patients. This can make discussions, particularly about sensitive subjects such as drugs, alcohol, nicotine, and sex, difficult. Recognizing and addressing these issues or referring adolescents to colleagues with greater experience and comfort with these matters would be appropriate.

The role of family physicians is to provide a supportive, sensitive, and instructive environment in which they neither ignore nor judge adolescent sexual activity but reassure, listen, clarify, and provide correct information about this important aspect of adolescent development. Consultation or referral is appropriate when it is in the best interest of the patient. Open and frank communication, ensuring confidentiality, nonjudgmental listening, and the provision of clear, accurate information help develop a successful physician-patient relationship. Ideally the goal should be to delay sexual activity until adolescents have the knowledge and tools needed to make healthy decisions about sex. However, identifying adolescents at risk, educating about safer sex, establishing sexual limits, and providing information about support and educational resources for adolescents who are currently sexually active are critical activities for the family physician.

### Web Sites

**For Patient Information**


**For Provider Information**


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Table 12-3. Adolescent sexual development.

<table>
<thead>
<tr>
<th></th>
<th>8-12 Years</th>
<th>13 Years and Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual knowledge</td>
<td>Knows correct terms for sexual parts, commonly uses slang.</td>
<td>Understands sexual intercourse, contraception, and sexually transmitted diseases (STDs).</td>
</tr>
<tr>
<td>Body parts and function</td>
<td>Should have complete understanding of sexual, reproductive, and elimination functions of body parts. All need anticipatory guidance on upcoming pubertal changes for both sexes, including menstruation and nocturnal emissions.</td>
<td>Important to discuss health and hygiene, as well as provide more information about contraceptives, STDs/HIV, and responsible sexual behaviors. Access to health care, especially gynecologic care, is important.</td>
</tr>
<tr>
<td>Gender identity</td>
<td>Gender identity is fixed. Encouragement to pursue individual interests and talents regardless of gender stereotypes is important.</td>
<td>Discuss men and women in social perception. Males tend to perceive social situations more sexually than females and may interpret neutral cues (eg, clothing, friendliness) as sexual invitations.</td>
</tr>
<tr>
<td>Sexual abuse prevention</td>
<td>Assess their understanding of an abuser and correct misconceptions. Explain how abusers, including friends, relatives, and strangers, may manipulate children. Help them to identify abusive situations, including sexual harassment. Practice assertiveness and problem-solving skills. Teach them to trust their body’s internal cues and to act assertively in problematic situations.</td>
<td>Teach them to avoid risky situations (eg, walking alone at night, unsafe parts of town). Discuss dating relationships and, in particular, date/acquaintance rape and its association with alcohol and drug use, including date rape drugs. Encourage parents to make themselves available for a ride home anytime their teenager finds himself or herself in a difficult or potentially dangerous situation. Consider a self-defense class for children.</td>
</tr>
<tr>
<td>Developmental issues: most sexual concerns are related to the developmental tasks.</td>
<td>Early adolescence (Tanner I and II): Physical changes, including menstruation and nocturnal emissions. Often ambivalent over issues of independence and protection and family relationships. Egocentric. Beginning struggles of separation and emerging individual identity. Seemingly trivial concerns to adults can reach crisis proportions in young adolescents. Common concerns include fears of too slow or too rapid physical development, especially breasts and genitalia; concern and curiosity about their bodies; sexual feelings; and sexual behavior of their peer group as well as adults around them. Although masturbation is very healthy and normal, reassurance may be needed given persistence of myths and mixed messages.</td>
<td>Middle adolescence (Tanner III and IV): Peer approval. Experimentation and risk-taking behavior arise out of the developmental task of defining oneself socially. Sexual intercourse may be viewed as requisite for peer acceptance. Curiosity, need for peer approval, self-esteem, and struggle for independence from parents can lead to intercourse at this stage. Feelings of invincibility lead to sexual activity that is impulsive and lacking discussion about sexual decision making, such as contraception, preferences for behavior, relationship commitment, or safe sex. Increasing insistence on control over decisions. Increasing conflict with parents.</td>
</tr>
</tbody>
</table>

(Continued)
## Table 12-3. Adolescent sexual development (Continued)

<table>
<thead>
<tr>
<th>8-12 Years</th>
<th>13 Years and Older</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Developmental tasks:</strong></td>
<td></td>
</tr>
<tr>
<td>1. Independence and separation from the family</td>
<td></td>
</tr>
<tr>
<td>2. Development of individual identity</td>
<td></td>
</tr>
<tr>
<td>3. Beginning to shift from concrete to abstract thinking</td>
<td></td>
</tr>
<tr>
<td><strong>Developmental tasks:</strong></td>
<td></td>
</tr>
<tr>
<td>1. Development of adult social relationships with both sexes</td>
<td></td>
</tr>
<tr>
<td>2. Continued struggle for independence</td>
<td></td>
</tr>
<tr>
<td>3. Continued development of individual identity</td>
<td></td>
</tr>
<tr>
<td>4. Continued shifting from concrete to abstract thinking</td>
<td></td>
</tr>
<tr>
<td><strong>Developmental tasks:</strong></td>
<td></td>
</tr>
<tr>
<td>1. Development of adult social relationships with both sexes</td>
<td></td>
</tr>
<tr>
<td>2. Continued struggle for independence</td>
<td></td>
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<tr>
<td>3. Continued development of individual identity</td>
<td></td>
</tr>
<tr>
<td>4. Continued shifting from concrete to abstract thinking</td>
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</tr>
</tbody>
</table>

Late adolescence (Tanner V): With cognitive maturation, issues regarding peer acceptance and conflicts with parents regarding independence lessen. Intimacy, commitment, and life planning, including thoughts of future parenthood. Self-identity continues to solidify, moral and ethical values, exploration of sexual identity. Crises over sexual orientation may surface at this stage. Increasing ability to recognize consequences of own behavior.

**Developmental tasks:**
1. Abstract (futuristic) thinking
2. Vocational plans
3. Development of moral and ethical values
4. Maturation toward autonomous decision making

*These are general categories; adolescents vary in their physical, psychosocial, and cognitive development.


Menstrual disorders are a heterogeneous group of conditions that are both physically and psychologically debilitating. Though they were once considered nuisance problems, it is now recognized that menstrual disorders take a significant toll on society, both in days lost from work, as well as the pain and suffering experienced by individual women. These disorders may arise from physiologic (ie, pregnancy), pathologic (ie, endocrine abnormalities), or iatrogenic (ie, secondary to contraceptive use) conditions.

Irregularities in menstruation may manifest as complete absence of menses, dysfunctional uterine bleeding, dysmenorrhea, or premenstrual syndrome. Since it is essential to know what is normal in order to define that which is abnormal, normal menstrual parameters are listed in Table 13-1.

### AMENORRHEA

**ESSENTIALS OF DIAGNOSIS**

- Primary amenorrhea: the absence of menses by 16 years of age in patient with secondary sex characteristics, or absence of menses by 13 years of age in a patient without secondary sex characteristics.
- Secondary amenorrhea: absence of menses for at least 6 months in a woman with previously normal mense, or at least 12 months or six cycles without a period in a woman with previously irregular menses.

**General Considerations**

Amenorrhea is a symptom, not a diagnosis, and may occur secondary to a number of endocrine and anatomic abnormalities. Classifying amenorrhea into primary and secondary amenorrhea can aid in evaluation and simplify diagnosis.

### 1. Primary Amenorrhea

The patient with primary amenorrhea is often brought to the physician by her mother who is concerned about the patient’s delay in reaching developmental milestones. The clinician must be sensitive to the fact that the adolescent patient may be uncomfortable discussing her sexuality, especially in the presence of a parent. The most common causes are gonadal dysgenesis, hypothalamic hypogonadism, and anatomic abnormality.

**Prevention**

Amenorrhea may be prevented by maintaining an appropriate body weight and treating the underlying conditions.

**Clinical Findings**

**A. Signs and Symptoms**

Key elements of the history are listed in Table 13-2. This targeted history will help to narrow the differential and eliminate unnecessary testing. Physical examination should focus on appearance of secondary sexual characteristics and pelvic examination findings—specifically the presence or absence of a uterus. The clinician should be careful to allay patient fears, as this will often be her first pelvic examination. BMI should also be calculated and compared with prior visits to assess both for rapid weight loss or weight gain. Presence or absence of breast development and presence or absence of the uterus and cervix are decision points for further testing and diagnostic categories.

**B. Laboratory Findings**

Choice of laboratory examination should be guided based on history and physical findings and are listed here based on etiology. A pregnancy test should be performed on all individuals presenting for primary amenorrhea that have secondary
sexual characteristics and functional anatomy. Though the initial cycles after menarche are often anovulatory, pregnancy can occur before the first recognized menstrual cycle.

Patients with a normal pelvic examination, but absent breast development should have serum FSH (follicle-stimulating hormone) measured to distinguish peripheral (gonadal) from central (pituitary or hypothalamic) causes of amenorrhea. A high FSH suggests gonadal dysgenesis. A karyotype should be performed to identify patients with a 46 XY karyotype, since these individuals have a high peripubertal risk for gonadoblastoma and dysgerminoma. If the uterus is absent, serum testosterone and karyotype should be performed. Elevated testosterone in the presence of a Y chromosome indicates presence of functional testicular tissue that should be excised to prevent later neoplastic transformation. In patients with both normal breast development and a normal pelvic examination, serum prolactin and TSH should be measured to rule out hyperprolactinemia and hypothyroidism. If these values are in the normal range, investigation should proceed according to the secondary amenorrhea algorithm. The etiologies for primary amenorrhea is listed in Table 13-3.

### C. Imaging Studies

Radiographic studies are targeted toward the diagnosis suggested by history, physical, and laboratory studies. Magnetic resonance imaging (MRI) is indicated in patients whom pituitary pathology is suspected. Computerized visual field testing may be added if examination or MRI indicates optic chiasm compression. Pelvic ultrasound should be performed in patients with suspected pelvic anomalies.

#### Table 13-1. Normal menstrual parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of menarche</td>
<td>&lt;16 y old</td>
</tr>
<tr>
<td>Age of menopause</td>
<td>&gt;40 y old; mean age 52</td>
</tr>
<tr>
<td>Length of menstrual cycle</td>
<td>22-45 d</td>
</tr>
<tr>
<td>Length of menstrual flow</td>
<td>3-7 days</td>
</tr>
<tr>
<td>Amount of menstrual flow</td>
<td>&lt;80 cc</td>
</tr>
</tbody>
</table>

#### Table 13-2. Key historical elements in the evaluation of primary amenorrhea.

- Recent medical history
- History of head trauma (damage to the hypothalamic-pituitary axis)
- History of weight loss and amount of regular physical activity (female athlete triad)
- Timeline of development of secondary sexual characteristics (if present)
- Past medical history
- Diabetes
- Juvenile rheumatoid arthritis
- Inflammatory bowel disease
- Malignancy
- Chronic infection
- Family history
- Time of menarche in the patient’s mother and sister(s)
- Family history of gonadal dysgenesis
- Medications
- Medication or supplement use (particularly hormonal)
- Social history
- Sexual activity
- History of psychosocial deprivation/abuse
- Symptoms
- Anosmia (Kallman syndrome)
- Monthly abdominal pain (imperforate hymen)

#### Table 13-3. Etiologies of primary amenorrhea.

<table>
<thead>
<tr>
<th>Category</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiologic</td>
<td>Constitutional delay</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Pathologic</td>
<td>Absent breast development, normal pelvic examination findings</td>
</tr>
<tr>
<td></td>
<td>Hypothalamic failure</td>
</tr>
<tr>
<td></td>
<td>Anorexia nervosa, excessive weight loss, excessive exercise, stress</td>
</tr>
<tr>
<td></td>
<td>Chronic illness (juvenile rheumatoid arthritis, diabetes, irritable bowel syndrome)</td>
</tr>
<tr>
<td></td>
<td>Gonadotropin deficiency</td>
</tr>
<tr>
<td></td>
<td>Kallman syndrome (associate with anosmia)</td>
</tr>
<tr>
<td></td>
<td>Pituitary dysfunction after head trauma or shock</td>
</tr>
<tr>
<td></td>
<td>Infiltrative or inflammatory processes</td>
</tr>
<tr>
<td></td>
<td>Pituitary adenoma</td>
</tr>
<tr>
<td></td>
<td>Cantiopharyngioma</td>
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<tr>
<td></td>
<td>Gonadal failure</td>
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<tr>
<td></td>
<td>Gonadal dysgenesis (ie, Turner syndrome)</td>
</tr>
<tr>
<td></td>
<td>Normal breast development, normal pelvic examination findings</td>
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<tr>
<td></td>
<td>Hypothyroidism</td>
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<tr>
<td></td>
<td>Hyperprolactinemia</td>
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<tr>
<td></td>
<td>Normal breast development, abnormal pelvic examination findings</td>
</tr>
<tr>
<td></td>
<td>Testicular feminization</td>
</tr>
<tr>
<td></td>
<td>Anatomic abnormalities (uterovaginal septum, imperforate hymen)</td>
</tr>
</tbody>
</table>

#### Treatment

#### A. Medical Therapy

Successful treatment of primary amenorrhea is based on correct diagnosis of the underlying etiology. The patient should be counseled as to the cause of their amenorrhea, implications for future fertility, and treatment options. Patients with functional hypothalamic amenorrhea due to physical or psychological stress can have this reversed by weight gain, resolution of emotional issues, or decrease in intensity of exercise. For patients with hypothyroidism, thyroid replacement should be started at a low dose and titrated up, being cautious to avoid over replacement. Patients with pituitary adenomas should be treated with the dopamine agonists bromocriptine or cabergoline, the former having the best established safety record and approved for use in pregnancy. Metformin can be
used in patients with polycystic ovarian syndrome (PCOS) who are insulin resistant. Cyclical estrogen-progesterone and combined estrogen-progesterone oral contraceptive pills, patches, or vaginal ring can be used in patients those with gonadal dysgenesis or hypoestrogenic state. Only providers experienced in this field should perform induction of puberty in patients with constitutional delay. Estrogen is responsible for epiphyseal closure as well as the adolescent growth spurt; mistimed administration could have significant effects on the final achieved height in these patients. For patients who desire fertility, ovulation induction with clomiphene citrate, exogenous gonadotropins, or pulsatile GnRH (gonadotropin-releasing hormone) may be required.

B. Surgical Intervention

Structural anomalies should be addressed surgically. In those patients with congenital absence of a uterus, investigation should be undertaken for associated renal anomalies. Gonadectomy should be performed after puberty in patient with Y chromosome material to prevent the development of subsequent gonadal neoplasia.

C. Behavioral Modification

Patients with hypothalamic failure due to rapid weight loss, excessive exercise, or stress should receive counseling to address the underlying cause of these problems.

2. Secondary Amenorrhea

The most common type of amenorrhea, secondary amenorrhea, is diagnosed when a woman with previously normal menses goes at least 6 months without a period, or when a woman with previously irregular menses goes at least 12 months or at least six cycles without a period.

Clinical Findings

A. Signs and Symptoms

Pertinent history in the evaluation of secondary amenorrhea includes (1) previous menstrual history (timing and quality of menses), (2) pregnancies (to include terminations and complicated deliveries), (3) symptoms of endocrine disease, (4) medication history, (5) weight loss or gain, (6) exercise level, (7) history of instrumentation or surgery to genital tract, and (8) masculinizing characteristics noticed by patient or family. Physical examination should assess pubertal development and secondary sexual characteristics while looking for evidence of hyperandrogenism. These latter findings may include oily skin, acne, and hirsutism.

B. Laboratory Findings

After the exclusion of pregnancy, initial labs should include fasting glucose, thyroid-stimulating hormone (TSH), and prolactin levels. In the absence of significant abnormalities in these values, a progestin challenge test should be performed to assess the patient’s estrogen status. FSH should be measured on women who do not experience withdrawal bleeding within 2 weeks. A high FSH value (>30 IU/L) is indicative of ovarian failure, whereas normal or low values indicate either an acquired uterine anomaly (Asherman syndrome) or hypothalamic-pituitary failure. Ovarian failure is confirmed with a low serum estradiol level, less than 30 pg/mL. A serum luteinizing hormone (LH) and FSH should be drawn on women who do not experience withdrawal bleeding after the progesterone challenge and have a normal estrogen level. An elevated LH value is highly suggestive of PCOS, especially in a woman with clinical features of virilization. If the LH level is normal, an LH to FSH ratio should be determined. This ratio is elevated, greater than 2.5, in women with PCOS even when FSH and LH values are within normal limits. This diagnosis can be confirmed by measurement of serum testosterone and dehydroepiandrosterone sulfate (DHEA-S), which should be normal or just mildly elevated in PCOS. An increased testosterone to DHEA-S ratio is suggestive of an adrenal source. This finding warrants further study with determination of 17-hydroxyprogesterone. This level is elevated in late onset congenital adrenal hyperplasia and Cushing syndrome. Cushing syndrome may be excluded with a 24-hour urinary free cortisol and dexamethasone suppression testing.

C. Imaging Studies

Hysterosalpingogram is indicated with history of uterine instrumentation and/or suggestion of anatomic anomaly as source of amenorrhea. Computed tomographic (CT) scanning of the adrenal glands and ultrasound of the ovaries should be performed in women with clinical features of virilization and increased testosterone (>200 ng/dL) or DHEAS-S (>7 μg/mL). A CT or MRI of the pituitary should be performed if pituitary pathology is suspected.

Differential Diagnosis

The differential diagnosis of secondary amenorrhea can be broken down into those etiologies with and those without evidence of hyperandrogenism.

A. With Evidence of Hyperandrogenism

1. Polycystic ovarian syndrome (PCOS)—Responsible for 20% of secondary amenorrhea, PCOS is the most common reproductive female endocrine disorder, occurring in 5%-7% of women. PCOS is associated with an increased risk of type 2 diabetes, abdominal obesity, hypertension, hypertriglyceridemia, and cardiovascular events.

2. Autonomus hyperandrogenism—Tumors of adrenal or ovarian origin may secrete androgens. Virilization is more pronounced than in PCOS and may manifest as frontal balding, increased muscle bulk, deep voice, clitorimegaly, and severe hirsutism.
3. Late-onset or mild congenital adrenal hyperplasia—
   This rare condition may be diagnosed with the finding of an increased 17-hydroxyprogesterone level in the setting of secondary amenorrhea and hyperandrogenism.

B. Without Evidence of Hyperandrogenism on Examination

1. Medication use—History should be reviewed for use of contraceptives, particularly progesterone-only preparations. These may take the form of oral contraceptives (OCPs), implants, injectables, or intrauterine devices. It is important to educate women on progestin-only pills that 20% of patients will become amenorrheic within the first year of use. Rates are even higher for those using injectable progesterone, with 55% of women at 1 year and 68% of women at 2 years reporting amenorrhea.

2. Functional hypothalamic amenorrhea—Amenorrhea in this setting, seen in patients who have experienced rapid weight loss, severely restricted calorie intake, or rigorous exercise, may be part of the female athlete triad of amenorrhea, disordered eating and osteoporosis addressed in Chapter 11.

3. Hypergonadotropic hypogonadism—Premature ovarian failure (cessation of ovarian function before 40 years of age) may be autoimmune or idiopathic, or may occur secondarily due to radiotherapy or chemotherapy (cyclophosphamide is associated with destruction of oocytes).

4. Hyperprolactinemia—Pituitary adenomas may present with amenorrhea and galactorrhea, and are responsible for 20% of cases of secondary amenorrhea. Prolactin secreted by these tumors acts directly on the hypothalamus to suppress GnRH secretion. Dopamine receptor–blocking agents, hypothalamic masses, and hypothyroidism are less common causes of hyperprolactinemia.

5. Thyroid disease—Profound hypothyroidism or hyperthyroidism affects the feedback control of LH, FSH, and estradiol on the hypothalamus, causing menstrual irregularities.

6. Hypogonadotropic hypogonadism—Head trauma, severe hypotension (shock), infiltrative or inflammatory processes, pituitary adenoma, or craniopharyngioma may damage the pituitary, resulting in decreased or absent gonadotropin (LH and FSH) release. These patients will often display symptoms relating to deficiency of other pituitary hormones as well.

A. Treat the Underlying Causes of Amenorrhea

Patients with identified hypothyroidism should be treated with thyroxine replacement. Patients with hyperprolactinemia secondary to prolactinoma may be treated with either surgical resection or dopamine agonist therapy. Bromocriptine is often used in women who desire to conceive, since there is no increased incidence of congenital malformations, and it has been used successfully for over 20 years. Patients found to have empty sella or Sheehan syndrome should be treated with replacement of pituitary hormones.

Women whose amenorrhea is secondary to absent ovarian function before 40 years of age have premature ovarian failure. Those who experience ovarian failure before 30 years of age should undergo karyotype testing to screen for Y-chromosome elements, which are associated with malignancies. These patients are at a high risk of osteoporosis and cardiovascular disease due to their hypoestrogenemic state. Estrogen replacement should be undertaken, with progesterone for those patients with an intact uterus, to prevent these sequelae.

Women with adrenal or ovarian androgen-secreting tumors should undergo appropriate surgical intervention. Likewise, women found to have Asherman syndrome as a cause for their amenorrhea should undergo lysis of adhesions followed by endometrial stimulation with estrogen. These patients are at increased risk of placenta accreta in subsequent pregnancies.

Patients with PCOS may achieve resumption of menses with weight loss. The assistance of a registered dietician should be sought to improve success rates in this daunting task. Metformin, a biguanide insulin sensitizer, has been used to treat PCOS, with reports of success in both inducing ovulation and improving laboratory markers for cardiovascular risk.

**DYSMENORRHEA**

**ESSENTIALS OF DIAGNOSIS**

- Affects 50% of all women, and between 20% and 90% of all adolescent women.
- Primary defined as painful menses in absence of pelvic disease; secondary defined as painful menses caused by pelvic disease.

**General Considerations**

Dysmenorrhea is the most common gynecologic complaint and is a leading cause of morbidity in women of reproductive age, resulting in absence from work and school, as well as nonparticipation in sports.

**Pathogenesis**

Primary dysmenorrhea is caused by the release of prostaglandin F2α from the endometrium at the time of menstruation.
Prostaglandins induce smooth muscle contraction in the uterus, as well as in the intestine, bronchi, and vasculature. As contractions cause the pressure within the uterus to exceed that of the systemic circulation, ischemia ensues, causing an anginal equivalent in the uterus. The cause of secondary dysmenorrhea varies with the underlying lying disease.

**Clinical Findings**

**A. Symptoms and Signs**

Symptoms of primary dysmenorrhea include pain beginning with the onset of menstruation and lasting for 12-72 hours, characterized as crampy and intermittent in nature, with radiation to the low back or upper thighs. Headache, nausea, vomiting, diarrhea, and fatigue may accompany the pain. Symptoms are most often worst on the first day of menses and then gradually resolving. The patient may report that her dysmenorrhea began gradually, with the first year of menses, and then became worse as her periods became regular. Conversely, women with secondary amenorrhea report symptoms beginning after age 20, lasting for 5-7 days and progressive worsening of pain with time. These patients may also report pelvic pain that is not associated with menstruation.

**B. Physical Findings**

A pelvic examination with cervical smear and cultures should be performed in all patients presenting with a chief complaint of dysmenorrhea. Findings of cul-de-sac induration and uterosacral ligament nodularity on pelvic examination are indicative of endometriosis. Adenexal masses could indicate endometriosis, neoplasm, hydrosalpinx, or scarring from chronic PID. Likewise uterine abnormalities or tenderness should raise the examiner’s index of suspicion for the underlying pathology as the cause for dysmenorrhea.

**C. Laboratory Findings**

Any woman with acute onset of pelvic pain should have a pregnancy test. Women with a history consistent with primary dysmenorrhea do not require initial labs. In those who fail to respond to therapy for primary dysmenorrhea or in whom a diagnosis of secondary dysmenorrhea is suspected, a complete blood count (CBC) and an erythrocyte sedimentation rate (ESR) may help in detection of the underlying infection or inflammation.

**D. Imaging Studies**

Patients with abnormal findings on pelvic examination who do not respond to therapy for primary dysmenorrhea or who have a history suggestive of pelvic pathology should undergo pelvic ultrasound.

**E. Special Examinations**

In patients whom endometriosis is suggested, diagnostic laparoscopy may be indicated. Due to high rates of treatment and diagnostic failure with laparoscopy, some authors recommend empirically treating patients with a presumptive diagnosis of endometriosis with GnRH analogues for 3 months. Proponents argue this provides both diagnostic and therapeutic functions, while forgoing surgical complications.

**Treatment**

**A. Medical Therapies**

Treatment for primary dysmenorrhea focuses on reducing endometrial prostaglandin production. This can be accomplished with medications that either inhibit prostaglandin synthesis (Table 13-4), with contraceptives that suppress ovulation, administered orally or intravaginally, by injection, by IUD, or by other hormonal means.

**B. Physical Modalities**

Physical modalities utilizing heat, acupuncture/acupressure, and spinal manipulation have been proposed for inclusion in the treatment of dysmenorrhea. A heated abdominal patch was demonstrated to have efficacy similar to ibuprofen (400 mg) for the treatment of dysmenorrhea, with quicker, but not greater, relief observed with the combination of ibuprofen and heat. Acupuncture relieved pain in 91% of patients with dysmenorrhea compared to 36% relief for control patients in a study with sham acupuncture. A systematic review of spinal manipulation in the treatment of dysmenorrhea failed to find evidence for the effectiveness of this approach.

**C. Supplement and Herbals**

A number of supplements and herbal formulations have been touted as relieving the symptoms of dysmenorrhea. While some small trials have showed promising results, the data is not strong enough at this time to recommend widespread use. A systematic review of Chinese herbal therapy for treatment of dysmenorrhea showed promising results with self-designed formulas in small studies, but not with commonly used herbal health products. Results were limited by poor methodological quality and small sample size.

**D. Behavioral Modification**

Strenuous exercise and caffeine intake are both lifestyle factors that can modulate prostaglandin-induced uterine contractions. Strenuous exercise can increase uterine tone, resulting in increased periods of uterine “angina” with accompanying increases in prostaglandins. Decreasing strenuous exercise in the first few days of a woman’s menses may reduce her dysmenorrhea. Conversely, caffeine decreases uterine tone by increasing uterine cyclic adenosine monophosphate levels.

**E. Surgical Therapy**

If a patient continues to have significant dysmenorrhea with this treatment, further testing for causes of secondary dysmenorrhea should be considered, and surgical options explored when applicable.
Table 13-4. Medications for the treatment of primary dysmenorrhea.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Primary Side Effects/Complications</th>
<th>Strength of Recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective</td>
<td></td>
<td></td>
<td>A*</td>
<td>Most effective when started before onset of pain</td>
</tr>
<tr>
<td>NSAIDs: diclofenac, ibuprofen, mefenamic acid, naproxen, ASA</td>
<td>Inhibits prostaglandin synthesis</td>
<td>GI upset, GI bleed</td>
<td>B*</td>
<td></td>
</tr>
<tr>
<td>Danazol</td>
<td>Suppression of menses</td>
<td>Amenorrhea, vaginal dryness, jaundice, eosinophilia</td>
<td>B*</td>
<td>Significant side effects; primarily for severe endometriosis</td>
</tr>
<tr>
<td>Probably effective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leuprolide acetate (Lupron)</td>
<td>Suppression of menses</td>
<td>Weight gain, hirsutism, elevation of BP</td>
<td>B*</td>
<td>Very expensive with significant side-effects. Not 1st line.</td>
</tr>
<tr>
<td>Depo-medroxyprogesterone acetate (Depo-Provera)</td>
<td>Suppression of menses</td>
<td>Amenorrhea, hypermenorrhea</td>
<td>B*</td>
<td>Weight gain may be significant</td>
</tr>
<tr>
<td>Possibly effective</td>
<td>Oral contraceptives: oral or intravaginal administration</td>
<td>Reduced prostaglandin release during menstruation</td>
<td>B*</td>
<td>Use with caution in pts &gt;35 y and smokers; not for pts desiring fertility</td>
</tr>
<tr>
<td>COX-2 inhibitors</td>
<td>Inhibits prostaglandin synthesis</td>
<td>Cardiovascular risk, acute renal failure</td>
<td>B*</td>
<td>Contains sulfa moiety; consider safer NSAIDs first</td>
</tr>
<tr>
<td>Levonorgestrel intrauterine device (Mirena)</td>
<td>Thins uterine lining through inhibition</td>
<td>Hypertension, acne, weight gain</td>
<td>B*</td>
<td>Effective for 5 y</td>
</tr>
<tr>
<td>Uncertain efficacy</td>
<td>Nifedipine (Procardia)</td>
<td>Induction of uterine relaxation</td>
<td>C</td>
<td>Moderate to good pain reduction but high rate side effects</td>
</tr>
<tr>
<td>Transdermal contraceptive patch</td>
<td>Reduced prostaglandin release during menstruation</td>
<td>Local irritation, irregular menses</td>
<td>B*</td>
<td>Less effective than OCPs, efficacy varies with pt weight</td>
</tr>
</tbody>
</table>

*A: consistent, good quality, patient-oriented evidence; B: inconsistent or limited-quality patient-oriented evidence; C: consensus, disease-oriented evidence, usual practice, opinion, or case series.


PREMENSTRUAL SYNDROME

ESSENTIALS OF DIAGNOSIS

- A cluster of affective, cognitive and physical symptoms that occurs before the onset of menses, and not at other times during the month.
- Premenstrual syndrome (PMS) may encompass any of the following disorders occurring during the luteal phase of the menstrual cycle:
  - Premenstrual dysphoric disorder.
  - Affective or cognitive disturbances.
  - Alterations in appetite.
  - Fluid retention.
  - Pain.
  - Absence of a symptom-free week in the time period just after menses suggests that a chronic psychiatric disorder may be present.

General Considerations

Forty percent of women experience PMS symptoms significant enough to interfere with daily life and relationships, while 5% of women experience severe impairment. Evaluation, diagnosis,
and treatment of PMS should be undertaken prudently, as it is often mistaken for other disorders, and sometimes treated with counterproductive and even harmful approaches. The clinician must be sensitive in addressing issues of reduced self-worth, frustration, and depression that may be present in women suffering from this condition.

Pathogenesis

Premenstrual syndrome is thought to be secondary to interactions between the ovarian hormones, estrogen and progesterone, and central neurotransmitters. Serotonin is the central neurotransmitter most often implicated in the manifestations of PMS. This would explain the cyclical mood changes that are synchronized with the changes in ovarian hormone levels. Systemic symptoms, such as bloating, may be produced through the peripheral effects of these hormones. Trace elements are also speculated to have a role in the pathogenesis of PMS symptoms, but their role is less clear.

Clinical findings

A. Symptoms and Signs

Symptoms may include irritability, bloating, depression, food cravings, aggressiveness, and mood swings. Abraham’s classification of premenstrual syndrome (Table 13-5) helps the clinician to organize history taking for patients with PMS.

Factors associated with an increased risk of PMS include stress, alcohol use, exercise, smoking, and the use of certain medications. It is not clear whether some of these factors are causative or are forms of self-medication used by sufferers. A prospective symptom diary kept for at least 2 months is helpful in assessing the relation of symptoms to the luteal phase of menses. The absence of a symptom-free week early in the follicular phase, the time period just after menses, suggests that a chronic psychiatric disorder may be present. A record of symptoms that are temporally clustered before menses and that decline or diminish 2-3 days after the start of menses is highly suggestive of PMS. Patients with PMS experience fluid retention and fluctuating weight gain in relation to their menses. Mild edema may or may not be evident on physical examination.

B. Laboratory Findings

There are no laboratory evaluations recommended in the diagnosis of PMS. Nutrient deficiency tests are not recommended, as they do not adequately assess the patients’ physiologic state.

C. Radiologic Studies

There are no radiologic studies recommended in the assessment of PMS.

Treatment

The treatment goals for PMS are to minimize symptoms and functional impairment while optimizing the patient’s overall health and sense of well-being. Therapy should take an integrative approach, including education, psychological support, exercise, diet, and pharmacological intervention, if necessary. By providing education about the prevalence and treatability of PMS, the clinician can destigmatize the disease and encourage the patient to take ownership of the treatment plan.

Many first-line treatments for PMS, while not based on well-designed prospective trials, also have general health benefits, are inexpensive, and have few side effects. These include dietary modifications, as recommended by the American Heart Association, and moderate exercise at least three times a week. Patients should begin to see the results of these lifestyle changes 2-3 months after initiation. Patients should be counseled to expect improvement in their symptoms, rather than cure. Multiple approaches may be required before finding the optimal treatment.

For those patients with continued symptoms, secondary treatment strategies may be employed. Dietary supplements, specifically vitamin B₆, calcium, and magnesium have been suggested to correct possible deficiencies. Current therapies are listed below, in Table 13-6, with their levels of supporting evidence, primary benefits, and potential side effects.
Table 13-6. Selected pharmacological and supplemental therapies for PMS.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Indication(s) for Use in PMS</th>
<th>Dosing</th>
<th>Primary Side Effects/Complications</th>
<th>Evidence Supporting Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mefenamic acid</td>
<td>Inhibits prostaglandin synthesis, competes for prostaglandin binding sites</td>
<td>Pain relief</td>
<td>500 mg loading dose, then 250 mg po qid for up to 7 d</td>
<td>Diarrhea, nausea, vomiting, drowsiness, decreased renal blood flow, renal papillary necrosis</td>
<td>RCCT</td>
</tr>
<tr>
<td>GnRH agonists (nafrelin, leuproli)</td>
<td>LH and FSH transient stimulation then prolonged suppression</td>
<td>Severe PMS; relief of all symptoms in 50% of patients</td>
<td>Nafrelin: 200 mg intranasal bid Leuprolide: 3.75 mg depot IM every 4 wk or 0.5 mg SQ qd</td>
<td>Vaginal dryness, accelerated bone loss, hot flashes</td>
<td>Controlled clinical trial</td>
</tr>
<tr>
<td>Danazol</td>
<td>Suppresses LH and FSH</td>
<td>Severe PMS</td>
<td>200 mg po qd in the luteal phase</td>
<td>Acne, weight gain, hirsutism, virilization</td>
<td>RCCTs</td>
</tr>
<tr>
<td>Alprazolam (second-line since it appears to treat only depressive symptoms and has high addictive potential)</td>
<td>Depressant effect on central nervous system</td>
<td>Depression caused by PMS</td>
<td>0.25 mg po tid during the late luteal phase of the cycle</td>
<td>Drowsiness, increased appetite, withdrawal (discontinue if patient exhibits withdrawal symptoms)</td>
<td>RCCT</td>
</tr>
<tr>
<td>SSRIs: fluoxetine, sertraline, paroxetine, venlafaxine, citalopram</td>
<td>Serotonin reuptake inhibitor</td>
<td>Depression, anger, and anxiety caused by PMS</td>
<td>Varies with drug: all month or just during luteal phase (start day 14, end at start of menses)</td>
<td>Nervousness, insomnia, drowsiness, nausea, anorexia</td>
<td>EBM review</td>
</tr>
<tr>
<td>Diuretics (metolazone, spironolactone)</td>
<td>Reduction in retained fluid</td>
<td>Bloating, edema, breast tenderness (especially in women with &gt;1.5 kg premenstrual weight gain)</td>
<td>Metolazone: 2.4 mg/d po Spironolactone: 25 mg po qid</td>
<td>Electrolyte imbalance</td>
<td>EBM review</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Dopamine agonist</td>
<td>Breast tenderness and fullness</td>
<td>2.5 mg po bid-tid</td>
<td>Postural hypotension, nausea</td>
<td>Use not supported by RCCT's</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Suppression of estrogen and progesterone</td>
<td>General symptoms</td>
<td>Varies by formulation</td>
<td>Varies by formulation</td>
<td>Use not supported by RCCTs for treatment of PMS</td>
</tr>
<tr>
<td>Vitamin B₆</td>
<td>Precursor in coenzyme for the biosynthesis of dopamine and serotonin</td>
<td>Depression and general symptoms</td>
<td>50 mg po qd or bid</td>
<td>Ataxia, sensory neuropathy</td>
<td>EBM review</td>
</tr>
<tr>
<td>γ-Linoleic acid</td>
<td>Prostaglandin E1 precursor that inhibits prostaglandin production and metabolism</td>
<td>Breast tenderness, bloating, weight gain, edema</td>
<td>3 g/d in late luteal phase of menstrual cycle</td>
<td>Headache, nausea</td>
<td>Efficacy not supported</td>
</tr>
<tr>
<td>Calcium</td>
<td>Restoration of calcium homeostasis</td>
<td>Depression, anxiety, and dysphoric states</td>
<td>800-1600 mg qd in divided doses</td>
<td>Bloating, nausea</td>
<td>RCCT</td>
</tr>
</tbody>
</table>
Alternative therapies include herbal medicine, dietary supplements, relaxation, massage, reflexology, manipulative therapy, and biofeedback. Though some small trials have shown promising results, there is no compelling evidence from well-designed studies supporting the use of these therapies in the treatment of PMS.


ESSENTIALS OF DIAGNOSIS

- Privacy, confidentiality, and legal disease reporting concerns affect detection and treatment.
- Suspicion or diagnosis of one sexually transmitted disease (STD) should prompt screening tests for others.
- Diagnosis of an STD should always include identification and treatment of partners, and education to reduce risk of future infection.

General Considerations

STDs include sexually transmitted infections and the clinical syndromes they cause. Based on estimates there are up to 19 million new STDs in the United States annually, almost half of them among persons aged 15–24 years. Rates in the United States are among the highest in the developed world. Although all sexually active individuals are susceptible to infection, adolescents and young adults are most commonly affected. Reasons for this include (1) adolescents’ biological susceptibility to increased morbidity (eg, cervical dysplasia in women exposed to human papillomavirus [HPV] as adolescent girls), (2) an attitude of invincibility, (3) lack of knowledge about the risks and consequences of STDs, and (4) barriers to health care access. *Chlamydia* and gonorrhea can result in infertility if left untreated. In many instances, these infections may be asymptomatic and not diagnosed. International travelers may be another population at increased risk for STDs and may benefit from pretravel counseling.

This chapter emphasizes the clinical presentation, diagnostic evaluation, and treatment of STDs commonly found in the United States. Readers of this chapter should be able to:

- Differentiate common STDs on the basis of clinical information and laboratory testing.
- Treat STDs according to current guidelines.
- Intervene in patients’ lives to reduce risk of future STD acquisition.

The discussion draws greatly from the most recent Centers for Disease Control and Prevention (CDC) guidelines for treatment of STDs. We are indebted to the individuals who worked to develop these recommendations.

Federal and state laws create disease-reporting requirements for many STDs. Gonorrhea, *Chlamydia*, chancroid, syphilis, and AIDS are reportable in every state. HIV is reportable in many states. Because reporting requirements for other diseases vary by state, clinicians should contact their local health department for pertinent information.

Privacy and confidentiality concerns are different for STDs than for general medical information. Patients generally experience greater anxiety about information pertaining to a possible diagnosis of an STD, and this may limit their willingness to disclose clinically pertinent information. Conversely, legal requirements for disease reporting and health department partner notification programs can inadvertently compromise patient confidentiality if not handled with the utmost professionalism. Furthermore, although minors generally require parental consent for nonemergent medical care in all states, minors can be diagnosed and treated for STDs without parental consent. Additionally, many US states legislation may permit physicians to prescribe treatment for the heterosexual partners of men or women with *Chlamydia* or gonorrhea without examining the partner. Thus, laws in different jurisdictions create additional options and complexities in treating STDs. Practitioners need to be familiar with local requirements.


Prevention

Intervening in patients’ lives to reduce their risk of disease due to STDs is no less important than reducing risk due to
smoking, inadequate exercise, poor nutrition, and other health risks. STD risk assessment should prompt providers to undertake discussion of risk reduction, and thus disease prevention. Physicians’ effectiveness depends on their ability to obtain an accurate sexual history employing effective counseling skills. Specific techniques include creating a trusting, confidential environment; obtaining permission to ask questions about STDs; demonstrating a nonjudgmental, optimistic attitude; and combining information collection with patient education, using clear, mutually understandable language (see Chapter 17). Prevention is facilitated by an environment of open, honest communication about sexuality.

A. Counseling

US Preventive Services Task Force (USPSTF) recommends high-intensity behavioral counseling to prevent sexually transmitted infections (STIs) for all sexually active adolescents and for adults at increased risk for STIs, for example, adults with current STIs or infections within the past year, who have multiple current sexual partners, or who are members of a population with a high rate of STIs. Recommendations for changes in behavior should be tailored to the patient’s specific risks and needs; simple suggestions such as keeping condoms available have been shown to be effective. Brief counseling using personalized risk reduction plans and culturally appropriate videos can significantly increase condom use and prevent new STDs, and can be conducted even in busy public clinics with minimal disruption to clinic operations. Effective interventions to reduce STDs in adolescents can extend beyond the examination room and include school-based and community-based education programs. Characteristics of successful interventions include: multiple sessions, most often in groups, with total duration from 3 to 9 hours, or two 20-minute counseling sessions before and after HIV testing. Individuals with chronic infections (eg, herpes simplex virus [HSV] and HPV) will need counseling tailored to help them understand their infection and effectively manage symptoms and transmission risk.

B. Condoms

For sexually active patients, male condoms are effective in reducing the sexual transmission of HIV infection. When used correctly and consistently, male latex condoms can reduce the risk of other STIs including Chlamydia, gonorrhea, and Trichomonas. Condoms may afford some protection against transmission of HSV, and may mitigate some adverse consequences of infection with HPV, as their use has been associated with higher rates of regression of cervical intraepithelial neoplasia and clearance of HPV in women.

Effectiveness depends on correct, consistent use. Patients should be instructed to use only water-based lubricants. Providers may need to demonstrate how to place a condom on the penis via a suitable model, especially for persons who may be inexperienced with condom use.

Nonoxynol-9 spermicide is not recommended for STI/HIV prevention. Some may confuse contraception with disease prevention; nonbarrier methods of contraception such as hormonal contraceptives or surgical sterilization do not protect against STDs. Women employing these methods should be counseled about the role of condoms in prevention of STDs.

C. Vaccination

Vaccination for hepatitis B virus (HBV) is indicated for all unvaccinated adolescents, all unvaccinated adults at risk for HBV infection, and all adults seeking protection from HBV infection. Other settings where all unvaccinated persons should receive vaccination include correctional facilities, drug abuse treatment and prevention services centers, health care settings serving men who have sex with men, and HIV testing and treatment facilities. Additionally, individuals with chronic liver disease (including chronic HBV or hepatitis C infection), end-stage renal disease, and potential occupational or travel exposure should be vaccinated. The prevalence of past exposure to HBV in homosexual men and injection drug users may render prevaccination testing cost effective, although it may lower compliance. For this reason, if prevaccination testing is employed, patients should receive their first vaccination dose when tested. If employed, HBV core antibody testing is an effective screen for immunity.

Vaccination for hepatitis A virus (HAV) is indicated for homosexual or bisexual men, persons with chronic liver disease (including hepatitis B and C), and persons who use illegal drugs; additionally, some individuals with occupational or travel exposure should be vaccinated. In cases of sexual or household contact with someone with HAV, hepatitis A vaccine or immune globulin should be administered as soon as possible after exposure. Information about the relative efficacy of vaccine compared with immune globulin postexposure is limited, and no data are available for persons aged older than 40 years or those with underlying medical conditions. (For additional information on hepatitis A and B, see Chapter 31.)

Two HPV vaccines are available and licensed for females aged 9–26 years to prevent cervical precancers and cancers, the quadrivalent HPV (Gardasil) and the bivalent HPV vaccine (Cervarix). Universal vaccination of females aged 11–12 years is recommended with either vaccine, as is catch-up vaccination for females aged 13–26 years. The quadrivalent HPV vaccine (Gardasil) may be given to males aged 9 through 26 years to prevent genital warts. Experimental vaccines are also being explored for other STDs.
D. Partner Treatment

Following treatment of an individual patient, treatment of asymptomatic partners of a diagnosed patient is commonly employed in STD treatment. For patients with multiple partners, it may be difficult to identify the source of infection. Partner treatment should be recommended for sexual contacts occurring prior to diagnosis within the time intervals indicated for each disease:

- Chancroid, 10 days
- Granuloma inguinale, 60 days
- Lymphogranuloma venereum, 30 days
- Syphilis, up to 90 days, even if the partner tests seronegative
- Chlamydia infection, 60 days
- Gonorrhea, 60 days
- Epididymitis, 60 days
- Pelvic inflammatory disease (PID), 60 days
- Pediculosis pubis, 30 days
- Scabies, 30 days

Although in general physicians must examine a patient directly before prescribing treatment, when prior medical evaluation and counseling is not feasible, or resource limitations constrain evaluation and diagnosis, other partner management options may be considered. One of these is partner-delivered therapy, in which the patient diagnosed with Chlamydia or gonorrhea delivers the prescribed treatment to his or her partner; this option is affected by state laws and regulations.

Repeat testing at 3 months following treatment is indicated for persons with Chlamydia or gonorrhea, due to the increased incidence of reinfection. Patients should also be instructed to avoid sexual contact for the duration of therapy to prevent further transmission. Patients taking single-dose azithromycin for Chlamydia infection should be instructed to avoid sexual contact for 7 days. Patients must also be instructed to avoid contact with their previous partner(s) until both patient and partner complete treatment.

E. Screening

Some form of STD screening, such as questions asked during the history interview or included in routine history forms, should be a universal practice for all patients, with periodic and regular updating. Content, frequency, and additional screening should be determined by individual patient circumstances, local disease prevalence, and research documenting effectiveness and cost-benefit. Table 14-1 summarizes current recommendations for STD screening from the USPSTF.

**Table 14-1. US Preventive Services Task Force (USPSTF) recommendations for STD screening.**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia</td>
<td>Screen all sexually active women aged 25 y and younger, and other asymptomatic women at increased risk for infection (eg, unmarried, having a prior history of STD, having new or multiple sex partners, having cervical ectopy)</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>Screen all sexually active women, including those who are pregnant, for gonorrhea infection if they are at increased risk for infection (eg, age &lt;25 y, previous gonorrhea, or other STD, new or multiple sex partners, inconsistent condom use, sex work, and drug use)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Screen all pregnant women at their first prenatal visit</td>
</tr>
<tr>
<td>HIV</td>
<td>Screen all pregnant women</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Screen persons at increased risk for syphilis infection (eg, men who have sex with men after 1975; men and women having unprotected sex with multiple partners; past or present injection drug users; men and women who exchange sex for money or drugs or have sex partners who do; individuals whose past or present sex partners were HIV-infected, bisexual, or injection drug users; persons being treated for STDs; persons with a history of blood transfusion between 1978 and 1985; persons seen in high-risk or high-prevalence clinical settings; and persons who request an HIV test)</td>
</tr>
</tbody>
</table>

The benefits of Chlamydia trachomatis screening in women have been demonstrated in areas where screening programs have reduced both the prevalence of infection and rates of PID. Evidence is insufficient to recommend routine screening for C. trachomatis in sexually active young men, based on feasibility, efficacy, and cost-effectiveness. However, screening of sexually active young men should be considered in clinical settings with a high prevalence of Chlamydia (eg, adolescent clinics, correctional facilities, and STD clinics).
2. Pregnancy—Recommendations for screening pregnant women vary somewhat depending on the source. According to the CDC, pregnant women should receive a serologic test for syphilis at the onset of prenatal care, again early in the third trimester, and at delivery for high-risk women. Hepatitis B surface antigen (HBsAg) testing should be performed at the onset of prenatal care and repeated late in pregnancy for unvaccinated HBsAg-negative women at high risk (ie, those who have had more than one sex partner in the previous 6 months; have been evaluated for an STD; are current injection drug users; or have an HBsAg-positive partner). Furthermore, women at risk for HBV infection should be vaccinated for hepatitis B.

Providers of obstetric care should test for Neisseria gonorrhoeae at the onset of care if local prevalence of gonorrhea is high or if the woman is at increased risk, and testing should be repeated in the third trimester if the woman is at continued risk. Providers should test for Chlamydia at the first prenatal visit. Women younger than 25 years and those at increased risk for chlamydial infection (ie, those who have multiple partners or who have a partner with multiple partners) should also be tested again in the third trimester. Evidence does not support routine testing for bacterial vaginosis. For asymptomatic pregnant women at high risk for preterm delivery, the current evidence is insufficient to assess the balance of benefits and harms of screening for bacterial vaginosis. Symptomatic women should be evaluated and treated.

3. HIV—HIV screening is recommended for patients aged 13-64 years in all health care settings after the patient is notified that testing will be performed unless the patient declines. Repeat annual testing for HIV is indicated for any high-risk patient, including patients with a diagnosed STD or with a history of behaviors that could expose them to HIV. Testing is also indicated for patients who present with a history and findings consistent with the acute retroviral syndrome (ARS), symptoms and frequency of which appear in Table 14-2. Appropriate testing regimens include an HIV-1 screening antibody test such as enzyme immunoassay, with a confirmatory test such as the Western immunoblot. HIV-2 prevalence in the United States is very low, so routine testing is not indicated although several commercial antibody tests screen for both HIV-1 and HIV-2; HIV-2 should be considered for persons coming from areas of high HIV-2 prevalence (eg, parts of West Africa, particularly Cape Verde, Ivory Coast, Gambia, Guinea-Bissau, Mali, Mauritania, Nigeria, and Sierra Leone).

Early diagnosis of ARS may present a very narrow window of opportunity to alter the course of HIV infection in the recently infected patient, and to block the source of most presumed new HIV transmission. Symptoms are common and nonspecific, making diagnosis difficult without a high index of suspicion; they include fever, malaise, lymphadenopathy, pharyngitis, and skin rash. Appropriate testing should include a nucleic acid test for HIV such as HIV-RNA polymerase chain reaction (PCR); routine HIV antibody tests are not sufficient, because they generally will not have become positive during ARS. Individuals with positive HIV tests should be referred immediately to an expert in HIV care.

HIV-infected individuals pose particular challenges for STD risk reduction. Reducing high-risk behaviors of known HIV-infected patients is a top priority, both to decrease the further spread of HIV and to limit the exposure of HIV patients to additional STDs. Persons with HIV also have substantial medical, psychological, and legal needs that are beyond the scope of this chapter.

4. Other STDs—Accepted national guidelines directing screening for other STDs do not exist. If undertaken, additional

### Table 14-2. Acute retroviral syndrome: associated signs and symptoms and expected frequency.

<table>
<thead>
<tr>
<th>Symptoms and Signs</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>96</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>74</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>70</td>
</tr>
<tr>
<td>Rash, including:</td>
<td>70</td>
</tr>
<tr>
<td>Erythematous maculopapular with lesions on face and trunk and sometimes extremities, including palms and soles</td>
<td></td>
</tr>
<tr>
<td>Mucocutaneous ulceration involving mouth, esophagus, or genitals</td>
<td></td>
</tr>
<tr>
<td>Myalgia or arthralgia</td>
<td>54</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
</tr>
<tr>
<td>Headache</td>
<td>32</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>27</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>14</td>
</tr>
<tr>
<td>Weight loss</td>
<td>13</td>
</tr>
<tr>
<td>Thrush</td>
<td>12</td>
</tr>
<tr>
<td>Neurologic symptoms, including:</td>
<td>12</td>
</tr>
<tr>
<td>Meningoencephalitis or aseptic meningitis</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy or radiculopathy</td>
<td></td>
</tr>
<tr>
<td>Facial palsy</td>
<td></td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td></td>
</tr>
<tr>
<td>Brachial neuritis</td>
<td></td>
</tr>
<tr>
<td>Cognitive impairment or psychosis</td>
<td></td>
</tr>
</tbody>
</table>

screening should be guided by local disease prevalence and an individual patient’s risk behaviors.


Web Sites

HIV InSite Knowledge Base: http://hivinsite.ucsf.edu/InSite.jsp?page=KB.


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**SEXUALLY TRANSMITTED INFECTIONS & SYNDROMES**

**ESSENTIALS OF DIAGNOSIS**

- Presenting clinical syndromes often guide diagnosis and treatment.
- History and findings can justify presumptive treatment while awaiting laboratory confirmation of a diagnosis.

Patients who are infected with STDs rarely present with accurate knowledge of their microbiological diagnosis. More commonly, patients present with clinical syndromes consistent with one or more diagnoses, so that providers frequently employ syndromic evaluation and treatment. This approach is useful for several reasons, including the fact that more than one disease may be present, and has been employed commonly in resource-poor settings with limited access to advanced diagnostic technology.

The following recommendations for testing strategies and use of empiric treatment pending laboratory results should be adapted to take into consideration local availability of specific tests, the probability of the diagnosis based on the history and examination, disease-associated morbidity, the risk of further transmission while awaiting diagnosis, and the likelihood that an untreated patient will return for laboratory test results and treatment. Treatment information is summarized in Table 14-3 and additional treatment information appears within the text description of specific diseases where applicable.

**GENITAL ULCER DISEASES**

**ESSENTIALS OF DIAGNOSIS**

- Herpes is the most common cause of genital ulcers in the United States.
- Most persons infected with herpes simplex virus type 2 (HSV-2) have not been diagnosed with genital herpes.
- All persons with genital ulcers need syphilis testing via serologic tests (rapid plasma reagin [RPR] or Venereal Disease Research Laboratories [VDRL]), darkfield microscopy; and culture or PCR tests for HSV).

**General Considerations**

In the United States, herpes simplex is the most common cause of genital ulcer diseases (GUD). Other causes such as syphilis, chancroid, lymphogranuloma venereum, and granuloma inguinale are much less common. Because this is not true throughout the world, physicians treating international travelers or recent arrivals to the United States may need to consider a broad spectrum of potential etiologies. The approach to diagnosis needs to include consideration of the likelihood of the different etiologies based on the patient’s history, physical examination, and local epidemiology. Furthermore, all types of GUD are associated with increased risk of HIV transmission, making HIV testing a necessary part of GUD evaluation.

**1. Herpes Simplex**

At least 50 million persons in the United States have genital HSV-2 infection.

The majority of persons infected with HSV-2 have not been diagnosed with genital herpes. Many such persons have mild or unrecognized infections but shed virus intermittently in the genital tract. The majority of genital herpes infections are transmitted by persons unaware that they have the infection or who are asymptomatic when transmission occurs. Herpes simplex virus type 1 is causing an increasing proportion of anogenital herpes and in some populations, such as young women and MSM, may now account for the majority of first episode anogenital infections.

**Clinical Findings**

**A. Symptoms and Signs**

A first episode of genital herpes classically presents with blisters and sores, with local tingling and discomfort. Visible lesions may be preceded by a prodrome of tingling or burning. Some patients also report dysesthesia or neuralgic-type pain in the buttocks or legs and malaise with fever. The clinical spectrum of disease can include atypical rashes, fissuring, excoration, and discomfort of the anogenital area, cervical
<table>
<thead>
<tr>
<th>Disease</th>
<th>Recommended Regimens</th>
<th>Dose/Route</th>
<th>Alternative Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomplicated infections in adults/adolescents&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Azithromycin or Doxycycline&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 g po</td>
<td>Erythromycin base 500 mg po qid x 7 d or Erythromycin ethylsuccinate 800 mg po qid x 7 d or Ofloxacin&lt;sup&gt;c&lt;/sup&gt; 300 mg po bid x 7 d or Levofloxacin 500 mg po qd x 7</td>
</tr>
<tr>
<td>Pregnant women&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Amoxicillin or Azithromycin</td>
<td>500 mg po tid x 7 d</td>
<td>Erythromycin base 250 mg po qid x 14 d or Erythromycin ethylsuccinate 800 mg p qid x 7 d or Erythromycin ethylsuccinate 400 mg po qid x 14 d Erythromycin base 500 mg po qid x 7 d</td>
</tr>
<tr>
<td>Gonorrhea&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomplicated infections in adults/adolescents</td>
<td>Ceftriaxone or Cefixime&lt;sup&gt;f&lt;/sup&gt; plus a Chlamydia recommended regimen listed above</td>
<td>250 mg IM 400 mg po</td>
<td>Ceftriaxone 500 mg IM or Cefotaxime 500 mg IM or Cefoxitin 2 g IM plus probenecid 1 g po or Spectinomycin&lt;sup&gt;h&lt;/sup&gt; 2 g IM plus&lt;sup&gt;a&lt;/sup&gt; a Chlamydia recommended regimen</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Ceftriaxone or Cefixime&lt;sup&gt;f&lt;/sup&gt; plus a Chlamydia recommended regimen listed above</td>
<td>250 mg IM 400 mg po</td>
<td>Spectinomycin&lt;sup&gt;h&lt;/sup&gt; 2 g IM plus&lt;sup&gt;a&lt;/sup&gt; a Chlamydia recommended regimen</td>
</tr>
<tr>
<td>Pelvic inflammatory disease&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Parenteral&lt;sup&gt;i&lt;/sup&gt; Parenteral&lt;sup&gt;i&lt;/sup&gt;</td>
<td>2 g IV q 12 h 2 g IV q 6 h</td>
<td>Parenteral Ampicillin/sulbactam 3 g IV q 6 h plus doxycycline&lt;sup&gt;b&lt;/sup&gt; 100 mg po 12 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg po or q 12 h 900 mg IV q 8 h</td>
<td>If parenteral cephalosporin therapy is not feasible, use of fluoroquinolones (levofloxacin 500 mg orally once daily or ofloxacin 400 mg bid for 14 d) with or without metronidazole (500 mg orally bid for 14 d) may be considered if the community prevalence and individual risk of gonorrhea is low. Tests for gonorrhea must be performed prior to instituting therapy and the patient managed as follows: If NAAT test is positive, parenteral cephalosporin is recommended. If culture for gonorrhea is positive, treatment should be based on results of antimicrobial susceptibility. If isolate is quinolone-resistant or antimicrobial susceptibility cannot be assessed, parenteral cephalosporin is recommended.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 mg/kg IV or IM followed by 1.5 mg/kg IV or IM q 8 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral treatment Ceftriaxone or Cefixime&lt;sup&gt;f&lt;/sup&gt; with Probenecid plus Doxycycline&lt;sup&gt;b&lt;/sup&gt; s Metronidazole</td>
<td>250 mg IM 2 g IM 1 g po 100 mg po bid x 14 d 500 mg bid x 14 d</td>
<td></td>
</tr>
<tr>
<td>Cervicitis&lt;sup&gt;j&lt;/sup&gt;</td>
<td>Azithromycin or Doxycycline&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 g po</td>
<td>Erythromycin base 500 mg po qid x 7 d or Erythromycin ethylsuccinate 800 mg po qid x 7 d or Ofloxacin&lt;sup&gt;c&lt;/sup&gt; 300 mg po bid x 7 d or Levofloxacin 500 mg po qd x 7 d</td>
</tr>
<tr>
<td>Nongonococcal urethritis&lt;sup&gt;j&lt;/sup&gt;</td>
<td>Azithromycin or Doxycycline&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 g po</td>
<td>Erythromycin base 500 mg po qid x 7 d or Erythromycin ethylsuccinate 800 mg po qid x 7 d or Ofloxacin&lt;sup&gt;c&lt;/sup&gt; 300 mg po bid x 7 d or Levofloxacin 500 mg po qd x 7 d</td>
</tr>
</tbody>
</table>

(Continued)
### Table 14-3. STD treatment guidelines for adults and adolescents. (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Recommended Regimens</th>
<th>Dose/Route</th>
<th>Alternative Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epididymitis</strong></td>
<td>Ceftriaxone plus doxycycline</td>
<td><strong>250 mg IM</strong></td>
<td>For men at risk for both enteric organisms and sexually transmitted pathogens (MSM who report insertive anal intercourse) Ceftriaxone 250 mg IM + doxycycline 100 mg po bid × 10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>100 mg po bid × 10 d</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>For acute epididymitis most likely caused by enteric organisms or with negative gonococcal culture or nucleic acid amplification test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ofloxacin or levofloxacin 300 mg orally bid for 10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Levofloxacin 500 mg orally once daily for 10 d</td>
</tr>
<tr>
<td><strong>Trichomoniasis</strong></td>
<td>Metronidazole or tinidazole</td>
<td><strong>2 g po</strong></td>
<td>Metronidazole 500 mg po bid × 7 d or for failure Tinidazole or metronidazole 2 g po × 5 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vulvovaginal candidiasis</strong></td>
<td>Butoconazole creamk</td>
<td><strong>2%, 5 g intravaginally × 3 d</strong></td>
<td>Fluconazole 150 mg po once</td>
</tr>
<tr>
<td></td>
<td>Butoconazole 2% cream (SR)k</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clotrimazole creamk</td>
<td><strong>1%, 5 g intravaginally × 7-14 d</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clotrimazole creamk</td>
<td><strong>2% cream 5 g intravaginally × 3 d</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Miconazole creamk</td>
<td><strong>2% 5 g intravaginally × 7 d</strong> 4% vag intravaginally × 3 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Miconazole vaginal suppositoryk</td>
<td><strong>100 mg intravaginally × 7 d</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>200 mg intravaginally × 3 d</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nystatin</td>
<td><strong>100,000 units intravaginal tablet × 14 d</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tioconazole creamk</td>
<td><strong>6.5% 5 g intravaginally once</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Terconazole creamk</td>
<td><strong>0.4% 5 g intravaginally × 7 d</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Terconazole vaginal suppositoryk</td>
<td><strong>0.8% 5 g intravaginally × 3 d</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>80 mg intravaginally × 3 d</strong></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
### Table 14-3. STD treatment guidelines for adults and adolescents. (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Recommended Regimens</th>
<th>Dose/Route</th>
<th>Alternative Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial vaginosis</strong></td>
<td><strong>Adults/adolescents</strong></td>
<td></td>
<td>Clindamycin 300 mg po bid × 7 d or Clindamycin ovules 100 g intravaginally qhs × 3 d or Tinidazole 2 gm po qd × 3 d or Or Tinidazole 1 gm po day × 5 d</td>
</tr>
<tr>
<td></td>
<td>Metronidazole or</td>
<td>500 mg po bid × 7 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clindamycin cream(^4) or</td>
<td>2%, one applicator full (5 g) intravaginally at bedtime × 7 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metronidazole gel</td>
<td>0.75%, one applicator full (5 g) intravaginally, bid × 5 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnant women</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
<td>250 mg po tid × 7 d or</td>
<td>Erythromycin base 500 mg po t id × 7 d</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>500 mg bid × 7 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 mg po bid × 7 d</td>
<td></td>
</tr>
<tr>
<td><strong>Chancroid</strong></td>
<td><strong>Azithromycin or</strong></td>
<td>1 g po</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone or</td>
<td>250 mg IM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin(^2)</td>
<td>500 mg po bid × 3 d</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphogranuloma venereum</strong></td>
<td>Doxycycline(^b)</td>
<td>100 mg po bid × 21 d</td>
<td>Erythromycin base 500 mg po qd × 21 d</td>
</tr>
<tr>
<td><strong>Human papillomavirus</strong></td>
<td></td>
<td></td>
<td>Azithromycin 1 g po q wk × 3 wk</td>
</tr>
<tr>
<td><strong>External genital/perianal warts</strong></td>
<td>Patient applied</td>
<td></td>
<td>Intralesional interferon or laser surgery</td>
</tr>
<tr>
<td></td>
<td>Podofilox(^1) 0.5% solution or gel or imiquimod 5% cream or Sinecathechins 15% ointment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Provider administered</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cryotherapy or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Podophyllin(^1) resin 10%-25% in tincture of benzoin or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trichloroacetic acid (TCA) or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bichloroacetic acid (BCA) 80%-90% or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical removal</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vaginal warts</strong></td>
<td>Cryotherapy or TCA or BCA 80%-90% or surgical removal</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urethral meatus warts</strong></td>
<td>Cryotherapy or podophyllin(^1) 10%-25% in tincture of benzoin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anal warts</strong></td>
<td>Cryotherapy or TCA or BCA 80%-90% or surgical removal</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Herpes simplex virus</strong>(^m)</td>
<td>Acyclovir(^n) or</td>
<td>400 mg po tid × 7-10 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acyclovir(^n) or</td>
<td>200 mg po 5 × qd × 7-10 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Famciclovir(^n) or</td>
<td>250 mg po tid × 7-10 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Valacyclovir(^n)</td>
<td>1 g po bid × 7-10 d</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
### Table 14-3. STD treatment guidelines for adults and adolescents. (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Recommended Regimens</th>
<th>Dose/Route</th>
<th>Alternative Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Episodic therapy for recurrent episodes</strong></td>
<td>Acyclovir&lt;sup&gt;m&lt;/sup&gt; or Acyclovir&lt;sup&gt;m&lt;/sup&gt; or Famiclovir&lt;sup&gt;m,n&lt;/sup&gt; or Famiclovir&lt;sup&gt;m,n&lt;/sup&gt; or Valacyclovir&lt;sup&gt;m,n&lt;/sup&gt; or Valacyclovir&lt;sup&gt;m,n&lt;/sup&gt;</td>
<td>400 mg po tid × 5 d 800 mg po bid × 5 d 800 mg po tid × 2 d 125 mg po bid × 5 d 1000 mg po bid × 1 d or 500 mg × 1, then 250 mg bid × 2 d 500 mg po bid × 3 d 1 g po qd × 5 d</td>
<td></td>
</tr>
<tr>
<td><strong>Suppressive therapy</strong></td>
<td>Acyclovir&lt;sup&gt;m&lt;/sup&gt; or Famiclovir&lt;sup&gt;n&lt;/sup&gt; or Valacyclovir&lt;sup&gt;n&lt;/sup&gt; or Valacyclovir&lt;sup&gt;n&lt;/sup&gt;</td>
<td>400 mg po bid 250 mg po bid 500 mg po qd 1 g po qd</td>
<td></td>
</tr>
<tr>
<td><strong>Syphilis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary, secondary, and early latent</td>
<td>Benzathine penicillin G</td>
<td>2.4 million units IM</td>
<td>Doxycycline&lt;sup&gt;a&lt;/sup&gt; 100 mg po bid × 2 wk or Tetracycline&lt;sup&gt;a&lt;/sup&gt; 500 mg po qid × 2 wk</td>
</tr>
<tr>
<td>Late latent and unknown duration</td>
<td>Benzathine penicillin G</td>
<td>7.2 million units, administered as 3 doses of 2.4 million units IM, at 1 wk intervals</td>
<td>Doxycycline&lt;sup&gt;a&lt;/sup&gt; 100 mg po bid × 4 wk or Tetracycline&lt;sup&gt;a&lt;/sup&gt; 500 mg po qid × 4 wk</td>
</tr>
<tr>
<td>Neurosyphilis&lt;sup&gt;o&lt;/sup&gt;</td>
<td>Aqueous crystalline penicillin G</td>
<td>18-24 million units daily, administered as 3-4 million units IV q 4 h × 10-14 d</td>
<td>Procaine penicillin G, 2.4 million units IM qd × 10-14 d plus Probenecid 500 mg po qid × 10-14 d or desensitization if penicillin allergic</td>
</tr>
<tr>
<td><strong>Pregnant women&lt;sup&gt;o&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary, secondary, and early latent</td>
<td>Benzathine penicillin G</td>
<td>2.4 million units IM</td>
<td>None</td>
</tr>
<tr>
<td>Late latent and unknown duration</td>
<td>Benzathine penicillin G</td>
<td>7.2 million units, administered as 3 doses of 2.4 million units IM, at 1 wk intervals</td>
<td>None</td>
</tr>
<tr>
<td>Neurosyphilis&lt;sup&gt;o&lt;/sup&gt;</td>
<td>Aqueous crystalline penicillin G</td>
<td>18-24 million units daily, administered as 3-4 million units IV q 4 h × 10-14 d</td>
<td>Procaine penicillin G, 2.4 million units IM qd × 10-14 d plus Probenecid 500 mg po qid × 10-14 d or desensitization if penicillin allergic</td>
</tr>
<tr>
<td>Congenital syphilis</td>
<td>Procaine penicillin G</td>
<td>50,000 U/kg IM daily for 10-14 d</td>
<td>Aqueous crystalline penicillin G 100,000-150,000 U/kg/d in doses of 50,000 U/kg IV q 12 h for 7 d then q 8 h for 3-7 d</td>
</tr>
<tr>
<td>Children: early (primary)</td>
<td>Benzathine penicillin G</td>
<td>50,000 U/kg IM once (max. 2.4 million units)</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
### Table 14-3. STD treatment guidelines for adults and adolescents. (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Recommended Regimens</th>
<th>Dose/Route</th>
<th>Alternative Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children: late latent or &gt;1 y late</td>
<td>Benzathine penicillin G</td>
<td>50,000 U/kg IM for 3 doses at 1 wk intervals, to max. total dose of 7.2 million units</td>
<td></td>
</tr>
<tr>
<td>HIV infection</td>
<td>Benzathine penicillin G</td>
<td>2.4 million units IM</td>
<td>The efficacy of nonpenicillin regimens in HIV-infected persons has not been well studied</td>
</tr>
<tr>
<td>Primary, secondary, and early latent</td>
<td>Benzathine penicillin G</td>
<td>7.2 million units, administered as 3 doses of 2.4 million units IM, at 1 wk intervals</td>
<td>None</td>
</tr>
<tr>
<td>Late latent and unknown duration(p)</td>
<td>Benzathine penicillin G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurosyphilis(p)</td>
<td>Aqueous crystalline penicillin G</td>
<td>18-24 million units daily, administered as 3-4 million units IV q 4 h × 10-14 d</td>
<td>Procaine penicillin G, 2.4 million units IM qd × 10-14 d plus Probenecid 500 mg po qid × 10-14 d</td>
</tr>
<tr>
<td>Pediculosis pubis “crab lice”</td>
<td>Permethrin cream rinse</td>
<td>1% applied to affected areas, rinsed after 10 min</td>
<td>Malathion 0.5% lotion applied for 8-12 h and washed off or Ivermectin 0.25 mg/kg po repeated in 2 wk</td>
</tr>
<tr>
<td></td>
<td>Pyrethrins with piperonyl butoxide</td>
<td>Apply to affected area, wash after 10 min</td>
<td></td>
</tr>
<tr>
<td>Scabies(q)</td>
<td>Permethrin cream</td>
<td>5% applied to entire body below neck, washed off after 8-14 h</td>
<td>Lindane 1% 1-oz lotion or 30 g cream applied thinly to entire body below neck, washed off after 8 h(q)</td>
</tr>
<tr>
<td></td>
<td>Ivermectin</td>
<td>0.2 mg/kg po repeated in 2 wk</td>
<td></td>
</tr>
</tbody>
</table>

bid, twice a day; d, day; h, hours; IM, intramuscularly; IV, intravenously; po, orally; q, every; qd, every day; qid, four times a day; SR, sustained release; tid, three times a day; wk, week.

\(a\)Screen adolescents and women younger than 25 y annually, especially if new or multiple partners.

\(b\)Contraindicated for pregnant and nursing women.

\(c\)Contraindicated for pregnant and nursing women, and children younger than 18 y.

\(d\)Test-of-cure follow-up recommended because the regimens are not highly efficacious (amoxicillin and erythromycin).

\(e\)Cotreatment for Chlamydia infection is indicated.

\(f\)Not recommended for pharyngeal gonococcal infection.

\(g\)If risk of gonorrhea is low and pre-treatment gonorrhea testing is available; if nucleic acid amplification test is positive, treat with cephalosporin, or if culture is positive, treat according to susceptibility.

\(h\)For patients who cannot tolerate cephalosporins or quinolones; not recommended for pharyngeal gonococcal infection.

\(i\)Discontinue 24 h after patient improves clinically and continue with oral therapy for a total course of 14 d.

\(j\)Testing for gonorrhea and Chlamydia is recommended because a specific diagnosis may improve compliance and partner management and these infections are reportable.

\(k\)Might weaken latex condoms and diaphragms because oil-based.

\(l\)Contraindicated during pregnancy.

\(m\)Counseling especially about natural history, asymptomatic shedding, and sexual transmission is an essential component of herpes management.

\(n\)Safety in pregnancy has not been established.

\(o\)Patients allergic to penicillin should be treated with penicillin after desensitization.

\(p\)Some experts recommend a second dose of 2.4 million units of benzathine penicillin G administered 1 wk after the initial dose.

\(q\)Bedding and clothing should be decontaminated (machine washed, machine dried, or dry cleaned) or removed from body contact for >72 h.

Source: CDC STD treatment guidelines.
lesions, urinary symptoms, and extragenital lesions. Recent data suggest that only 37% of patients who acquire HSV-2 have symptoms associated with initial infection, although overt disease may follow. In immunocompromised persons, HSV can manifest as large, chronic, hyperkeratotic ulcers. If lesions persist despite antiviral therapy, acyclovir-resistant HSV should be suspected.

Both HSV-1 and HSV-2 cause genital disease, although HSV-1 produces fewer clinical recurrences and may be less severe. Symptoms during recurrences are generally less intense and shorter in duration. Infectious virus is shed intermittently and unpredictably in some asymptomatic patients. Latex condoms, when used correctly and consistently, may reduce the risk of genital HSV transmission.

**B. Laboratory Findings**

Diagnosis of HSV is based on either culture of the vesicle base or ulcer, or PCR test for HSV DNA. PCR assays for HSV DNA are more sensitive and have been increasingly used. Cytologic detection of cellular changes of herpes virus infection is insensitive and nonspecific, both in genital lesions (Tzanck smear) and cervical Papanicolaou (Pap) smears, and so should not be relied on. Type-specific serologic assays may be useful in patients with recurrent symptoms and negative HSV cultures, those with a clinical diagnosis of genital herpes without laboratory confirmation, or in patients who have a partner with genital herpes.

**Treatment**

Treatment of HSV can be episodic (ie, in response to an episode of disease) or suppressive, with daily medication continuing for months or years. Treatment for an initial outbreak consists of 7-10 days of oral medication (see Table 14-3). Episodic treatment is effective when medication is started during the prodrome or on the first symptomatic day. No benefit will be seen if treatment of recurrences is delayed; thus, patients should be given a prescription to have available for use when needed.

Suppressive therapy is traditionally indicated for patients with frequent recurrences, although this may be individualized based on the stress and disability caused by recurrences. Available experience suggests that long-term suppression is safe and is not associated with development of antiviral resistance.Suppressive therapy seems to reduce but not eliminate asymptomatic shedding. Daily treatment with valacyclovir, 500 mg, has been shown to decrease the rate of HSV-2 transmission in discordant heterosexual couples in which the source partner has a history of genital HSV-2 infection. Suppression does not change the natural history of a patient’s infection; however, because the frequency of recurrences diminishes with time, suppression may be particularly useful during the time period immediately following initial infection. Available therapies appear to be safe in pregnant women, although data for valacyclovir and famciclovir are limited.

2. Syphilis

**General Considerations**

Syphilis cases reported to the CDC had declined since the early 1950s until a resurgence was noted in the 1990s. In 1999, the CDC launched “The National Plan to Eliminate Syphilis from the United States.” In 2008, 13,500 cases of primary and secondary syphilis were reported, a 17.7% increase over the previous year. Of concern, national numbers have increased every year since 2000 and men who have sex with men now account for almost two-thirds of new cases of primary and secondary syphilis. Recent resurgences of syphilis in some populations and geographic areas indicate the need for continued vigilance.

**Clinical Findings**

**A. Symptoms and Signs**

Syphilis infection is characterized by stages, and accurate staging is vital to determine appropriate therapy. Primary syphilis is characterized by the appearance of a painless, indurated ulcer—the chancre—occurring 10 days to 3 months after infection with Treponema pallidum. The chancre usually heals by 4-6 weeks, although associated painless bilateral lymphadenopathy may persist for months.

Secondary syphilis has variable manifestations, but usually includes symmetric mucocutaneous macular, papular, papulosquamous, or pustular lesions with generalized non-tender lymphadenopathy. In moist skin areas such as the peri-anal or vulvar regions, papules may become superficially eroded to form pink or whitish condylomata lata. Constitutional symptoms such as fever, malaise, and weight loss occur commonly. Less common complications include meningitis, hepatitis, arthritis, nephropathy, and iridocyclitis.

Latent syphilis is diagnosed in persons with serologic evidence of syphilis infection without other current evidence of disease. “Early” latent syphilis is defined as infection for less than 1 year. A diagnosis of early latent syphilis is demonstrated by seroconversion, a definitive history of primary or secondary syphilis findings within the past year, or documented exposure to primary or secondary syphilis in the past year. Asymptomatic patients with known infection of more than 1 year or in whom infection of less than 1 year cannot be conclusively demonstrated are classified as having late latent syphilis or latent syphilis of unknown duration, respectively. These two categories of syphilis are treated equivalently. The magnitude of serologic test titers cannot reliably differentiate early from late latent syphilis.

Neurosyphilis is difficult to diagnose, as no single test can be used in all instances. The cerebrospinal fluid (CSF) VDRL test is highly specific but insensitive. The diagnosis depends on a combination of serologic tests, elevated CSF cell count or protein, or a reactive VDRL. CSF fluorescent treponemal antibody absorption (FTA-ABS) is less specific, but highly sensitive. CSF pleocytosis (>5 white blood cells [WBCs]/mm³) is
usually evident, although HIV infection and other conditions may also cause increased WBCs in the CSF.

**Tertiary syphilis** is diagnosed in patients with syphilitic aortitis, and in patients with one or more gummas, a syphilitic granuloma.

Patients are infectious during primary, secondary, and early latent stages of syphilis.

**B. Laboratory Findings**

Positive darkfield examination or direct fluorescent antibody tests of lesion exudates definitively diagnose primary syphilis. More typically, syphilis is diagnosed by positive serologic results of both a nontreponemal test (VDRL or RPR) and a treponemal test (T pallidum particle agglutination [TP-PA] or FTA-ABS).

Nontreponemal tests may be falsely positive due to other medical conditions (eg, some collagen vascular diseases). When positive due to syphilis, their titers generally rise and fall in response to T pallidum infection and treatment, respectively, and usually return to normal (negative) following treatment, although some individuals remain “serofast” and have persistent low positive titers. Treponemal tests usually yield persistent positive results throughout the patient’s life following infection with T pallidum. Treponemal test titers do not correlate with disease activity or treatment.

Lumbar puncture is indicated for (1) neurologic or ophthalmologic signs or symptoms, (2) active aortitis or gumma, or (3) treatment failure (a fourfold increase in titer or a failure to decline fourfold or more within 12-24 months).

**Treatment**

Treatment for syphilis as described in Table 14-3 is based on current CDC guidelines. Follow-up testing of patients diagnosed with syphilis is a vital part of care, as it determines the effectiveness of therapy and provides useful information to differentiate potential future serofast patients from those with recurrent infection.

The nontreponemal test titer should have fallen fourfold or more (eg, from 1:32 to 1:8 or less) for persons with primary or secondary syphilis in 6-12 months post therapy. If it does not, consider this a treatment failure or an indication of reinfection. In evaluating such a potential treatment failure, the patient should, at minimum, receive continued serologic follow-up, and repeat HIV serology if previously negative. Lumbar puncture should also be considered, and if the results are normal, the patient should be treated with 2.4 million units of benzathine penicillin weekly for 3 weeks and followed as described above.

**3. Chancroid**

Chancroid has declined in the United States and worldwide. In 2008, a total of 25 cases of chancroid were reported in only eight states in the United States. These data should be interpreted with caution, however, in view of the fact that Haemophilus ducreyi is difficult to culture, and thus this condition may be substantially underdiagnosed.

Definitive diagnosis is difficult, requiring identification of H ducreyi on special culture medium that is generally not readily available. Presumptive diagnosis rests on the presence of painful genital ulcer(s) with a negative HSV test and negative syphilis serology, with or without regional lymphadenopathy.

Treatment consists of oral antibiotics as listed in Table 14-3. Healing of large ulcers may require more than 2 weeks. If patients do not show clinical improvement after 7 days, consider the accuracy of the diagnosis, medication nonadherence, antibacterial resistance, or a combination of these. Flucluant lymphadenopathy may require drainage via aspiration or incision.

Although definitive diagnosis generally rests on laboratory testing, history and examination often lead to a presumptive diagnosis. Table 14-4 summarizes findings for different causes of GUD.

**4. Other Causes of GUD**

Granuloma inguinale or donovonosis is caused by Calymmatobacterium granulomatis, which is endemic in some tropical nonindustrialized parts of the world and is rarely reported in the United States. The bacterium does not grow on standard culture media; diagnosis rests on demonstration of so-called Donovan bodies in a tissue specimen. Infection causes painless, progressive, beefy red, highly vascular lesions without lymphadenopathy. Treatment is often prolonged, and relapse can occur months after initial treatment and apparent cure.

Lymphogranuloma venereum is caused by serovars L1, L2, and L3 of Chlamydia trachomatis. The small ulcer arising at the site of infection is often unnoticed or unreported. The most common clinical presentation is painful unilateral lymphadenopathy. Rectal exposure in women and in men who have sex with men may result in proctocolitis (mucus or hemorrhagic rectal discharge, anal pain, constipation, fever, or tenesmus). Diagnosis rests on clinical suspicion, epidemiologic information, exclusion of other etiologies, and C trachomatis tests. In addition to antibiotics, treatment may require aspiration or incision and drainage of buboes, and despite this patients may still experience scarring.


Chapter 14

Urethritis

# Essentials of Diagnosis

- Coinfection with *C. trachomatis* is common in those with *N. gonorrhoeae*, justifying treatment for both.
- Nucleic acid amplification tests have largely supplanted cell culture tests for diagnosis.

The best estimates from population studies of adolescents and young adults suggest 3%-5% have chlamydial infection and 0.4% have gonorrhea, although prevalence for each of these infections in some populations may exceed 10%.

STDs causing urethritis are typically diagnosed in men, although women may also experience urethritis as a consequence of an STD. For clinical management, urethritis can be divided into “nongonococcal urethritis” (NGU) and urethritis due to *N. gonorrhoeae* infection.

## 1. Nongonococcal Urethritis

One frequent cause of NGU is *C. trachomatis*. In 2008, 313,779 *Chlamydia* cases were reported in males; female cases were more than threefold greater at 893,004, and, although significant, these numbers likely dramatically underestimate actual cases of *C. trachomatis* infection. The spectrum of *C. trachomatis*-caused disease includes extragenital manifestations, among them ophthalmic infection and a reactive arthritis.

Causes of nonchlamydial NGU may include *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, *herpes simplex*, and *adenovirus*. Diagnosis of NGU can be based on (1) purulent urethral discharge; (2) urethral secretions with 5 or more WBCs per high-power field (HPF) and no gram-negative intracellular diplococci (which if present would indicate gonorrhea); (3) first-void urine with positive leukocyte esterase, or more than 10 WBCs/HPF. Nucleic acid amplification tests (*Chlamydia* or gonorrhea) offer greater convenience and better sensitivity than culture and represent the best tests currently available.

In patients presenting with recurrent urethritis, diagnostic evaluation may be necessary to identify the etiology. In evaluating recurrent urethritis, the physician should assess medication compliance and potential reexposure; perform wet mount, culture, or both, for *T. vaginalis*; and treat as indicated by findings, or empirically as per Table 14-3.

Treatment of NGU generally employs azithromycin or doxycycline, with alternatives as listed in Table 14-3. If findings of urethritis are present, treatment is generally indicated pending results of diagnostic tests. Because diagnostic testing typically does not look for all potential causes of urethritis, patients with negative tests for gonorrhea and *C. trachomatis* may also benefit from treatment. Empiric treatment of symptoms without documentation of urethritis findings is recommended only for patients at high risk for infection who are unlikely to return for a follow-up evaluation. Such patients should be treated for gonorrhea and *Chlamydia*. Partners of patients treated empirically should be evaluated and treated. If treatment is not offered at the initial visit, diagnostic testing should use the most sensitive test available, with follow-up treatment as indicated by test results and symptom persistence.

### Table 14-4. Differentiation of common causes of genital ulcers.

<table>
<thead>
<tr>
<th>Ulcer(s) Appearance</th>
<th>Herpes</th>
<th>Syphilis</th>
<th>Chancroid</th>
<th>Lymphogranuloma Venereum</th>
<th>Granuloma Inguinale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Usually multiple</td>
<td>Single</td>
<td>Often multiple</td>
<td>Single or multiple</td>
<td>Multiple</td>
</tr>
<tr>
<td>Pain</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Ulcer: no</td>
<td>No</td>
</tr>
<tr>
<td>Preceded by</td>
<td>Papule, then vesicle</td>
<td>Papule</td>
<td>Papule</td>
<td>Papule; ulcer often unnoticed</td>
<td>Nodule(s)</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>Painful with primary outbreak</td>
<td>Painless</td>
<td>Painful; may suppurate</td>
<td>Painful; may suppurate</td>
<td>No, unless secondary bacterial infection</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>Often with primary outbreak</td>
<td>Usually not</td>
<td>Occasionally</td>
<td>Usually not</td>
<td>No</td>
</tr>
</tbody>
</table>

*a* A diagnosis based solely on medical history and physical examination is often inaccurate.

*b* Up to 40% of patients with primary syphilis have more than one chancre.
2. Gonorrhea

► General Considerations

In 2008, 336,742 cases of gonorrhea were reported in the United States. Rates have been stable for the past 10 years, more common in the South (152.4 cases per 100,000 population vs 111.6 cases per 100,000 for the country) and somewhat more common in women than in men (119.7 vs 103.3 cases per 100,000, respectively).

► Clinical Findings

A. Symptoms and Signs

If symptomatic, gonorrhea typically causes dysuria and a purulent urethral discharge; however, it may also cause asymptomatic infection or disseminated systemic disease, including skin lesions, septic arthritis, tenosynovitis, arthralgias, perihepatitis, endocarditis, and meningitis. In these cases, there is usually minimal genital inflammation.

Clinical differentiation between gonorrhea and Chlamydia may be difficult. Characteristically, urethral exudate in gonorrhea is thicker, more profuse, and more purulent in appearance than the exudate caused by C trachomatis, which is often watery with mucus strands. However, differentiation of etiology based on clinical appearance is notoriously unreliable.

B. Laboratory Findings

Nucleic acid amplification technology has largely supplanted culture for diagnosis due to enhanced sensitivity and excellent specificity. Tests can be performed on a urine specimen, eliminating more invasive specimen collection, for example, urethral swab.

Diagnostic evaluation identifies disease etiology and may facilitate the public health missions of contact tracing and disease eradication. For an individual patient, however, the physician may treat empirically if follow-up cannot be assured and test methodology is insensitive. Decisions about diagnostic testing should consider both public health goals and how information obtained will influence patient (and partner) treatment.

► Treatment

When treating for gonorrhea, practitioners should treat also for C trachomatis, as coinfection is common. Quinolone-resistant N gonorrhoeae strains are now widely disseminated throughout the United States and the world. As of April 2007, quinolones are no longer recommended in the United States for the treatment of gonorrhea and associated conditions such as PID. Decreased susceptibility of N gonorrhoeae to cefalosporins and other antimicrobials is expected to continue to spread; therefore, state and local surveillance for antimicrobial resistance is crucial for guiding local therapy recommendations. Ceftriaxone 250 mg IM is effective for the treatment of uncomplicated gonorrhea at all anatomic sites. A cefixime 400-mg oral dose does not provide as high, nor as sustained, bactericidal level as that provided by the 250-mg dose of ceftriaxone. The advantage of cefixime is that it can be administered orally; however, cefixime (as well as other oral cephalosporins) have insufficient efficacy at the pharyngeal site to be recommended for gonococcal infections of the pharynx.

Treatment failures should be followed by (repeat) culture and sensitivity testing, and any resistance should be reported to the public health department.

EPIDIDYMITIS

The cause of epididymitis varies with age. It is most commonly due to gonorrhea or C trachomatis in men 35 years of age or younger, or to gram-negative enteric organisms in men 35 years of age or older who engage in unprotected insertive anal intercourse, who have undergone recent urologic surgery, or who have anatomic abnormalities. Patients usually present with unilateral testicular pain and inflammation with onset over several days. The clinician must differentiate epididymitis from testicular torsion, since the latter is a surgical emergency requiring immediate correction. The laboratory evaluation of suspected epididymitis is essentially the same as for urethritis, and includes Gram stain, nucleic acid amplification test, and serologic testing for HIV and syphilis.

PROCTITIS, PROCTOCOLITIS, & ENTERITIS

Proctitis, proctocolitis, and enteritis may arise from anal intercourse or oral-anal contact. Depending on organism and anatomic location of infection and inflammation, symptoms can include pain, tenesmus, rectal discharge, and diarrhea. Etiologic agents of proctitis include C trachomatis (lymphogranuloma venereum), N gonorrhoeae, T pallidum, and HSV. Other agents may cause proctitis or enteritis including Giardia lamblia, Campylobacter, Shigella, and Entamoeba histolytica. In HIV-infected patients, additional etiologic agents include cytomegalovirus, Mycobacterium avium intracellulare, Salmonella, Cryptosporidium, Microsporidium, and Isospora. Symptoms may also arise as a primary effect of HIV infection.

Diagnosis involves examination of stool for ova, parasites, occult blood, and WBCs; stool culture; and anoscopy or sigmoidoscopy.

Treatment should generally be based on results of diagnostic studies. However, if the onset of symptoms occurs within 1-2 weeks of receptive anal intercourse, and there is evidence of purulent exudates or polymorphonuclear neutrophils on Gram stain of anorectal smear, the patient can be treated presumptively for gonorrhea and chlamydial infection. If painful perianal ulcers are present or mucosal ulcers are detected on anoscopy, presumptive therapy should include a regimen for genital herpes and lymphogranuloma venereum.

**VAGINITIS**

**ESSENTIALS OF DIAGNOSIS**

- A careful history, examination, and laboratory testing should be performed to determine the etiology of vaginal complaints. Information on sexual behaviors and practices, gender of sex partners, menses, vaginal hygiene practices (such as douching or use of douche products), and other medications should be elicited.
- Examination of vaginal discharge by wet mount, potassium hydroxide (KOH) preparation, pH, and odor.
- Disease-specific point-of-care test or vaginal fluid culture if indicated.

Patients with vaginitis may present with vaginal discharge, vulvar itching, irritation, or all of these, and sometimes with complaints of abnormal vaginal odor. Common etiologies include *Candida albicans*, *T vaginalis*, and bacterial vaginosis. Diagnostic evaluation typically includes physical examination and evaluation of a saline wet mount and potassium hydroxide (KOH) preparation. Differences between common causes of vaginitis are summarized in Table 14-5 and described next.

### 1. Vulvovaginal Candidiasis

Vulvovaginal candidiasis (VVC) is typically caused by *C albicans*, although occasionally other species are identified. More than 75% of all women will have at least one episode of VVC during their lifetime. The diagnosis is presumed if the patient has vulvovaginal pruritus and erythema with or without a white discharge, and is confirmed by wet mount or KOH preparation showing yeast or pseudohyphae, or culture showing a yeast species.

VVC can be classified as uncomplicated, complicated, or recurrent. Uncomplicated VVC encompasses sporadic, non-recurrent, mild to moderate symptoms due to *C albicans* that, in an otherwise healthy patient, are responsive to routine therapy. Complicated VVC implies recurrent or severe local disease in a patient with impaired immune function (eg, diabetes or HIV), or infection with resistant yeast species. Recurrent VVC is defined as four or more symptomatic episodes annually.

Treatment is summarized in Table 14-3. Uncomplicated candidiasis should respond to short-term or single-dose therapies as listed. Complicated VVC may require prolonged treatment. Treatment of women with recurrent vulvovaginal candidiasis should begin with an intensive regimen (7-14 days of topical therapy or a multi-dose fluconazole regimen) followed by 6 months of maintenance therapy to reduce the likelihood of subsequent recurrence. Symptomatic candidal vaginitis is more frequent in HIV-infected women and correlates with severity of immunodeficiency.

VVC is not usually acquired through sexual intercourse. There are no data to support treatment of sex partners. Some male sex partners have balanitis and may benefit from topical antifungal agents.

### 2. Trichomoniasis

Vaginitis due to *T vaginalis* presents with a thin, yellow or yellow-green frothy malodorous discharge and vulvar irritation that may worsen following menstruation. Diagnosis can often be made via prompt examination of a freshly obtained wet mount, which reveals the motile trichomonads. Although culture is more sensitive, it may not be as readily available, and results are delayed. Point-of-care tests (eg, Osom *Trichomonas* Rapid Test and Affirm VPIII) are also available and tend to be more sensitive than vaginal wet prep. Partners of women with *Trichomonas* infection require treatment.

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Findings Characteristics of</th>
<th>Candida albicans</th>
<th>Trichomonas vaginalis</th>
<th>Bacterial Vaginosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pH</strong></td>
<td></td>
<td>&lt;4.5</td>
<td>&gt;4.5</td>
<td>&gt;4.5</td>
</tr>
<tr>
<td>KOH to slide</td>
<td>Yeast or pseudohyphae</td>
<td></td>
<td>Amine or “fishy” odor</td>
<td></td>
</tr>
<tr>
<td>Saline to slide</td>
<td>Yeast or pseudohyphae</td>
<td>Motile <em>T vaginalis</em> organisms</td>
<td>“Clue” cells</td>
<td></td>
</tr>
<tr>
<td>Culture</td>
<td>Yeast species</td>
<td><em>T vaginalis</em></td>
<td>Nonspecific (not recommended)</td>
<td></td>
</tr>
</tbody>
</table>
3. Bacterial Vaginosis

Bacterial vaginosis arises when normal vaginal bacteria are replaced with an overgrowth of anaerobic bacteria. Although not thought to be an STD, it is associated with having multiple sex partners or a new sex partner.

Diagnosis can be based on the presence of three of four clinical criteria: (1) a thin, homogeneous vaginal discharge, (2) a vaginal pH value of more than 4.5, (3) a positive KOH test, and (4) the presence of clue cells in a wet mount preparation.

Treatment is recommended for women with symptoms. Potential benefits of therapy include reducing the risk for infectious complications associated with bacterial vaginosis during pregnancy and reducing the risk for other infections. Routine treatment of sex partners is not recommended.

4. Cervicitis

Cervicitis is characterized by purulent discharge from the endocervix, which may or may not be associated with vaginal discharge or cervical bleeding. The diagnostic evaluation should include testing for *Chlamydia*, gonorrhea, bacterial vaginosis, and *Trichomonas*. Absence of symptoms should not preclude additional evaluation and treatment, as approximately 70% of chlamydial infections and 50% of gonococcal infections in women are asymptomatic.

Nucleic acid amplification tests are the preferred diagnostic test and can be performed on vaginal, cervical, or urine specimens. Empiric treatment should be considered in areas with high prevalence of *C. trachomatis* or gonorrhea, or if follow-up is unlikely.


PELVIC INFLAMMATORY DISEASE

**ESSENTIALS OF DIAGNOSIS**

- Diagnosis is challenging, requiring the clinician to balance underdiagnosis with overtreatment.
- Consequences of untreated PID can include chronic pain, infertility, and death.

PID is defined as inflammation of the upper genital tract, including pelvic peritonitis, endometritis, salpingitis, and tuboovarian abscess due to infection with gonorrhea, *C. trachomatis*, or vaginal or bowel flora; etiology is often polymicrobial. Diagnosis is challenging due to often vague symptoms, lack of a single diagnostic test, and the invasive nature of technologies needed to make a definitive diagnosis. Lower abdominal tenderness and uterine, adnexal, or cervical motion tenderness with signs of lower genital tract inflammation increase the specificity of a PID diagnosis. Other criteria enhance the specificity of the diagnosis (but reduce diagnostic sensitivity):
  - Fever higher than 38.3°C (101°F)
  - Abnormal cervical or vaginal discharge
  - Abundant WBCs in saline microscopy of vaginal secretions
  - Elevated sedimentation rate
  - Elevated C-reactive protein
  - Cervical infection with gonorrhea or *C. trachomatis*

Definitive diagnosis rests on techniques that are not always readily available and that are not generally used to make the diagnosis. These include laparoscopic findings consistent with PID, evidence of endometritis on endometrial biopsy, and ultrasonographic findings showing thickened fluid-filled tubes with or without free pelvic fluid or tuboovarian complex.

Determination of appropriate therapy should consider pregnancy status, severity of illness, and patient compliance. Less severe disease can generally be treated with oral antibiotics in an ambulatory setting, whereas pregnant patients and those with severe disease may need hospitalization. Options are listed in Table 14-3.


HPV INFECTION AND EXTERNAL GENITAL WARTS

**ESSENTIALS OF DIAGNOSIS**

- Diagnosis of genital warts is usually made by visual inspection. Biopsy may be indicated if diagnosis is uncertain.
- Treatment does not eradicate HPV infection, but treatment may reduce risk of neoplastic change.
General Considerations

It is estimated that over 20 million Americans are infected with HPV, with 1 million new infections and 250,000 initial visits to physicians for genital warts occurring annually. Even this estimate may be low; overall HPV prevalence among US females aged 14-59 years was estimated to be 26.8% based on 2003-2004 NHANES data. Over 100 types of HPV have been identified, and over 40 types cause genital lesions. Types 6, 11, and others typically produce benign exophytic warts, whereas types 16, 18, 31, 33, 35, and others are associated with dysplasia and neoplasia. Thus, cervical and anogenital squamous cancer can be considered STDs; other cancers may also be sexually transmitted.

Clinical Findings

Diagnosis is almost always based on physical examination with bright light and magnification, and rarely requires biopsy. If the diagnosis is uncertain, consider referral to a physician with extensive experience in external genital warts. Biopsy should be considered for warts that are larger than 1 cm; indurated, ulcerated, or fixed to underlying structures; atypical in appearance; pigmented; or resistant to therapy. Application of 3%-5% acetic acid as an aid to visualization is generally not useful, and the resulting nonspecific acetowhite reaction may lead to overdiagnosis of genital warts.

Cancer screening via cervical Pap smear is indicated if not done in the past 12 months, and may be collected after other specimens (eg, cervical culture swabs). Regular cervical Pap smears are also indicated for women who have sex with women, a population sometimes erroneously felt to have limited risk for cervical cancer. Genital warts are not an indication for screening more frequently than every 12 months.

Type-specific HPV DNA tests may be useful in the triage of women with atypical squamous cells of undetermined significance (ASCUS) or in screening women 30 years of age or older in conjunction with the Pap test. Abnormal Pap results should be managed according to current recommendations.

Because of the increased incidence of anal cancer in HIV-infected homosexual and bisexual men and high-risk women, screening for anal cytologic abnormalities may be considered. However, there are limited data on the natural history of anal intraepithelial neoplasias, the reliability of screening methods, the safety of and response to treatments, and the programmatic considerations that would support this screening approach.

Treatment

The therapeutic goal in treatment of external genital warts is elimination of warts. Treatment strives to eliminate symptoms, and a potential theoretical benefit is reduced likelihood of transmission. Clinicians should be certain of the diagnosis prior to instituting therapy, and should not apply treatments to skin tags, pearly penile papules, sebaceous glands, or other benign findings that do not require (and will not respond to) genital wart treatment.

No evidence suggests any treatment is superior to others. The possibility of spontaneous resolution may justify no treatment, if that is the patient’s wish.

Treatments can be categorized as provider applied or patient applied. Physicians should familiarize themselves with at least one or two treatments in each category, as described in Table 14-3. Most treatments work via tissue destruction. Imiquimod uses a different mechanism; by inducing production of interferon, it may be more effective than other therapies in treating some genital warts or other skin conditions, including molluscum contagiosum. Patients unresponsive to an initial course of treatment may require another round of treatment, more aggressive treatment, or referral to a specialist.

Patients with HPV need to understand the chronic nature of this infection, its natural history, and treatment options, and should receive adequate education and counseling to achieve optimal treatment outcomes. The chronic nature of HPV infection combined with the serious, albeit relatively infrequent, complication of cancer creates significant challenges to patient coping and provider counseling.

Molluscum Contagiosum

Molluscum contagiosum appears in individuals of all ages and from all races, but has been reported more commonly in the white population and in males. Lesions are due to infection with poxvirus, which is transmitted through direct skin contact, as occurs among children in a nursery school and among adults during sexual activity. Diagnosis is typically based on inspection, which reveals dimpled or umbilicated flesh-colored or pearly papules several millimeters in diameter; if needed, a smear of the core stained with Giemsa reveals cytoplasmic inclusion bodies. Lesions usually number less than 10-30, but may exceed 100, especially in HIV-infected patients who may have verrucous, warty papules, as well as molluscus greater than 1 cm in diameter. Lesions usually resolve spontaneously within months of appearance, but can be treated with cryotherapy, cautery, curettage, or removal of the lesion’s core, with or without local anesthesia.

Hepatitis

Vaccines for prevention of viral hepatitis and indications have been previously described. Diagnostic and treatment considerations of viral hepatitis are reviewed in Chapter 32.
ECTOPARASITES

Pediculosis pubis results from infestation with “crab lice” or Phthirus pubis. Affected patients usually present with pubic or anogenital pruritus, and may have identified lice or nits. The physician should be able to identify lice or nits with careful examination, and their absence calls into question the diagnosis despite compatible history.

Scabies, resulting from infestation with Sarcoptes scabiei, usually presents with pruritus not necessarily limited to the genital region. The intensity of pruritus may be increased at bedtime, and may be out of proportion to modest physical findings of erythematous papules, burrows, or excoriation from scratching. A classic finding on physical examination is the serpiginous burrow present in the web space between fingers, although this finding is frequently absent in individuals with scabies.

Scabies can be sexually transmitted in adults; sexual contact is not the usual route of transmission in children. Pruritus may persist for weeks after treatment. Retreatment should be deferred if intensity of symptoms is diminishing and no new findings appear. In HIV-infected patients with uncomplicated scabies, treatment is the same as for HIV-uninfected patients. However, HIV-infected patients are at risk for a more severe infestation with Norwegian scabies, which should be managed with expert consultation.


GENERAL PRINCIPLES OF THERAPY

ESSENTIAL FEATURES

▶ Presumptive treatment while awaiting laboratory test results is common practice.
▶ Coexisting HIV infection may modify STD treatment regimens.
▶ Patient education and partner treatment are essential to reduce disease spread.

Treatments may be empirically targeted to agents most likely causing the presenting clinical syndrome, or targeted to a specific infection diagnosed definitively. Regardless, there are overarching concerns affecting STD treatment that pertain to adherence and treatment success, HIV status, partner treatment, test of cure, and pregnancy.

Adherence considerations may favor shorter or single-dose regimens. For example, although single-dose azithromycin is more expensive than 7-day doxycycline therapy, reduced medication compliance and attendant costs of follow-up evaluation for patients treated with doxycycline may favor the use of azithromycin.

With HIV coinfection, treatments are generally the same as for uninfected patients unless stated otherwise. One potential difference is that HSV often causes more significant and prolonged symptoms in HIV-infected than in uninfected patients, so that HIV-infected patients may require longer treatment or higher medication dosages, or both. Syphilis treatment is the same as for HIV-uninfected patients regardless of stage. However, careful follow-up is important, as treatment failure or progression to neurosyphilis may be more common in the presence of HIV.

Ulcerative and nonulcerative STDs can increase the risk of HIV transmission approximately three- to fivefold. Pregnancy imposes constraints and special considerations for therapy. Where applicable, these are noted in the treatment recommendations in Table 14-3.

As previously described, patients often present with a clinical syndrome potentially attributable to more than one infectious agent, and optimally focused therapy depends on microbiological identification. However, delaying therapy may allow symptoms to continue, resulting in untreated infection or continued spread (if the patient fails to return for follow-up or heed advice to avoid sexual contact until cured), and contribute to increased long-term morbidity. Consequently, it may be desirable to treat at the initial presentation for the infectious agents considered most likely.

Management of victims of sexual assault encompasses much more than treatment or prevention of STDs. Providers must heed legal requirements and effectively manage the psychological trauma, while not compromising the best course of medical care.

Proper medical management of sexual assault victims includes collection of evidence, diagnostic evaluation, counseling, and medical therapies to treat infection and unintended pregnancy. The diagnostic evaluation should include the following:

▶ Nucleic acid amplification tests for N gonorrhoeae and C trachomatis from specimens collected from any sites of penetration or attempted penetration.
▶ Vaginal wet mount and culture for T vaginalis if vaginal discharge, malodor, or pruritus is present.
▶ Serum tests for syphilis, hepatitis B, and HIV can be collected on an individual basis.

Evaluation for STDs may be repeated in 1-2 weeks after the initial evaluation to detect organisms that may have been undetected, unless the patient was treated prophylactically.

Web Sites

American Social Health Association (ASHA): http://www.ashastd.org/

SEXUAL ASSAULT
Providers should also consider testing for hepatitis C virus, transmission of which has been documented following sexual assault.

Prophylactic treatment for STDs may be offered or recommended as compliance with follow-up visits is poor. Hepatitis B vaccine should be administered according to the routine schedule; hepatitis B immune globulin is not necessary. Azithromycin, 1 g orally, plus ceftriaxone 250 mg intramuscularly, plus metronidazole, 2 g orally, may be offered to treat *C. trachomatis*, *N. gonorrhoea*, and *Trichomonas*. Gastrointestinal side effects, especially when combined with postcoital oral contraceptive pills, may make this regimen intolerable, and alternative therapies or watchful waiting may be preferable.

Need for and benefit from HIV postexposure prophylaxis is difficult to predict. If instituted, the greatest benefit results from initiation of therapy as soon after exposure as possible. For guidance in deciding whether to begin postexposure HIV prophylaxis and in selecting appropriate treatment and monitoring, providers may contact the National Clinician's Post-Exposure Prophylaxis Hotline (PEPline) at 888-HIV-4911 (888-448 4911).

After the neonatal period, STDs in children most commonly result from sexual abuse. In addition to vaginal gonococcal infection, pharyngeal and anorectal infection may occur and are often asymptomatic. Specific diagnostic techniques should rely only on existing guidelines as data on nucleic acid amplification tests for *Chlamydia* and gonorrhea is limited and performance may be test dependent. Specimen preservation is essential for future testing when needed.


On the average, each day longer you live the longer you are likely to live, yet the closer to dying you become.

The goal of health maintenance (HM) is to help people live longer and healthier lives.

In this chapter, the findings and positions of the United States Preventative Service Task Force (USPSTF) are emphasized because it generates the most comprehensive and evidence-based recommendations of any organization. Hence, knowing the USPSTF grading system for its recommendations is important (Table 15-1). The USPSTF is sponsored by the Agency for Healthcare Research and Quality (AHRQ) and is the leading independent panel of private-sector experts in prevention and primary care. The rest of this chapter lays out HM by the age groups 18-39, 40-49, 50-59, 60-74, and 75 years or older. USPSTF Grade A & B recommendations are emphasized with highlights some areas of special interest or controversy, including sections on immunizations and aspirin. Health maintenance involves three types of prevention: primary, secondary, and tertiary (Figure 15-2).

**Prevention**

**A. Primary Prevention**

Targets individuals who may be at risk to develop a medical condition and intervenes to prevent the onset of that condition (eg, childhood vaccination programs, water fluoridation, smoking prevention programs, clean water, and sanitation). The disease does not exist. The goal is to prevent development of disease.

**B. Secondary Prevention**

Targets individuals who have developed an asymptomatic disease and institutes treatment to prevent complications (eg, routine Papanicolaou smears, and screening for hypertension, diabetes, or hyperlipidemia). The disease does exist, but the person is unaware (asymptomatic). The goal is to identify and treat people with disease.

**C. Tertiary Prevention**

Targets individuals with a known disease, with the goal of limiting or preventing future complications (eg, rigorous treatment of diabetes mellitus, and post–myocardial infarction treatment with β-blockers and aspirin). The disease exists and there are symptoms. The goal is to prevent complications.

Secondary and tertiary prevention require some type of screening: who should get screened, for which disease(s), and with what test(s)? (Table 15-2.)

1. **The disease**—The disease must have a period of being detectable before the symptoms start so it can be found and treated, for example, colon cancer has no early symptoms but can be detected with screening. The disease cannot appear too quickly (eg, a cold, certain lung cancers). The disease must be common in the target population, for example, stomach cancer is not screened for in the United States (uncommon), but it is screened for in Japan where it is more common.

2. **The test**—Ideally the screening test will identify all people with disease and only people with disease will test positive. The reality: screening tests are acceptable if they do the job well enough—sensitive enough to have few false negatives and specific enough to have few false positives. Screening test should also be cost-efficient, easy, reliable, and as painless as possible.

**Treatment**

When screening for disease, treatment must be available, acceptable, and have benefits that outweigh the risk. Mortality is the most often used endpoint. If a group of people who are screened and then treated live longer or better than a group of people who are not screened, then the screening test may be good for that population. If the two groups of people die at the same rate, there is usually no point in screening for the disease.
A. Health Maintenance: Across the Ages—What Not to Do

Conditions for which the USPSTF recommends against routine screening in asymptomatic adults:

- Aspirin to prevent myocardial infarction in men younger than 45 years old
- Asymptomatic bacteriuria in men and nonpregnant women
- Bladder cancer
- Carotid artery stenosis
- Chronic obstructive pulmonary disease
- Electrocardiography (ECG)
- Genital herpes
- Gonorrhea in low-risk men and women
- Heart disease in low-risk men and women using ECG, EBCT
- Hemochromatosis
- Hepatitis B
- Hepatitis C
- Ovarian cancer
- Pancreatic cancer
- Peripheral arterial disease
- Routine aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) for primary prevention of colorectal cancer for average risk
- Scoliosis
- Stress echocardiogram
- Syphilis
- Testicular cancer
- Vitamin supplements with β-carotene to prevent cancer and cardiovascular disease (CVD)

B. Health Maintenance: Across the Ages—Insufficient Evidence

Conditions for which the USPSTF found insufficient evidence to promote routine screening in asymptomatic adults at low risk:

- Chlamydia in men
- Dementia
- Diabetes mellitus
- Drug abuse
- Family violence
- Glaucoma
- Lung cancer
- Oral cancer
- Prostate cancer
- Skin cancer
- Suicide
- Thyroid disease
- Vitamin supplements with A, C, E, multi to prevent cancer and heart disease

C. Health Maintenance: Across the Ages—Aspirin

The role of aspirin in health maintenance and promotion is dependent on whether it is used for primary or secondary/tertiary prevention. For the latter it is generally beneficial (Table 15-3). For primary prevention it is not that simple (Tables 15-4 through 15-6). Evidence is unclear in terms of risk-to-benefit for the role of aspirin in colorectal cancer prevention.

D. Health Maintenance: Age 18-39

Table 15-7 summarizes USPSTF recommendations for average risk 18- to 39-year-olds.

- Screening tests in focus: hypertension, cervical cancer, Chlamydia, lipid disorders, depression, tobacco, and risk-targeted.
1. Hypertension—Hypertension is a common disease that contributes to significant adverse health outcomes, including premature deaths, heart attacks, renal insufficiency, and stroke. Blood pressure measurement identifies individuals at increased risk for cardiovascular disease. Treatment of hypertension decreases the incidence of cardiovascular disease events.

Hypertension in adults is defined as a systolic blood pressure of 140 mm Hg or higher, or a diastolic blood pressure of 90 mm Hg or higher on at least two separate obtained on at least two visits over a period of one to several weeks.

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends screening every 2 years in persons with blood pressure less than 120/80 mm Hg and every year with systolic blood pressure of 120-139 mm Hg or diastolic blood pressure of 80-90 mm Hg. The American Heart Association (AHA) has issued similar recommendations beginning at age 20.


3. Chlamydia screening—The USPSTF recommends screening for Chlamydia infection for all sexually active women 24 years of age and younger and for women 25 years of age and older who are at increased risk, regardless of pregnancy status. Chlamydia trachomatis infection is the most common sexually transmitted bacterial infection in the United States. In women, genital infection may result in urethritis, cervicitis, pelvic inflammatory disease (PID), infertility, ectopic pregnancy, and chronic pelvic pain. Infection during pregnancy is related to adverse pregnancy outcomes, including miscarriage, premature rupture of membranes, preterm labor, low birth weight, and infant mortality. The benefits of screening and subsequent treatment in high-risk pregnant and nonpregnant individuals are substantial.

The USPSTF found no evidence of benefit of screening women who are not at increased risk for Chlamydia infection in a lower-risk population the certainty is moderate that the benefits outweigh the harms of screening to only a small degree.

Nucleic acid amplification tests (NAAT) for Chlamydia have high specificity and sensitivity as screening tests. However, in low-prevalence populations, a positive test is more likely to be a false positive than a true positive: low positive predictive value. NAAT can be used with urine and vaginal swabs, enabling screening when a pelvic examination is not performed.

Screening of pregnant women for Chlamydia infection is recommended at the first prenatal visit. For pregnant women who remain at increased risk and acquire a new risk factor, such as a new sexual partner, a screening should occur during the third trimester. The optimal screening interval for nonpregnant women is unknown. The CDC recommends at least annual screening for women at increased risk.

4. Lipid disorders—High levels of total cholesterol and LDL and low levels of HDL are important risk factors for coronary heart disease. Men older than the age of 35 should be screened for lipid disorders. This age may be reduced to 20 if there is an increased risk for coronary heart disease. Screening for women does not need to start until age 45. At least two serum lipid measurements are necessary to ensure that true values are within 10% of the mean of the measurements.

**Table 15-2. USPSTF grade definitions.**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Suggestions for Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is substantial.</td>
<td>Offer or provide this service.</td>
</tr>
<tr>
<td>B</td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.</td>
<td>Offer or provide this service.</td>
</tr>
<tr>
<td>C</td>
<td>The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is at least moderate certainty that the net benefit is small.</td>
<td>Offer or provide this service only if other considerations support the offering or providing the service in an individual patient.</td>
</tr>
<tr>
<td>D</td>
<td>The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.</td>
<td>Discourage the use of this service.</td>
</tr>
<tr>
<td>I</td>
<td>The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.</td>
<td>Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.</td>
</tr>
</tbody>
</table>
Table 15-3. Indications for aspirin (ASA) therapy summary of available guidelines and recent evidence in selected disease states and concomitant therapies.

<table>
<thead>
<tr>
<th>Topic</th>
<th>Available Guidelines and Recent Evidence</th>
</tr>
</thead>
</table>
| **Diabetes** Secondary prevention | ADA Diabetes Guidelines 2010:  
- Men > 50 (women > 60) years of age and one of the following: family history of CVD, smoking, hypertension, dyslipidemia, albuminuria  
BMJ 2009 Meta-analysis:  
- No difference in risk of major CV events, CV mortality, or all-cause mortality between ASA and placebo → Role of ASA in this population questioned  
- Decreased risk of MI in men, but not in women (significant study heterogeneity) |
| **Heart failure** Secondary prevention | ACC/AHA Update to Heart Failure Guidelines 2009:  
No recommendation at this time due to controversial evidence  
- Aspirin may negate the positive effect of angiotensin-converting enzyme (ACE) inhibitor therapy |
| **Dual therapy (ASA + warfarin)** Secondary prevention | ACCP Antithrombotic and Thrombolytic Therapy Guidelines 2008:  
- Patients with mechanical heart valves  
  1. And a history of coronary artery disease, peripheral arterial disease, or other risk factors for atherosclerotic disease (1B)  
  2. Who have additional risk factors for thromboembolism: atrial fibrillation, hypercoagulable state, or low ejection fraction (1B)  
  a. Consider if bioprosthetic heart valves and additional risk factors for thromboembolism (2C)  
  b. Particularly in patients with a history of atherosclerotic disease.  
  c. Following clopidogrel discontinuation in patients on triple therapy.  
  d. No dual therapy if at high risk for bleeding—history of GI bleed or age > 80 years (2C) |
| **Dual antiplatelet therapy (ASA + clopidogrel)** Secondary and tertiary prevention | ACCP Antithrombotic and Thrombolytic Therapy Guidelines 2008: primary prevention  
- Recommend against routine use of aspirin and clopidogrel (1A)  
ACCP Antithrombotic and Thrombolytic Therapy Guidelines 2008: secondary prevention  
- NSTE ACS: clopidogrel × 12 months (1A)  
- Symptomatic coronary artery disease (2B)  
- PCI with bare-metal stent: clopidogrel × 12 mo (1A)  
- PCI with drug-eluting stent: clopidogrel × 12 mo (1B)  
- Indefinitely if low risk of bleeding and combination tolerable (2C). |
| **Triple therapy (ASA + clopidogrel + warfarin)** Tertiary prevention | ACCP Antithrombotic and Thrombolytic Therapy Guidelines 2008:  
- PCI with bare-metal stent and strong indication for warfarin: clopidogrel × 4 wk (2C)  
- PCI with drug-eluting stent and strong indication for warfarin: clopidogrel × 12 mo (2C)  
- Consider warfarin INR goal of 2.0-2.5 |

ADA, American Diabetes Association; AHA, American Heart Association; CVD, Cardiovascular disease; BMJ, British Medical Journal; CV, Cardiovascular; MI, myocardial infarction; ACC, American College of Cardiology; ACCP, American College of Chest Physicians; GI, gastrointestinal; NSTE ACS, non-ST-elevated acute coronary syndrome; PCI, percutaneous coronary intervention.

<table>
<thead>
<tr>
<th>ACCP 2008 Grades of Recommendation</th>
<th>1A</th>
<th>1B</th>
<th>1C</th>
<th>2A</th>
<th>2B</th>
<th>2C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Strong recommendation, high-quality evidence</td>
<td>Strong recommendation, moderate-quality evidence</td>
<td>Strong recommendation, low- or very-low-quality evidence</td>
<td>Weak recommendation, high-quality evidence</td>
<td>Weak recommendation, moderate-quality evidence</td>
<td>Weak recommendation, low- or very-low-quality evidence</td>
</tr>
</tbody>
</table>
The optimal interval for screening is uncertain. Reasonable options include every 5 years, with shorter intervals for those with risk factor and/or lipid levels close to those warranting therapy.

While high levels of total cholesterol and low-density lipoprotein-cholesterol (LDL-C) and low levels of high-density lipoprotein-cholesterol (HDL-C) are important risk factors for coronary heart disease (CHD), the risk for CHD is highest in those with a combination of risk factors. Therefore, a careful review of the complete risk factor profile is necessary to assess the benefit of screening and subsequent lowering of high cholesterol levels with medications. (Please see the Chapter 21 for a fuller discussion of lipid disorders.)

5. Depression screening—The USPSTF recommends screening adults for depression only when staff-assisted depression care supports are in place to assure accurate diagnosis, effective treatment, and follow-up (Grade B). It recommends against routinely screening adults for depression when staff-assisted depression care supports are not in place (Grade C). There may be considerations that support screening for depression in an individual patient.

6. Tobacco use counseling—Cessation of tobacco use may be the single most important lifestyle intervention for the maintenance and improvement of health. All adults should be assessed for tobacco use and tobacco cessation interventions provided for those who use tobacco products. Tobacco use, cigarette smoking in particular, is the leading cause of preventable death in the United States, resulting in more than 400,000 deaths annually from cardiovascular disease, respiratory disease, and cancer. Smoking during pregnancy results in the deaths of about 1000 infants annually and is associated with an increased risk for premature birth and intrauterine growth retardation. Environmental tobacco smoke may contribute to death in up to 38,000 people annually.

Cessation of tobacco use is associated with a corresponding reduction in the risk of heart disease, stroke, and lung disease. Tobacco cessation at any point during pregnancy yields substantial health benefits for the expectant mother and baby.

<table>
<thead>
<tr>
<th>Prevention Outcome &amp; Increased Risk</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Myocardial infarctions</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Cardiovascular mortality or all-cause mortality</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>


### Table 15-4.
Evidence for the use of aspirin for primary prevention of cardiovascular events and associated increased risk of adverse events in men versus women.

### Table 15-5.
When to use aspirin for primary prevention of myocardial infarction (men) and stroke (women) based on age and 10-year Framingham risk for event.

<table>
<thead>
<tr>
<th>Men (Years)</th>
<th>10-Year MI Risk</th>
<th>&lt; 45</th>
<th>45-59</th>
<th>60-69</th>
<th>70-79</th>
<th>&gt; 80</th>
<th>Risk:Benefit Consideration for Patients with GI Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (Years)</td>
<td>10-Year Stroke Risk</td>
<td>&lt;55</td>
<td>55-59</td>
<td>60-69</td>
<td>70-79</td>
<td>&gt; 80</td>
<td>Evidence lacking</td>
</tr>
<tr>
<td>Framingham Score</td>
<td>4%-8%</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Evidence lacking</td>
</tr>
<tr>
<td></td>
<td>3%-7%</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Evidence lacking</td>
</tr>
<tr>
<td></td>
<td>9%-11%</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Evidence lacking</td>
</tr>
<tr>
<td></td>
<td>8%-10%</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Evidence lacking</td>
</tr>
<tr>
<td></td>
<td>&gt;12%</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Evidence lacking</td>
</tr>
<tr>
<td></td>
<td>&gt;11%</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Evidence lacking</td>
</tr>
</tbody>
</table>

Smoking cessation interventions, including brief (<10 minutes) behavioral counseling sessions and pharmacotherapy delivered in primary care settings, are effective in increasing the proportion of smokers who successfully quit and remain abstinent for 1 year. Even minimal counseling interventions (<3 minutes) are associated with improved quit rates. One of several screening strategies aimed at engaging patients in smoking cessation discussions is the “five As” behavioral counseling framework:

1. Ask about tobacco use
2. Advise to quit through clear personalized messages
3. Assess willingness to quit
4. Assist to quit
5. Arrange follow-up and support

7. Screening and counseling targeted for those at increased risk—
   - BRCA mutation testing for breast and ovarian cancer
   - Gonorrhea: Women who are pregnant or at increased risk
   - Healthy diet: Adults with hyperlipidemia and other risk factors for coronary heart disease (CHD)
   - Sexually transmitted infections: Behavioral counseling for sexually active adolescents and adults at increased risk
   - Type 2 diabetes mellitus: Men and women with sustained more than or equal to BP 135/80 mm Hg
   - Syphilis: Men and women at increased risk
   - Lipid disorders in adults: Screening women aged 20–44 and men 20–34 years at increased risk for CHD

<table>
<thead>
<tr>
<th>One of the Following</th>
<th>Two of the Following</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant other NSAID use</td>
<td>Age ≤60 y</td>
</tr>
<tr>
<td>History of ulcer complication</td>
<td>Corticosteroid steroid use</td>
</tr>
<tr>
<td>History of ulcer disease</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td>Concomitant antiplatelets</td>
<td>Gastroesophageal reflux disease symptoms</td>
</tr>
<tr>
<td>Concomitant anticoagulants</td>
<td></td>
</tr>
<tr>
<td>History of gastrointestinal bleeding</td>
<td></td>
</tr>
</tbody>
</table>

*Aspirin therapy: proton pump inhibitor therapy recommended based on gastrointestinal risk factors.

Smoking cessation interventions, including brief (<10 minutes) behavioral counseling sessions and pharmacotherapy delivered in primary care settings, are effective in increasing the proportion of smokers who successfully quit and remain abstinent for 1 year. Even minimal counseling interventions (<3 minutes) are associated with improved quit rates. One of several screening strategies aimed at engaging patients in smoking cessation discussions is the “five As” behavioral counseling framework:

1. Ask about tobacco use
2. Advise to quit through clear personalized messages
3. Assess willingness to quit
4. Assist to quit
5. Arrange follow-up and support

7. Screening and counseling targeted for those at increased risk—
   - BRCA mutation testing for breast and ovarian cancer
   - Gonorrhea: Women who are pregnant or at increased risk
   - Healthy diet: Adults with hyperlipidemia and other risk factors for coronary heart disease (CHD)
   - Sexually transmitted infections: Behavioral counseling for sexually active adolescents and adults at increased risk
   - Type 2 diabetes mellitus: Men and women with sustained more than or equal to BP 135/80 mm Hg
   - Syphilis: Men and women at increased risk
   - Lipid disorders in adults: Screening women aged 20–44 and men 20–34 years at increased risk for CHD

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-24</td>
<td>Cervical cancer, start at age 21 if has had sexual debut (A)</td>
<td>Hypertension (A)</td>
</tr>
<tr>
<td>Screen</td>
<td>Chlamydia, if sexually active (A)</td>
<td>Tobacco use and counsel as needed (A)</td>
</tr>
<tr>
<td></td>
<td>Tobacco use and counsel as needed (A)</td>
<td>Obesity (B)</td>
</tr>
<tr>
<td></td>
<td>Alcohol use disorders (B)</td>
<td>Alcohol use disorders (B)</td>
</tr>
<tr>
<td></td>
<td>Depression if system in place to manage (B)</td>
<td>Depression (B)</td>
</tr>
<tr>
<td></td>
<td>Rubella susceptibility by history of vaccination or serology (B)</td>
<td></td>
</tr>
<tr>
<td>25-34</td>
<td>Same as 18-24</td>
<td>Same as 18-24</td>
</tr>
<tr>
<td>Screen for Chlamydia if high risk (A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-39</td>
<td>Same as 25-34</td>
<td>Same as 25-34</td>
</tr>
<tr>
<td>Screen for hyperlipidemia (A)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 15-6. When to add proton pump inhibitor therapy to ASA.

E. Health Maintenance: Age 40-49 with a Highlight on Breast Cancer and Lipid Screening

Tables 15-8 (A-C) summarize USPSTF recommendations for average risk 40- to 49-year-olds.

1. Breast cancer—Please see Chapter 26 for discussion of screening for breast cancer.

2. Lipid screening—Women aged 45 years and older should be screened for lipid disorders if they are at increased risk for coronary heart disease (CHD). Increased risk, for this recommendation, is defined by the presence of any of the following risk factors: diabetes, previous personal history of CHD or noncoronary atherosclerosis (eg abdominal aorta aneurysm, peripheral artery disease, carotid artery stenosis), a family history of cardiovascular disease before age 50 in male relatives or age 60 in female relatives, tobacco use, hypertension, obesity (BMI >30). (Further discussion of dyslipidemia is found in section Health Maintenance: Age 18-39, earlier and Chapter 21.)

F. Health Maintenance: Age 50-59

Table 15-9 summarizes USPSTF recommendations for average risk 50- to 59-year-olds.

1. Colorectal cancer screening—This should occur from age 50-75 years using a variety of tests.

   Sensitivity: Hemoccult II < fecal immunochemical tests < Hemoccult SENSA = flexible sigmoidoscopy < colonoscopy

   Specificity: Hemoccult SENSA < fecal immunochemical tests = Hemoccult II < flexible sigmoidoscopy = colonoscopy

   Screening with fecal occult blood testing, sigmoidoscopy, or colonoscopy reduce mortality assuming 100% adherence to any of these regimens: (1) annual high-sensitivity fecal occult blood testing, (2) sigmoidoscopy every 5 years combined with high-sensitivity fecal occult blood testing every 3 years, or (3) screening colonoscopy at intervals of 10 years. Evidence is insufficient regarding screening with fecal DNA or CT colonography.

   For a more complete discussion of colorectal cancer screening, see Chapter 39.

2. Hypertension—Screen every 2 years if blood pressure is less than 120/80 mm Hg and every year with systolic blood pressure of 120-139 mm Hg or diastolic blood pressure of 80-90 mm Hg.

3. Aspirin—Benefits must outweigh risk. See earlier ASA discussion and tables. It should not be initiated in women younger than 55 years of age to prevent stroke.

4. Prostate cancer screening (I recommendation)—Prostate cancer is the most common non-skin cancer in US males. If they live to be 90 years old, 1 out of 6 US males will be diagnosed with prostate cancer. Risk factors for development of prostate cancer include advanced age, family history, and race. Nearly 70% of prostate cancer diagnoses occur in men age 65 and older. The risk of developing prostate cancer is nearly 2.5 times greater in men with a family history of prostate cancer in a first-degree relative. Rates of prostate cancer occurrence are lower in Asian and Hispanic males than in white males. Black men are at twice the risk of white men. While US men have an approximately 16% lifetime risk of being diagnosed with prostate cancer, they have only about 3% risk of dying from it.

   Digital rectal examination (DRE) and prostate-specific antigen (PSA) testing are the most commonly used prostate cancer screening tools. Physician performed DRE is limited in that it allows only a portion of the prostate gland to be palpated and has poor inter-rater reliability. Sensitivity of DRE is low (53%-59%) and positive predictive value (PPV) is only 18%-28%. The PPV of PSA for prostate cancer screening is similarly low at about 30%. Proposed prostate cancer screening methods include using PSA cutoff of 4 ng/mL, measuring PSA velocity, and percent free PSA. No currently available data demonstrates a mortality benefit with any of these.

   DRE and PSA screening can lead to detection of clinically insignificant prostate cancers, exposing patients to undue psychological distress and potentially harmful procedures and treatments, such as biopsy and radical prostatectomy. Unfortunately, DRE and PSA screening can also miss aggressive prostate cancers. As discussed earlier, an effective screening test should detect disease early and early treatment should improve morbidity and mortality. There is no conclusive evidence that treatment of prostate cancers detected by screening improves outcomes. Recognition of the fact that most men with prostate cancer die with, rather than from, their disease and acknowledgement of the limitations of currently available prostate screening tests has led to debate regarding the best prostate screening practices.

   Based upon the lack of evidence that treatment of prostate cancer detected by screening improves outcomes, the USPSTF has concluded that evidence is insufficient to determine the balance between benefits and harms associated with prostate cancer screening in men less than 75 years of age (1 recommendation). Furthermore, USPSTF recommends against screening for prostate cancer in men older than 75 years (Grade D) due to evidence that harms outweigh benefits. The American Academy of Family Physicians (AAFP) supports the USPSTF guidelines. The American Urologic Association (AUA) and American Cancer Society (ACS) recommend offering DRE and PSA annually to all men age 50 and older who have a life expectancy of greater than or equal to 10 years. ACS goes on to recommend that screening begin at age 45 for men at high risk for prostate cancer.

   The strength of support of these various organizations for prostate cancer screening varies. All recommendations, however, emphasize the importance of discussing this complicated issue with patients and reaching a shared, patient-centered decision regarding prostate cancer screening. This discussion should include information about the risks and benefits of screening, the limitations of screening, and what additional testing will follow in the event of an abnormal
### Table 15-8A. Health promotion and preventive screening for adults aged 40-49.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Target Group, a</th>
<th>Screening Interval, b</th>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin to prevent CVD</td>
<td>Men 45-79, every 5 y or when other cardiovascular risk factors are detected</td>
<td>A</td>
<td>Aspirin daily when the potential benefit due to a reduction in myocardial infarctions outweighs the potential harm due to an increase in gastrointestinal hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Physical exam</td>
<td>1-2 y depending on BP</td>
<td>A</td>
<td>Screen every 2 y in persons with BP &lt;120/80 mm Hg and every year in persons with BP 120-130/80-90 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Blood pressure (BP)</td>
<td>Men &gt; 35, every 5 y women &gt; 45 if risk for CHD, every 5 y</td>
<td>A</td>
<td>For women, the risk factors include diabetes, previous personal history of CHD or non-coronary atherosclerosis, a family history of cardiovascular disease before 50 in males and 60 in females, tobacco, hypertension, obesity (BMI &gt;30)</td>
<td></td>
</tr>
<tr>
<td>Testing</td>
<td>Every 1-3 y</td>
<td>A</td>
<td>Screen for cervical cancer in women who have been sexually active and have a cervix</td>
<td></td>
</tr>
<tr>
<td>Lipid disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pap smear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>If high risk</td>
<td>A</td>
<td>Risks include men having sex with men, unprotected sex with multiple partners, injection drug use, sex worker, history of sex with partners who are HIV+, bisexual, or injection drug users, history of STI, transfusion between 1978 and 1985</td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>If high risk</td>
<td>A</td>
<td>Risks include men who have sex with men and engage in high-risk sexual behavior, commercial sex workers, persons who exchange sex for drugs, and those in adult correctional facilities</td>
<td></td>
</tr>
<tr>
<td>Chlamydia</td>
<td>If high risk</td>
<td>A</td>
<td>Risks factors include a history of Chlamydia or other STI, new or multiple sexual partners, inconsistent condom use, and exchanging sex for money or drugs</td>
<td></td>
</tr>
<tr>
<td>Counsel</td>
<td>Against routine screening in normal-risk women aged 40-49 y</td>
<td>C</td>
<td>Offer mammography to an individual patient if she is at higher risk of breast cancer (<a href="http://www.cancer.gov/bcrisktool/">http://www.cancer.gov/bcrisktool/</a>)</td>
<td></td>
</tr>
<tr>
<td>Tobacco use</td>
<td>All with sustained blood pressure greater than 135/80 mm Hg.</td>
<td>B</td>
<td>Screen asymptomatic adults with sustained blood pressure &gt; 135/80 mm Hg.</td>
<td></td>
</tr>
<tr>
<td>Testing</td>
<td>All with sustained blood pressure greater than 135/80 mm Hg.</td>
<td>B</td>
<td>Clinicians screen all adult patients for obesity and offer intensive counseling and behavioral interventions to promote sustained weight loss for obese adults</td>
<td></td>
</tr>
<tr>
<td>Mammogram</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counsel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>obesity: BMI&gt;30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol misuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STI</td>
<td>If high risk</td>
<td>B</td>
<td>Screen adults with STI in past year or multiple current sexual partners</td>
<td></td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease; CHD, coronary heart disease; BMI, body mass index; HIV, human immunodeficiency virus; STI, sexually transmitted infection.

aTarget group: if none noted, includes men and women aged 40-49.

bScreening interval: if none noted, unknown.

screening test. Several organizations including AAFP, ACS, and AUA have created patient-friendly education material that is readily available online and can aid in the discussion of prostate cancer screening with your patient (Figure 15-2). Additionally, the Agency for Healthcare Quality and Research has a video for providers, “How to Talk with Your Patients When Evidence is Insufficient” at http://www.ahrq.gov/CLINIC/uspstf/uspsprca.htm.

G. Health Maintenance: Age 60-74
Table 15-10 summarizes USPSTF recommendations for average-risk 60- to 74-year-olds.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td></td>
</tr>
<tr>
<td>≥75</td>
<td>15</td>
</tr>
<tr>
<td>65-74</td>
<td>9</td>
</tr>
<tr>
<td>55-64</td>
<td>5</td>
</tr>
<tr>
<td>45-54</td>
<td>0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>9</td>
</tr>
<tr>
<td>60-69</td>
<td>3</td>
</tr>
<tr>
<td>≥70</td>
<td>0</td>
</tr>
<tr>
<td>Current estrogen use</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
</tbody>
</table>

Women with a total score of 9 or greater would be selected for bone densitometry.

Note: The Osteoporosis Risk Assessment Instrument (ORAI) uses age, weight, and the use of estrogen as an aid to selecting postmenopausal patients for bone density testing. A score greater than 9 would indicate testing is warranted. Source: Cadarette 2000. Development and validation of the Osteoporosis Risk Assessment Instrument to facilitate selection of women for bone densitometry—Reprinted from CMAJ 02-May-00: 162(9), 1289-1294 by permission of the publisher. ©2000 Canadian Medical Association.

1Risk factors: Low body weight (<70 kg) is the single best predictor of low bone mineral density; next best is no current use of estrogen therapy; others supported by less evidence include smoking, weight loss, family history, decreased physical activity, alcohol or caffeine use, or low calcium and vitamin D intake.

H. Health Maintenance: Age 75 or Older
Perhaps the most important aspect of health maintenance in patients 75 years and older is lifestyle. HM recommendations for this age group is summarized in Table 15-11 and discussed below.

In patients aged 75 years and older, health maintenance decisions become more complex. The focus remains both primary and secondary prevention, however there are relatively few studies evaluating the utility and impact of health maintenance interventions in this population. Therefore, it becomes increasingly important to work with geriatric patients to make...

<table>
<thead>
<tr>
<th>Population</th>
<th>Age 40-49 y</th>
<th>Age 50-74 y</th>
<th>Age ≥75 y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommend</strong></td>
<td>Do not screen routinely. Individualize decision to begin biennial screening according to the patient’s context, risk, and values. Grade: C</td>
<td>Screen every 2 y Grade: B</td>
<td>No recommendation</td>
</tr>
<tr>
<td><strong>Risk assessment</strong></td>
<td>Recommendation applies to women aged ≥40 y not at increased risk by virtue of a known genetic mutation or history of chest radiation. Increasing age is the most important risk factor for most women.</td>
<td></td>
<td>Grade: I (insufficient evidence)</td>
</tr>
<tr>
<td><strong>Screening tests</strong></td>
<td>Standardization of film mammography has led to improved quality. Refer patients to facilities certified under the Mammography Quality Standards Act (MQSA).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Timing of screening</strong></td>
<td>Evidence indicates that biennial screening is optimal. This preserves most of the benefit of annual screening and cuts the harms nearly in half. A longer interval may reduce the benefit.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Balance of harms and benefits</strong></td>
<td>There is convincing evidence that screening with film mammography reduces breast cancer mortality, with a greater absolute reduction for women aged 50-74 y than for younger women. Harms of screening include psychological harms, additional medical visits, imaging, and biopsies in women without cancer, inconvenience due to false-positive screening results, harms of unnecessary treatment, and radiation exposure. Harms seem moderate for each age group.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>False-positive results are a greater concern for younger women; treatment of cancer that would not become clinically apparent during a woman’s life (overdiagnosis) is an increasing problem as women age.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nothing specific recommended (Grade I)</strong></td>
<td></td>
<td></td>
<td>Among women 75 y or older, evidence of benefit is lacking</td>
</tr>
</tbody>
</table>
Table 15-9. Health promotion and preventive screening for adults aged 50-59.

<table>
<thead>
<tr>
<th>USPSTF Grade</th>
<th>Recommended Health Promotion or Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>A°</td>
<td>Aspirin to prevent CVD: men age 45-79 to prevent myocardial infarctions</td>
</tr>
<tr>
<td>A'</td>
<td>Cervical cancer: screen sexually active women ≥21 q3y as long as normal</td>
</tr>
<tr>
<td>A'</td>
<td>Chlamydia: screening—women ages 24 and younger or women ages ≥25 at increased risk</td>
</tr>
<tr>
<td>A</td>
<td>Colorectal cancer: screening—adults, beginning at age 50 and continuing until age 75</td>
</tr>
<tr>
<td>A</td>
<td>HIV: screening—adults and adolescents at increased risk</td>
</tr>
<tr>
<td>A</td>
<td>High blood pressure: screening—adults ≥18</td>
</tr>
<tr>
<td>A</td>
<td>Lipid disorders in adults: screening—men ≥35</td>
</tr>
<tr>
<td>A</td>
<td>Lipid disorders in adults: screening—women ≥45, increased risk for CHD</td>
</tr>
<tr>
<td>A</td>
<td>Syphilis: screening—men and women at increased risk</td>
</tr>
<tr>
<td>A°</td>
<td>Tobacco use: counseling and interventions for adults</td>
</tr>
<tr>
<td>B</td>
<td>Alcohol misuse: screening and behavioral counseling—men, women, and pregnant women</td>
</tr>
<tr>
<td>B</td>
<td>BRCA mutation testing for breast and ovarian cancer: women, increased risk</td>
</tr>
<tr>
<td>B</td>
<td>Breast cancer: preventive medication discussion—women, increased risk</td>
</tr>
<tr>
<td>B°</td>
<td>Breast cancer: screening with mammography—women aged 50-74</td>
</tr>
<tr>
<td>B°</td>
<td>Depression: screening—adults age ≥18—when staff-assisted depression care supports are in place</td>
</tr>
<tr>
<td>B</td>
<td>Gonorrhea: screening—pregnant women and women at increased risk</td>
</tr>
<tr>
<td>B</td>
<td>Healthy diet: counseling—adults with hyperlipidemia and other risk factors for CVD</td>
</tr>
<tr>
<td>B</td>
<td>Obesity: screening and intensive counseling—obese men and women</td>
</tr>
<tr>
<td>B</td>
<td>Sexually transmitted infections: behavioral counseling—sexually active adolescents and adults at increased risk</td>
</tr>
<tr>
<td>B</td>
<td>Type 2 diabetes mellitus: screening men and women if sustained BP &gt; 135/80 mm Hg</td>
</tr>
</tbody>
</table>

*See earlier discussion and tables.
informed, individualized health maintenance decisions. Amongst people aged 75 years and older, there exist wide variations in the number and severity of comorbid conditions, functional status, life expectancy and patients’ overall goals of care and preferences. Each of these factors must be considered when discussing health maintenance interventions in older patients. Consideration of both risks and harms of any health maintenance intervention is also essential.

Guidelines regarding cancer screening in patients aged 75 and older especially require individualized, patient-specific discussions and decisions. The American College for Gastroenterology (ACG) recommends colon cancer screening at age 50 and does not suggest when to discontinue screening. USPSTF suggests that the benefits of colon cancer screening in adults over the age of 75 do not outweigh the harms, and explicitly recommends against it in patients older than 85 years. For prostate cancer, USPSTF recommends against screening for prostate cancer in men over the age of 75 while the American Urologic Association (AUA) and American Cancer Society (ACS) recommend offering DRE and PSA annually to all men age 50 and older who have a life expectancy of 10 years and greater. The American Geriatric

### Figure 15-2. Websites with Prostate Cancer Patient Education.

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| **Women 60-74 y** | Pap smear: at least every 3 y (A)  
Mammogram: every 1-2 y (B)  
Colorectal cancer screening* (A)  
Osteoporosis screen: all women aged ≥ 65 and high-risk women starting at age 60: screen using DEXA or bone densitometry testing (B)  
Weight and BMI: screen for obesity using BMI (body mass index) (B)  
Blood Pressure: annually for all adults (A)  
Tobacco: counsel about quitting (A)  
Alcohol: counsel to reduce alcohol misuse (B)  
Aspirin chemoprevention: postmenopausal women and all with increased coronary heart disease risk (A) |
| **Men 60-74 y** | Cholesterol: test every 5 y (A)  
Abdominal aortic aneurysm (AAA): ultrasound once in men who have ever smoked (B, C)  
Colorectal cancer: screening* (A)  
Weight and BMI: screen for obesity using BMI (B)  
Blood pressure: annually for all adults (A)  
Tobacco: counsel about quitting (A)  
Alcohol: counsel to reduce alcohol misuse (B)  
Aspirin chemoprevention: postmenopausal women and all with increased coronary heart disease risk (A) |

*See colon cancer screening discussion in section Health Maintenance: Age 50-59.
Society (AGS) recommends screening mammography every 3 years after age 75 with no upper age limit for women with an estimated life expectancy of four or more years. USPSTF recommends neither for nor against screening mammography in women 75 years and older. ACS and USPSTF agree that older women with previously negative Pap results do not require continuation of screening for cervical cancer over the age of 75.

Screening for hearing impairment using simple subjective patient questioning was recommended in the 1996 USPSTF guidelines, but this recommendation is currently being revised. There is no recommendation for or against screening for vision impairment in asymptomatic patients. Similarly, USPSTF does not recommend for or against screening for dementia individuals without symptoms.

### I. Health Maintenance: Adult Immunizations

Tables 15-12 and 15-13 are summary of vaccination recommendations for adults.

**Table 15-11. Health promotion & preventive screening for adults Aged ≥75.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>USPSTF Screening Recommendations (Grade)</th>
<th>Alternate Recommendations from Other Organizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco abuse</td>
<td>Recommended (A)</td>
<td></td>
</tr>
<tr>
<td>Alcohol misuse</td>
<td>Recommended (A)</td>
<td></td>
</tr>
<tr>
<td>Nutrition screening and counseling</td>
<td>Recommended (B)—for patients with risk factors for cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Recommended (A)</td>
<td></td>
</tr>
<tr>
<td>Lipids</td>
<td>Recommended (A)</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>Recommended (B)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Recommended (B)</td>
<td></td>
</tr>
<tr>
<td>Aspirin for prevention of cardiovascular disease</td>
<td>Recommended (A)—up to age 79</td>
<td></td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Not recommended routinely (C), but in select patients up to age 85; Recommendation against (D) age &gt;85</td>
<td>ACG: indefinite screening after age 50</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Recommendation against (D)</td>
<td>AUA, ACS: DRE and PSA annually for men ≥age 50 with life expectancy ≥10 y</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Neither for nor against (I)</td>
<td>AGS: mammogram every 3 y after age 75 with estimated life expectancy of ≥4 y</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Recommendation against (D)</td>
<td>ACS = same</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>Update in progress</td>
<td></td>
</tr>
<tr>
<td>Vision impairment</td>
<td>Neither for nor against (I)</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>Neither for nor against (I)</td>
<td></td>
</tr>
</tbody>
</table>

USPSTF, US Preventive Services Task Force; CDC, Centers for Disease Control; ACG, American College for Gastroenterology; AUA, American Urologic Association; ACS, American Cancer Society; AGS, American Geriatrics Society.
Table 15-12. Immunizations for adults aged ≥18 y: general recommendations.

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Tdap/Td</th>
<th>HPV 0, 2, 6 mo</th>
<th>Varicella 0, ≥4 wk LIVE</th>
<th>Zoster 1 Dose LIVE</th>
<th>MMR 1-2 Doses LIVE</th>
<th>Influenza 1 Dose/y Nasal=LIVE</th>
<th>Pneumococcal 1 Dose</th>
<th>Hep A 0, 6-12 mo</th>
<th>Hep B 0, 1, 6 mo</th>
<th>Meningococcal 1-2 Doses (5 y Apart)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-39 ↓</td>
<td>Tdap × 1, then Td</td>
<td>Age ≤26</td>
<td>Patients without immunity</td>
<td>Patients without immunity</td>
<td>Nasal or IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Give</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49 ↓</td>
<td>Tdap × 1, then Td</td>
<td>Tdap × 1, then Td</td>
<td>Patients without immunity</td>
<td>Patients without immunity</td>
<td>Nasal or IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Give</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59 ↓</td>
<td>Tdap × 1, then Td</td>
<td>Tdap × 1, then Td</td>
<td>Patients without immunity</td>
<td>Patients without immunity</td>
<td>Nasal or IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Give</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-75 ↓</td>
<td>&lt;65 Tdap × 1 then Td every 10 y ≥65 Td only</td>
<td>Patients without immunity</td>
<td>Born before 1957 and without immunity</td>
<td>≥65 priority IM only</td>
<td>≥65: if received dose &lt;65 and 5 y passed, give 2nd dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Give</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;75 ↓</td>
<td>Td</td>
<td>Td</td>
<td>Patients without immunity</td>
<td>IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Give</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Separate LIVE vaccines by 28 days or give on same day.
### Table 15-13. Immunizations for adults aged ≥18 y: compelling and special indications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Tdap/Td 10 y Every</th>
<th>HPV 0, 2, 6 mo</th>
<th>Varicella 0, ≥4 wk LIVE²</th>
<th>Zoster 1 dose LIVE³</th>
<th>MMR 1-2 doses LIVE³</th>
<th>Influenza 1 dose/y Nasal-LIVE³</th>
<th>Pneumococcal 1 dose</th>
<th>Hep A 0, 6-12 mo</th>
<th>Hep B 0, 1, 6 mo</th>
<th>Meningococcal 1-2 Doses (5 y Apart)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Tdap post-partum 2 y from last Td</td>
<td>Do not give; could cause harm</td>
<td>Do not give; could cause harm</td>
<td>Only post-partum; could cause harm before</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health care workers</td>
<td>Tdap x 1, 2 y from last Td</td>
<td>2 doses (if not immune)</td>
<td></td>
<td>If work with HAV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact with children</td>
<td>Infants &lt;12 mo Tdap x 1, 2 y from last Td</td>
<td></td>
<td>Children &lt;5 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>International travel to certain countries</td>
<td></td>
<td>2 doses (if not immune)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 doses if residing in endemic countries</td>
</tr>
<tr>
<td>Students in post-secondary school</td>
<td></td>
<td>2 doses (if not immune)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Students living in dormitories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immuno-suppressed</td>
<td></td>
<td></td>
<td></td>
<td>2 doses (5 y apart)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nursing home residents</td>
<td></td>
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<td></td>
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<tr>
<td>Certain chronic disease states²</td>
<td></td>
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<tr>
<td>Renal disorders</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Asplenia</td>
<td></td>
<td></td>
<td></td>
<td>2 doses (5 y apart)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Men who have sex with men</td>
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<td></td>
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<tr>
<td>Illegal drug use</td>
<td></td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

*aSeparate LIVE vaccines by 28 days or give on same day.

*bIncluding chronic pulmonary, cardiovascular, hepatic, renal, hematological, neurologic, neuromuscular, or metabolic disorders (including diabetes).


Centers for Disease Control and Prevention: Recommended adult immunization schedule—United States, 2009. MMWR 2008;57(53).


Web Sites
http://epss.ahrq.gov/ePSS/search.jsp
http://www.ahrq.gov/CLINIC/uspsstk/uspsprca.htm
http://www.ahrq.gov/clinic/uspsstk.htm
http://www.asccp.org/pdfs/consensus/algorithms_cyto_07.pdf
http://chealth.canoe.ca/channel_section_details.asp?text_id=1222&channel_id=7&relation_id=24636
http://epss.ahrq.gov/ePSS/search.jsp
http://generalmedicine.suite101.com/article.cfm/screening_tests
http://info.cancerresearchuk.org/cancerstats/types/breast/riskfactors
http://www.ahrq.gov/CLINIC/uspsstk/uspsprca.htm
http://www.ahrq.gov/clinic/uspsstk.htm
http://www.asccp.org/pdfs/consensus/algorithms_cyto_07.pdf
http://www.gptraining.net/training/tutorials/management/audit/screen.htm
Preconception Care

Essam Demian, MD, FRCOG
Magued Rizk, MD

There were 4,317,119 births in the United States in 2007, the highest number of births ever registered. Although most infants are born healthy, of critical importance is that the infant mortality rate in the United States ranks 29th among developed nations. Preconception care has been advocated as a measure to improve pregnancy outcomes. In 2006, the Centers for Disease Control and Prevention (CDC) published a report aimed at improving preconception care. This report outlined the following 10 recommendations: (1) individual responsibility across the life span, (2) consumer awareness, (3) preventive visits, (4) intervention for identified risks, (5) interconception care, (6) prepregnancy checkup, (7) health insurance coverage for women with low incomes, (8) public health programs and strategies, (9) research, and (10) monitoring improvements. Preconception care can be provided most effectively as part of ongoing primary care. It can be initiated during visits for routine health maintenance, during examinations for school or work, at premarital or family planning visits, after a negative pregnancy test, or during well child care for another family member.


NUTRITION

A woman’s nutritional status before pregnancy may have a profound effect on reproductive outcome. Obesity is the most common nutritional disorder in developed countries. Obese women are at increased risk for prenatal complications such as hypertensive disorders of pregnancy, gestational diabetes, and urinary tract infections. They are more likely to deliver large-for-gestational age infants and, as a result, have a higher incidence of intrapartum complications. Maternal obesity is also associated with a range of congenital malformations, including neural tube defects, cardiovascular anomalies, cleft palate, hydrocephalus, and limb reduction anomalies. Because dieting is not recommended during pregnancy, obese women should be encouraged to lose weight prior to conception.

On the other hand, underweight women are more likely than women of normal weight to give birth to low-birth-weight infants. Low birth weight may be associated with an increased risk of developing cardiovascular disease and diabetes in adult life (the “fetal origin hypothesis”).

At the preconception visit, the patient’s weight and height should be assessed and inquiries should be made regarding anorexia, bulimia, pica, vegetarian eating habits, and use of megavitamin supplements.

Vitamin A is a known teratogen at high doses. Supplemental doses exceeding 5000 IU/d should be avoided by women who are, or who may become, pregnant. The form of vitamin A that is teratogenic is retinol, not β-carotene, so large consumption of fruits and vegetables rich in β-carotene is not a concern.

Folic acid supplementation: Neural tube defects (NTDs), including spina bifida, anencephaly, and encephalocele, affect approximately 4000 pregnancies each year in the United States. Although anencephaly is almost always lethal, spina bifida is associated with serious disabilities including paraplegia, bowel and bladder incontinence, hydrocephalus, and intellectual impairment.

Over the past 30 years, multiple studies conducted in various countries have shown a reduced risk of NTDs in infants whose mothers used folic acid supplements. The strongest evidence was provided by the Medical Research Council Vitamin Study in the United Kingdom, which showed a 72% reduction of recurrence of NTDs with a daily dose of 4 mg of folic acid started 4 weeks prior to conception and continued through the first trimester of pregnancy. Additionally, other studies showed a reduction in the incidence of first occurrence...
NTD with lower doses of folic acid (0.36-0.8 mg). Since 1992, the CDC has recommended that all women of childbearing age who are capable of becoming pregnant take 0.4 mg of folic acid daily to reduce the risk of NTDs in pregnancy. It is also recommended that patients who had a previous pregnancy affected by an NTD take 4 mg of folic acid daily starting 1-3 months prior to planned conception and continuing through the first 3 months of pregnancy.

As of 1998 and in an effort to ensure an increased intake of folic acid, the US Food and Drug Administration (FDA) mandated the fortification of cereals and grains with folic acid at doses of 0.14 mg per 100 g of grain, an amount estimated to increase folic acid consumption by an average of 0.1 mg/d.

A recent report from the CDC showed that from the early postfortification period (1999-2000) to the most recent period of analysis (2003-2005), the prevalence of spina bifida decreased 6.9%. There was significant decrease in prevalence among infants born to non-Hispanic black mothers (19.8%), but not among infants born to non-Hispanic white or to Hispanic mothers. In order to further reduce the prevalence of spina bifida in the United States, public health efforts will need to focus on women with higher risks, such as obesity, Hispanic ethnicity, and certain genetic factors.

EXERCISE

More and more women wish to continue with their exercise programs during pregnancy. Among a representative sample of US women, 42% reported exercising during pregnancy. Walking was the leading activity (43% of all activities reported), followed by swimming and aerobics (12% each).

Available data suggest that moderate exercise is safe for pregnant women who have no medical or obstetric complications. A meta-analysis review of the literature on the effects of exercise on pregnancy outcomes found no significant difference between active and sedentary women in terms of maternal weight gain, infant birth weight, length of gestation, length of labor, or Apgar scores.

Exercise may actually reduce pregnancy-related discomforts and improve maternal fitness and sense of self-esteem. The American College of Obstetricians and Gynecologists (ACOG) recommends that exercise in the supine position and any activity that increases the risk of falling (gymnastics, horseback riding, downhill skiing, and vigorous racquet sports) be avoided during pregnancy. Contact sports (such as hockey, soccer, and basketball) should also be avoided as they can result in trauma to both the mother and the fetus. Scuba diving is contraindicated during pregnancy because the fetus is at risk for decompression sickness. Absolute contraindications to exercise during pregnancy are significant heart or lung disease, incompetent cervix, premature labor or ruptured membranes, placenta previa or persistent second- or third-trimester bleeding, and preeclampsia or pregnancy-induced hypertension.

MEDICAL CONDITIONS

Diabetes

Congenital anomalies occur two to six times more often in the offspring of women with diabetes mellitus and have been associated with poor glycemic control during early pregnancy. Preconceptional care with good diabetic control during early embryogenesis has been shown to reduce the rate of congenital anomalies to essentially that of a control population. In a meta-analysis of 18 published studies, the rate of major anomalies was lower among preconception care recipients (2.1%) than nonrecipients (6.5%).

According to the American Diabetes Association recommendations, the goal for blood glucose management in the preconception period and in the first trimester is to reach the lowest A1c level possible without undue risk of hypoglycemia to the mother. A1c levels that are less than 1% above the normal range are desirable. Suggested pre- and postprandial goals are as follows: before meals, capillary plasma glucose 80-110 mg/dL; 2 hours after meals, capillary plasma glucose less than 155 mg/dL.

Prior to conception, a baseline dilated eye examination is recommended, because diabetic retinopathy can worsen during pregnancy. Hypertension, frequently present in diabetic patients, needs to be controlled. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics should be avoided as they have been associated with adverse effects on the fetus. Insulin is used almost exclusively in pregnancy for patients with either type 1 or type 2 diabetes. Despite the emerging evidence about the safety of oral hypoglycemic drugs during pregnancy, the ACOG recommends that their use for control of type 2 diabetes during pregnancy should be limited until more data become available.

Hypothyroidism

Approximately 2.5% of pregnant women in the United States have hypothyroidism. Before 12 weeks’ gestation, the fetal thyroid is unable to produce hormones and the fetus is dependent on maternal thyroxine that crosses the placenta.
During pregnancy, maternal thyroid hormone requirements increase as early as the fifth week of gestation, typically before the first obstetrical visit. Inadequately treated maternal hypothyroidism is associated with impaired cognitive function in the offspring, as well as pregnancy complications including increased rates of miscarriage, preeclampsia, placental abruption, preterm birth, and low birth weight. Treatment with levothyroxine should be optimized before conception in women with hypothyroidism and they should be advised of the need for increased dosage should they become pregnant.

**Epilepsy**

Epilepsy occurs in 1% of the population and is the most common serious neurologic problem seen in pregnancy. There are approximately 1 million women of childbearing age with epilepsy in the United States, of whom around 20,000 deliver infants every year. Much can be done to achieve a favorable outcome of pregnancy in women with epilepsy. Ideally, this should start before conception. Menstrual disorders, ovulatory dysfunction, and infertility are relatively common problems in women with epilepsy and should be addressed.

Women with epilepsy must make choices about contraceptive methods. Certain antiepileptic drugs (AEDs), such as phenytoin, carbamazepine, phenobarbital, primidone, and topiramate, induce hepatic cytochrome P450 enzymes, leading to an increase in the metabolism of the estrogen and progesterin present in the oral contraceptive pills. This increases the risk of breakthrough pregnancy. The American Academy of Neurology recommends the use of oral contraceptive formulations with at least 50 μg of ethinyl estradiol or mestranol for women with epilepsy who take enzyme-inducing AEDs.

Both levonorgestrel implants (Norplant) and the progestin-only pill have reduced efficacy in women taking enzyme-inducing AEDs. Other AEDs that do not induce liver enzymes (eg, valproic acid, lamotrigine, vigabatrin, gabapentin, and felbamate) do not cause contraceptive failure.

Because many AEDs interfere with the metabolism of folic acid, all women with epilepsy who are planning a pregnancy should receive folic acid supplementation at a dose of 4-5 mg/d. Withdrawal of AEDs can be considered in any woman who has been seizure free for at least 2 years and has a single type of seizure, normal neurologic examination and intelligence quotient, and an electroencephalogram that has normalized with treatment. Because the risk of seizure relapse is greatest in the first 6 months after discontinuing AEDs, withdrawal should be accomplished before conception. If withdrawal is not possible, monotherapy should be attempted to reduce the risk of fetal malformations. Offspring of women with epilepsy are at increased risk for intrauterine growth restriction, congenital malformations that include craniofacial and digital anomalies, and cognitive dysfunction. The term *fetal anticonvulsant syndrome* encompasses various combinations of these findings and has been associated with use of virtually all AEDs. Some recent studies have indicated a higher risk for birth defects as well as for lower verbal intelligence in association with valproic acid compared with other AEDs, mainly carbamazepine.

**Phenylketonuria**

Phenylketonuria (PKU) is one of the most common inborn errors of metabolism. It is associated with deficient activity of the liver enzyme phenylalanine hydroxylase, leading to an accumulation of phenylalanine in the blood and other tissues. If untreated, PKU can result in mental retardation, seizures, microcephaly, delayed speech, eczema, and autistic-like behaviors. All states have screening programs for PKU at birth. When diagnosed early in the newborn period and when treated with a phenylalanine-restricted diet, affected infants have normal development and can expect a normal life span.

Dietary control is recommended for life in individuals with PKU and especially in women planning conception. High maternal phenylalanine levels are associated with facial dysmorphism, microcephaly, developmental delay and learning difficulties, and congenital heart disease in the offspring. The results of the Maternal Phenylketonuria International Study have shown that the achievement of pre- and periconceptional dietary control with a phenylalanine-restricted diet significantly decreased morbidity in the infants of women with hyperphenylalaninemia.

**GENETIC COUNSELING**

The ideal time for genetic counseling is before a couple attempts to conceive, especially if the history reveals advanced maternal age, previously affected pregnancy, consanguinity, or family history of genetic disease.

Certain ethnic groups have a relatively high carrier incidence for certain genetic disorders. For example, Ashkenazi Jews have a 1:25 chance of being a carrier for Tay-Sachs disease, a severe degenerative neurologic disease that leads to death in early childhood. Carrier status can easily be determined by a serum assay for the level of the enzyme hexosaminidase A. Screening for Tay-Sachs disease is recommended prior to conception, because testing on serum is not reliable in pregnancy and the enzyme assay on white blood cells that is used in pregnancy is more expensive and labor intensive. Ashkenazi Jews are at risk not only for Tay-Sachs disease, but also for Canavan disease, Gaucher disease, and cystic fibrosis, all of which can be screened for by DNA analysis.
Cystic fibrosis (CF) is the most common autosomal-recessive genetic disorder among whites in the United States, with a carrier rate of 1:22-25. It is characterized by the production of thickened secretions throughout the body, but particularly in the lungs and the gastrointestinal tract. The ACOG recommends that CF carrier screening should be offered before conception or early in pregnancy when both partners are of Caucasian, European, or Ashkenazi Jewish ethnicity. Additionally, ACOG considers it reasonable to offer CF carrier screening to all couples regardless of race or ethnicity as an alternative to selective screening.

Other common genetic disorders for which there is a reliable screening test for carriers are sickle cell disease in African Americans, β-thalassemia in individuals of Mediterranean descent, and α-thalassemia in Southeast Asians. Sickle cell carriers can be detected with solubility testing (Sickledex) for the presence of hemoglobin S. However, ACOG recommends hemoglobin electrophoresis screening in all patients considered at risk for having a child affected with a sickling disorder. Solubility testing is described as inadequate because it does not identify carriers of abnormal hemoglobins such as the β-thalassemia trait or the HbB, HbC, HbD, or HbE traits. A complete blood count with indices is a simple screening test for the thalassemias and will show a mild anemia with a low mean corpuscular volume.

Fragile X syndrome is the most common cause of mental retardation after Down syndrome and is the most common inherited cause of mental retardation. It affects approximately 1 in 4000 men and 1 in 8000 women and results from a mutation in a gene on the long arm of the X chromosome. The X-linked inheritance is atypical in that unaffected males can transmit the disorder and up to 30% of female carriers are affected.

In addition to mental retardation, fragile X syndrome is characterized by physical features such as macroorchidism, large ears, a prominent jaw, and autistic behaviors. Preconception screening should be offered to women with a known family history of fragile X syndrome or a family history of unexplained mental retardation, and to women who have learning disabilities or mental retardation.

**IMMUNIZATIONS**

The preconception visit is an ideal time to screen for rubella immunity, because rubella infection in pregnancy can result in miscarriage, stillbirth, or an infant with congenital rubella syndrome (CRS). The risk of developing CRS abnormalities (hearing impairment, eye defects, congenital heart defects, and developmental delay) is greatest if the mother is infected in the first trimester of pregnancy. From 2001 through 2004, only four cases of CRS were reported to the CDC; the mothers of three of the children were born outside the United States. In 2005, the United States was the first country in the Americas to declare it had eliminated endemic rubella virus transmission.

Immunization should be offered to any woman with a negative rubella titer and advice given to avoid conception for 1 month due to the theoretical risk to the fetus. Inadvertent immunization of a pregnant woman with rubella vaccine should not be a reason to consider termination of pregnancy as there is no evidence that the vaccine causes any malformations or CRS.

If a pregnant woman acquires varicella before 20 weeks’ gestation, the fetus has a 1%-2% risk of developing fetal varicella syndrome, which is characterized by skin scarring, hypoplasia of the limbs, eye defects, and neurologic abnormalities. Infants born to mothers who manifest varicella 5 days before to 2 days after delivery may experience a severe infection and have a mortality rate as high as 30%.

At the preconception visit, patients who do not have a prior history of chickenpox and who are seronegative should be offered vaccination. In 1995, the live attenuated varicella vaccine was introduced and the recommended regimen for patients older than 13 years is two doses 4 weeks apart. Patients should avoid becoming pregnant for at least 4 weeks after the second dose.

Since 1988, the CDC has recommended universal screening of pregnant women for hepatitis B. Although hepatitis B vaccine can be given during pregnancy, women with social or occupational risks for exposure to hepatitis B virus should ideally be identified and offered immunization prior to conception.

**LIFE-STYLE CHANGES**

**Caffeine**

Caffeine is present in many beverages, in chocolate, and in over-the-counter medications such as cold and headache medicines. One cup of coffee contains approximately 120 mg of caffeine, a cup of tea has 40 mg of caffeine, and soft drinks such as cola contain 45 mg of caffeine per 12-oz serving. Consumption of caffeine during pregnancy is quite common, but its metabolism is slowed. Cigarette smoking increases caffeine metabolism, leading to increased caffeine intake.

Several epidemiologic studies have suggested that caffeine intake may be associated with decreased fertility, increased spontaneous abortions, and decreased birth weight. As a result, in 1980, the FDA advised pregnant women to avoid caffeine during pregnancy. However, a recent extensive literature review
of the effects of caffeine concluded that pregnant women who consume moderate amounts of caffeine (55-6 mg/kg/d) spread throughout the day and do not smoke or drink alcohol have no increase in reproductive risks.

▶ Tobacco

Between 12% and 22% of pregnant women smoke during pregnancy, subjecting themselves and their infants to a number of adverse health effects. Smoking during pregnancy has been associated with spontaneous abortion, prematurity, low birth weight, intrauterine growth restriction, placental abruption, placenta previa, as well as an increased risk for sudden infant death syndrome. Accumulating evidence also indicates that maternal tobacco use is associated with birth defects such as oral clefts and foot deformities. Paradoxically, smoking during pregnancy has reportedly been associated with a reduced risk of preeclampsia. However, the smoking-related adverse outcomes of pregnancy outweigh this benefit.

The use of nicotine-replacement products to help with smoking cessation has not been sufficiently evaluated during pregnancy to determine its safety. Nicotine gum is rated category C during pregnancy while nicotine patches, inhaler, and nasal spray are category D. If nicotine-replacement therapy is used during pregnancy, products with intermittent delivery (gum or inhaler) are preferred as they provide a smaller daily dose than continuous delivery products such as the patch. If the nicotine patch is used, it is recommended that it be removed at night to limit fetal nicotine exposure. Women who are contemplating pregnancy should be advised to quit smoking prior to conception, and nicotine replacement could then be prescribed. Smoking cessation either before pregnancy or in early pregnancy is associated with improvement in maternal airway function and an infant birth weight comparable to that observed among nonsmoking pregnant women.

▶ Alcohol

In 1981, the surgeon general of the United States recommended that women abstain from drinking alcohol during pregnancy and when planning a pregnancy, because such drinking may harm the fetus. Despite that, approximately 15% of pregnant women report drinking alcohol.

The most severe consequence of exposure to alcohol during pregnancy is fetal alcohol syndrome (FAS), characterized by a triad of prenatal or postnatal growth retardation, central nervous system neurodevelopmental abnormalities, and facial anomalies (short palpebral fissures, smooth philtrum, thin upper lip, and midfacial hypoplasia). FAS is the largest preventable cause of birth defects and mental retardation in the Western world. In the United States, the prevalence of FAS is estimated to be between 0.5 and 2 cases per 1000 births.

Some ethnic groups are disproportionately affected by FAS. American Indians and Alaska Native populations have a prevalence of FAS 30 times higher than white populations. It also appears that binge drinking produces more severe outcomes in offspring than more chronic exposure, possibly because of in utero withdrawal and its concomitant effects.

At the preconception visit, physicians should counsel their patients that there is no safe level of alcohol consumption during pregnancy and that the harmful effects on the developing fetal brain can occur at any time during pregnancy. High alcohol consumption in women has also been associated with infertility, spontaneous abortion, increased menstrual symptoms, hypertension, and stroke. Mortality and breast cancer are also increased in women who report drinking more than two drinks daily.

▶ Illicit Drugs

Illicit drug use during pregnancy remains a major health problem in the United States. Among pregnant women aged 15-44 years, 5.1% report using illicit drugs. At the preconception visit, all patients should be questioned about drug use and offered counseling, referral, and access to recovery programs.

Marijuana is the most frequently used illicit drug in pregnancy. It does not appear to be teratogenic in humans and there is no significant association between marijuana usage and preterm birth or congenital malformations. Prenatal exposure to marijuana is associated with increased hyperactivity, impulsivity, and inattention symptoms in children at age 10 years.

Cocaine use during pregnancy has been associated with spontaneous abortion, premature labor, intrauterine growth restriction, placental abruption, microcephaly, limb reduction defects, and urogenital malformations. Initial reports that suggested “devastating” outcomes for prenatal exposure to cocaine have not been substantiated. A meta-analysis of 36 studies concluded that cocaine exposure in utero has not been demonstrated to affect physical growth and that it does not appear to independently affect developmental scores from infancy to age 6 years.

Maternal use of heroin and other opiates is associated with low birth weight due to premature delivery as well as intrauterine growth restriction, preeclampsia, placental abruption, fetal distress, and sudden infant death syndrome.

Infants born to heroin-dependent mothers often develop a syndrome of withdrawal known as neonatal abstinence syndrome within 48 hours of delivery. Neonatal withdrawal is characterized by central nervous system hyperirritability, respiratory distress, gastrointestinal dysfunction, poor feeding, high-pitched cry, yawning, and sneezing. Methadone has long been used to treat opioid dependence in pregnancy because of its long half-life. It has been associated with increases in birth weight. However, the use of methadone is controversial because more than 60% of neonates born to methadone-maintained mothers require treatment for withdrawal. Also, a substantial number of patients on methadone maintenance continue to use street narcotics and other illicit drugs. Buprenorphine, a recently developed partial opiate agonist, may have important advantages over methadone,
including fewer withdrawal symptoms and a lower risk of overdose.

Women are increasingly affected by HIV. In untreated HIV-infected pregnant women, the risk of mother-to-child transmission varies from 16% to 40%. However, it is possible to dramatically reduce the transmission rates by using highly active antiretroviral therapy (HAART) during pregnancy, by offering elective cesarean delivery at 38 weeks if the viral load at term is higher than 1000 copies/mL, and by discouraging breast-feeding. In developed countries, transmission rates as low as 1%-2% have been achieved.


\section*{SEXUALLY TRANSMITTED DISEASES}

The latest estimates suggest that there are up to 19 million new cases of sexually transmitted diseases (STDs) in the United States each year. The preconception visit is a good opportunity to screen for genital infections such as \textit{Chlamydia}, gonorrhea, syphilis, and HIV.

\textit{Chlamydia} and gonorrhea are two of the most prevalent STDs and both are often asymptomatic in women. In pregnancy, both \textit{Chlamydia} and gonorrhea have been associated with premature rupture of membranes, preterm labor, postabortion and postpartum endometritis, and congenital infection.

Infants whose mothers have untreated \textit{Chlamydia} infection have a 30%-50% chance of developing inclusion conjunctivitis and a 10%-20% chance of developing pneumonia. Inclusion conjunctivitis typically develops 5-14 days after delivery and is usually mild and self-limiting. Pneumonia due to \textit{Chlamydia} usually has a slow onset without fever and can have a protracted course if untreated. Long-term complications may be significant. Ophthalmia neonatorum is the most common manifestation of neonatal gonococcal infection. It occurs 2-5 days after birth in up to 50% of exposed infants who did not receive oculcar prophylaxis. Corneal ulceration may occur, and unless treatment is initiated promptly, the cornea may perforate, leading to blindness.

Congenital syphilis occurs when the spirochete \textit{Treponema pallidum} is transmitted from a pregnant woman with syphilis to her fetus. Untreated syphilis during pregnancy may lead to spontaneous abortion, nonimmune hydrops, stillbirth, neonatal death, and serious sequelae in liveborn infected children. After 14 years of decline in the United States, the rate of congenital syphilis increased 15.4% between 2006 and 2007. In 2007, 430 cases were reported compared to 373 cases in 2006.
conversion of \( T_4 \) to triiodothyronine (\( T_3 \)). Methimazole crosses the placenta in larger amounts and has been associated with aplasia cutis, a congenital defect of the scalp. If the patient is taking methimazole, it is reasonable to switch to propylthiouracil prior to conception.

**Isotretinoin**

Isotretinoin is indicated for severe recalcitrant nodular acne unresponsive to conventional therapy. As many as 50% of fetuses exposed to the drug develop severe congenital anomalies of the ears, central nervous system (CNS), heart, and thymus. In 2005, the FDA approved a computer-based risk management program called iPledge to prevent fetal exposure to isotretinoin (available at http://www.ipledgeprogram.com). Female patients of childbearing age must have two negative pregnancy tests and use two appropriate forms of contraception before starting therapy. They also have to wait at least a month before considering pregnancy after completing a course of isotretinoin.

**Risk Categories**

The FDA has defined five risk categories (A, B, C, D, and X) that are used by manufacturers to rate their products for use during pregnancy.

**A. Category A**

Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of risk in later trimesters), and the possibility of fetal harm appears remote (eg, folic acid and thyroxine).

**B. Category B**

Either animal reproduction studies have not demonstrated fetal risk but no controlled studies in pregnant women have been conducted, or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of risk in later trimesters (eg, acetaminophen, penicillins, and cephalosporins).

**C. Category C**

Either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) but no controlled studies in women have been reported, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus (eg, acyclovir and zidovudine).

**D. Category D**

Positive evidence of human fetal risk exists, but the benefits from use in pregnant women may be acceptable despite the risk, especially if the drug is used in a life-threatening situation or for a severe disease for which safer drugs cannot be used or are ineffective (eg, tetracycline and phenytoin).

**E. Category X**

Studies in animals or humans have demonstrated fetal abnormalities, or evidence of fetal risk exists based on human experience, or both, and the risk of using the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may be pregnant (eg, isotretinoin, misoprostol, warfarin, and statins).

**OCCUPATIONAL EXPOSURES**

Increasing numbers of women are entering the work-force worldwide, and most are in their reproductive years. This has raised concerns for the safety of pregnant women and their fetuses in the workplace. The preconception visit is the best time to identify and control exposures that may affect parental health or pregnancy outcome. The three most common occupational exposures reported to affect pregnancy are video display terminals, organic solvents, and lead.

**Video Display Terminals**

In 1980, a cluster of four infants with severe congenital malformations was reported in Canada. The cluster was linked to the fact that the mothers had all worked with video display terminals (VDTs) during their pregnancy, at a newspaper department in Toronto. Many epidemiologic studies have since investigated the effects of electromagnetic fields emitted from VDTs on pregnancy outcome. Most studies found only equivocal or no associations of VDTs with birth defects, preterm labor, and low birth weight. Thus, it is reasonable to advise women that there is no evidence that using VDTs will jeopardize pregnancy.

**Organic Solvents**

Organic solvents comprise a large group of chemically heterogeneous compounds that are widely used in industry and common household products. Occupational exposure to organic solvents can result from many industrial applications, including dry cleaning, painting, varnishing, degreasing, printing, and production of plastics and pharmaceuticals. Smelling the odor of organic solvents is not indicative of a significant exposure, because the olfactory nerve can detect levels as low as several parts per million, which are not necessarily associated with toxicity. A recent meta-analysis of epidemiologic studies demonstrated a statistically significant relationship between exposure to organic solvents in the first trimester of pregnancy and fetal malformations. There was also a tendency toward an increased risk for spontaneous abortion. Women who plan to become pregnant should minimize their exposure to organic solvents by routinely using ventilation systems and protective equipment.
Lead

Despite a steady decline in average blood levels of lead in the US population in recent years, approximately 0.5% of women of childbearing age may have blood levels of lead higher than 10 μg/dL. The vast majority of exposures to lead occur in artists using glass staining and in workers involved in paint manufacturing for the automotive and aircraft industries. Other occupational sources of exposure to lead include smelting, printing, and battery manufacturing. The most worrisome consequence of low to moderate lead toxicity is neurotoxicity. A review of the literature suggested that low-dose exposure to lead in utero may cause developmental deficits in the infant. However, these effects seem to be reversible if further exposure to lead is avoided. It is crucial to detect and treat lead toxicity prior to conception because the chelating agents used (dimercaprol, ethylenediaminetetraacetate, and penicillamine) can adversely affect the fetus if used during pregnancy.


DOMESTIC VIOLENCE

Domestic violence is increasingly recognized as a major public health issue. In the United States, 1.5 million women are raped or physically assaulted by an intimate partner every year. Domestic violence crosses all socioeconomic, racial, religious, and educational boundaries. Even physicians are not immune: in a survey, 17% of female medical students and faculty had experienced abuse by a partner in their adult life, an estimate comparable to that of the general population. Victims of domestic violence should be identified preconceptionally, because the pattern of violence may escalate during pregnancy. The prevalence of domestic violence during pregnancy ranges from 0.9% to 20.1%, with most studies identifying rates between 3.9% and 8.3%. Whereas violence in nonpregnant women is directed at the head, neck, and chest, the breasts and the abdomen are frequent targets during pregnancy. Physical abuse during pregnancy is a significant risk factor for low birth weight and maternal complications of low weight gain, infections, anemia, smoking, and alcohol or drug usage. If it is identified that a patient is the victim of domestic violence, the physician should assess her immediate safety and make timely referrals to local community resources and shelters.

According to the 2002 National Survey of Family Growth (NSFG) approximately one-half of all pregnancies in the United States were unintended and almost one-half of these occurred in women using some form of reversible contraception. These rates have remained relatively unchanged since the previous survey reported in 1995. Addressing family planning and contraception is an important issue for providers of care to reproductive-age women. An increasing number of contraceptive options are becoming available on the US market. It is dependent on physicians and other health care providers to maintain currency with the recent advances in information concerning counseling, efficacy, safety, and side effects.


**COMBINED ORAL CONTRACEPTIVES**

According to the 2002 NSFG, the combined oral contraceptive pill is the leading contraceptive method among women, with 19% of women between the ages of 15 and 44 choosing the pill. The introduction of lower-dose combination oral contraceptives (COCs) (<50 μg ethinyl estradiol) has provided many women a highly effective, safe, and tolerable method of contraception.

COCs suppress ovulation by diminishing the frequency of gonadotropin-releasing hormone pulses and halting the luteinizing hormone surge. They also alter the consistency of cervical mucus, affect the endometrial lining, and alter tubal transport. Most of the antiovulatory effects of COCs derive from the action of the progestin component. The estrogen doses are not sufficient to produce a consistent antiovulatory effect. The estrogenic component of COCs potentiates the action of the progestin and stabilizes the endometrium so that breakthrough bleeding is minimized. When administered correctly and consistently, they are greater than 99% effective at preventing pregnancy. However, failure rates are as high as 8%-10% during the first year of typical use. Noncompliance is the primary reason cited for the difference between these rates, frequently secondary to side effects such as abnormal bleeding and nausea.

**Hormonal Content**

The estrogenic agent most commonly used in COCs is ethinyl estradiol (EE), in doses ranging from 20 to 35 μg. Mestranol, which is infrequently used, is less potent than ethinyl estradiol such that a 50-μg dose of mestranol is equivalent to 30-35 μg of ethinyl estradiol. It appears that decreasing the dose of estrogen to 20 μg reduces the frequency of estrogen-related side effects, but increases the rate of breakthrough bleeding. In addition, there may be less margin for error with low-dose preparations such that missing pills may be more likely to result in breakthrough ovulation.

Multiple progestins are used in COC formulations. Biphasic and triphasic oral contraceptives, which vary the dose of progestin over a 28-day cycle, were developed to decrease the incidence of progestin-related side effects and breakthrough bleeding, although there is no convincing evidence that multiphasics indeed cause fewer adverse effects. The most commonly used progestins include norgestrel, levonorgestrel, and norethindrone. As with estrogens, some progestins (norethindrone and levonorgestrel) are biologically active, while others are pro-drugs that are activated by metabolism. Norethindrone acetate is converted to norethindrone and norgestimate is metabolized into several active steroids including levonorgestrel. Progestins that do not require hepatic transformation tend to have better bioavailability and a longer serum half-life. For example, levonorgestrel has a longer half-life than norethindrone. Norgestimate and desogestrel, have lower androgenic potential than other progestins.

Drospirenone, a derivative of spironolactone, differs from other progestins because it has mild antimineralocorticoid activity. Contraceptive efficacy, metabolic profile, and cycle control are comparable to other COCs. The clinical
implications of the diuretic-like potential of drospirenone are not yet clear. Because of its antimineralocorticoid effects and the potential for hyperkalemia, drospirenone should not be used in women with severe renal disease or hepatic dysfunction.

COCs are traditionally dosed cyclically with 21 days of hormone and 7 days of placebo during which a withdrawal bleed occurs. To address the potential of escape ovulation in the lowest estrogen formulations (20 μg), many regimens reduce the number of hormone-free days to 2-4 days. Extended cycle regimens or continuous hormonal regimens are safe and acceptable forms of contraception and may be more efficacious than cyclic regimens. Extended cycle regimens result in fewer scheduled bleeding episodes, however they also result in more unscheduled bleeding and/or spotting episodes that decrease with time. Women who may particularly benefit from these regimens are those who have symptoms exacerbated by their menses. These include women who have seizure disorders, endometriosis, menstrual headaches, premenstrual dysphoric disorder, menorrhagia, or dysmenorrhea. There are several extended cycle regimens approved by the FDA (Seasonal, Seasonique, Lybrel); however, traditionally packaged COCs may also be prescribed as extended cycle regimens. Women are advised to use the active pills and then start a new pack, ignoring the placebo pills. This regimen gives women the option of cycling as she desires, modifying the timing of individual periods on a month-by-month basis for personal reasons. Based on a Cochrane review there are no differences between the traditional and extended cycles in satisfaction, compliance, pregnancy rates, and safety.

**Side Effects**

Side effects may be due either to the estrogen component, the progestin component, or both. Side effects attributable to progestin include androgenic effects, such as hair growth, male-pattern baldness, and nausea. Switching to an agent with lower androgenic potential may decrease or resolve these problems. Estrogenic effects include nausea, breast tenderness, and fluid retention. Weight gain is commonly thought to be a side effect of COCs, however, multiple studies have failed to confirm a significant effect. Weight gain can be managed by switching to a different formulation, however, appropriate diet and exercise should be emphasized.

Bleeding irregularities is the side effect most frequently cited as the reason for discontinuing COCs. Patients should be counseled that irregular bleeding/spotting is common in the first 3 months of COC use and will diminish with time. Spotting is also related to missed pills. Patients should be counseled regarding the importance of taking the pill daily. If the bleeding does not appear to be related to missed pills, the patient should be evaluated for other pathology such as infection, cervical disease, or pregnancy. If this evaluation is negative the patient may be reassured. Another approach would be to change the pill formulation to increase the estrogen or progestin component. The doses can be tailored to the time in the cycle when the bleeding occurs. If the bleeding precedes the menses, consider a triphasic pill that increases the dose of estrogen (Estrostep) or progestin (eg, Ortho-Novum 7/7/7) sequentially through the cycle. If the bleeding follows the menses consider Micrette which has only 2 hormone-free days. Increase the estrogen and/or the progestin midcycle for midcycle bleeding (eg, Triphasil).

Combined oral contraceptives may cause a small increase in blood pressure in some patients. The risk increases with age. The hypertension usually resolves within 3 months if the COC is discontinued. Both estrogens and progestins are known to affect blood pressure. Therefore, switching to a lower-estrogen formulation or a progestin-only pill may not resolve the problem.

**Major Sequelae**

Use of most oral contraceptives with less than 50 μg of estrogen approximately triples one’s risk of venous thromboembolism. Before 1995, the progestin component of COCs was not generally thought to contribute to the risk of thrombosis. However, more recent studies with formulations containing gestodene (not available in the United States) or desogestrel have shown approximately a sevenfold increased risk of thrombosis compared with nonusers of COCs. Bias and confounding in these studies do not explain the consistent epidemiologic findings of an increased risk. Obesity and increasing age are contributing risk factors. The factor V Leiden mutation is another risk factor. As compared with the baseline risk for women who do not use COCs and who do not carry the mutation, the risk of venous thromboembolism is increased by a factor of 35 in women who carry the mutation and also use COCs. The best approach to identify women at higher risk of venous thromboembolism before taking COCs is controversial. Universal screening for factor V Leiden is not cost-effective. Furthermore, family history of venous thromboembolism has unsatisfactory sensitivity and positive predictive value for identifying carriers of other common defects.

The risk of thrombotic or ischemic stroke among users of COCs appears to be relatively low. There is no evidence that the type of progestin influences risk or mortality associated with ischemic stroke. The risk of ischemic stroke does appear to be directly proportional to estrogen dose, but even with the newer low-estrogen preparations there is still a slightly increased risk compared with nonusers. Hypertension, cigarette smoking, and migraine headaches interact with COC use to substantially increase the risk of ischemic stroke. The risk of hemorrhagic stroke in young women is low and is not increased by the use of COCs in the absence of risk factors. The major risk factors are hypertension and cigarette smoking. History of migraine without focal neurologic signs is not a contraindication to hormonal contraception.

Current use of COCs is associated with an increased risk of acute myocardial infarction (AMI) among women with
known cardiovascular risk factors (diabetes, cigarette smoking, hypertension) and among those who have not been effectively screened for risk factors, particularly for blood pressure. There is no increased risk for AMI with increasing duration of use or with past use of COCs.

Many epidemiologic studies have reported an increased risk of breast cancer among COC users. For current users of COCs, the relative risk of breast cancer compared with never-users is 1.24. This small risk persists for 10 years, but essentially disappears after this time period. Although COC users have a modest increase in risk of breast cancer, the disease tends to be localized. The pattern of disappearance of risk after 10 years coupled with the tendency toward localized disease suggests that the overall effect may represent detection bias or perhaps a promotional effect. A population-based, case-control study with over 8000 women enrolled was conducted to evaluate risk of breast cancer in COC users later in life when the risk of cancer is higher. This study, reported in 2002, showed that among women from 35 to 64 years of age, current or previous contraceptive use was not associated with a significantly increased risk of breast cancer.

### Noncontraceptive Health Benefits

Most studies evaluating the relationship between COCs and ovarian cancer have shown a protective effect for oral contraceptives. There appears to be a 40%-80% overall decrease in risk among users, with protection beginning 1 year after starting use, with a 10%-12% decrease annually in risk for each year of use. Protection persists between 15 and 20 years after discontinuation. The mechanisms by which COCs may produce these protective effects include suppression of ovulation and the suppression of gonadotropins.

The use of COCs conveys protection against endometrial cancer as well. The reduction in risk of up to 50% begins 1 year after initiation, and persists for up to 20 years after COCs are discontinued. The mechanism of action is likely reduction in the mitotic activity of endometrial cells because of postgestational effects.

A number of epidemiologic studies demonstrate that the use of COCs will reduce the risk of salpingitis by 50%-80% compared with the risk to women not using contraception or who use a barrier method. There is no protective effect against the acquisition of lower genital tract sexually transmitted diseases. The purported mechanism for protection include progestin-induced thickening of the cervical mucus, so that ascent of bacteria is inhibited, and a decrease in menstrual flow, resulting in less retrograde flow to the fallopian tubes. Other noncontraceptive benefits of COCs include decreased incidence of benign breast disease, relief from menstrual disorders (dysmenorrhea and menorrhagia), reduced risk of uterine leiomyomata, protection against ovarian cysts, reduction of acne, improvement in bone mineral density, and a reduced risk of colorectal cancer.


### Transdermal Contraceptive System

A transdermal contraceptive patch containing norelgestromin, the active metabolite of norgestimate, and ethinyl estradiol is marketed by Ortho-McNeil under the trade name “Ortho-Evra.” The system is designed to deliver 150 μg of norelgestromin and 20 μg of ethinyl estradiol daily directly to the peripheral circulation. The treatment regimen for each cycle is three consecutive 7-day patches (21 days) followed by 1 patch-free week so that withdrawal bleeding can occur. The patch can be applied to one of four sites on a woman’s body: abdomen, buttocks, upper outer arm, or torso (excluding the breast).

Ortho Evra’s efficacy is comparable to that of COCs. Compliance with the patch is much higher than with COC, which may result in fewer pregnancies overall. However, pregnancy is more likely to occur in women weighing greater than 198 lb. Breakthrough bleeding, spotting, and breast tenderness are slightly higher for Ortho-Evra than COCs in the first two cycles, but there is no difference in later cycles. Amenorrhea occurs in only 0.1% of patch users. Patch-site reactions occur in 2%-3% of women.

Initiation of patch use is similar to initiation of COC use. Women apply the first patch on day 1 of their menstrual cycle. Another option is to apply the first patch on the Sunday after their menses begins. This becomes their patch change day. Subsequently, they change patches on the same day of the week. After three cycles they have a patch-free week during which they can expect their menses. A backup contraceptive should be used for the first 7 days of use.

The US Food and Drug Administration (FDA) requires labeling on the Ortho Evra patch to warn health care providers and patients that this product exposes women to higher levels of estrogen than most birth control pills. Average concentration at steady state for ethinyl estradiol is approximately 60% higher in women using Ortho Evra compared with women using an oral contraceptive containing 35 μg of ethinyl estradiol. In contrast, peak concentrations for ethinyl estradiol are approximately 25% lower in women using Ortho Evra. In general, increased estrogen exposure may increase the risk of blood clots. The potential risks related to increased estrogen exposure with the patch should be balanced against the risk of pregnancy if patients have difficulty following the daily regimen associated with typical birth control pills.

INTRAVAGINAL RING SYSTEM

NuvaRing vaginal contraceptive ring is a flexible, transparent ring made of ethylene vinylacetate copolymers, delivering an average of 120 µg of etonorgestrel and 15 µg of ethinyl estradiol per day. A woman inserts the NuvaRing herself, wears it for three weeks, then removes and discards the device. After one ring-free week, during which withdrawal bleeding occurs, a new ring is inserted. Small studies have shown that the ring can be used for extended periods (6 or 12 weeks of continuous use) without an increase in the pregnancy rates. However, there is an increase in irregular bleeding with extended use regimens. Rarely, NuvaRing can slip out of the vagina if it has not been inserted properly or while removing a tampon, moving the bowels, straining, or with severe constipation. If the NuvaRing has been out of the vagina for more than three hours, breakthrough ovulation may occur. Patients may be counseled to check the position of the NuvaRing before and after intercourse.

Peak serum concentrations of etonorgestrel and ethinyl estradiol occur about 1 week after insertion and are 60%-70% lower than peak concentrations produced by standard COCs. The manufacturer recommends using backup birth control for the first 7 days of use if not switching from another hormonal contraceptive. NuvaRing prevents pregnancy by the same mechanism as COCs. Pregnancy rates for users of NuvaRing are between 1 and 2 per 100 women-years of use.

The side effects of NuvaRing are similar to that of COC pills with the main adverse effect being disrupted bleeding. Breakthrough bleeding/spotting occurs in 2.6%-11.7% of cycles and absence of withdrawal bleeding occurs in 0.6%-3.8% of cycles. Fewer than 1%-2% of women experience discomfort or reported discomfort from their partners with NuvaRing. NuvaRing is associated with increased vaginal secretions, which is a result of both hormonal and mechanical effects. Twenty-three percent of ring users reported vaginal discharge; however, the normal vaginal flora appears to be maintained. The ring is not associated with either adverse cytologic effects or bacteriologic colonization of the vaginal canal. The contraindications to NuvaRing are similar to those of COCs. In addition, the ring may not be an appropriate choice for women with conditions that make the vagina more susceptible to irritation or that make expulsion of the ring more likely to occur, such as vaginal stenosis, cervical prolapse, cystocele, or rectocele.


PROGESTIN-ONLY PILL

Progestin-only oral contraceptives (POPs), sometimes called the “minipill,” are not widely used in the United States. Their use tends to be concentrated in select populations, notably breast-feeding women and those with contraindications to estrogen. Two formulations of POPs are available: one containing norgestrel, the other with norethindrone. POPs appear to prevent conception through several mechanisms including suppression of ovulation, thickening of cervical mucus, alteration of the endometrium, and inhibition of tubal transport. Efficacy of POPs requires consistent administration. The pills should be taken at the same time every day without interruption (no hormone-free week). If a pill is taken more than 3 hours late, a backup method of contraception should be used for the next 48 hours. No increase in the risk for thromboembolic events has been reported for POPs. The World Health Organization has deemed this contraceptive method to be acceptable for use in women with a history of venous thrombosis, pulmonary embolism, diabetes, obesity, or hypertension. Vascular disease is no longer considered a contraindication to use. The most common side effects of POPs are menstrual cycle disruption and breakthrough bleeding. Other common side effects include headache, breast tenderness, nausea, and dizziness. In general, POP use protects against ectopic pregnancy by lowering the chance of conception. If POP users do get pregnant, an average of 6%-10% of pregnancies are extrauterine—higher than in women not using contraception. Therefore POP users should be aware of the symptoms of ectopic pregnancy.

INJECTABLE CONTRACEPTIVES

Injectable long-acting contraception offers users convenient, safe, and reversible birth control as effective as surgical sterilization. Depo-Provera (DMPA), a 3-month progestin-only formulation, contains 150 mg medroxyprogesterone acetate per injection. It is administered by deep intramuscular injection into the gluteus or deltoid muscle. Depo-SubQ Provera 104 is a formulation of medroxyprogesterone acetate that patients can be taught to self-administer subcutaneously 4 times per year. Self-administration facilitates access to injectable contraception for many women, eliminating the need for an office visit. In addition to contraception, Depo-SubQ Provera is also indicated for the treatment of pain associated with endometriosis.

Depo-Provera acts primarily by inhibiting ovulation. With typical use, the failure rate of DMPA is 0.3 per 100 woman-years, which is comparable to that of levonorgestrel implants, copper intrauterine devices, or surgical sterilization. Neither increasing weight nor use of concurrent medications has been noted to alter efficacy, apparently because of high circulating levels of progestin.

The first injection of DMPA should be administered within five days of the onset of menses or within five days of a first-trimester abortion. If a woman is postpartum and breastfeeding then the drug should not be administered until at least six weeks postdelivery. When switching from COCs, the first injection may be given any time while the active pills are being taken or within 7 days of taking the last active pill. Repeat injections of DMPA should be administered
every 12 weeks. If a patient presents at 13 weeks or later, the manufacturer recommends excluding pregnancy before administering a repeat injection.

Use of DMPA has no permanent impact on fertility; however, return of fertility may be delayed after cessation of use. Fifty percent of women who discontinue DMPA will have conceived within 10 months of the last injection. In a small proportion of women fertility is not reestablished until 18 months after the last injection.

Menstrual changes are the most common side effects reported by users of DMPA. After 1 year of use, approximately 75% of women receiving DMPA report amenorrhea with the remainder reporting irregular bleeding or spotting. Some women, especially adolescents, view amenorrhea as a potential benefit of use. Women who voice concern over this side effect can be reassured that the amenorrhea is not harmful. Patients with persistent bleeding or spotting should be evaluated for genital tract neoplasia and infection as appropriate. If these are excluded and the symptoms are bothersome to the patient, a 1-3 month trial of low-dose estrogen can be considered. Options include conjugated equine estrogen (0.625, 1.25, or 2.5 mg), ethinyl estradiol 20 μg or a combined oral contraceptive. Early reinjection (e.g., every 8-10 weeks) does not seem to decrease bleeding.

Other side effects attributed to DMPA include weight changes, mood swings, reduced libido, and headaches. Due to concerns regarding decreased bone mineral density after prolonged use, the manufacturer no longer recommends use for greater than 2 years. Reassuringly, results from several studies indicate almost complete recovery of BMD 2 years after discontinuation. Many clinicians recommend users take supplemental calcium and vitamin D. DMPA may be used safely by smokers 35 years or older, and by other women at increased risk for arterial or venous events. Use of DMPA has not been associated with clinically significant alterations in hepatic function.

### INTRAUTERINE DEVICES

Throughout the world, the most common form of reversible contraception is the intrauterine device (IUD), however relatively few women in the United States use IUDs, although those that do express a high degree of satisfaction. Currently there are two IUDs marketed for use in the United States. The most common IUD used is the copper T 380A (Paragard) made of polyethylene with fine wire copper wrapped around the stem and copper in the sleeves of each horizontal arm. It is approved for 10 years of use. The levonorgestrel IUD (Mirena) has a polyethylene frame which releases 20 μg of levonorgestrel per day for as long as five years. Both IUDs are visible on x-ray.

The contraceptive action of IUDs is probably a result of a combination of factors. The IUD induces an inflammatory, foreign body reaction within the uterus that causes prostaglandin release. This release results in altered uterine activity, inhibited tubal motility, and a direct toxic effect on sperm. The copper present in the Paragard enhances the contraceptive effects by inhibiting transport of ovum and sperm. IUDs containing progesterin produce a similar effect and, in addition, thicken cervical mucus and suppress ovulation. IUDs are not abortifacients; they prevent fertilization. The IUD is one of the most effective methods of reversible contraception available. Among women who use the IUD perfectly (checking strings regularly to detect expulsion), the probability of pregnancy in the first year of use is 0.6% for Paragard, and 0.1% for Mirena. The progestational activity of the levonorgestrel IUD results in contraceptive benefits. It improves menorrhagia, and early investigations indicate it will likely benefit women with endometriosis, adenomyosis, and fibroids.

Screening is critical for identifying women at risk for IUD-associated complications. The main goal of patient selection is to prevent insertion of an IUD in a patient who has a STD or is at high risk for exposure to one. Women who have more than one sexual partner or whose partner has other sexual partners are at high risk for acquiring a STD and are more likely to develop PID if they use an IUD instead of other barrier or hormonal methods of birth control. The risk of developing PID associated with IUD use is related to insertion of the IUD and subsequent exposure to STDs. The greatest risk of PID occurs during the first few weeks following insertion possibly because of contamination of the endometrial cavity at the time of insertion. The use of prophylactic antibiotics at the time of IUD insertion has not been shown to decrease the risk of PID. Concern about the potential risk of PID and subsequent tubal infertility has led to the recommendation that they not be placed in women who have never been pregnant. However, IUDs can be used safely in appropriately selected nulligravid women with no increased risk of tubal infertility.

The most common side effects reported by IUD users are cramping and bleeding. These symptoms can be minimized with the use of a nonsteroidal anti-inflammatory drug. However, if symptoms are persistent or severe the patient should be evaluated for infection or perforation. Patients can be reassured that the amount of bleeding and cramping usually decreases with time.

Expulsion occurs in 2%-10% of women in the first year of use, with most expulsions occurring in the first 3 months. Nulliparity, abnormal amount of menstrual flow, and severe dysmenorrhea are risk factors for expulsion. In addition, the expulsion rate may be higher when the IUD is inserted at the time of the menses. Pregnancy may be the first sign of expulsion. Therefore, patients should be taught to check for the IUD strings after each menstrual cycle. If a pregnancy does occur with an IUD in place, the IUD should be removed as soon as possible. In the presence of an IUD, 50%-60% of pregnancies spontaneously abort. The risk drops to 20% when the IUD is removed. Septic abortion is 26 times more common in women with an IUD. The copper-T IUD protects against ectopic pregnancy, whereas the progesterone IUD increases the risk of ectopic pregnancy almost twofold.
The management of actinomyces discovered on routine Pap smear is one of the most controversial areas in the IUD literature. This finding on cervical cytology is more common in IUD users than in other women. There was concern that actinomyces was associated with IUD-related PID. However, this relationship has been questioned. If actinomyces is detected on Pap smear and the patient has signs or symptoms of PID, the IUD should be removed immediately and the patient treated with doxycycline. If the patient is asymptomatic, antibiotic treatment is not recommended and the Pap smear is repeated in 1 year.


BARRIER CONTRACEPTION

The percentage of women who used a method of contraception at their first premarital intercourse increased from 43% in the 1970s to 79% in 1999-2002. Most of this increase was due to an increase in the use of the male condom at first premarital intercourse, from 22% in the 1970s to 67% in 1999-2002 (NSFG 2002). Condoms are inexpensive, easy to use, and are available without a prescription. Most commercially available condoms were manufactured from either latex or polyurethane condoms. While polyurethane and latex condoms offer similar protection against pregnancy, breakage and slippage rates appear to be higher with the polyurethane condom. Natural membrane condoms (made from sheep intestine) are also available, however they do not offer the same degree of protection from STDs. Because couples vary widely in their ability to use condoms consistently and correctly, the failure rate also varies. The percentage of women experiencing an unintended pregnancy within the first year of use ranges from 3% with perfect use to 14% with typical use. Women relying on condoms for contraception and protection from STDs should be reminded that oil-based lubricants reduce the integrity of a latex condom and facilitate breakage. Because vaginal medications (eg, for yeast infections) often contain oil-based ingredients, they can damage latex condoms as well.

There are several vaginal barrier contraceptives available that are easy to use and effective. The contraceptive efficacy of all barrier methods depends on their consistent and correct use. The percentage of women experiencing an unintended pregnancy within the first year of typical use ranges from 15% to 32%.

The female condom is a soft, loose fitting polyurethane sheath with two flexible polyurethane rings at either end. One ring is inserted into the vagina and lies adjacent to the cervix. The other ring remains outside of the vagina, against the perineum. Sperm is captured within the condom. The sheath is coated on the inside with a silicone-based lubricant. It is available without a prescription and is intended for one-time use. Female and male condoms should not be used together because the two condoms can adhere to one another causing slippage and displacement. With correct and consistent use, the female condom can decrease the transmission of STDs, including HIV/AIDS.

The diaphragm is a dome-shaped latex rubber cup with a flexible rim. It is inserted, with a spermicide, into the vagina before intercourse. Once in position, the diaphragm provides contraceptive protection for 6 hours. If a longer interval has elapsed, insertion of additional spermicide is required. After intercourse the diaphragm must be left in place for 6 hours, but no longer than 24 hours. Use of the diaphragm has been associated with an increase risk of uterine tract infections (UTI). Spermicide exposure is an important risk factor for UTI (due to alterations in vaginal flora), although it is possible mechanical factors in diaphragm use also may contribute to the risk of UTI. Use of the diaphragm requires an appointment with a health care provider for education, fitting, and a prescription. Oil-based vaginal products should not be used with the latex diaphragm.

The contraceptive sponge is a small, pillow-shaped polyurethane sponge containing a spermicide. The sponge protects for up to 12-24 hours, no matter how many times intercourse occurs. After intercourse, the sponge must be left in place for at least 6 hours before it is removed and discarded. The sponge comes in one universal size and does not require a prescription.

Lea’s Shield is a reusable elliptical bowl made of medical-grade silicone rubber that is used with spermicide. It has an anterior loop to assist with removal and a centrally located valve that allows passage of cervical secretions. Lea’s Shield offers several advantages over other vaginal barriers. Because the device is made of silicone, latex allergy and reaction with vaginal medications are not a concern. The device comes in only one size simplifying the fitting process. The device can be worn for up to 48 hours and, unlike the diaphragm, additional spermicide is not required for each repeated act of intercourse. Lea’s Shield is available by prescription only.

Spermicides are an integral component of several of the barrier contraceptives. Nonoxynol-9, the active chemical agent in spermicides available in the United States, is a surfactant that destroys the sperm cell membrane. It comes in a variety of formulations including gel, foam, creme, film, suppository, or tablet. Spermicide use may lower the chance of becoming infected with a bacterial STD by as much as 25%. However, women at high risk for acquiring HIV should not use products containing nonoxynol-9. Some studies have shown it causes vaginal lesions which could then be entry points for HIV.

EMERGENCY CONTRACEPTION

As many as half of the unintended pregnancies in the United States result from condom failure, missed birth control pills, or incorrect or inconsistent use of barrier contraception. Optimal use of emergency contraception could reduce unintended pregnancy in the United States by as much as 50%. Emergency contraception, available as combined oral contraceptives, progestin-only pills, and the copper intrauterine device, are safe and effective. When taken as directed, emergency contraceptive pills (ECP) can reduce the risk of pregnancy by 75%-89% after a single act of unprotected intercourse, while a copper IUD inserted within 5 days of intercourse can reduce the risk by 99%.

Emergency contraception is appropriate when no contraception was used or when intercourse was unprotected due to contraceptive failure. Since pill regimens involve only limited exposure to hormones, ECPs are safe. They have not been shown to increase the risk of venous thromboembolism, stroke, myocardial infarction, or other cardiovascular event. In addition, ECPs will not disrupt an implanted pregnancy and will not cause birth defects. ECPs work primarily by inhibiting ovulation, with some effects on sperm motility and thickening of cervical mucus. They will not disrupt an implanted pregnancy. Unfortunately ECPs do not protect against sexually transmitted diseases.

Combined oral contraceptive for use as EC is frequently referred to as the Yuzpe method. Commercially available COCs containing ethinyl estradiol and levonorgestrel or norgestrel can be used as emergency contraception. Each of two doses separated by 12 hours must contain at least 100 μg ethinyl estradiol plus 0.5 mg levonorgestrel or 1.0 mg norgestrel (eg, Lo/Ovral four white pills per dose). When used correctly, the Yuzpe method decreases expected pregnancies by 75%. More specifically, 8 out of every 100 women who have unprotected intercourse once during the second or third week of their cycles will become pregnant. Two out of 100 will become pregnant if the Yuzpe method is used. The most common adverse effects are nausea (50%) and vomiting (20%). Antiemetics taken 30-60 minutes before each dose help to minimize these symptoms. Other side effects include delayed or early menstrual bleeding. Some women also experience heavier menses.

When used for emergency contraception, the initial dose of the progestin-only pill is 0.75 mg levonorgestrel taken no more than 72 hours after unprotected intercourse and repeated in 12 hours. This regimen is marketed under the trade name “Plan B.” If Plan B is not available the dosage can be formulated from commercially available progestin-only pills. The initial dose of Ovrette, for example, is 20 pills, which is repeated 12 hours later. The progestin-only regimen may be somewhat more effective than the Yuzpe method preventing 85% of expected pregnancies in one study. In addition, nausea occurs in less than 25% of patients and vomiting is reduced to about 5% in women taking the progestin-only regimen. Recent trials have found that treatment is effective when initiated up to 5 days after unprotected intercourse and that a single dose of 1.5 mg is as effective as two 0.75-mg doses 12 hours apart.

To prevent pregnancy, a copper-containing IUD can be inserted up to 5 days after unprotected intercourse. The IUD is highly effective and can be used for long-term contraception. An IUD is not recommended for anyone at risk for sexually transmitted diseases, ectopic pregnancy, or if long-term contraception is not desired. The IUD is the most effective method of EC, with failure rates of less than 1%.

Screening patients for ECP use is based on the time of unprotected intercourse and the date of the last normal menstrual period. There are no preexisting disease contraindications and inadvertent use in pregnancy has not been linked to birth defects. Neither a pregnancy test nor a pelvic examination is required, although may be done for other reasons (eg, screening for STDs). In contrast, IUD insertion for emergency contraception is an office-based procedure that requires appropriate counseling and screening as for any patient desiring an IUD for contraception.

Counseling regarding the availability of emergency contraception can occur anytime that contraception or family planning issues are discussed. It is especially appropriate if the patient is relying on barrier methods or does not have a regular form of contraception. The counseling can be reinforced when patients present with contraceptive “mishaps.” Information that should be discussed includes: the definition of emergency contraception, indications for use, mechanism of action, lack of protection against STDs, instructions on use, and follow-up plans including ongoing contraception.


IMPLANTS

Implanon is an implantable contraceptive containing the progestin etonogestrel which provides up to 3 years of contraception. A single rod is inserted subdermally on the inside of the upper arm. Implanon contains 68 mg of etonogestrel which is the active metabolite of desogestrel. The implant releases etonogestrel at a rate of 60-70 μg per day initially, which decreases to 25-30 μg by the end of 3 years. Etonogestrel levels are undetectable one week after removal. Like other progestin-only contraceptives, the mechanism of action is by inhibition of gonadotropin secretion, inhibition of endometrial proliferation, and changes in cervical mucus. Implanon is effective with a pregnancy rate of less than 1%. Irregular bleeding is the primary reason cited for discontinuation, accounting for 13%-19% of discontinuations. Other adverse effects include headache, weight gain, acne, breast and abdominal pain, mood swings, depression, and decreased libido.
Timing of insertion depends on the patient’s recent history. If she is not currently using contraception, insert during the menstrual cycle. If she is using COCs, insert during the pill-free week. If insertion occurs at other times, backup contraception is recommended for the first seven days after insertion. In comparative trials, Implanon was easier to insert and remove than Norplant. Correct placement of the rod can be confirmed by palpation. Only health care providers who receive training from the manufacturer are allowed to order and insert the implant.

Two additional contraceptive implants, Norplant and Jadelle, which both contain levonorgestrel, are FDA-approved but not marketed in the United States.


### SPECIAL POPULATIONS

#### Adolescents

Adolescent pregnancy continues to be a serious public health problem in the United States. Almost 1 in 10 adolescent females becomes pregnant each year, with half ending in abortion. Improved contraceptive practices has contributed to an almost 40% decrease in the teen pregnancy rate. The general approach to adolescent contraception should focus on keeping the clinician-patient encounter interactive. Several suggestions include: avoiding “yes/no” questions, keeping clinician speaking time short and focused, and avoiding the word “should.”

Abstinence deserves emphasis, especially in young teenagers. Counseling should focus not on “just say no” but rather “know how to say no.” Oral contraceptives (COCs) and condoms are the most common contraceptive methods chosen by teens. These methods should be promoted simultaneously as an approach to pregnancy and STD prevention. COC use is associated with health benefits that are especially important during adolescence including treatment for acne and menstrual cycle irregularity, decreased risk of pelvic inflammatory disease and functional ovarian cysts, and decreased dysmenorrhea. The main concern adolescents have regarding COCs is the development of side effects, especially weight gain. They can be reassured that many studies have proven that COCs do not cause weight gain. Another issue that may contribute to the reluctance of adolescents to seek contraception is fear of a pelvic examination. Contrary to popular belief, a pelvic examination is not necessary when contraception is prescribed, especially if it will delay the sexually active teens’ access to needed pregnancy prevention. Adolescents should be counseled regarding missed pills and given anticipatory guidance about breakthrough bleeding and amenorrhea. Considering adolescents miss on average up to 3 pills per month, the contraceptive patch and the vaginal ring may be attractive alternatives for some adolescents.

DMPA (“Depo-Provera”) is in some ways an ideal contraceptive for adolescents. The dosing schedule allows flexibility and minimal maintenance and the failure rate is extremely low. However, concerns regarding bone loss in long-term users have prompted the recommendation that use not extend past two years. Although available data on adolescents are scant, they indicate that this group may be especially vulnerable to bone mineral density loss. It is not known whether bone loss before achieving peak bone density is recoverable, or to what extent the loss impacts on future risk of fracture. In addition, adolescents are likely to demonstrate other risk behaviors for bone loss including early sexual activity, smoking, alcohol use, and poor diet choices. Until the results of larger studies are available definitive recommendations in teenagers can not be made.

Vaginal barrier contraceptives are not ideal choices for several reasons. Many adolescents are not prepared to deal so intimately with their own bodies and do not wish to prepare so carefully for each episode of intercourse. However, they can be an effective method for highly motivated, educated adolescents. The IUD is normally not appropriate for adolescents because of the risk of PID in this population.

A discussion of emergency contraception (EC) should be part of contraceptive counseling for all adolescents. To increase the availability of EC, teens may be given a replaceable supply of EC pills to keep at home. Several studies in adolescents have shown that direct access to emergency contraception increases its rate of use but does not result in repetitive use. Although concern for improper use persists, women who are provided education on the method, use the method correctly, and incorrect use does not pose a health risk beyond unintended pregnancy.

#### Breast-Feeding Women

The lactational amenorrhea method is a highly effective, temporary method of contraception. However, to maintain effective protection against pregnancy, another method must be used as soon as menstruation resumes, the frequency or duration of breast-feeds is reduced, bottle-feeds or regular food supplements are introduced, or the baby reaches 6 months of age. Other good contraceptive options for lactating women include barrier methods, progestin-only methods, or an IUD. Some experts recommend that breast-feeding women delay using progestin-only contraception until 6 weeks postpartum. This recommendation is based on a theoretical concern that early neonatal exposure to exogenous steroids should be avoided if possible. The combined pill is not a good option for lactating women because estrogen decreases breast milk supply.

#### Perimenopausal Women

Women over the age of 40 have the second highest proportion of unintended pregnancies, exceeded only by girls 13-14 years old. Although women still need effective contraception during
perimenopause, issues including bone loss, menstrual irregularity, and vasomotor instability also need to be addressed. Oral contraceptives offer many benefits for healthy, non-smoking perimenopausal women. They have been found to decrease the risk of postmenopausal hip fracture, regularize menses in women with dysfunctional uterine bleeding, and decrease vasomotor symptoms.

Progestin-only pills can be used by women who have contraindications to estrogen. However, irregular bleeding patterns can create problems for perimenopausal women. Abnormal bleeding that is persistent, even if contraceptive hormone exposure is the most likely cause, will need to be evaluated. Other contraceptive options include condoms, vaginal barriers, and IUDs.

Physiologically, menopause is the permanent cessation of menstruation as a consequence of termination of ovarian follicular activity. Determining the exact onset of menopause in a woman using hormonal contraception can be tricky. Many clinicians measure the level of follicle-stimulating hormone (FSH) during the pill-free interval to diagnose menopause. However, because suppression of ovulation can vary from month to month, a single FSH value is unreliable. In addition, in women using COCs, FSH levels can be suppressed even on the seventh pill-free day. Given that most women do not become menopausal until after age 50 and considering the limited utility of FSH testing, one approach to managing this transition avoids FSH testing entirely. Women continue to use their COCs until age 50-52 at which time they can discontinue use or transition to hormone replacement therapy.


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2. “I/We certify that all individuals who qualify as authors have been listed; each has participated in the conception and design of this work, the analysis of data (when applicable), the writing of the document, and the approval of the submission of this version; that the document represents valid work; that if we used information derived from another source, we obtained all necessary approvals to use it and made appropriate acknowledgements in the document; and that each takes public responsibility for it.”

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Sexual dysfunction is a disturbance in one or more aspects of the sexual response cycle. It is a common problem that can result from communication difficulties, misunderstandings, and side effects of medical or surgical treatment, as well as underlying health problems. Because sexual difficulties often occur as a response to stress, fatigue, or interpersonal difficulties, addressing sexual health requires an expanded view of sexuality that emphasizes the importance of understanding individuals within the context of their lives and defining sexual health across physical, intellectual, emotional, interpersonal, environmental, cultural, and spiritual aspects of their lives and their sexual orientation. Family physicians are ideally situated to address the sexual health needs of both men and women, and it is likely that the therapeutic options for addressing these needs will continue to expand over the next decade.

Sexual dysfunction is positively correlated with low physical and emotional relationship satisfaction, as well as low general happiness. Despite this, only 10% of men and 20% of women with sexual dysfunction seek medical care for their sexual difficulties. The key to the identification of sexual function disorders is for the provider to inquire about their presence. A discussion of sexual health can be initiated in a variety of ways. Educational material or self-administered screening forms, placed in the waiting area or the examination rooms, send the message that sexual health is an important topic that is discussed in the clinician’s office. Table 18-1 lists several questionnaires that can be incorporated into self-administered patient surveys for office practices.

Sexual history can be included as part of the social history, as part of the review of systems under genitourinary systems, or in whatever manner seems most appropriate to the clinician. There are many other opportunities to bring a discussion of sexual health into the clinical encounter, as outlined in Table 18-2. Clinician anxiety may be reduced by asking the patient for permission prior to taking the sexual history.

Once the history confirms the existence of sexual difficulties, obtain as clear a description as possible of the following elements: the aspect of the sexual response cycle most involved, the onset, the progression, and any associated medical problems. Asking the patient what he or she believes to be the cause can help the clinician identify possible relationship, health, and iatrogenic etiologies. Asking the patient what he or she has tried to do to resolve the problems and clarifying the patient’s expectations for resolution can help facilitate an appropriate therapeutic approach. Involving the partner in both identification and subsequent management can be very valuable.

Sexual dysfunction is associated with many factors, including medical conditions and therapies and lifestyle choices (Table 18-3). In some instances the underlying medical condition may be the cause of the sexual dysfunction (eg, arterial
vascular disease causing erectile dysfunction). In other instances the sexual dysfunction contributes to the associated condition (eg, erectile dysfunction leads to loss of self-esteem and depression). Sexual difficulties can begin with one aspect of the sexual response cycle and subsequently affect other aspects; for example, arousal difficulties can lead to depression, which can then negatively affect sexual interest.


### DISORDERS OF DESIRE

#### General Considerations

Difficulties with sexual desire are the most common sexual concern. Over 33% of women and 16% of men in the general population report experiencing an extended period of lack of sexual interest. Other investigators have reported prevalence rates as high as 87% in specific populations. Women who were younger, separated, black, less educated, and of lower socioeconomic status reported the highest rates. Among men, the same demographics as well as increasing age were associated with the highest rates.

Table 18-3. Factors associated with sexual dysfunction.

<table>
<thead>
<tr>
<th>Factor</th>
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<tr>
<td>Aging</td>
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<td>Chronic disease</td>
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<td>Diabetes mellitus</td>
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<td>Heart disease</td>
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<td>Hypertension</td>
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<td>Lipid disorders</td>
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<td>Renal failure</td>
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<td>Vascular disease</td>
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<td>Endocrine abnormalities</td>
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<td>Hypogonadism</td>
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<td>Hyperprolactinemia</td>
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<tr>
<td>Hypo/hyperthyroidism</td>
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<td>Life style</td>
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<tr>
<td>Cigarette smoking</td>
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<td>Chronic alcohol abuse</td>
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<tr>
<td>Neurogenic causes</td>
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<tr>
<td>Spinal cord injury</td>
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<tr>
<td>Multiple sclerosis</td>
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<tr>
<td>Herniated disc</td>
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<tr>
<td>Penile injury/disease</td>
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<tr>
<td>Peyronie plaques</td>
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<tr>
<td>Priapism</td>
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<tr>
<td>Pharmacologic agents</td>
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<tr>
<td>Psychological issues</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Anxiety</td>
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<tr>
<td>Social stresses</td>
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<tr>
<td>Trauma/injury</td>
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<td>Pelvic trauma/surgery</td>
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<td>Pelvic radiation</td>
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It can also be a marker for extrarelationship affairs or domestic violence.

**Pathogenesis**

Changes in or a loss of sexual desire can be the result of biological, psychological, or social and interpersonal factors. Numerous medical conditions directly or indirectly affect sexual desire (Table 18-4). Illnesses and medications that decrease relative androgen levels, increase the level of sex hormone-binding globulin, or interfere with endocrine and neurotransmitter functioning can negatively affect desire. Examples include exogenous hormones (eg, estrogens and progesterones), diabetes, and depression, as well as erectile difficulties due to arterial vascular disease or dyspareunia due to estrogen deficiency–induced atrophic vaginitis. In both men and women, sexual desire is linked to levels of androgens, testosterone, and dehydroepiandrosterone (DHEA). In men, testosterone levels begin to decline in the fifth decade and continue to do so steadily throughout later life. For both genders, DHEA levels begin to decline in the thirties, decrease steadily thereafter, and are quite low by age 60.

Decreased sexual desire is a common manifestation of some psychiatric conditions, particularly affective disorders. Several medications can negatively affect desire and the sexual response cycle (Table 18-5). The agents most commonly associated with these changes are psychoactive drugs, particularly antidepressants, and medications with antiandrogen effects. Many psychosocial issues affect sexual desire. Factors as widely varied as religious beliefs, primary sexual interest in individuals outside of the main relationship, specific sexual phobias or aversions, fear of pregnancy, lack of attraction to partner, and poor sexual skills in the partner can all diminish sexual desire.

**Clinical Findings**

**A. Symptoms and Signs**

The evaluation of decreased sexual desire should include a detailed sexual problem history, which may clarify difficulties with sexual desire, identify predisposing conditions, and help establish a therapeutic plan. In addition to loss of desire, a diminished sense of well being, depression, lethargy, osteoporosis, loss of muscle mass, and erectile dysfunction are other manifestations of androgen deficiency.

The physical examination in patients with an acquired generalized loss of desire should be directed toward the

<table>
<thead>
<tr>
<th>Table 18-4. Common medical conditions that may affect sexual desire.</th>
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<tbody>
<tr>
<td><strong>Pituitary/hypothalamic</strong></td>
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<tr>
<td>Infiltrative diseases/tumors</td>
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<td>Endocrine</td>
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<td>Testosterone deficiency</td>
</tr>
<tr>
<td>Castration, adrenal disease, age-related bilateral</td>
</tr>
<tr>
<td>salpingoophorectomy, adrenal disease</td>
</tr>
<tr>
<td>Thyroid deficiency</td>
</tr>
<tr>
<td>Endocrine-secreting tumors</td>
</tr>
<tr>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>Psychiatric</td>
</tr>
<tr>
<td>Depression and stress</td>
</tr>
<tr>
<td>Substance abuse</td>
</tr>
<tr>
<td>Neurologic</td>
</tr>
<tr>
<td>Degenerative diseases/trauma of the central nervous system</td>
</tr>
<tr>
<td>Urologic/gynecologic (indirect cause)</td>
</tr>
<tr>
<td>Peyronie plaques, phimosis</td>
</tr>
<tr>
<td>Gynecologic pain syndromes</td>
</tr>
<tr>
<td>Renal</td>
</tr>
<tr>
<td>End-stage renal disease, renal dialysis</td>
</tr>
<tr>
<td>Conditions that cause chronic pain, fatigue, malaise</td>
</tr>
<tr>
<td>Arthritis, cancer, chronic pulmonary or hepatic disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 18-5. Drugs most commonly associated with sexual dysfunction.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Class</strong></td>
</tr>
<tr>
<td>Antihypertensives</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Thiazides</td>
</tr>
<tr>
<td>Spironolactone</td>
</tr>
<tr>
<td>Sympatholytics</td>
</tr>
<tr>
<td>Central agents (methyldopa, clonidine)</td>
</tr>
<tr>
<td>Peripheral agents (reserpine)</td>
</tr>
<tr>
<td>α-Blockers</td>
</tr>
<tr>
<td>β-Blockers (particularly nonselective agents)</td>
</tr>
<tr>
<td>Psychiatric medications</td>
</tr>
<tr>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>MAO inhibitors</td>
</tr>
<tr>
<td>SSRI</td>
</tr>
<tr>
<td>Anxiolytics</td>
</tr>
<tr>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Antiandrogenic agents</td>
</tr>
<tr>
<td>Digoxin</td>
</tr>
<tr>
<td>H2 receptor blockers</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Alcohol (long-term, heavy use)</td>
</tr>
<tr>
<td>Ketocanazole</td>
</tr>
<tr>
<td>Niacin</td>
</tr>
<tr>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Phenytoin</td>
</tr>
</tbody>
</table>

MAO, monoamine oxidase; SSRI, selective serotonin reuptake inhibitor.
identification of unrecognized conditions such as endocrine abnormalities (e.g., hypogonadism, hypothyroidism).

**B. Laboratory Findings**

An assessment of hormone status may be helpful. In men, an assessment of androgen status is indicated. In women, an assessment of both androgens and estrogens is indicated.

Assessment of the total plasma testosterone level, obtained in the morning, is the most readily available study. In most men, levels below 300 ng/dL are symptomatic of hypogonadism; however, 200 ng/dL might be a more appropriate cutoff for diagnosis in older men. Free testosterone more accurately reflects bioavailable androgens. Levels less than 50 pg/mL suggest hypogonadism.

Measurement of other androgenic agents formed earlier in the steroid hormone synthesis pathway are advocated by some authorities. If low testosterone is confirmed, further endocrine assessment and imaging is indicated to determine the specific underlying etiology.

**Treatment**

Treatment is directed at the underlying etiology and consists of both nonspecific and specific therapy. Asking sex partners about each other’s sexual function can be useful.

Educating couples about the impact of extraneous influences—fatigue, preoccupation with child rearing, work stress, and interpersonal conflict—can improve awareness of these issues. Encouraging couples to set time aside for themselves, to schedule “dates,” can be very effective. Educating partners about gender generalities and encouraging communication about sexual needs and desires can be helpful. The quality of the relationship appears to be a critical component in women’s sexual response cycle.

Although largely unstudied, the quality of the relationship is likely of equal import in men’s sexual interaction. An emotionally and physically satisfying relationship enhances sexual desire and arousal and has a positive feedback on the quality of the relationship. The importance of allowing time for sexual relations, incorporating the senses, understanding what is pleasing to one’s partner, and incorporating seduction cannot be overemphasized.

The impact of potentially reversible medical conditions or medications on sexual desire should be addressed. Treating organic etiologies such as depression, hypothyroidism, hyperprolactinemia, and androgen deficiency can often restore sexual interest.

Options available when decreased sexual desire is attributed to medical therapy can be challenging. Treatment approaches can include lowering the dosage, suggesting drug holidays, discontinuing potentially offensive medications, or switching to a different agent. Where continuation of therapy is indicated, adding specific agents to address the sexual manifestations can be useful.

In men and women with acquired decreased sexual interest, hormone supplementation may be considered.

**A. Androgen Replacement**

The goal of replacement therapy is to raise the level to the lowest physiologic range that promotes satisfactory response (Table 18-6). For both genders, oral testosterone is not recommended due to the prominent first-pass phenomenon and the potential for significant liver toxicity. Intramuscular injections result in dramatic fluctuations in blood levels. Topical preparations offer the advantage of consistent levels in the normal range. Local skin reactions are common with patches. Topical gels tend to have fewer skin side effects.

A diagnosis of androgen insufficiency should only be made in women who are adequately estrogenized, whose free testosterone is at or below the lowest quartile of the normal range for the reproductive age (20-40 years), and who present with clinical symptoms.

Androgen supplementation can be helpful for desire and arousal difficulties in both men and women. Dehydroepiandrosterone sulfate (DHEAS) is available over the counter and is dosed 25-75 mg/d based on response. Transdermal testosterone can be compounded as 1%-2% cream, gel, or lotion that can be applied to the labial and clitoral area. Oral methyltestosterone, available as Estratest for women, has been used safely for years. Oral administration of methyltestosterone is a less preferred route given erratic absorption and concerns about liver effects.

Exogenous estrogens and progestins, in the form of hormone replacement therapy, lower physiologically available androgens and can contribute to decreased sexual interest. Addition of androgens, methyltestosterone, or DHEAS can offset this negative impact. If no benefit occurs from this change, the physician should reassess the quality of the sexual relationship and also consider discontinuing the exogenous hormones. All oral contraceptive agents lower bioavailable androgen levels as a result of high sex hormone–binding globulin levels. Changing to oral contraceptive pills with greater androgen activity, such as those containing norgestrel, levonorgestrel, and norethindrone acetate, may be an effective change (Table 18-7).

**B. Contraindications and Risk of Testosterone Therapy**

Because testosterone treatment may stimulate tumor growth in androgen-, estrogen-, or progesterone-dependent cancers, it is contraindicated in men with prostate cancer and in men and women with a history of breast cancer. Although it is known that testosterone accelerates the clinical course of prostate cancer and may stimulate the growth of previously undiagnosed prostate tumors, there is no conclusive evidence in short-term studies that testosterone therapy increases the incidence of prostate cancer.

Certain patient populations such as the elderly and patients who have a first-degree relative with prostate cancer may be at increased risk. Preexisting sleep apnea and hyperviscosity, including deep venous thrombosis or pulmonary...
embolism, are relative contraindications to testosterone use. Serious hepatic and lipid changes have been associated with the use of oral preparations available in the United States. Benign prostatic hypertrophy, lipid changes, gynecomastia, sleep apnea, and increased oiliness of skin or acne are other reported side effects.

If androgen therapy is initiated for both men and women, close follow-up is recommended to assess androgen levels, lipid profile, hematocrit levels, and liver function. Periodic assessment of the prostate-specific antigen level may be considered. Until more data regarding long-term use are available, it is probably most prudent to check androgen, hematocrit, liver, and lipid levels every 3-6 months.


### DISORDERS OF EXCITEMENT & AROUSAL

#### General Considerations

Arousal disorders appear to affect 18.8% of women and 5% of men in the general population. The prevalence of arousal difficulties for both men and women is much higher in patient populations with coexisting illnesses such as depression,

<table>
<thead>
<tr>
<th>Route/Agent</th>
<th>Dosage for Women</th>
<th>Dosage for Men</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyltestosterone</td>
<td>10 mg: 1/4, 1/2 tablet daily or 10 mg Monday, Wednesday, Friday</td>
<td>10-50 mg/d</td>
</tr>
<tr>
<td>Fluoxymesterone</td>
<td>2 mg: 1/2 tablet daily or 1 tablet every other day</td>
<td>5-20 mg/d</td>
</tr>
<tr>
<td>Estratest and Estratest HS</td>
<td>Either 1.25 or 0.625 mg</td>
<td></td>
</tr>
<tr>
<td>Dehydroepiandrosterone</td>
<td>25-75 mg 3 times weekly to daily</td>
<td></td>
</tr>
<tr>
<td><strong>Buccal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyltestosterone</td>
<td>5-25 mg daily</td>
<td>5-25 mg/d</td>
</tr>
<tr>
<td><strong>Sublingual</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyltestosterone</td>
<td>0.25 mgb</td>
<td></td>
</tr>
<tr>
<td>Testosterone micronized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USP tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Transdermal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone patch</td>
<td>2.5-5.0 mg applied every day or every other day</td>
<td>4-6 mg/d</td>
</tr>
<tr>
<td>Topical testosterone</td>
<td>1% vaginal cream daily to clitoris and labia</td>
<td>5-10 mg/d (Androderm)</td>
</tr>
<tr>
<td>Testosterone micronized</td>
<td>1-2% gel daily to clitoris and labia</td>
<td></td>
</tr>
<tr>
<td><strong>Intramuscular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone enanthate</td>
<td>200 mg/mL: 0.25-0.5 mL every 3-5 wk</td>
<td>50-400 mg every 2-4 wk</td>
</tr>
<tr>
<td>Testosterone propionate</td>
<td>100 mg/mL: 1/4-1/2 mL every 3-4 weeks</td>
<td>25-50 mg 2-3 times weekly</td>
</tr>
</tbody>
</table>

aOral methyltestosterone, aside from the combination estratest, should be used only short term due to the risk of hepatotoxicity.
bMust be compounded by a pharmacist.


### Table 18-7. Relative androgenicity of progestational components of oral contraceptive agents.

<table>
<thead>
<tr>
<th>Androgenicity</th>
<th>Norethindrone (0.4-0.5 mg)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least</td>
<td>Norgestrel (0.18-0.25 mg)</td>
</tr>
<tr>
<td></td>
<td>Desogestrel (0.15 mg)</td>
</tr>
<tr>
<td></td>
<td>Ethynodiol diacetate (1.0 mg)</td>
</tr>
<tr>
<td>Medium/neutral</td>
<td>Norethindrone (0.5-1.0 mg)a</td>
</tr>
<tr>
<td>Greatest</td>
<td>Levonorgestrel (0.1-0.15 mg)</td>
</tr>
<tr>
<td></td>
<td>Norgestrel (0.075-0.5 mg)</td>
</tr>
<tr>
<td></td>
<td>Norethindrone acetate (1.0-1.5 mg)</td>
</tr>
</tbody>
</table>

aNorethindrone (0.35 mg) without estrogen, in progestin-only oral contraceptive pills, has medium relative androgenicity.

Pathogenesis

Arousal difficulties most likely result from a mix of organic and psychogenic etiologies. Organic causes include vascular, neurogenic, and hormonal etiologies. Vascular arterial or inflow problems are by far the most common. Regardless of the primary etiology, a psychological component frequently coexists. Although influenced by other systems, arousal is primarily a neurovascular process. Optimal function requires an intact nervous system and responsive arterial vasculature. Sexual stimulation results in nitric oxide release, which initiates a cascade of events leading to a dramatic increase in blood flow to the penis in men and the vagina and clitoris in women. Nitric oxide enters into vascular smooth muscle cells causing an increase in the production of cyclic guanosine monophosphate (cGMP). As cGMP concentrations rise, vascular smooth muscle relaxes, allowing increased arterial blood flow. The cGMP buildup is countered by the enzyme phosphodiesterase type 5 (PDE-5).

Inhibiting the action of PDE-5 results in higher levels of cGMP, causing increased and sustained vasodilation. Arousal disorders appear to increase with age, but it is more likely that increase in chronic illnesses and their therapeutic intervention are the root cause. Life style factors such as tobacco, alcohol, exercise, and diet also contribute.

Clinical Findings

A. Symptoms and Signs

The first step in assessment is to ensure that arousal problems are the primary problem. Some men may complain of erectile difficulties but on detailed questioning may not be experiencing erections due to lack of desire or may not be able to sustain the erection due to premature ejaculation. Detailed information about onset, duration, progression, severity, and association with medical conditions, medications, and psychosocial factors will enable the provider to identify if the patient's problem has a primarily organic or psychogenic etiology.

Physical examination should be focused and directed by the history. The clinician should assess overall health, including life style topics such as exercise, tobacco use, and alcohol use. Additionally, screening for manifestations of affective, cardiovascular, neurologic, or hormonal etiology should be performed.

B. Laboratory Findings

If not previously done, basic laboratory studies such as lipid profile and fasting blood glucose should be considered to identify unrecognized systemic disease that may predispose to vascular disease. Measurement of androgen levels (including DHEA) should be performed if androgen supplementation is being considered.

Treatment

Chronic medical conditions should be treated or controlled to reverse or slow the progression of associated conditions. Medications contributing to arousal problems (eg, antihypertensive agents) should be replaced with other agents, if possible, or reduced in dosage. Potentially reversible causes should be addressed.

Maximizing glucose control in diabetic patients, moderating alcohol consumption, encouraging exercise, and smoking cessation are important life style changes necessary to maintain healthy sexual response. Nitric oxide appears to be androgen sensitive, so correction of androgen levels may be necessary before PDE-5 inhibitors will be successful. Sexual lubricants such as Astro-glide, Replens, and K-Y jelly can add lubrication and enhance sensuality.

A. Oral Agents

Sildenafil, vardenafil, and tadalaf are PDE-5 inhibitors approved for the treatment of male erectile dysfunction. Inhibitors do not result in spontaneous erection and require erotic or physical stimulation, or both, to be effective. PDE-5 inhibitors are contraindicated in patients who take organic nitrates of any type. Nitrates are nitric oxide donors. The concomitant use of a PDE-5 inhibitor and a nitrate can result in profound hypotension. PDE-5 inhibitors are also contraindicated in patients with recent cardiovascular events or who are clinically hypotensive.

The side effects of PDE-5 inhibitors are related to the presence of PDE-5 in other parts of the body and cross-reactivity with other PDE enzyme subtypes. A transient disturbance in color vision, characterized typically by a greenish-blue hue, is due to a slight cross-reactivity with PDE-5 isoenzyme in the retina. Because of this cross-reactivity, PDE-5 inhibitors should not be used in patients with retinitis pigmentosa. Side effects tend to be mild and transient, and include headache, flushing, dyspepsia, and rhinitis.

Although PDE-5 inhibitors are not approved by the Food and Drug Administration for use in women, it is likely that these agents will have a role in treating female arousal difficulties. One study reported significant effectiveness in improving arousal and orgasm in a group of young premenopausal women with arousal difficulties. Additionally, the frequency of sexual fantasies, sexual intercourse, and enjoyment improved. Studies of genital stimulation devices and topical warming gels have shown these adjuncts to be beneficial to sexual functioning.

B. Vacuum Constriction Devices

These devices are effective for most causes of erectile dysfunction, are noninvasive, and are a relatively inexpensive treatment option. The device consists of a cylinder, vacuum
pump, and constriction band. The flaccid penis is placed in the cylinder. Pressing the cylinder against the skin of the perineum forms an airtight seal. Negative pressure from the pump draws blood into the penis, resulting in increased firmness. When sufficient blood has entered the erectile bodies, a constriction band is placed around the base of the penis preventing the escape of blood. Following intercourse the band is removed. Side effects include penile pain, bruising, numbness, and impaired ejaculation.

C. Intracavernosal Injection

With this method, synthetic formulations of prostaglandin E₃ (alprostadil alone or in combination with other vasoactive agents) is injected directly into the corpus cavernosum. This results in spontaneous erection. Intracavernosal injection is effective in producing erection in most patients with erectile dysfunction, including some who failed to respond to oral therapy.

D. Penile Prosthesis

In patients not responding to other therapies, a permanent penile prosthesis has proven to be safe and effective in many patients. Current models have a 7- to 10-year life expectancy or longer. Overall patient satisfaction is excellent.

Sexual Pain Syndromes

Sexual pain syndromes can negatively affect arousal for both men and women. Sexual pain syndromes occur in 14% of women and 3% of men in the general population, and over 70% of samples of female patients. Peyronie plaques or other penile deformity, priapism, and lower urinary tract symptoms can be etiologic in male sexual pain syndrome. For women, vaginitis, vestibulitis, pelvic pathology, vaginismus, and inadequate vaginal lubrication are among the etiologies of sexual pain syndromes for women. Sexual pain syndromes negatively affect desire, arousal, and thus orgasm.

Premature ejaculation results from a shortened plateau phase. In addition to heightened sensitivity to erotic stimulation and, often, learned behavior from rushed sexual encounters, organic etiology is also likely. The ejaculatory reflex involves a complex interplay between central serotonergic and other neurons. From studies of rodents, premature ejaculation is speculated to be a dysfunction of serotonergic receptors.

Although premature ejaculation tends to improve with age by the natural lengthening of the plateau phase, it persists well into aging for many men. Like erectile dysfunction, premature ejaculation is often associated with shame and depression. Orgasmic difficulties can feed back negatively on arousal and then desire. A man with premature ejaculation can develop erectile dysfunction and ultimately have decreased sexual desire because of the emotional effects.

Difficulty or inability to achieve orgasm affects a greater number of women than men and typically results from a prolonged arousal phase caused by inadequate stimulation. Medications can also interfere. Selective serotonin reuptake inhibitors (SSRIs) raise the threshold for orgasm, which makes them highly effective treatment options for men with premature ejaculation, but highly problematic for both genders who have difficulty achieving orgasm. Medications that lower the threshold for orgasm can be very problematic for men with premature ejaculation but can be very effective for treating problems with orgasm. These include cyproheptadine, bupropion, and possibly PDE-5 inhibitors. These agents can be helpful for men with delayed ejaculation. Psychotropic agents and alcohol often cause delayed ejaculation. Medications used as rescue agents for treating sexual side effects of psychotropic agents or to lower the threshold for orgasm for women having difficulty with orgasm are also useful for treating delayed ejaculation (Table 18-8).

Retrograde ejaculation occurs when the seminal fluid is ejaculated from the posterior urethra into the bladder. This is caused by abnormal function of the internal sphincter of the urethra and can result from anatomic disruption (eg, transurethral prostatectomy), sympathetic nervous system disruptions (eg, damage from surgery), lymph node invasion, or diabetes. Retrograde ejaculation can result from interference with the sphincter function from medications such as antipsychotics, antidepressants, and antihypertensive agents as well as alcohol use. Dextroamphetamine, ephedrine, phenylpropanolamine, and pseudoephedrine are potentially effective in treating retrograde ejaculation.

Evaluation should include a history of sexual problems, medications, and quality of the relationship. Treatment approaches include discontinuing, decreasing the dosage of, or drug holidays from offending medications. Small studies have shown a benefit from rescue agents that can be added as standing (or as needed) medications (see Table 18-8). SSRIs are the treatment of choice for premature ejaculation. It is helpful if women become familiar with the type of stimulation they require for orgasm and communicate that to their partners. An excellent reference for patients is the book *Becoming Orgasmic*. 

DISORDERS OF EJACULATION & ORGASM

Premature ejaculation affects 29% of men in the general population, and orgasm difficulties affect 8% of men and 24% of women. Over 80% of women in patient populations report difficulties with orgasm.
The resolution phase is typically not problematic for either gender, but misunderstandings of age-related changes can occur. Men, and their partners, need to understand that with increasing age the refractory period to sexual stimulation lengthens, sometimes up to 24 hours. Men may require more direct penile stimulation for sexual response as they age.


### Sexual Activity & Cardiovascular Risk

Sexual activity and intercourse are associated with physiologic changes in heart rate and blood pressure. A patient’s ability to meet the physiologic demands related to sexual activity should be assessed, particularly if the patient is not accustomed to the level of activity associated with sex or may be at increased risk of a cardiovascular event. Typical sexual intercourse is associated with an oxygen expenditure of 3-4 metabolic equivalents (METS), whereas vigorous sexual intercourse can expend 5-6 METS. Patients unaccustomed to the level of exercise associated with sexual activity and who have risk factors for cardiovascular events present a clinical challenge. An algorithm based on expert opinion can assist clinicians in determining which patients can be safely advised that sexual activity and treatment can be undertaken without further risk stratification and which should have further evaluation. In this algorithm patients are classified as low risk if they have fewer than three risk factors (age, hypertension, diabetes, obesity, cigarette smoking, dyslipidemias, and sedentary lifestyle). Patients in the intermediate risk group should undergo risk stratification into either the low-risk or high-risk group. This assessment may include cardiac stress testing.


### Table 18-8. Antidotes for psychotropic-induced sexual dysfunction.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yohimbine</td>
<td>5.4-16.2 mg, 2-4 h prior to sexual activity</td>
</tr>
<tr>
<td>Bupropion</td>
<td>100 mg as needed or 75 mg three times daily</td>
</tr>
<tr>
<td>Amantadine</td>
<td>100-400 mg as needed or daily</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>2-16 mg a few hours before sexual activity</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>5-25 mg as needed</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>5 mg sublingually 1 h prior to sex</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>150 mg 1 h prior to sex</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>50-100 mg as needed</td>
</tr>
</tbody>
</table>

Acute coronary syndrome (ACS) encompasses unstable angina, ST-elevation myocardial infarction (STEMI), and non–ST-elevation myocardial infarction (NSTEMI). It is the symptomatic cardiac end-product of cardiovascular disease (CVD) resulting in reversible or irreversible cardiac injury, and even death.

**Diagnosis**

The diagnosis of ACS requires two of the following: ischemic symptoms, diagnostic electrocardiogram (ECG) changes, and elevated serum marker of cardiac injury.

**A. Symptoms**

By themselves, signs and symptoms are not sufficient to diagnose or rule out acute coronary syndrome, but they start the investigatory cascade. Having known risk factors for coronary artery disease (CAD) (Table 19-1) increases the likelihood of ACS. Up to one-third of people with CAD progress to ACS with chest pain. Chest pain is the predominant symptom of ACS, but is not always present. Symptoms include:

- Typical or stable angina: substernal pain that occurs with exertion and alleviates with rest
- Chest pain for >20 minutes
- Dull, heavy pressure in or on the chest
- Sensation of a heavy object on the chest
- Chest pain radiating to the back, neck, jaw, left arm, or shoulder
- Chest pain unaffected by inspiration
- Chest pain not reproducible with chest palpation
- Accompanying diaphoresis
- Pain initiated by stress, exercise, large meals, sex, or any activity that increases the body’s demand upon the heart for blood
- Extreme fatigue or edema after exercise
- Shortness of breath
  - This can be the only sign in the elderly
  - More common in black that white patients
  - More common in women than men
- Right-sided chest pain, occasionally
  - More common in black patients
- Levine’s sign: chest discomfort described as a clenched fist over the sternum (the patient will clench his/her fist and rest it on or hover it over his/her sternum)
- Angor Anami: great fear of impending doom/death
- Pain high in the abdomen or chest, nausea, extreme fatigue after exercise, back pain, and edema can occur in anyone, but are more common in women
- Nausea, lightheadedness, or dizziness
- Less commonly:
  - Mild, burning chest discomfort
  - Sharp chest pain
  - Pain that radiates to the right arm or back or a sudden urge to defecate in conjunction with chest pain
  - Chest pain that is present for days, pleuritic, or positional or that radiates to the lower extremities or above the mandible is less likely to be cardiac in origin.

**B. Physical Findings**

Examination findings that increase the probability that symptoms are from ACS include hypotension, diaphoresis, and systolic heart failure indicated by a new S3 gallop, new or worsening mitral valve regurgitation, pulmonary edema, and jugular venous distention.

Chest pain reproducible with palpation is significantly less likely to be ACS.
Table 19-1. Risk Factors for Coronary Artery Disease

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>Age: men ≥45 years old women ≥55 years old or postmenopausal</td>
</tr>
<tr>
<td>Positive family history of CAD</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Overweight and obesity</td>
</tr>
<tr>
<td>Left ventricle hypertrophy</td>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Dyslipidemias:</td>
<td>Smoking (risk abates after 3 y quit)</td>
</tr>
<tr>
<td>HDL &lt;35 mg/dL</td>
<td>Low fruit and vegetable intake</td>
</tr>
<tr>
<td>LDL &gt;130 mg/dL</td>
<td>Excessive alcohol intake</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Stress</td>
<td>Elevated uric acid</td>
</tr>
<tr>
<td>Depression</td>
<td>Lp (a) lipoprotein</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>Elevated high sensitivity C-reactive protein</td>
</tr>
<tr>
<td>Hyperreninemia</td>
<td></td>
</tr>
</tbody>
</table>

>2 drinks/d in men, >1 drink/d in women and lighter weight persons. 1 drink = 0.5 oz (15 mL) of ethanol: 12 oz beer, 5 oz wine, or 1.5 oz 80-proof whiskey.

C. Diagnostic Testings

Anyone suspected of having ACS should be evaluated with a 12-lead electrocardiogram (ECG) and serum cardiac biomarkers (eg, troponin, CPK-MB).

1. Electrocardiogram—Notable ECG findings: ST-T segment (>1-mm elevation or depression) and T-wave (inversion) changes suggest ischemia; Q-wave suggests accomplished infarction; ST-elevation is absent in unstable angina and NSTEMI; new bundle branch block or sustained ventricular tachycardia indicates a higher risk of progression to infarction.

Accurate ECG interpretation is essential for diagnosis, risk stratification, and guiding the treatment plan. Many findings are nonspecific, and the preexisting presence of bundle branch block (BBB), interventricular conduction delay (IVCD), or Wolff-Parkinson-White syndrome reduce the diagnostic reliability of an ECG in patients with chest pain. If there is a recent ECG for comparison the presence of a new BBB or IVCD raises the suspicion of ACS.

A normal ECG does not exclude ACS. Up to 25%-50% of people with angina or silent ischemia have a normal ECG; 10% of ACS is subsequently diagnosed with an MI after an initial normal ECG.

2. Cardiac biomarkers—Cardiac biomarkers are blood tests that indicate myocardial damage. Troponin T and Troponin I are preferred because of their high sensitivity and specificity for myocardial injury. Troponin I is most preferred because Troponin T can also be elevated by renal disease, polymyositis, or dermatomyositis. Until recently, due to its decreased sensitivity during the first 4-6 hours of ACS, a negative troponin did not reliably “rule out” ACS; however, newer highly sensitive troponin I assays have a negative predictive value of 97%-99%, depending on the chosen cut-off value, as early as 3-hours after the onset of symptoms. The trade-off is lower specificity. In essence, less false negatives afford earlier diagnosis at the cost of more false positives. The potential impact of this will be discussed in the treatment section of this chapter. Troponin remains elevated for 7-10 days, and can therefore help identify prior recent infarctions.

When initial ECG and cardiac markers are normal these tests should be repeated within 6-12 hours of symptom onset. If those are normal, exercise or pharmacological cardiac stress testing should be done to evaluate for inducible ischemia. Exercise stress testing is preferred, but stress testing with chemicals (dobutamine, dipyridamole, or adenosine) can be used to simulate the cardiac effects of exercise in those unable to exercise enough to produce a test adequate for interpretation.

3. Exercise ECG—Exercise ECG, also called exercise stress testing (EST), is the main test for evaluating those with suspected angina or heart disease (Table 19-2). Interpretation of the test is based upon the occurrence of signs of stress-induced impairment of myocardial contraction, including ECG changes (Table 19-3) and/or symptoms and signs of angina. The false positive rate is 10%.

4. Radionuclide myocardial perfusion imaging—Adding radionuclide myocardial perfusion imaging (Table 19-4) to EST can improve sensitivity, specificity, and accuracy, especially in patients with a nondiagnostic exercise test or limited exercise ability. Acute rest myocardial perfusion imaging is very similar, but is performed during or shortly after resolution of angina symptoms that were not induced by a stress test. Radionuclide EST can be advantageous in women because EST is less accurate in women compared to men.

5. Chest radiography—Chest radiography (CXR) is used to assess for non-ACS causes of chest pain (eg, aortic dissection, pneumothorax, pulmonary embolus, pneumonia, rib fracture).

6. Echocardiography—Echocardiography can be used to determine left ventricle ejection fraction, assess cardiac valve function, and detect regional wall motion abnormalities which correspond to areas of myocardial damage. Its high sensitivity but low specificity makes it most useful to exclude ACS if the study is normal. It can also be used as an adjunct to stress testing. Since stress-induced impairment of myocardial contraction precedes ECG changes and angina, stress echocardiography, done and interpreted by experienced clinicians, can be superior to EST.

7. Cardiac magnetic resonance imaging—Cardiac magnetic resonance imaging does not yet have a clinical role because its sensitivity and specificity for detecting significant CAD plaque do not eclipse angiography, the gold standard.
8. **Electron-beam computer tomography**—Electron-beam computer tomography (EBCT) currently lacks utility since a positive test does not correlate well to an ACS episode. The future role of EBCT may change as more studies are done with higher resolution (64 and 128 slice) CT machines.

9. **Coronary angiography**—Coronary angiography is the gold standard. Main indications are in Table 19-5. Risks include death (1 in 1400), stroke (1 in 1000), coronary artery dissection (1 in 1000), arterial access complications (1 in 500), and minor risks such as arrhythmia. Ten to 30% of angiography studies are normal.

### Table 19-2. Exercise Stress Testing

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Confirm suspected angina</td>
<td>• Cardiac failure</td>
</tr>
<tr>
<td>• Evaluation of extent of myocardial ischemia and prognosis</td>
<td>• Any febrile illness</td>
</tr>
<tr>
<td>• Risk stratification after myocardial infarction</td>
<td>• Left ventricular outflow tract obstruction or hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>• Detection of exercise induced symptoms (such as arrhythmias or syncope)</td>
<td>• Severe aortic or mitral stenosis</td>
</tr>
<tr>
<td>• Evaluation of outcome of interventions (such as PCI or CABG)</td>
<td>• Uncontrolled hypertension</td>
</tr>
<tr>
<td>• Assessment of cardiac transplant</td>
<td>• Pulmonary hypertension</td>
</tr>
<tr>
<td>• Rehabilitation and patient motivation</td>
<td>• Recent myocardial infarction</td>
</tr>
<tr>
<td>• Confirm suspected angina</td>
<td>• Severe tachyarrhythmias</td>
</tr>
<tr>
<td>• Evaluation of extent of myocardial ischemia and prognosis</td>
<td>• Dissecting aortic aneurysm</td>
</tr>
<tr>
<td>• Risk stratification after myocardial infarction</td>
<td>• Left main stem stenosis or equivalent</td>
</tr>
<tr>
<td>• Detection of exercise induced symptoms (such as arrhythmias or syncope)</td>
<td>• Complete heart block</td>
</tr>
</tbody>
</table>


### Pathogenesis & Epidemiology

Cardiovascular disease (CVD) includes all diseases of the heart and vascular (eg, stroke and hypertension). CAD, synonymous with coronary heart disease (CHD), affects the coronary arteries, diminishing their ability to supply oxygenated blood to the heart.

### A. Atherosclerosis Progression

Atherosclerotic disease is the thickening and hardening (loss of elasticity) of the arterial wall due to the accumulations of lipids, macrophages, T-lymphocytes, smooth muscle cells,

### Table 19-3. Main End Points for Abnormal Exercise ECG

<table>
<thead>
<tr>
<th>Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Target heart rate achieved (&gt;85% of maximum predicted heart rate)</td>
</tr>
<tr>
<td>• ST-segment depression &gt;1 mm (downsloping or planar depression of greater predictive value than upsloping depression)</td>
</tr>
<tr>
<td>• Slow ST recovery to normal (&gt;5 min)</td>
</tr>
<tr>
<td>• Decrease in systolic blood pressure &gt;20 mm Hg</td>
</tr>
<tr>
<td>• Increase in diastolic blood pressure &gt;15 mm Hg</td>
</tr>
<tr>
<td>• Progressive ST-segment elevation or depression</td>
</tr>
<tr>
<td>• ST-segment depression &gt;3 mm without pain</td>
</tr>
<tr>
<td>• Arrhythmias (atrial fibrillation, ventricular tachycardia)</td>
</tr>
</tbody>
</table>

**Features indicative of a strongly positive exercise test**

| Exercise limited by angina to <6 min of Bruce protocol                    |
| Failure of systolic blood pressure to increase >10 mm Hg, or fall with evidence of ischemia |
| Widespread marked ST-segment depression >3 mm                             |
| Prolonged recovery time of ST changes (>6 min)                            |
| Development of ventricular tachycardia                                    |
| ST elevation in absence of prior myocardial infarction                    |


### Table 19-4. Some Indications for the Use of Radionuclide Perfusion Imaging Rather Than Exercise Electrocardiography

<table>
<thead>
<tr>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complete left bundle-branch block</td>
</tr>
<tr>
<td>• Electronically paced ventricular rhythm</td>
</tr>
<tr>
<td>• Preexcitation (Wolff-Parkinson-White) syndrome or other, similar electrocardiographic conduction abnormalities</td>
</tr>
<tr>
<td>• More than 1 mm of ST-segment depression at rest</td>
</tr>
<tr>
<td>• Inability to exercise to a level high enough to give meaningful results on routine stress electrocardiography†</td>
</tr>
<tr>
<td>• Angina and a history of revascularization‡</td>
</tr>
</tbody>
</table>

*The guidelines were developed by the American College of Cardiology, the American Heart Association, the American College of Physicians, and the American Society of Internal Medicine.*

†Patients with this factor should be considered for pharmacologic stress tests.

‡In patients with angina and a history of revascularization, characterizing the ischemia, establishing the functional effect of lesions, and determining myocardial viability are important considerations.

extracellular matrix, calcium, and necrotic debris. Figures 19-1 to 19-3 grossly depict the multifactorial and complex depository, inflammatory, and reactive processes that collaborate to occlude coronary arteries.

### B. Genetic Predisposition

The best marker for CAD risk is having a family history of CAD. Some inherited risk factors (eg, dyslipidemia and propensity for diabetes mellitus) are modifiable; others (eg, age and sex) are not. Genes affect the development and progression of disease and its response to risk factor modification and lifestyle decisions: nature (genetics) meets nurture (environment) and they responsively interrelate (Table 19-6).

### Prevention: Primary, Secondary, and Tertiary

The cascade of events of CHD that lead to ACS can be interrupted, delayed, or treated. **Primary prevention** tries to prevent disease before it develops, that is, prevent or delay development of risk factors. **Secondary prevention** attempts to prevent disease progression by identifying and treating risk factors or preclinical, asymptomatic disease. **Tertiary prevention** is treatment of established disease to restore and maintain highest function, minimize negative disease effects, and prevent complications, i.e., help recover from and prevent recurrence of ACS.

Primary prevention of ACS should begin in childhood by preventing tobacco use, eating a diet rich in fruits and vegetable and low in saturated fats, exercising regularly for 20-30 minutes five times a week, and maintaining a BMI 18-25 kg/m².

Secondary and tertiary preventions involve progressively more aggressive management of those who have known risk factors for or have experienced ACS (Figure 19-4 and Table 19-7). Although the association between cholesterol and ACS death is weaker in those older than 65 years, HMG-CoA reductase inhibitors drugs (statins) still positively impacts morbidity and mortality in this demographic. This may be due to their effects that go beyond their lipid lowering: pleiotropic effects such as anti-inflammation and endothelial stabilizing.

Some once-touted therapies have been found to be ineffective. Due to lack of effect and potential harm, estrogen +/− progestin hormone replacement therapy should not be used as primary, secondary, or tertiary prevention of CAD. **Antibiotics** and the **antioxidants vitamins C and E** do not improve ACS morbidity and mortality.

### Cardiac Rehabilitation

Cardiac rehabilitation, an example of tertiary prevention, is a multidisciplinary attempt to prevent future ACS by focusing on three areas: exercise, risk factor modification, and psychosocial intervention. Optimal medical management is part of this process. Patient adherence to the plan is integral to long-term success.

1. **Exercise-based rehabilitation programs**—Exercise-based rehabilitation programs reduce both all-cause and cardiac mortality in patients with a history of myocardial infarction, surgical intervention (PCI, CABG), or stable CAD.

2. **Risk factor modification**—Risk factor modification addresses the content of Figure 19-4 and Table 19-7, involves dietician-led nutritional training, and emphasizes smoking cessation via counseling, drug therapy (bupropion, varenicline), nicotine replacement, and formal cessation programs.

---

**Table 19-5. Main Indications for Coronary Angiography**

- Uncertain diagnosis of angina (coronary artery disease cannot be excluded by noninvasive testing)
- Assessment of feasibility and appropriateness of various forms of treatment (percutaneous intervention, bypass surgery, medical)
- Class I or U stable angina with positive stress test or class III or W angina without positive stress test
- Unstable angina or non-Q-wave myocardial infarction (medium- and high-risk patients)
- Angina not controlled by drug treatment
- Acute myocardial infarction—especially cardiogenic shock, ineligibility for thrombolytic treatment, failed thrombolytic reperfusion, reinfarction, or positive stress test
- Life-threatening ventricular arrhythmia
- Angina after bypass surgery or percutaneous intervention
- Before valve surgery or corrective heart surgery to assess occult coronary artery disease

**Source:** Grech ED: Pathophysiology and investigation of coronary artery disease. BMJ 2003; 326:1027-1031.

**Figure 19-1. Atheromatous plaque progression.**


Figure 19-3. Mechanism of coronary artery thrombosis. Hypothetical methods of possible trigger for coronary thrombosis: (1) physical or mental stress leads to hemodynamic changes, which in turn lead to plaque rupture; (2) activities causing an increase in coagulability; and (3) stimuli leading to vasoconstriction. The role of coronary thrombosis in unstable angina, MI, and sudden cardiac death has been well described. (From Muller JE et al: Triggers, acute risk factors and vulnerable plaques: the lexicon of a new frontier. J Am Coll Cardiol 1994; 23:809. Reprinted with permission from the American College of Cardiology. Chasen CA, Muller JE: Triggers of myocardial infarction. Cardiol Special Ed 1997; 3:57.)
3. **Psychosocial intervention**—Psychosocial intervention emphasizes the identification and management of the psychological and social effects that can follow ACS. These effects can include depression, anxiety, family issues, and job-related problems. Depression has been linked to worse mortality in patients with CHD. Psychosocial intervention alone does not affect total or cardiac mortality, but does decrease depression and anxiety which may impact quality of life.

### Differential Diagnosis of ACS Signs & Symptoms

- Anemia
- Aortic aneurysm
- Aortic dissection
- Cardiac tamponade
- Cardiac valve rupture
- Cardiomyopathy
- Cholecystitis
- Chostochondritis
- Coronary artery anomaly or aneurysm
- Diaphragmatic irritation/inflammation due to:
  - Hepatitis
  - Infection
  - Mass effect from nearby cancer
  - Pancreatitis
  - Pulmonary edema/effusion
- Duodenal ulcer
- Esophageal spasm

### Table 19-6. Genetic and Environmental Influences on CHD Predisposition

<table>
<thead>
<tr>
<th>Gene-Environment Interaction</th>
<th>Favorable Genes</th>
<th>Unfavorable Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable environment</td>
<td>Low risk</td>
<td>Moderate risk</td>
</tr>
<tr>
<td>Unfavorable environment</td>
<td>Moderate risk</td>
<td>High risk</td>
</tr>
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<td>High risk</td>
</tr>
</tbody>
</table>


### Neurohormonal

- β-blocker
- ACE inhibitor

### Anti-inflammatory

- Statins
- Niacin

### Anti-Thrombotic

- Aspirin
  - or clopidroglre, ticlopidine, dipyridamol + aspirin
- Anticoagulants
  - (eg, warfarin, glycoprotein IIb/IIIa inhibitors)
- Thrombolytics
- Coronary angioplasty +/- stent

**CAD treatment after onset angina, post-MI**

### Metabolic

- Lipid lowering
- Folate
- Omega-3-Fatty acids*

### Blood pressure lowering

- Diuretics (non-loop)
- β-blocker
- ACE inhibitors
- ARBs
- CCBs (last choice; favor dihydropyridine)

**Figure 19-4.** Tertiary prevention for CAD.
Table 19-7. Guide to Comprehensive Risk Reduction for Patients with Coronary Artery Disease

<table>
<thead>
<tr>
<th>Risk Intervention</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking:</td>
<td>Strongly encourage patient and family to stop smoking. Provide counseling, nicotine replacement, bupropion, and formal cessation programs as appropriate.</td>
</tr>
<tr>
<td>Lipids:</td>
<td>Start AHA Step II Diet in all patients: (30% fat, &lt;200 mg/d cholesterol). Assess fasting lipid profile. In past-MI patients, lipid profile may take 4 to 6 weeks to stabilize. Add drug therapy according to the following table:</td>
</tr>
<tr>
<td>LDL &lt;100 mg/dL</td>
<td>No drug therapy, unless after an MI. Then use statin. Statins as 1st line suggestion drug therapy</td>
</tr>
<tr>
<td>LDL 100-130 mg/dL</td>
<td>Consider adding drug therapy to diet, as follows:</td>
</tr>
<tr>
<td>TG &lt;200 mg/dL</td>
<td>Statin Resin Niacin</td>
</tr>
<tr>
<td>LDL &gt;130 mg/dL</td>
<td>Add drug therapy to diet, as follows:</td>
</tr>
<tr>
<td>TG 200-400 mg/dL</td>
<td>Statin Niacin</td>
</tr>
<tr>
<td>TG &gt;400 mg/dL</td>
<td>Consider combined drug therapy (niacin, fibrate, statin)</td>
</tr>
<tr>
<td>Physical activity:</td>
<td>If LDL goal not achieved, consider combination therapy</td>
</tr>
<tr>
<td>Minimum goal:</td>
<td>Assess risk, preferably with exercise test, to guide prescription. Encourage minimum of 30-60 minutes of moderate-intensity activity three to four times weekly (walking, jogging, cycling, or other aerobic activity) supplemented by an increase in daily life-style activities (eg, walking breaks at work, using stairs, gardening, household work). Maximum benefit 5 to 6 hours a week. Advise medically supervised programs or moderate- to high-risk patients.</td>
</tr>
<tr>
<td>Weight Management</td>
<td>Start intensive diet and appropriate physical activity intervention, as outlined above, in patients &gt;120% of ideal weight for height. Particularly emphasize need for weight loss in patients with hypertension, elevated triglycerides, or elevated glucose levels. Desirable waist-to-hip ratio for men, &lt;0.9: for middle-aged and elderly women, &lt;0.8.</td>
</tr>
<tr>
<td>Ideal BMI: 18.5-25 kg/m²</td>
<td>Start aspirin 80 to 325 mg/d if not contraindicated. Manage warfarin to international normalized ratio=2-3.5 for post-MI patients not able to take or fails aspirin, then consider ticlopidine, clopidogrel, or dipyridamole + aspirin</td>
</tr>
<tr>
<td>Antiplatelet agents/anticoagulants:</td>
<td>Start early post-MI in stable patients, especially those with anterior MI, CHF, renal insufficiency, EF &lt;40%, (LV dysfunction). Maximize dose as tolerated indefinitely. Use as needed to manage blood pressure or symptoms in all other patients.</td>
</tr>
<tr>
<td>ACE inhibitors Post-MI:</td>
<td>For all patients, especially post-MI, as tolerated.</td>
</tr>
<tr>
<td>β-blockers:</td>
<td>No role. More evidence of harm than help.</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Initiate life-style modification: weight control, physical activity, and alcohol moderation in all patients with blood pressure &gt;140 mm Hg systolic or 90 mm Hg diastolic. Add blood pressure medication, individualize to other patient requirements and characteristics (i.e., age, race, need for drugs with specific benefits) if blood pressure is not less than 140 mm Hg systolic or 90 mm Hg diastolic in 3 months of if initial blood pressure is &gt;160 mm Hg systolic or 100 mm Hg diastolic.</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; MI, myocardial infarction; TG, triglycerides; LV, left ventricular; CHF, congestive heart failure; BMI, body mass index; EF, ejection fraction; LFTs, liver function tests; TFTs, thyroid function tests; UA, uric acid; CHD, coronary heart disease. Source: Modified and reproduced from Smith SC Jr et al: AHA consensus panel statement. Preventing heart attack and death in patients with coronary disease. In Dedwania PC, Gheorghiade M (eds), Therapeutic Options for Effective Management of Coronary Artery Disease. May 1999.
• Esophagitis
• Gastritis
• Generalized anxiety disorder (GAD)
• Gastroesophageal reflux disease (GERD)
• Hiatal hernia
• High altitude exposure
• Hyperthyroidism
• Panic attack
• Peptic ulcer disease
• Pericardial effusion
• Pleurisy/pleuritis
• Pneumothorax
• Prinzmetal angina (coronary vasospasm): more common in women
• Pulmonary embolus
• Pulmonary hypertension
• Radiculopathy
• Shoulder arthropathy
• Stress reactional anxiety
• Supraventricular tachycardia
• Vasculitis

ACS Complications

Number 1: Death.
Number 2: Myocardial infarction.
Number 3: Hospitalization.
Number 4: Cardiac disability: Lifestyle and activity options are diminished because the heart is unable to supply the oxygenated blood the body needs to fulfill its demand because the coronary arteries are unable to supply the heart muscle.

Treatment: Time = Tissue!

ACS causes myocardial infarction (MI) in three ways:
1. Plaque buildup increases till the artery is totally occluded.
2. An atheromatous plaque ruptures or tears leading to occlusions via inflammatory response and thrombus formation as platelets adhere to the site to seal off the plaque.
3. Superimposition of thrombus upon a disrupted atherosclerotic plaque.

The goal of treatment is to save cardiac muscle by reducing myocardial oxygen demand and/or increasing oxygen supply.

All patients with ACS should be hospitalized, medically stabilized and receive further cardiac evaluation to determine STEMI versus NSTEMI versus unstable angina and then treatment appropriate to the diagnosis. Immediate PCI can be beneficial for STEMI, but can be safely delayed in low-risk NSTEMI. All ACS patients should receive medical management, which starts with HOBANACS.

- **H**eparin (low-molecular-weight heparin—less MIs and deaths)
- **O**xygen
- **B**eta-blocker (if hemodynamically stable: metoprolol, timolol, propranolol, or carvedilol; if decreased: ejection fraction)
- **A**spirin (initially 166-325 mg then 70-160 mg indefinitely)
- **N**itroglycerin (for pain; stop if hypotension occurs)
- **C**lopidogrel (up to 1 year; not within 5 days of CABG)
- **S**tatins (HMG-CoA reductase inhibitors; goal LDL <70 mg/dL)

**Morphine** may be added for pain and anxiety relief. It also provides some afterload reduction.

Anticoagulation with heparin starts with low-molecular-weight heparin if PCI is not planned. Unfractionated heparin should be used if creatinine clearance <60 mL/min or if early PCI or CABG is planned within 24 hours. Fondaparinux is as effective as enoxaparin with less major bleeding and lower long-term mortality.

**β-Blockers** decrease the workload on the heart by slowing is and decreasing blood pressure. The goal should be <130/85 mm Hg or <130/80 mm Hg if diabetes or chronic kidney disease is present; optimal blood pressure may be 115/75 mm Hg.

**Aspirin** (ASA) should be continued indefinitely. Once ACS is stabilized a dose of 81 mg should suffice. If ASA is not tolerated clopidogrel should be used. If there is a history of history of gastrointestinal bleeding and either ASA or clopidogrel is used, drugs to decrease the risk of recurrent gastrointestinal bleeding (eg, proton-pump inhibitors) should be given.

**Clopidogrel** requires a loading dose (300-600mg) followed by daily maintenance dose (75 mg). If there is no plan for PCI, it should be added to aspirin and anticoagulant therapy as soon as possible after admission. If PCI is likely, it can be added before the procedure. Duration of treatment should be for at least 1 month and ideally up to 1 year. Ticagrelor (180 mg load then 90 mg twice daily) compared to clopidogrel resulted in lower all-cause mortality, vascular mortality, and MI rate without increase in major bleeding or stroke. It is not yet approved for use in the United States, but if further research is similar it could eventually supplant clopidogrel.

**Platelet glycoprotein IIB/IIIA (GP IIB/IIIA) receptor inhibitors** should be used judiciously if there is no plan for revascularization: 100 STEMI need to be treated to prevent 1 MI or death, but for every one prevention there is one major bleeding complication. Specifically, abciximab should only be used if PCI is planned.
**ACUTE CORONARY SYNDROME**

**PCI: immediate versus delayed.** If cardiac tissue is to survive, blood flow must be restored. STEMI (active infarctions) require medical thrombolysis or emergent angioplasty to achieve this. When necessary, thrombolytic agents should be started within 30-60 minutes, and PCI or CABG initiated within 60-90 minutes. If blood flow is not restored with thrombolitics, then PCI/CABG should be moved to within 2-3 hours. A “cooling off” period, i.e., delaying PCI or CABG because of failed medical thrombolysis, increases mortality without decreasing bleeding complications.

While there is a modest decrease in recurrent ischemia, early PCI within 24 hours of symptom onset for lower risk NSTEMI patients does not decrease mortality compared to late PCI within 36 hours. Higher risk patients (ST >1-mm depression, T-wave inversion, impaired renal function, hemodynamically unstable, TIMI score >4, presence of heart failure) with NSTEMI benefit from early PCI within 24 hours. There is no difference in NSTEMI mortality between PCI in 70 minutes compared to 21 hours in higher risk patients (TIMI score >4).

The 2-year risk of death or recurrent MI is the same for PCI and CABG, but about 5% with a CABG get angina.

Post-MI care should center around tertiary care (see cardiac rehabilitation, Figure 19-4, and Table 19-7). Optimal blood pressure is closer to 115/75, since in 40-70-year-olds each increment of 20 mm Hg in systolic BP or 10 mm Hg in diastolic BP doubles the risk of CVD across the entire BP range from 115/75 to 185/115 mm Hg.

COX-2 (cyclooxygenase-2) nonsteroidal anti-inflammatory drugs and naproxen should be avoided because they increase risk for ACS.

For some individuals, using warfarin (goal INR 2.0-3.0) together with aspirin or warfarin alone (goal INR 3.0-4.0) results in a better all-cause mortality than taking aspirin alone. It reduces the risk of myocardial infarction and stroke but increases risk of major bleeding.

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**Prognosis**

An estimated 60% of myocardial infarction deaths occur within the first hour of symptom onset. Prognosis following a survived MI without subsequent intervention carries a mortality rate of 10% the first year and 5% each additional year. Sudden death, more common in patients with a lower ejection fraction, following ACS occurs in 1.4% of patients during the first month, and decreases to 0.14% per month after 2 years.

When either Troponin T and I levels is normal at 2, 4, and 6 hours after the onset of chest pain in patients with a normal ECG, the 30-day risk of cardiac death and non-fatal acute MI is nearly zero.

Normal Troponin T levels at 10-12 hours after symptom onset in patients with chest pain and a normal ECG indicate a low-risk of adverse events for the next twelve months. Even slight elevations in cardiac troponin levels in patients with unstable angina and NSTEMI help identify high-risk patients who may benefit the most from early invasive treatment.

Web site accessible scoring systems can help risk-stratify patients with chest pain and help determine prognosis given a range of different circumstances by analyzing individual patient characteristics and test results. Prognostic tools are valuable when educating patients about possible outcomes, and when discussing and deciding upon treatment options.

**Cultural Considerations**

Cultural issues can affect the diagnosis, treatment, and outcome of ACS. Some clinical symptoms are more common in certain patient populations (see prior symptoms list). Overall, atypical symptoms are more prevalent in women and elderly patients. Symptoms may include jaw and neck pain, dyspnea, fatigue, palpitations, indigestion, cough, nausea, and emesis. Maybe because atypical symptoms occur more frequently in women and older adults, they tend to experience delayed diagnosis, less aggressive treatment, and increased rates of in-hospital mortality.

Other notable differences exist between patient populations that relate to diagnosis and treatment of cardiac disease. Both men and women with ACS respond to early invasive treatment. Women tend to have more severe first ACS, are less likely to receive thrombolysis, and are at greater risk for death and hospital readmission at 6 months. Patients with symptoms of acute MI are less often hospitalized if they are non-white or have a normal or nondiagnostic ECG. Patients experiencing ACS who are women younger than 55 years of age, are non-white, have shortness of breath as their chief complaint, or have a normal or indeterminate ECG are less often hospitalized, thus increasing their morality. After ACS, women are more likely than men to experience depression and hence its ramifications.

Patients are more likely to adhere to treatment plans they can afford. This should be taken into account when deciding which medication to prescribe and which diets and exercise plans to recommend. Exercise can be done without joining a gym, and some diet approaches are less expensive than others.


**GRACE:** Global Registry of Acute Coronary Events calculator. Available at: http://www.outcomes-umassmed.org/grace/.

Balady GJ et al: Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: A scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. Circulation 2007; 115:2679-2682. [PMID: 17513578]


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U.S. Department of Health and Human Services. National Institutes of Health

National Heart, Lung, and Blood Institute. National High Blood Pressure Education Program


Web Sites for ACS & CVD

American College of Cardiology http://www.acc.org
American Heart Association http://www.americanheart.org
Aspirin Foundation of America http://www.aspirin.org
Centers for Disease Control http://www.cdc.gov
Facts about Coronary Artery Disease http://home.mdconsult.com/das/patient/body/0/10041/5558.htm
Family Practice Notebook http://fpnotebook.com/CV.htm
National Heart, Lung, and Blood Institute http://www.nhlbi.nih/health/public/heart/other/chdfacts.htm
Healthfinder http://www.healthatoz.com
Mayo Clinic.com http://www.mayoclinic.com
MEDLINE Plus http://www.medlineplus.gov
Medtronic http://www.medtronic.com/cad
National Institutes of Health - Health Topics http://health.nih.gov/
National Women's Health Information Center http://www.4woman.gov/faq/coronary.htm
UPMC Patient Information http://patienteducation.upmc.com/C.htm#Cardiology
**Heart Failure**

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Richard E. Rodenberg, Jr., MD

**ESSENTIALS OF DIAGNOSIS**

- Left ventricular failure.
- Paroxysmal nocturnal dyspnea, orthopnea, dyspnea on exertion, fatigue, and peripheral edema.
- Third or fourth heart sound, increased jugular venous pressure, hepatojugular reflux, displaced cardiac apex, rales, wheezing, murmur, or peripheral edema.
- Any electrocardiographic (ECG) abnormality, radiographic evidence of pulmonary venous congestion, cardiomegaly, or pleural effusion; elevated B-type natriuretic peptide; echocardiographic evidence of left ventricular dysfunction.
- Right ventricular failure: increased jugular venous pressure, hepatomegaly, peripheral edema.

**General Considerations**

Increased survivorship after acute myocardial infarction (MI) and improved treatment of hypertension, valvular heart disease, and coronary artery disease (CAD) have led to a significant increase in the prevalence of heart failure in the United States. Overall prevalence of any congestive heart failure (CHF) diagnosis is estimated at 2.6% (2.7% in men; 1.7% in women). In addition, 10% of the population may have isolated moderate to severe diastolic dysfunction, with age greater than 65 years and female gender being consistent predictors of preserved left ventricular systolic function. Diastolic dysfunction is rarely associated with acute MI. Based on this apparent bias, the possibility of biological changes associated with increasing age and female gender have been proposed as underlying reasons for the increased likelihood of diastolic heart failure in these populations.

The prevalence of any type of heart failure increases with age. Asymptomatic left ventricular systolic dysfunction (LVSD) has been found to be as prevalent as symptomatic LVSD: 1.4% and 1.5%, respectively. Moderate or severe isolated diastolic dysfunction appears to be as common as systolic dysfunction, and systolic dysfunction appears to increase with the severity of diastolic dysfunction.

**Pathogenesis**

As defined by the American Heart Association (AHA) and the American College of Cardiology (ACC), heart failure is “a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.”

Heart failure results from a complex interplay of compensatory mechanisms used by the body to adjust for decreased cardiac output in response to stresses placed on the myocardium (Table 20-1). These compensatory mechanisms are rooted in the activation of the sodium-retaining renin-angiotensin-aldosterone and sympathetic nervous systems (neurohormonal adaptations). The purpose is to maintain blood pressure and tissue perfusion. However, these compensatory mechanisms, which increase afterload, lead to myocardial deterioration and worsening myocardial contractility. The heart then enters into a vicious cycle of increasing release of neurohormones (norepinephrine, angiotensin II, aldosterone, endothelin, vasopressin, and cytokines) that further increases afterload, allowing the heart to spiral into failure in a progressive fashion through cardiac remodeling. These neurohormones act both in an indirect and a directly toxic fashion to affect hemodynamic stressors and myocardial cell performance and phenotype.

**Causes of Cardiac Failure**

With the advent of improved hypertension treatment, earlier identification of valvular heart disease, and improved survival following MI, CAD and diabetes mellitus are now the leading causes of heart failure in the United States. It is estimated that 66% of patients having systolic heart failure have coronary heart disease as the underlying etiology. CAD is a substantial
Table 20-1. Possible causes of heart failure.

<table>
<thead>
<tr>
<th>Cause of Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease, including myocardial infarction</td>
</tr>
<tr>
<td>Diabes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Increased BMI (overweight)</td>
</tr>
<tr>
<td>Increased age</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Primary valvular heart disease</td>
</tr>
<tr>
<td>Congenital heart disease</td>
</tr>
<tr>
<td>Cardiomyopathies (dilated [idiopathic], hypertrophic, and restrictive)</td>
</tr>
<tr>
<td>Viral myocarditis (including HIV)</td>
</tr>
<tr>
<td>Pericardial disease</td>
</tr>
<tr>
<td>Infiltrative disease (hemochromatosis, sarcoidosis, amyloidosis)</td>
</tr>
<tr>
<td>Recent pregnancy</td>
</tr>
<tr>
<td>Connective tissue disease</td>
</tr>
<tr>
<td>Hyperthyroid or hypothyroid disease</td>
</tr>
<tr>
<td>Toxin (chemotherapy, substance abuse [especially alcohol or cocaine], heavy metal)</td>
</tr>
<tr>
<td>High-output failure secondary to anemia or thiamine deficiency (beriberi)</td>
</tr>
<tr>
<td>Cor pulmonale and pulmonary hypertension (in right-sided failure)</td>
</tr>
</tbody>
</table>

BMI, body mass index.

predictor of developing clinically evident heart failure or symptomatic versus asymptomatic LVSD. CHF has also been found to be twofold higher in all diabetic patients. Diabetes mellitus is one of the most significant factors for developing heart failure in women. Even in women with increased hyperglycemia but no diagnosis of diabetes mellitus, the risk of heart failure is increased compared with normoglycemic women. Evidence points to a diabetic cardiomyopathy independent of CAD that is more prominent in diabetic women. This raises the question of the direct effect of diabetes on the myocardium and endothelium. This association could also be related to the overt effect of diabetes on progression of CAD. It is also unknown whether treatment of long-standing diabetes mellitus decreases the risk of developing heart failure.

Poorly controlled hypertension and valvular heart disease remain major precipitants of heart failure. Often-overlooked risk factors in the development of heart failure are smoking, physical inactivity or obesity, and lower socioeconomic status. Tobacco is estimated to cause approximately 17% of CHF cases in the United States. The effect of cigarettes may be direct or indirect in relation to promoting CAD risk. Lower socioeconomic status may limit access to higher quality health care, resulting in decreased adherence to treatment of modifiable risk factors such as hypertension, diabetes mellitus, and CAD.


### Classification & Prevention

The American College of Cardiology (ACC)/American Heart Association (AHA) classification of heart failure emphasizes the progressive nature of the syndrome. This classification replaced the New York Heart Association (NYHA) classification with four stages that help define appropriate therapy at each level. The new classification recognizes that there are risk factors and structural prerequisites for the development of heart failure and that therapeutic interventions initiated early in the disease process can reduce morbidity and mortality and delay the onset of clinically evident disease (Table 20-2).

Patients in ACC/AHA stages A and B do not have clinical heart failure but are at risk for developing heart failure. Stage A includes those at risk but not manifesting structural heart disease. Early identification and aggressive treatment of modifiable risk factors remain the best prevention for heart failure. Lifestyle modification, pharmacologic therapy, and counseling can improve or correct conditions such as CAD, hypertension, diabetes mellitus, hyperlipidemia, obesity, tobacco abuse, and alcohol or illicit substance abuse. Stage B represents persons who are asymptomatic but have structural heart disease or impaired left ventricular function. Stage C comprises the bulk of persons with heart failure who have past or current symptoms and associated underlying structural heart disease. Stage D includes refractory patients with heart failure who may need advanced and specialized treatment strategies.

The NYHA classification gauges the severity of symptoms for patients with stage C and D heart failure. This is a subjective assessment that can change frequently, secondary to treatment response.

### Clinical Findings

A high index of suspicion is necessary to diagnose the syndrome of heart failure early in its clinical presentation, because it is frequently manifested by nonspecific signs and symptoms.
symptoms. Patients are often elderly with comorbidity, symptoms may be mild, and routine clinical assessment lacks specificity. A prompt diagnosis allows for early treatment with therapies proven to delay the progression of heart failure and improve quality of life.

Evaluation is directed at confirming the presence of heart failure, determining cause, identifying comorbid illness, establishing severity, and guiding response to therapy. Heart failure is a clinical diagnosis for which no single examination or test can establish the presence or absence with 100% certainty.

### A. Symptoms and Signs

The primary manifestations of symptomatic heart failure are dyspnea and fatigue, with dyspnea being the most common.
Limited exercise tolerance and fluid retention may eventually lead to pulmonary congestion and peripheral edema. Neither of these symptoms necessarily dominates the clinical picture at the same time. Dyspnea, whether at rest or with exertion, is present in nearly all patients with heart failure and indicates left ventricular dysfunction. Its absence makes heart failure highly unlikely. The absence of dyspnea on exertion essentially rules out the presence of heart failure due to left ventricular dysfunction in a predominantly asymptomatic population with a reported 100% sensitivity.

Other symptoms that are helpful in diagnosing heart failure include orthopnea, paroxysmal nocturnal dyspnea (PND), and peripheral edema. PND has the highest specificity of any symptom for heart failure. Likewise, if PND, orthopnea, or edema is not present, the likelihood of heart failure decreases. Nonspecific symptoms include chronic nonproductive cough, wheezing, and nocturia. Patients with right ventricular failure may present with right upper quadrant pain secondary to hepatic congestion and peripheral edema.

No single clinical symptom has been shown to be both sensitive and specific. A substantial portion of the population has asymptomatic left ventricular dysfunction and the history alone is insufficient to make the diagnosis of heart failure. However, a detailed history and review of symptoms remain the best approach in identifying the cause of heart failure and assessing response to therapy.

B. Physical Examination

The clinical examination can provide important information concerning the degree to which cardiac output is reduced and the degree of volume overload and ventricular enlargement. It can also provide clues to non-cardiac causes of dyspnea. The presence of a third heart sound, \( S_3 \) (ventricular filling gallop), increases the likelihood of heart failure with the most specificity of any physical examination finding. An \( S_4 \) or a fourth heart sound, \( S_4 \) (atrial gallop), are specific for increased left ventricular end-diastolic pressure and decreased left ventricular ejection fraction. The presence of an \( S_3 \) has been found to be superior to \( S_4 \) in identifying patients with abnormal left ventricular function. Gallop rhythm (\( S_3 \) and \( S_4 \)) and displacement of cardiac apex have also been found to be specific predictors of left ventricular dysfunction.

The presence of jugular venous distention, pulmonary rales, pitting peripheral edema, and hepatomegaly also helps to make the diagnosis, and the absence of the first three of these findings is useful for lowering the likelihood of heart failure. Cardiac murmurs may be an indication of primary valvular disease. Asymmetric rales or rhonchi on the pulmonary examination may indicate primary pulmonary pathology such as pneumonia or chronic obstructive pulmonary disease (COPD). Examination of the thyroid can exclude thyromegaly or goiter-causes of abnormal thyroid function that can precipitate heart failure. Dullness to percussion or auscultation of the lungs could indicate pleural effusion. Hepatomegaly can indicate passive hepatic congestion.

The absence of any of these findings alone does little to help rule out heart failure.

The patient’s appearance and vital signs may be affected by heart failure. Acute increases in body weight are indicative of fluid overload versus changes in body mass. Early in the disease of heart failure, blood pressure may be elevated or normotensive; and as the disease progresses, the blood pressure usually becomes low.

C. Laboratory Findings

Objective tests can be performed for further confirmation of heart failure by assessing the differential diagnosis by excluding other possible causes for the signs and symptoms or clearly defining the heart failure.

A complete blood count is necessary to rule out anemia as a cause of high-output failure. Electrolyte (including magnesium and calcium) analysis may reveal deficiencies, commonplace with treatment, which can make the patient prone to arrhythmias. Hyponatremia is a poor prognostic sign indicating significant activation of the renin-angiotensin system. Abnormalities on liver tests can indicate hepatic congestion. Thyroid function tests can detect hyper- or hypothyroidism. Fasting lipid profile, fasting glucose, and hemoglobin \( A_g \) level can reveal comorbid conditions that may need to be better controlled. Iron studies can detect iron deficiency or overload. If the patient is malnourished or an alcoholic and presents with high-output failure, thiamine testing is indicated to rule out deficiency related to beriberi. Further testing to determine etiologic factors of heart failure must be based on historical findings.

1. B-type natriuretic peptide—Specific laboratory testing includes evaluation of B-type natriuretic peptide (BNP) levels. BNP is a cardiac neurohormone secreted from the ventricles and, to some extent, the atrial myocardium in response to volume and pressure overload. Circulating BNP levels are increased in patients with heart failure and have rapid turnover, indicating that BNP responds in proportion to the size of the exacerbation and in turn increases and decreases with each individual exacerbation. Although no BNP threshold indicates the presence or absence of heart failure with 100% certainty, the BNP level is the most accurate predictor of heart failure and, in conjunction with the history and physical examination, helps differentiate between pulmonary and cardiac causes of dyspnea (Table 20-3). Factors to take into consideration when interpreting BNP levels: they are lower in men than women, they are inversely related to body weight, and they increase with age.

The likelihood of heart failure increases with BNP levels greater than 100 pg/mL, as follows:

- Less than 100 pg/mL: Negative predictive value high excluding the diagnosis of heart failure; consider alternate diagnoses.
- 100-400 pg/mL: Increased likelihood of heart failure; history, physical examination, and other tests are required to improve the probability of the diagnosis.
NYHA, New York Heart Association.

Adjusted levels are based on glomerular filtration rate (GFR). GFR 60-89 mL/min: no adjustment in the 100 pg/mL threshold (see text). GFR 30-59 mL/min: BNP >201. GFR 15-29 mL/min: BNP >225. GFR <15 mL/min: unknown utility of BNP levels.


Table 20-3. Factors influencing B-type natriuretic peptide (BNP) levels.

<table>
<thead>
<tr>
<th>Factors That Cause Elevated BNP (&lt;100 pg/mL)</th>
<th>Factors That Lower BNP in the Setting of Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Acute pulmonary edema</td>
</tr>
<tr>
<td>Advanced age</td>
<td>Stable NYHA class I disease with low ejection fraction</td>
</tr>
<tr>
<td>Renal failure&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Acute mitral regurgitation</td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td>Mitral stenosis</td>
</tr>
<tr>
<td>Lung disease with cor pulmonale</td>
<td>Atrial myxoma</td>
</tr>
<tr>
<td>Acute large pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>High-output cardiac states</td>
<td></td>
</tr>
</tbody>
</table>


D. Imaging Studies

1. Chest radiography—The chest radiograph can provide valuable clues in patients presenting with acute dyspnea. The presence of venous congestion, interstitial edema, alveolar edema, cardiomegaly, or pleural effusion increases the likelihood of heart failure in dyspneic patients. Cardiomegaly (cardiac-to-thoracic width ratio >50%) was the best predictor of decreased ejection fraction, whereas redistribution (upper lobe pulmonary vein dilation and lower lobe pulmonary vein constriction in response to a rise in pulmonary venous pressure secondary to increased left ventricular preload) and hilar haze were the best predictors of increased preload. The absence of cardiomegaly and pulmonary venous congestion were the most useful findings on chest radiography for lowering the likelihood of heart failure.

2. Cardiac Doppler echocardiography—Echocardiography is of undeniable utility in the evaluation of suspected and newly diagnosed heart failure (Table 20-4). An echocardiography study is recommended for all patients diagnosed with heart failure. It provides important information concerning cardiac systolic (ejection fraction or fractional shortening) and diastolic function.

Echocardiographic findings can help differentiate among the various causes of heart failure, including ischemic heart disease, idiopathic cardiomyopathy, hypertensive heart disease, and valvular heart disease. Echocardiography helps to distinguish segmental wall motion abnormalities, which can correlate with ischemia. An increase in cardiac mass (left ventricular hypertrophy) can be associated with hypertensive cardiomyopathy versus cardiac remodeling, which is an adaptive phenomenon associated with myocardial injury. The echocardiogram also helps to elucidate differences between dilated (idiopathic), hypertrophic, and restrictive cardiomyopathies. Diastolic changes can be elucidated by Doppler imaging. Left ventricular hypertrophy and a dilated left atrium are clues to the possible presence of left ventricular diastolic dysfunction. Dobutamine stress echocardiography
is an important tool to assess for myocardial ischemia and viability in the form of ischemic, stunned, or hibernating myocardium. In addition to ischemia and valvular abnormalities, potential reversible etiologies of heart failure that echocardiography can help to uncover include pericardial disorders such as effusion or tamponade. It can help determine appropriate timing of therapy by uncovering asymptomatic LVSD in high-risk populations. The degree of left ventricular dysfunction, ventricular size, and shape add important prognostic information.

The routine reevaluation with echocardiography of clinically stable patients in whom no change in management is contemplated is not recommended. If the body habitus of the patient makes echocardiography impractical, radionuclide ventriculography can be performed to assess left ventricular ejection fraction and volumes.

### 3. Cardiac catheterization—

Coronary angiography is recommended for patients with new-onset heart failure of uncertain etiology, despite the absence of anginal symptoms or negative findings on exercise stress testing. Coronary angiography should be strongly considered for patients with LVSD and a strong suspicion of ischemic myocardium based on noninvasive testing (echocardiography or nuclear imaging). Wall motion abnormalities seen on echocardiography or hibernating myocardium detected by dobutamine stress echocardiography are particularly useful indicators because they appear shortly after ischemia or infarction. The extent and severity of wall motion abnormalities have been shown to correlate with the size of the myocardium at risk. A strong association has been demonstrated between decreased mortality and revascularization (80% relative reduction in risk of death) only in patients found to have myocardial viability by thallium perfusion imaging, dobutamine echocardiography, or positron emission tomography scanning, with no apparent benefit in the absence of demonstrated viability. Therefore, evaluation of these abnormalities may have significant implications for urgency of treatment, resultant pump function, and subsequent morbidity and mortality.

Using clusters of clinical findings from the history, physical examination, and diagnostic tests is a better diagnostic strategy than using isolated findings. The clinical examination enables the clinician to categorize patients as having low, intermediate, and high pretest probabilities for the diagnosis of heart failure. More specialized testing, such as BNP results, helps clarify the diagnosis in patients determined to have an intermediate probability of heart failure.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Information Provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular function</td>
<td>Normal value: ≥ 55%-60% Abnormal value: &lt; 50% Significant systolic dysfunction value: ≤ 35%-40%</td>
</tr>
<tr>
<td>Diastolic function</td>
<td>Alteration of left ventricular compliance Estimation of left ventricular filling pressure</td>
</tr>
<tr>
<td>Pulmonary artery pressure</td>
<td>Normal value: ≤ 30-35 mm Hg</td>
</tr>
</tbody>
</table>


### Differential Diagnosis

Because heart failure is estimated to be present in only about 30% of patients with dyspnea in the primary care setting, clinicians need to consider differential diagnoses for dyspnea such as asthma, COPD, infection, interstitial lung disease, pulmonary embolism, anemia, thyrotoxicosis, carbon monoxide poisoning, arrhythmia, anginal equivalent (CAD), valvular heart disease, cardiac shunt, obstructive sleep apnea, and severe obesity causing hypoventilation syndrome.

### Treatment

Most evidence-based treatment strategies have focused on patients with systolic rather than diastolic heart failure; hence, stage-specific outpatient management of patients with chronic systolic heart failure is the focus of the discussion that follows. Although stages A through D of the ACC/AHA heart failure classification represent progressive cardiac risk and dysfunction, the treatment strategies recommended at earlier stages are applicable to and recommended for later stages (see Table 20-2).

### A. Systolic Heart Failure

#### 1. High risk for systolic heart failure (stage A)

Individuals with conditions and behaviors that place them at high risk for heart failure but who do not have structurally abnormal hearts are classified as ACC/AHA stage A and should be treated with therapies that can delay progression of cardiac dysfunction and development of heart failure. Optimizing hypertension treatment based on the current guidelines from the Seventh Report of the Joint National...
CHAPTER 20

Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) can reduce new-onset heart failure by 50%. Therapies such as diuretics, \( \beta \)-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs) are proven to be more effective than calcium channel blockers and doxazosin in preventing heart failure. Use of hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors or statin therapy in CAD patients based on current hyperlipidemia guidelines (the updated Adult Treatment Panel III [ATP III]) can also reduce the incidence of heart failure by 20%.

Evidence-based disease management strategies for diabetes mellitus, atherosclerotic vascular disease, and thyroid disease, as well as patient avoidance of tobacco, alcohol, cocaine, amphetamines, and other illicit drugs that can be cardiotoxic, are also important components of early risk modification for prevention of heart failure. In diabetic patients, both ACEIs and ARBs (specifically losartan and irbesartan) have been shown to reduce new-onset heart failure compared with placebo. In CAD or atherosclerotic vascular disease patients without heart failure, reviews of the EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease) and HOPE (Heart Outcomes Prevention Trial) results show a 23% reduction in heart failure with ACEI therapy as well as reduced mortality, MIs, and cardiac arrest.

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981. [PMID: 12479763]


2. Asymptomatic with cardiac structural abnormalities or remodeling (stage B)—Patients who do not have clinical symptoms of heart failure but who have a structurally abnormal heart, such as a previous MI, evidence of left ventricular remodeling (left ventricular hypertrophy or low ejection fraction), or valvular disease, are at a substantial risk of developing symptomatic heart failure. Prevention of further progression in these at-risk patients is the goal, and appropriate therapies are dependent on the patient’s cardiac condition.

In all patients with a recent or remote history of MI, regardless of ejection fraction, ACEIs and \( \beta \)-blockers are the mainstay of therapy. Both therapies have been demonstrated in randomized control trials to cause a significant reduction in cardiovascular death and heart failure. These therapies are vital in post-MI patients, as is evidence-based management of an ST-elevation MI and chronic stable angina, to help further achieve reduction in heart failure morbidity and mortality.

In asymptomatic patients who have not had an MI but have a reduced left ventricular ejection fraction (nonischemic cardiomyopathy), clinical trials reported an overall 37% reduction in heart failure when treated with ACEI therapy. The SOLVD (Studies of Left Ventricular Dysfunction) trial and a 12-year follow-up study confirmed the long-term benefit of ACEIs regarding onset of symptomatic heart failure and mortality. A substudy of the SOLVD trial showed how enalapril attenuates progressive increases in left ventricular dilation and hypertrophy, thus inhibiting left ventricular remodeling. Despite a lack of evidence from randomized controlled trials, the ACC/AHA guidelines recommend \( \beta \)-blockers in patients with stage B heart failure given the significant survival benefit these agents provide in worsening stages of heart failure. The RACE (Ramipril Cardioprotective Evaluation) trial provided a clue to why ACEIs are advantageous over \( \beta \)-blockers for nonischemic cardiomyopathy by demonstrating that ramipril is more effective than the \( \beta \)-blocker atenolol in reversing left ventricular hypertrophy in hypertensive patients.

There is no clear evidence for use of ARBs in asymptomatic patients with reduced left ventricular ejection fraction; however, ARB therapy is a reasonable alternative in ACEI-intolerant patients. The VALIANT (Valsartan in Acute Myocardial Infarction) trial showed that the ARB valsartan was as effective as but not superior to captopril, an ACEI, in reducing cardiovascular morbidity and mortality in post-MI patients with heart failure or a reduced left ventricular ejection fraction. The combination of both therapies was no better than captopril alone.

Agabiti-Rosei E et al: ACE inhibitor ramipril is more effective than the beta-blocker atenolol in reducing left ventricular mass in hypertension. Results of the RACE (ramipril cardioprotective evaluation) study on behalf of the RACE study group. J Hypertens 1995;13:1325. [PMID: 8984131]


3. Symptomatic systolic heart failure (stage C)—Patients with a clinical diagnosis of heart failure have current or prior symptoms of heart failure and comprise ACC/AHA stage C. This stage encompasses NYHA classes II, III, and IV, excluding patients who develop refractory end-stage heart failure (see Table 20-2). In symptomatic patients with heart failure, neurohormonal activation creates deleterious effects on the heart, leading to pulmonary and peripheral edema, persistent increased afterload, pathologic cardiac remodeling, and a progressive decline in cardiac function. The overall goals in this stage are to improve the patient’s symptoms, slow or reverse the deterioration of cardiac functioning, and reduce the patient’s long-term morbidity and mortality.

Accurate assessment of the cause and severity of heart failure, the incorporation of previous stage A and B treatment recommendations, and correction of any cardiovascular, systemic, and behavioral factors (Table 20-5) are important to achieve control in patients with symptomatic heart failure. Moderate dietary sodium restriction (3-4 g daily) with daily weight measurement further enhance volume control and allow for lower and safer doses of diuretic therapies. Exercise training is beneficial and should be encouraged to prevent physical deconditioning, which can contribute to exercise intolerance in patients with heart failure.

Patients with symptomatic heart failure should be routinely managed with a standard therapy of a diuretic, an ACEI (or ARB if intolerant), and a β-blocker (see Table 20-2). The addition of other pharmacologic therapies should be guided by the need for further symptom control versus the desire to enhance survival and long-term prognosis. A stepwise approach to therapy is presented in Table 20-6 and expanded upon below.

A. Diuretics—Patients with heart failure who present with common congestive symptoms (pulmonary and peripheral edema) are given a diuretic to manage fluid retention and achieve and maintain a euvolemic state. Diuretic therapy is specifically aimed at treating the compensatory volume expansion driven by renal tubular sodium retention and activation of the renin-angiotensin-aldosterone system.

Loop diuretics are the treatment of choice because they increase sodium excretion 20%-25% and substantially enhance free water clearance. Furosemide is most commonly used, but patients may respond better to bumetanide or torsemide because of superior, more predictable absorptions and longer durations of action. To minimize the risk of over- and underdiuresis, the diuretic response should guide the dosage of loop diuretics (Table 20-7), with dose increases until a response is achieved. Frequency of dosing is guided by the time needed to maintain active diuresis and sustained volume and weight control.

Thiazide diuretics also have a role in heart failure, principally as antihypertensive therapy, but they can be used in combination with loop diuretics to provide a potentiated or synergistic diuresis. As a lone treatment, however, they increase sodium excretion only 5%-10% and tend to decrease free water clearance overall.

Symptom improvement with diuretics occurs within hours to days as compared with weeks to months for other heart failure therapies. For long-term clinical stability, diuretics are not sufficient and exacerbations can be greatly reduced when they are combined with ACEI and β-blocker therapies.

B. ACE inhibitors—ACEIs are prescribed to all patients with symptomatic heart failure unless contraindicated and have proven benefit in alleviating heart failure symptoms, reducing hospitalization, and improving survival. Current ACC/AHA guidelines recommend that all patients with left ventricular dysfunction be started on low-dose ACEI therapy to avoid side effects and raised to a maintenance or target dose (see Table 20-7). There is, however, some uncertainty regarding target doses achieved in clinical trials, and whether these are more beneficial than lower doses. For ACEIs as a class, there does not appear to be any difference in agents in terms of effectiveness at improving heart failure outcomes.

C. β-Blockers—In patients with NYHA class II or III heart failure, the β-blockers bisoprolol, metoprolol succinate (sustained release), and carvedilol have been shown to improve mortality and event-free survival. These benefits are in addition to ACEI therapy and support the use of β-blockers as part of standard therapy in these patients. A similar survival benefit has been shown for patients with stable NYHA class IV heart failure.

### Table 20-5. Factors contributing to worsening heart failure.

<table>
<thead>
<tr>
<th>Cardiovascular Factors</th>
<th>Systemic Factors</th>
<th>Patient-Related Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superimposed ischemia or infarction</td>
<td>Inappropriate medications</td>
<td>Medication noncompliance</td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
<td>Superimposed infection</td>
<td>Dietary indiscretion</td>
</tr>
<tr>
<td>Unrecognized primary valvular disease</td>
<td>Anemia</td>
<td>Alcohol consumption</td>
</tr>
<tr>
<td>Worsening secondary mitral regurgitation</td>
<td>Uncontrolled diabetes mellitus</td>
<td>Substance abuse</td>
</tr>
<tr>
<td>New-onset or uncontrolled atrial fibrillation</td>
<td>Thyroid dysfunction</td>
<td></td>
</tr>
<tr>
<td>Excessive tachycardia</td>
<td>Electrolyte disorders</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Pregnancy</td>
<td></td>
</tr>
</tbody>
</table>

**Source:** Colucci WS. Overview of the therapy of heart failure due to systolic dysfunction. In Rose BD, ed: UpToDate Version 13.3. UpToDate, 2005.
β-Blocker therapy should be initiated near the onset of a diagnosis of left ventricular dysfunction and mild heart failure symptoms, given the added benefit on survival and disease progression. Titrating ACEI therapy to a target dose should not preclude the initiation of β-blocker therapy. Starting doses should be very low (see Table 20-7) but doubled at regular intervals, every 2-3 weeks as tolerated, to achieve target doses. There is no proven value to achieving a specific resting heart rate, but low doses are beneficial and there appears to be a dose-dependent improvement.

Traditionally the negative inotropic effects of β-blockers were thought to be harmful in heart failure, but this impact is outweighed by the beneficial effect of inhibiting sympathetic nervous system activation. Current evidence suggests that these beneficial effects are not necessarily equivalent among proven β-blockers. The COMET (Carvedilol or Metoprolol European Trial) findings showed that carvedilol (an α₁-, β₁-, and β₂-receptor inhibitor) is more effective than twice-daily dosed immediate-release metoprolol tartrate (a highly specific β₁-receptor inhibitor) in reducing heart failure mortality (40% vs 34%, respectively). Previous trials had investigated metoprolol succinate (sustained-release, once-daily dosing), but the COMET trial showed a mortality reduction even with metoprolol tartrate, a very cost-effective alternative.

Because β-blockers may cause a 4- to 10-week increase in symptoms before improvement is noted, therapy should be initiated when patients have no or minimal evidence of fluid retention. Relative contraindications include bradycardia, hypotension, hypoperfusion, severe peripheral vascular disease, a P-R interval greater than 0.24 seconds, second- or third-degree atrioventricular block, severe COPD, or a history of asthma. Race or gender differences in efficacy of β-blocker therapy have not been noted.

D. Angiotensin II receptor blockers—ARBs have been shown in clinical trials to be nearly as effective as, but not superior to, ACEIs as first-line therapy for symptomatic heart failure. ARBs should be utilized in ACEI-intolerant patients but not preferentially over ACEIs given the volume of evidence validating ACEIs. Despite unclear evidence, the
ACC/AHA guidelines recommend that ARB therapy be considered in addition to ACEI and standard therapy for patients who have persistent symptoms of heart failure.

E. Aldosterone antagonists—For selected patients with moderately severe to severe symptoms who are difficult to control (NYHA class III with decompensations or class IV), additional treatment options include the aldosterone antagonists spironolactone and eplerenone (see Table 20-7). There is no clear evidence to support the use of these therapies in patients with mild to moderate heart failure.

The addition of aldosterone antagonist therapy can cause life-threatening hyperkalemia in patients with heart failure, who are often already at risk because of reduced left ventricular function and associated renal insufficiency. Current guidelines recommend careful monitoring to ensure that creatinine is less than 2.5 mg/dL in men or less than 2.0 mg/dL in women and that potassium is maintained below 5.0 mEq/L (levels >5.5 mEq/L should trigger discontinuation or dose reduction). Higher doses of aldosterone antagonists and ACEI therapy should also raise concern for possible hyperkalemia, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, and potassium supplements should be avoided if possible. If the clinical situation does not allow for proper monitoring, the risk of hyperkalemia may outweigh the benefit of aldosterone antagonist therapy.

F. Digoxin—Digoxin therapy is only indicated to reduce hospitalizations in patients with uncontrolled symptomatic heart failure or as a ventricular rate control agent if a patient has a known arrhythmia. The DIG (Digitalis Investigation Group) trial proved the benefit of digoxin added to diuretic and ACEI therapy in improving heart failure symptom control and

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Initial Daily Dose</th>
<th>Target or Maximum Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loop Diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>1.0 mg/dose</td>
<td>4-8 mg/dose</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40 mg/dose</td>
<td>160-200 mg/dose</td>
</tr>
<tr>
<td>Torsemide</td>
<td>10 mg/dose</td>
<td>100-200 mg/dose</td>
</tr>
<tr>
<td><strong>ACE Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg three times daily</td>
<td>50-100 mg three times daily</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg twice daily</td>
<td>10-20 mg twice daily</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>2.5 mg once daily</td>
<td>20-40 mg once daily</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>5-10 mg once daily</td>
<td>20 mg once daily</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg once daily</td>
<td>8-16 mg once daily</td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg twice daily</td>
<td>20 mg twice daily</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25-2.5 mg once daily</td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg once daily</td>
<td>4 mg once daily</td>
</tr>
<tr>
<td><strong>Angiotensin II Receptor Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4-8 mg once daily</td>
<td>32 mg once daily</td>
</tr>
<tr>
<td>Losartan</td>
<td>25-50 mg once daily</td>
<td>50-100 mg once daily</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20-40 mg twice daily</td>
<td>160 mg twice daily</td>
</tr>
<tr>
<td><strong>β-Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg once daily</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice daily</td>
<td>25 mg once daily (50 mg twice daily, if &gt; 85 kg [187 lb])</td>
</tr>
<tr>
<td>Metoprolol succinate, extended release</td>
<td>12.5-25 mg once daily</td>
<td>200 mg once daily</td>
</tr>
<tr>
<td>Metoprolol tartrate, immediate release</td>
<td>12.5-25 mg twice daily</td>
<td>100 mg twice daily</td>
</tr>
<tr>
<td><strong>Aldosterone Antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg once daily</td>
<td>50 mg once daily</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5-25 mg once daily</td>
<td>25 mg once or twice daily</td>
</tr>
<tr>
<td><strong>Other Medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.125-0.25 mg once daily</td>
<td>Serum concentration 0.5-1.1 ng/mL</td>
</tr>
<tr>
<td>Hydralazine plus isosorbide dinitrate</td>
<td>37.5 mg/20 mg three times daily</td>
<td>75 mg/40 mg three times daily</td>
</tr>
</tbody>
</table>

decreasing the rate of hospitalization by 6%, but there was no overall mortality benefit. Subsequent retrospective subgroup analysis of the trial discovered some survival improvement at a serum digoxin concentration of 0.5–0.8 ng/mL in men. A similar but nonsignificant survival trend was also noted in women. Because survival is clearly worse when the serum digoxin concentration is greater than 1.2 ng/mL, patients are best managed within the range noted to avoid potential adverse outcomes given the narrow risk/benefit ratio. Digoxin should be used cautiously in elderly patients, who may have impaired renal function that adversely affects drug levels.

G. Hydralazine and nitrates—The combination of hydralazine and isosorbide dinitrate (H-I) is a reasonable treatment in patients, particularly blacks, who have persistent heart failure symptoms with standard therapy. In V-HeFT I (Vasodilator Heart-Failure Trial), the mortality of black patients receiving H-I combination therapy was reduced, but mortality of white patients was not different than that of the placebo group. In V-HeFT II, a reduction in mortality with the H-I combination was seen only in white patients who had been receiving enalapril therapy. No effect on hospitalization was found in either trial.

The A-HeFT (African-American Heart Failure Trial) findings further supported the benefit of a fixed dose H-I combination (see Table 20-7) by showing a reduction in mortality and heart failure hospitalization rates as well as improved quality of life scores in patients with moderate to severe heart failure (NYHA class III or IV) who self-identified as black. The H-I combination was in addition to standard therapies that included ACEIs or ARBs, β-blockers, and spironolactone.

H. Anticoagulation—It is well established that patients with heart failure are at an increased risk of thrombosis from blood stasis in dilated hypokinetic cardiac chambers and peripheral blood vessels. Despite this known risk the yearly incidence of thromboembolic events in patients with stable heart failure is between 1% and 3%, even in those with lower left ventricular ejection fractions and evidence of intracardiac thrombi. Such low rates limit the detectable benefit of warfarin therapy, and retrospective data analysis of warfarin with heart failure show conflicting results, especially given the major risk of bleeding. Warfarin therapy is only indicated in heart failure patients with a history of a thromboembolic event or those with paroxysmal or chronic atrial fibrillation or flutter. Likewise, the benefit of antplatelet therapies, such as aspirin, has not been clearly proven, and these therapies could possibly be detrimental because of their known interaction with ACEIs. Aspirin can decrease ACEI effectiveness and potentially increase hospitalizations from heart failure decompensation.

I. Adverse therapies—Therapies that adversely affect the clinical status of patients with symptomatic heart failure should be avoided. Other than for control of hypertension, calcium channel blockers offer no morbidity or mortality benefit in heart failure. Nondihydropyridine calcium channel blockers (eg, diltiazem and verapamil) and older, short-acting dihydropyridines (eg, nicardipine and nisoldipine) can worsen symptoms of heart failure, especially in patients with moderate to severe heart failure. The newer long-acting dihydropyridine calcium channel blockers amlodipine and felodipine appear to be safe when used in the treatment of hypertension but do not improve heart failure outcomes. NSAIDs can also exacerbate heart failure through peripheral vasoconstriction and by interfering with the renal effects of diuretics and the unloading effects of ACEIs. Most antiarrhythmic drugs (except amiodarone and dofetilide) have an adverse impact on heart failure and survival because of their negative inotropic activity and proarrhythmic effects. Phosphodiesterase inhibitors (cilostazol, sildenafil, vardenafil, and tadalafil) can cause hypotension and are potentially hazardous in patients with heart failure. Thiazolidinediones and metformin, both used in treatment of diabetes, can be detrimental in patients with heart failure because they increase the risk of excessive fluid retention and lactic acidosis, respectively.

J. Implantable devices—Nearly one-third of all heart failure deaths occur as a result of sudden cardiac death. The ACC/AHA recommendations include use of implantable cardioverter-defibrillators (ICDs) for secondary prevention of sudden cardiac death in patients with symptomatic heart failure, a reduced left ventricular ejection fraction, and a history of cardiac arrest, ventricular fibrillation, or hemodynamically destabilizing ventricular tachycardia. ICDs are recommended for patients with NYHA class II or III heart failure, a left ventricular ejection fraction less than 35%, and a reasonable 1-year survival with no recent MI (within 40 days).

As heart failure progresses, ventricular dysynchrony can also occur. This is defined by a QRS duration greater than 0.12 msec in patients with a low left ventricular ejection fraction (usually <35%) and NYHA class III or IV heart failure. Clinical trials have shown that cardiac resynchronization therapy with biventricular pacing can improve quality of life, functional class, exercise capacity, exercise distance, left ventricular ejection fraction, and survival in these patients. Patients who meet criteria for cardiac resynchronization therapy and an ICD should receive a combined device, unless contraindicated.


4. Refractory end-stage heart failure (stage D)—Despite optimal medical therapy some patients deteriorate or do not improve and experience symptoms at rest (NYHA class IV). These patients can have rapid recurrence of symptoms, leading to frequent hospitalizations and a significant or permanent reduction in their activities of daily living. Before classifying patients as being refractory or having end-stage heart failure, providers should verify an accurate diagnosis, identify and treat contributing conditions that could be hindering improvement, and maximize medical therapy.

Control of fluid retention to improve symptoms is paramount in this stage, and referral to a program with expertise in refractory heart failure or referral for cardiac transplantation should be considered. Other specialized treatment strategies, such as mechanical circulatory support, continuous intravenous positive inotropic therapy, and other surgical management can be considered, but there is limited evidence in terms of morbidity and mortality to support the value of these therapies. Careful discussion of the prognosis and options for end-of-life care should also be initiated with patients and their families. In this scenario, patients with ICDs should receive information about the option to inactivate defibrillation.

B. Diastolic Heart Failure

Clinically, diastolic heart failure is as prevalent as LVSD, and the presentation of clinically evident diastolic heart failure is indistinguishable from clinically apparent LVSD. Elderly women, usually with a heavy prevalence of hypertension and diabetes mellitus, appear to be most at risk. When considering the diagnosis of diastolic heart failure, conditions that mimic heart failure—including obesity, lung disease, poorly controlled atrial fibrillation, and occult coronary ischemia—have to be ruled out. Management focuses on controlling systolic and diastolic blood pressure, ventricular rate, and volume status, and reducing myocardial ischemia, because these entities are known to exert effects on ventricular relaxation. Diuretics are used to control symptoms of pulmonary congestion and peripheral edema, but care must be taken to avoid overdiuresis, which can cause decreased volume status and preload, manifesting as worsening heart failure.


Prognosis

Despite favorable trends in survival and advances in treatment of heart failure and associated comorbidities, 50% of patients die within 5 years of diagnosis. Mortality increases in patients both with and without CHF as systolic function declines. Even patients with diastolic heart failure have significantly higher mortality rates compared with persons who have normal left ventricular systolic function and no CHF.

Web Sites

American College of Cardiology clinical guidelines: http://www.acc.org/clinical/statements.htm
American Heart Association (AHA): http://www.americanheart.org
AHA patient information: http://www.americanheart.org/presenter.jhtml?identifier=1486
Dyslipidemias

Brian V. Reamy, MD, Colonel (Ret), USAF, MC

ESSENTIALS OF DIAGNOSIS

- Serum cholesterol values greater than ideal for the prevention of atherosclerotic cardiovascular disease (ASCVD).
- Ideal values vary based on the risk status of the individual patient.

General Considerations

The Framingham Heart Study firmly established an epidemiologic link between elevated serum cholesterol and an increased risk of morbidity and mortality from ASCVD. Although the benefits of lowering cholesterol were assumed for many years, not until the past decades has enough evidence accumulated to show unequivocal benefits from using lifestyle and pharmacologic therapy to lower serum cholesterol. Evidence in support of using statin agents is particularly strong and has revolutionized the treatment of dyslipidemias.

The efficacy of lipid reduction for the secondary prevention of ASCVD, (reducing further disease related morbidity in those with manifest disease) is supported by multiple trials and is appropriate in all patients with ASCVD. The efficacy of primary prevention, (reducing the risk of disease occurrence in those without overt cardiovascular disease) is now supported in any patients at more than a low risk of ASCVD by the 10-year Framingham risk assessment available at: http://hp2010.nhlbihin.net/atp3i/calculator.asp.

The National Cholesterol Education Program (NCEP), Adult Treatment Panel (ATP) III released guidelines in 2001 and an update in July 2004. These guidelines emphasize aggressive treatment of dyslipidemias with the intensity of treatment titrated to the patients risk status.

Pathogenesis

Serum cholesterol is carried by three major lipoproteins: high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL). Most clinical laboratories measure the total cholesterol, total triglycerides (TG), and the HDL fraction.

The triglyceride fraction, and to a lesser extent the HDL level, varies considerably depending on the fasting status of the patient. The NCEP/ATP III guidelines recommend that only fasting measurements including total cholesterol, triglycerides, HDL cholesterol, and a LDL cholesterol be used to guide management decisions.

Different populations have different median cholesterol values. For example, Asian populations tend to have total cholesterol values 20%-30% lower than populations living in Europe or the United States. It is important to recognize that unlike a serum sodium electrolyte value, there is no normal cholesterol value. Instead, there are cholesterol values that predict higher morbidity and mortality from ASCVD if left untreated, and cholesterol values that correlate with less likelihood of cardiovascular disease if they are below certain levels.

Atherosclerosis is an inflammatory disease in which cells and mediators participate at every stage of atherogenesis from the earliest fatty streak to the most advanced fibrous lesion. Elevated glucose, increased blood pressure, and inhaled cigarette by-products can trigger inflammation. But, one of the key factors triggering this inflammation is oxidized LDL. When LDL is taken up by macrophages it triggers the release of inflammatory mediators which can lead to thickening and/or rupture of plaque lining the arterial walls. Ruptured or unstable plaques are responsible for clinical events such as myocardial infarction and stroke. Lipid lowering, whether by diet or medication, can therefore be thought of as an anti-inflammatory and plaque stabilizing therapy.

1The opinions contained herein are those of the author. They do not represent the opinions or official policy of the Department of the Air Force, the Department of Defense, or the Uniformed Services University.
Clinical Findings

A: Symptoms and Signs

The majority of patients with dyslipidemias have no signs or symptoms of disease and is usually detected by routine laboratory screening in an asymptomatic individual. Rarely, patients with familial forms of hyperlipidemia may present with yellow xanthomas on the skin or in tendon bodies, especially the patellar tendon, Achilles tendon, and the extensor tendons of the hands.

There are a few associated conditions that can cause a secondary hyperlipidemia (Table 21-1). These conditions should be considered before lipid lowering therapy is begun or when the response to therapy is much less than predicted. In particular, poorly controlled diabetes and untreated hypothyroidism can lead to an elevation of serum lipids resistant to pharmacologic treatment.

B. Screening

The US Preventive Services Task Force (USPSTF) bases its screening recommendations on the age of the patient. It strongly recommends (rating A) routinely screening men 35 years and older and women 45 years of age and older for lipid disorders.

The USPSTF recommends (rating B) screening younger adults, (men 20-35 years of age and women 20-45 years of age), if they have other risk factors for coronary disease. They make no recommendation for or against screening in younger adults in the absence of known risk factors.

In contrast, the NCEP guidelines advise that screening should occur in adults aged 20 years or older with a fasting, lipid profile once every 5 years.

Table 21-1. Secondary causes of lipid abnormalities.

<table>
<thead>
<tr>
<th>I. Hypercholesterolemia</th>
<th>II. Hypertriglyceridemia</th>
<th>III. Hypocholesterolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>Diabetes mellitus</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Alcohol use</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Obstructive liver disease</td>
<td>Obesity</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td>Chronic renal insufficiency</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Drugs (oral contraceptives, diuretics)</td>
<td></td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>Drugs (estrogens, isotretinoin)</td>
<td></td>
</tr>
</tbody>
</table>

Screening children and adolescents is controversial and expert opinion recommends screening only those children older than 2 years of age with significant family histories of hypercholesterolemia or premature ASCVD.

Treatment

The current NCEP/ATP III treatment guidelines released on 15 May 2001 and the update from July 2004 are as rooted in evidence as possible. They are available online at www.nhlbi.nih.gov.

The NCEP/ATP III guidelines follow a 9-step process (Table 21-2). The first step begins after obtaining fasting lipoprotein levels. The profile is categorized based on the LDL, HDL, and total cholesterol values:

<table>
<thead>
<tr>
<th>LDL Cholesterol (mg/dL)</th>
<th>HDL Cholesterol (mg/dL)</th>
<th>Total Cholesterol (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 Optimal</td>
<td>&lt;40 Low</td>
<td>&lt;200 Desireable</td>
</tr>
<tr>
<td>100-129 Near Optimal</td>
<td>&gt;60 High</td>
<td>200-239 Borderline high</td>
</tr>
<tr>
<td>130-159 Borderline high</td>
<td></td>
<td>&gt;240 High</td>
</tr>
<tr>
<td>160-189 High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;190 Very high</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Step 1 Determine lipoprotein levels after a 9-12 h fast.
Step 2 Identify the presence of coronary heart disease or equivalents (coronary artery disease, peripheral arterial disease, abdominal aortic aneurysm, diabetes mellitus).
Step 3 Determine the presence of major risk factors, other than LDL (smoking, hypertension, HDL <40 mg/dL, family history of premature coronary disease, men >45 y and women > 55 y).
Step 4 Assess level of risk: use Framingham risk tables if 2+ risk factors and no coronary heart disease (or equivalent) is present.
Step 5 Determine risk category, LDL goal, and the threshold for drug treatment.
Step 6 Initiate therapeutic lifestyle changes (TLC) if LDL is above goal.
Step 7 Initiate drug therapy if LDL remains above goal.
Step 8 Identify the presence of the metabolic syndrome and treat. Determine the triglyceride and HDL goals of therapy.
Step 9 Treat elevated triglycerides and reduced HDL with TLC and drug therapy to achieve goals.

TLC, therapeutic lifestyle changes.
Step 2 focuses on determining the presence of clinical atherosclerotic disease such as: coronary heart disease, peripheral arterial disease, or diabetes mellitus.

In Step 3 the clinician should determine the presence of other major CAD risk factors including: smoking, age greater than 45 years in men, (55 years in women), hypertension, HDL cholesterol less than 40 mg/dL, a family history of premature CHD in a male first degree relative less than 55 years or a female first degree relative less than 65 years of age. An HDL cholesterol greater than 60 mg/dL negates one risk factor.

Step 4 uses the Framingham coronary risk calculator to classify the patient into one of four risk categories: high-risk, having coronary artery disease or a 10-year risk of greater than 20%, moderately high risk, having a 10-year risk of 10%-20%, moderate-risk, having greater than 2 risk factors, but a 10-year risk of less than 10%, or low-risk, having 0-1 risk factors. The Framingham risk calculator can be found at: http://hp2010.nhlbihin.net/atpiii/calculator.asp.

Step 5 is the key step that determines the patient’s suggested LDL cholesterol treatment goals. Table 21-3 summarizes risk category determination and treatment goals.

### A. Behavior Modification

Step 6 reviews the contents of Therapeutic Lifestyle Changes (TLC). Saturated fat is limited to less than 7% of total calories, cholesterol intake to less than 200 mg/d. In addition, weight management and increased physical activity are encouraged. TLC also includes advice to increase the consumption of soluble fiber (10-25 gm/d) and the intake of plant sterols (sitostanol approximately 2 g/d). Several margarines (Benecol™ Take Control™) contain these plant sterols, and evidence exists that they work in conjunction with cholesterol lowering drugs. Excellent information sources of soluble fiber can be found at: www.nhlbi.nih.gov/chd/tipsheets/solfiber.htm.

The cultural background of the patient will impact the choice of dietary recommendations. A skilled nutritional medicine consultant can easily adapt the fat/cholesterol intake recommendations to a variety of culturally normative diets. Indeed, components of some cultures’ diets that encourage the consumption of soluble fiber, plant sterols, soy protein, or fish oils have cholesterol lowering effects. Dietary advice given without regard to a patient’s culturally accepted diet is counterproductive.

### B. Pharmacotherapy

Step 7 reviews the options for drug therapy if required (Table 21-4). Of note, NCEP/ATPIII now recommends the simultaneous use of TLC and drugs in patients at the highest risk. Medications should be added to TLC after 3 months if goal LDL levels are not reached in lower risk patients. Given their proven efficacy, and enhanced patient compliance over other classes of medications, statin agents are the drugs of first choice. In particular, patients with diabetes or those in the highest risk category derive special benefits from their use due to their innate anti-inflammatory effects. Myopathy and increased liver enzymes are the main potential side effects from statin agents. An increase of serum aminotransferase levels to more than three times normal (ULN) occurs in 1% of patients taking high doses of statins. Discontinuation of the agent is only required if liver enzymes increase to more than three times ULN. Monitoring of liver function tests at 12 weeks, 6 months, and annually thereafter can help identify patients with hepatic side effects and facilitate prompt discontinuation. Rhabdomyolysis occurs in less than 0.1% of cases. It can be prevented by the prompt discontinuation of the agent when muscle pain and elevated muscle enzymes occur. Unexplained pain in large muscle groups should prompt investigation for myopathy, however routine monitoring of muscle enzymes is not supported by any evidence. Side effects from statins may not be class-specific. Therefore, a side effect with one agent should not prevent a trial with another statin agent. Prior concerns about statins causing cataracts or cancer have been alleviated by the release of several meta-analyses.

### Table 21-3. Risk category determination and LDL cholesterol goals.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
<th>LDL Level at Which To Begin Therapeutic Lifestyle Changes (TLC)</th>
<th>LDL Level at Which To Consider Drug Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk: CHD or equivalent (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL (&lt;70 mg/dL optional)</td>
<td>&gt;100 mg/dL</td>
<td>&gt;100 mg/dL or &lt;100 mg/dL</td>
</tr>
<tr>
<td>Moderately high risk: 10-year risk 10%-20%</td>
<td>&lt;130 mg/dL (&lt;100 mg/dL optional)</td>
<td>&gt;130 mg/dL</td>
<td>&gt;130 mg/dL or (consider if 100-129 mg/dL)</td>
</tr>
<tr>
<td>Moderate risk: 2+ risk factors (10-year risk &lt;10%)</td>
<td>&lt;160 mg/dL</td>
<td>&gt;160 mg/dL</td>
<td>&gt;160 mg/dL</td>
</tr>
<tr>
<td>0-1 risk factor</td>
<td>&lt;160 mg/dL</td>
<td>&gt;160 mg/dL</td>
<td>&gt;190 mg/dL (160-189 mg/dL drug use optional)</td>
</tr>
</tbody>
</table>

Adapted from 2001 NCEP/ATPIII Treatment Guidelines and 2004 update.
Statin agents can be combined with fibrates and nicotinic acid, but the potential for side effects is increased. When a statin is combined with a fibrate the use of fenofibrate is preferred over gemfibrozil due to a much lower rate of rhabdomyolysis. Fibrate agents have special efficacy in patients with low HDL and elevated triglycerides.

Nicotinic acid is the most potent HDL-elevating agent. Yet, long-term patient compliance is difficult due to flushing, nausea, and abdominal discomfort. Additionally, nicotinic acid can cause an increase in blood glucose, which can limit its use in diabetic patients.

The bile acid sequestrants cause gastrointestinal side effects and can lead to decreased absorption of other medications. Given their relative low potency they are mainly useful as adjuncts. Ezetimibe is a cholesterol absorption inhibitor that lowers LDL and is ideally used in combination with a statin agent. However, recent trials have not demonstrated benefits in reducing cardiovascular outcomes.

C. Complementary and Alternative Therapies

Several complementary or alternative therapies are employed for cholesterol reduction but, the evidence supporting their use is variable. Several are harmless and some could lead to significant side effects. Oat bran (1/2 cup/d) is a soluble fiber that can reduce TC by 5 mg/dL and TG by 5%. Fish oil (1 g daily of unsaturated omega-3 fatty acids) can reduce triglycerides by up to 30% and raise HDL slightly with long-term use.

Garlic has few side effects but several trials have shown that it changes lipids minimally. Soy can reduce LDL by up to 15%, with an intake of 25 g/d. This amount is unlikely to be achieved in a western-style diet. Went yeast is the natural source for statin agents. As such, it is effective at lowering lipid values, but carries the same side effect profile as statins.

Of concern is that most patients do not undergo monitoring for potential hepatic or muscle side effects. Red wine can raise HDL, however, in amounts greater than two glasses per day, red wine will raise TG and potentially cause hepatic damage and other deleterious health effects. Several other supplements such as ginseng, chromium, and myrrh all have putative cholesterol-lowering effects but little patient-oriented clinical outcome evidence supporting their use.

Step 8 of the NCEP/ATP III guidelines encourages clinicians to look for the “metabolic syndrome”. The components of this syndrome are abdominal obesity, hypertriglyceridemia, low HDL, hypertension, and glucose intolerance. Aggressive treatment of inactivity, obesity, hypertension, and the use of low-dose aspirin are encouraged in these patients.

Step 9 is the final step of the algorithm. This step focuses on treating elevated triglycerides and low HDL as secondary endpoints of cholesterol therapy. Triglycerides are classified as follows:

- <150 mg/dL: Normal
- 150-199 mg/dL: Borderline high
- 200-499 mg/dL: High
- >500 mg/dL: Very high

The initial steps are to employ TLC, (weight reduction, increase physical activity, dietary change) and then to add a fibrate or nicotinic acid to reach goal levels.

D. Treatment of Special Groups

The treatment of dyslipidemias in special groups presents problems because less trial data is available.

1. Women—Several statin trials included women although they accounted for only 15%-20% of the total enrolled patient population. Subset analysis and meta-analysis reveal...
that statins reduced coronary events by a similar proportion in women as in men.

2. Elderly—Given that ASCVD is more common in the elderly it is expected that the benefits of cholesterol lowering would extend to this subgroup. Due to the increased frequency of ASCVD events in this population, the number needed to treat (NNT) is reduced from approximately 35:1, in patients aged 40-55 years of age, to just 4:1 in patients from 65 to 75 years of age. The 2002 Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study, 2003 Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study, and the 2002 Heart Protection Study (HPS) study confirmed the benefits of lipid lowering with statins for the primary and secondary prevention of ASCVD in patients from 65 to 84 years of age.

3. Children—There are accumulating studies showing the safety of statins in adolescents. However, given concerns of interrupting cholesterol synthesis in the growing body, therapy is usually confined to the very high risk. Therapeutic lifestyle interventions are safe, and can have a profound impact on the long-term health of the child if they are followed. Cholesterol levels should not be checked below 2 years of age.

4. Patients less than 35 years of age—Numerous studies have shown pathoanatomic evidence of ASCVD at all ages. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study has demonstrated the ability to correlate degrees of arterial intimal narrowing with the risk factors present in a patient across all ages.

Cholesterol treatment studies have not enrolled patients younger than 35 years of age because the frequency of clinical endpoints would be reduced and the duration of the studies would need to increase. The elevation of the NNT in young patients also makes treatment less economically attractive. The NCEP/ATP III guidelines specifically address this issue for patients from 20 to 35 years of age. They state that even though clinical CHD is rare in young adults, coronary atherosclerosis may progress rapidly, and young men who smoke and have an LDL from 160-189 mg/dL may be candidates for drug therapy. In addition, drug therapy should be considered in young men and women with an LDL greater than 190 mg/d.

E. Indications for Referral

Patients who do not respond to combination therapy or have untoward side effects on therapy should be considered for specialty consultation. Combinations of multiple agents or lipid plasmapheresis may sometimes be required.


Web Site
American Heart Association: www.americanheart.org (Best peer-reviewed source for diet, exercise, and lifestyle information for physicians and patients)
Urinary tract infections (UTIs) are among the most common bacterial infections encountered in medicine. Accurately estimating incidence is difficult because UTIs are not reportable, but estimates range from 650,000 to seven million office visits per year.

A UTI is defined by urologists as any infection involving the urothelium, which includes urethral, bladder, prostate, and kidney infections. Some of these are diseases that have been clearly characterized (eg, cystitis and pyelonephritis), whereas others (eg, urethral and prostate infections) are not as well understood or described.

The terms simple UTI and uncomplicated UTI are often used to refer to cystitis. In this chapter UTI is used to refer to any infection of the urinary tract, and cystitis is used to specify a bladder infection. The generic term complicated UTI is often used to refer to cystitis occurring in a person with pre-existing metabolic, immunologic, or urologic abnormalities, including kidney stones, diabetes, and AIDS, or caused by multidrug resistant organisms.

Asymptomatic bacteriuria, uncomplicated cystitis, complicated cystitis, two urethral syndromes, four prostatitis syndromes, and pyelonephritis are discussed in this chapter. Although separated into different diagnoses, differentiating among syndromes and deciding treatment is left to the clinician’s discretion.

Antibiotic resistance is a topic that has been left mostly to the reader. General recommendations about specific antibiotics are inappropriate, given that antibiotic resistance differs from location to location. It is the responsibility of the individual physician to be familiar with local antibiotic resistances, and to determine the best first-line therapies for his or her practice. Always keep in mind that antibiotic use breeds resistance, and try to keep first-line drugs as simple and narrow-spectrum as possible.

pyelonephritis. In the United States, screening is usually done by urine culture because dipstick screening can miss patients without pyuria or with unusual organisms.

### Treatment

Treatment should be guided by local rates of resistance. The usual first-line treatment in the absence of significant resistance or penicillin allergy is a 7-day course of amoxicillin. Nitrofurantoin or a cephalosporin is suggested for penicillin-allergic pregnant patients, again for 7 days.

**Treatment**


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### General Considerations

Acute, uncomplicated cystitis is most common in women. Approximately one-third of all women have experienced at least one episode of cystitis by the age of 24 years, and nearly half will experience at least one episode during their lifetime. When a young woman presents to a health care provider with one or more symptoms, her probability of UTI is approximately 50%. Young women’s risk factors include sexual activity, use of spermicidal condoms or diaphragm, and genetic factors such as blood type or maternal history of recurrent cystitis. Healthy, noninstitutionalized older women can also experience recurrent cystitis. Risk factors among these women include changes in the perineal epithelium and vaginal microflora after menopause, incontinence, diabetes, and history of cystitis before menopause.

Although men can also suffer from cystitis, it is rare (annual incidence: <0.01% of men aged 21-50 years) in men with normal urinary anatomy who are younger than 35 years. Urethritis from sexually transmitted pathogens should always be considered in this age group, and prostatitis should always be ruled out in the older age group by a rectal examination. Any cystitis in a man is complicated, due to the presence of the prostate gland, and should be treated for 10-14 days to prevent a persistent prostatic infection.

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### Prevention

**A. Young Women**

Considering the frequency and morbidity of cystitis among young women, it is hardly surprising that the lay press and medical literature contain a host of ideas about how to prevent recurrent cystitis. These range from the suggestion that cotton underwear is “healthier” to wiping habits, voiding habits, and choice of beverage. Unfortunately, the vast majority of these preventive measures do not hold up to scientific study (Table 22-1).

---

### Table 22-1. UTI risk in young women.

<table>
<thead>
<tr>
<th>Factors With No Evidence of Effect on Cystitis</th>
<th>Factors With Evidence for Effect on Cystitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Promote</strong></td>
<td><strong>Prevent</strong></td>
</tr>
<tr>
<td>Precoital voiding</td>
<td>Spermicide&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Underwear fabric</td>
<td>Diaphragm&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Wiping pattern</td>
<td>Cervical cap&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Doucheing</td>
<td>Sexual activity</td>
</tr>
<tr>
<td>Hot tub use</td>
<td>Genetic predisposition</td>
</tr>
<tr>
<td>Delayed postcoital voiding&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Recent studies have shown no effect of back-to-front wiping, precoital voiding, tampon use, underwear fabric choice, or use of noncotton hose or tights. Behaviors that do appear to have an impact on frequency of cystitis in young women include sexual activity (four or more episodes per month in one study), delayed postcoital voiding, use of spermicidal condoms (several studies), use of un lubricated condoms (one study), use of diaphragms or cervical caps, and intake of cranberry juice.

It can be concluded from Table 22-1 that there are few behaviorally oriented strategies that can be offered to young women who suffer from recurrent cystitis. Recommending a change in contraception to oral contraceptive pills, intravaginal devices, or nonspermicidal, lubricated condoms may be helpful.

Cranberry juice and cranberry extract have long been proposed as a possible way to prevent UTIs. Cranberries are thought to contain a substance that changes the surface properties of *E. coli* and prevents it from adhering to the bladder wall. A recent Cochrane Review identified 10 studies comparing the effects of cranberry products with placebo, juice, or water. There was evidence to show cranberries in the form of juice or capsules could prevent recurrent UTIs in women. A reasonable dose in capsule form is 300–400 mg twice daily. As for juice, 8 oz three times daily of unsweetened juice is recommended. It is unclear how long the duration should be.

Prophylactic antibiotics, either low-dose daily antibiotics or postcoital antibiotics, remain the mainstay of prevention of recurrent UTIs for young women and can reduce recurrence rates up to 95%.

### B. Postmenopausal Women

Risk factors for cystitis in older women include urologic factors such as incontinence, cystocele, and postvoid residual; hormonal factors resulting in a lack of protective lactobacillus colonization; and a prior history of cystitis. For the above-mentioned risk factors, the most easily administered effective prevention is estrogen.

There are many possible ways to administer estrogen. These include traditional oral hormone replacement therapy, which is still considered indicative (after thorough discussion with the patient of risks and benefits) for menopausal symptoms; vaginal estrogen rings; or vaginal creams.

The only form of estrogen which has been proven to decrease recurrent UTIs in postmenopausal women is vaginal. The usual side effects of estrogen can be seen with vaginal use as well as oral. These include breast tenderness, vaginal bleeding, vaginal discharge, and vaginal irritation. Contraindications (as with oral estrogens) include a history of endometrial carcinoma, breast carcinoma, thromboembolic disorders, and liver disease. Consideration should be made of patients’ functional and cultural abilities before prescribing vaginal applications.

One study compared the effects of cranberry extract (500 mg daily) to trimethoprim for the prevention of recurrent UTIs in older women. There was only a slight advantage of the antibiotic over cranberry extract.

### C. Young Men

The only studies focusing on prevention of UTI in young men have investigated infant circumcision; because the risk of UTI is so low in normal men these studies are prohibitively expensive. The risk of UTI in normal boys hovers around 1% in the first 10 years of life, given that the number needed to treat (NNT) for circumcision is 111. In boys with recurrent UTI or high-grade ureteral reflux, the NNTs are 11 and 4, respectively. The complication rate of circumcision is 2%–10%, with adverse sequelae ranging from minor transient bleeding (common) to amputation of the penis (extremely rare).

### D. Future Trends in Prevention

Several investigators are currently evaluating the use of probiotics and vaccines for the prevention of UTI. Probiotics are benign living organisms, which in this case are used to boost the vaginal flora. They then defend against pathologic bacteria by competing for adhesion receptors and nutrients. Some species, such as *Lactobacillus*, even produce antimicrobial substances. Vaginal vaccines are working their way through clinical trials and are not yet commercially available; whether they will prove to be more efficacious than prophylactic antibiotics is yet to be determined. There are also studies looking at intentional colonization of the urothelium with *Escherichia coli* 83972. This looks promising, but needs more research.

#### Clinical Findings

### A. Symptoms and Signs

Symptoms include dysuria, ideally felt more internally than externally, and of sudden onset; suprapubic pain; cloudy, smelly urine; frequency; and urgency.

Physical examination in the afebrile, otherwise healthy patient with a classic history is done essentially to rule out other diagnoses and to ensure that “red flags” are not present. The examination might range from checking a temperature and percussing the costovertebral angles to a full pelvic examination, depending on where the history leads. There are no pathognomonic signs on physical examination for cystitis.

### B. Laboratory Findings

Laboratory studies include dipstick test of urine, urinalysis, and urine culture. In some cases laboratory tests are not required to diagnose cystitis with high accuracy; however, they should probably only be omitted in settings where follow-up can be easily arranged in case of failure of treatment, which would of course indicate further workup. Figure 21-1 provides a diagnostic algorithm for cystitis.

1. **Urine dipstick testing**—Dipstick findings are positive for leukocyte esterase or nitrite, or both. Several references
Women with $\geq$1 symptoms of UTI\(^a\)

Risk factors for complicated infection?\(^b\)

Back pain or fever?

Vaginal discharge?

Most elements of the history (and physical examination\(^c\)) positive?

Perform dipstick urinalysis

Dipstick results positive?

Low to intermediate probability of UTI (~20%)

Consider urine culture to establish diagnosis

Consider initiating empirical treatment

Probability of UTI moderate (~60%) and probability of pyelonephritis unknown

Consider urine culture to establish diagnosis

Consider empirical treatment

Low to intermediate probability of UTI (~20%)

Pelvic examination (including cervical cultures when appropriate) and urine culture to establish diagnosis

High probability of UTI (~90%)

Consider empirical treatment without urine culture

High probability of UTI (~80%)

Consider empirical treatment without urine culture

\(\text{Figure 22-1. Diagnostic algorithm for cystitis. STD, sexually transmitted disease; UTI, urinary tract infection.}\)

\(^a\)In women who have risk factors for sexually transmitted diseases (STDs), consider testing for \textit{Chlamydia}. The US Preventative Services Task Force recommends screening for \textit{Chlamydia} for all women 25 years or younger and women of any age with more than one sex partner, a history of STD, or inconsistent use of condoms.

\(^b\)For a definition of complicated UTI, see text.

\(^c\)The only physical examination finding that increases the likelihood of UTI is costovertebral angle tenderness, and clinicians may consider not performing this test in patient with typical symptoms of acute uncomplicated UTI (as in telephone management).
now support treatment of simple, uncomplicated UTI in the young, nonpregnant woman on the grounds of clinical history alone, if that history leads to high suspicion for cystitis (and low suspicion of STD). For women with an equivocal clinical history, urine dipstick analysis may be enough to reassign the women to high or low suspicion and treat or not treat accordingly.

2. Urinalysis—Urinalysis will be positive for WBCs, with few or no epithelial cells. It should be noted, however, that urinalysis is more expensive than dipstick analysis and only minimally more accurate.

3. Urine culture—The gold standard of diagnosis is a culture growth of 100,000 ($10^5$) organisms in a midstream clean-catch sample. However, there are some patients who have classic clinical cases of UTI and only 100 ($10^2$) organisms on culture. Most laboratories are not equipped to detect anything fewer than $10^4$ organisms. Culture is strongly suggested if a relapsing UTI or pyelonephritis is suspected to be sure of sensitivities and eradication (see Figure 22-1).

C. Imaging Studies

Imaging studies generally are not required for patients with simple uncomplicated UTIs.

D. Special Tests

These tests are generally required only for failures of treatment, symptoms suggesting a diagnosis other than cystitis, or complicated cystitis (see section Complicated Cystitis, later).

Differential Diagnosis

See Table 22-2.

Complications

There are virtually no complications from repeated uncomplicated cystitis if it is recognized and treated. Delay in treatment may lead to ascending infection and pyelonephritis, but this has not been confirmed. In the case of infection with urea-splitting bacteria, “infection stones” of struvite with bacteria trapped in the interstices may be formed. These stones lead to persistent bacteriuria and must be completely removed to clear the infection. *Proteus mirabilis*, *S saprophyticus*, and *Klebsiella* bacteria can all split urea and lead to stones.

Treatment

A. Acute Cystitis

There is a lot of evidence from randomized clinical trials to support 3-day antibiotic therapy as superior to 1-day treatment and equivalent to therapy for longer periods of time, with the exception of nitrofurantoin. This is true for treatment of older, noninstitutionalized women as well. Trimethoprim-sulfamethoxazole, in the absence of allergies to sulfa and local resistance rates greater than 10%-20%, should be considered first-line therapy. Risk factors for trimethoprim-sulfamethoxazole resistance include recent antibiotic exposure, recent hospitalization, diabetes mellitus, three or more UTIs in the past year, and possibly use of oral contraceptive pills or estrogen replacement therapy. For patients who are allergic to sulfa drugs, a 5-7 day course of nitrofurantoin or a 3-day course of a fluoroquinolone (eg, ciprofloxacin) can be used. However, due to the concern of fluoroquinolone resistance and frequency of cystitis, they should be used sparingly. β-Lactam antibiotics are not as effective as other classes of drugs against urinary pathogens and should not be used as first-line agents except in pregnant patients.

B. Acute Cystitis in the Pregnant Woman

Treatment with amoxicillin, a cephalosporin, nitrofurantoin, or another pregnancy-safe antibiotic for 7 days remains the

<table>
<thead>
<tr>
<th>Table 22-2. Red flag symptoms and differential diagnoses.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>If Patient Has</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Vaginal discharge</td>
</tr>
<tr>
<td>External burning pain</td>
</tr>
<tr>
<td>Costovertebral angle tenderness</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Recent UTI (&lt;2 wk)</td>
</tr>
<tr>
<td>Dyspareunia</td>
</tr>
<tr>
<td>Recent trauma or instrumentation</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Severe, colicky flank pain</td>
</tr>
<tr>
<td>Joint pains, sterile urine</td>
</tr>
<tr>
<td>History of childhood infections, urologic surgery</td>
</tr>
<tr>
<td>History of kidney stones</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Immunosuppression</td>
</tr>
</tbody>
</table>
standard, with follow-up cultures to demonstrate bacterial eradication. Asymptomatic bacteriuria, if found on cultures, is treated in pregnant women with the same antibiotics (see section Asymptomatic Bacteriuria, earlier).

C. Prophylaxis for Recurrent Cystitis

Low-dose, prophylactic antibiotics have been shown to decrease recurrences by up to 95%. Most recommendations suggest starting prophylaxis after a patient has had more than three documented UTIs in 1 year. Prophylactic antibiotics are usually administered for 6 months to 1 year but can be given for longer periods of time. Antibiotics can be taken daily at bedtime or used postcoitally by women whose infections are associated with intercourse (Table 22-3). Unfortunately, prophylaxis does not change the propensity of these women for recurrent UTIs; when prophylaxis is stopped, approximately 60% of women develop a UTI within 3-4 months. Prophylaxis should not start until cultures have shown no growth after treatment, to rule out bacterial persistence.

Table 22-3. Prophylactic antibiotics for recurrent UTI in women.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drug and Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>Trimethoprim, 100 mg every day</td>
</tr>
<tr>
<td></td>
<td>Nitrofurantoin, 50 mg every day</td>
</tr>
<tr>
<td></td>
<td>Nitrofurantoin macrocrystals, 100 mg every day</td>
</tr>
<tr>
<td></td>
<td>Cotrimoxazole, 240 mg every day</td>
</tr>
<tr>
<td></td>
<td>Cranberry juice, 8 oz three times a day</td>
</tr>
<tr>
<td></td>
<td>Cranberry tablets, 1:30 twice a day</td>
</tr>
<tr>
<td>Postcoital</td>
<td>One dose of any of the above antibiotics after coitus</td>
</tr>
</tbody>
</table>

*Preferred if patient could become pregnant. Trimethoprim should be avoided in the first trimester.

LONG-TERM PROGNOSIS

Long-term prognosis in terms of kidney function is excellent; prognosis of arresting recurrent cystitis without permanent prophylaxis is not as good. New preventative treatments are currently being explored and it is hoped these will prove beneficial.


ESSENTIALS OF DIAGNOSIS

▶ Any cystitis not resolved after 3 days of appropriate antibiotic treatment.
▶ Any cystitis in a special population, such as:
▶ A diabetic patient.
▶ A man.
▶ A patient with an abnormal urinary tract.
▶ A patient with stones.
▶ A pregnant woman.
▶ Any cystitis involving multidrug resistant bacteria.

General Considerations

These are the infections for which a physician should consider further workup or referral to a urologist. These infections should all be cultured to be sure the antibiotics used are appropriate and that the organisms are sensitive to the chosen antibiotic.

Clinical Findings

Special tests should include x-ray or computed tomography (CT) to evaluate for stones, intravenous pyelogram (IVP) to evaluate anatomy and stones, and cystoscopy and biopsy to rule out interstitial cystitis, cancer, or unusual pathogens.

Treatment

Patients with complicated UTIs should be treated with long-course (10- to 14-day or more), appropriate antibiotics. Single-dose or 3-day regimens are not appropriate for this group of patients.
ACUTE URETHRAL SYNDROME

**ESSENTIALS OF DIAGNOSIS**

- Dysuria.
- Frequency and urgency.
- No vaginal discharge.
- Urine dipstick analysis may be negative or positive.
- Negative culture.

**General Considerations**

*Acute urethral syndrome* is a term used by some to describe a young, healthy, sexually active woman who complains of recent-onset symptoms of cystitis but does not meet strict guidelines for diagnosis of cystitis (growth of $\leq 10^4$ or $10^5$ organisms on culture). Some authors now feel that even 100 CFU found on culture of a dysuric woman represent a true UTI. Because most laboratories are equipped to detect only $10^4$ organisms or more, these are patients in usual practice found to have “negative” cultures. They may have positive or negative urine dipstick analysis and positive or negative spun urine for bacteria, although bacteria and white blood cells (WBCs) in the urine are more convincing for cystitis than a completely negative workup.

**Clinical Findings**

Testing depends on the physician’s assessment of the patient. In patients at low risk of acquiring a sexually transmitted disease (STD), no testing might be appropriate or maybe only after failure of empirical treatment for cystitis. In patients at higher risk of acquiring an STD, *Chlamydia* testing, either by cervical swab or urine polymerase chain reaction (PCR) or ligase chain reaction (LCR) might be appropriate.

**Differential Diagnosis**

This syndrome is not well defined. It is usually taken to represent an early cystitis, but it can also be an STD (*C. trachomatis* has been noted in women with the previously described symptoms).

**Treatment**

There is some evidence that the acute urethral syndrome will respond to antibiotics commonly used in the treatment of UTIs. Because the prevalence of *C. trachomatis* was found to be high in at least one study of women with these symptoms, use of antibiotics effective against STDs or *Chlamydia* testing for patients who do not respond completely to a course of antibiotics is highly recommended.

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URETHRITIS

**ESSENTIALS OF DIAGNOSIS**

- Pain or irritation on urination.
- No frequency or urgency.
- Discharge from the urethra (predominantly males).
- Vaginal discharge possible.

**General Considerations**

Isolated urethritis in men or women is almost always an STD, most often caused by *C. trachomatis*. This syndrome is differentiated from acute urethral syndrome by the time course of symptoms: symptoms that have a gradual onset or persist without evolution into classic cystitis symptoms, including suprapubic symptoms such as pain, urgency, or frequency, are more indicative of urethritis than of acute urethral syndrome.

**Clinical Findings**

It can be very difficult to differentiate a symptomatic chlamydial infection from bacterial cystitis with coliform organisms, and testing for both may be required. The advent of *Chlamydia* urine PCR or LCR tests makes ruling out *Chlamydia* much easier than in the past, as the same urine sample can be sent for both tests.

**Treatment**

See Chapter 14 for current diagnosis and treatment of STDs such as *Chlamydia*.

ACUTE BACTERIAL PROSTATITIS

**ESSENTIALS OF DIAGNOSIS**

- Dysuria, frequency, urgency.
- Tender prostate.
- Systemic symptoms such as fever, nausea, vomiting.
- Leukocyte esterase or nitrite on urine dipstick analysis.
- Positive urine culture.
General Considerations

Prostatitis is a very common disease among men, with a prevalence and incidence among men ranging between 11% and 16%. Some two million office visits a year are made for prostatitis (1% of all primary care office visits), so it is useful for the primary care practitioner to be able to evaluate men for symptoms of prostatitis.

Previously, prostatitis was simply described as “acute,” “chronic,” or “nonbacterial.” In 1995 the National Institutes of Health (NIH) revised the categorization of prostatitis and the disease is now differentiated into four categories, as follows:

- Category I: acute bacterial prostatitis
- Category II: chronic bacterial prostatitis
- Category IIIA: inflammatory chronic pelvic pain syndrome
- Category IIIB: noninflammatory chronic pelvic pain syndrome
- Category IV: asymptomatic inflammatory prostatitis

The last category is a diagnosis made incidentally, while working up other symptoms, and is not felt to require treatment. Discussion of category I, or acute bacterial prostatitis, follows. The other categories are discussed separately, later in this chapter.

Acute bacterial prostatitis is different from other types of prostatitis in that it is a well-defined entity with a relatively clear-cut etiology, diagnosis, and treatment. Acute bacterial prostatitis is caused by typical uropathogens and responds well to antibiotic treatment.

Prevention

There is no evidence for interventions that will prevent spontaneous prostatitis.

Clinical Findings

Symptoms and signs include dysuria, frequency, and urgency; low back, perineal, penile, or rectal pain; or tense or “boggy” tender prostate. Fever and chills may be present.

Laboratory findings include a urine dipstick analysis that is positive for leukocyte esterase or nitrites, or both, and urine culture that is positive for a single uropathogen. Imaging studies usually are not performed for acute uncomplicated prostatitis.

Prostatic massage is not generally performed in patients with acute bacterial prostatitis because it may lead to acute bacteremia.

Differential Diagnosis

Abnormal anatomy may include urethral strictures, polyps, diverticula, redundancies, or valves anywhere in the system from the penis to the kidneys (Table 22-4).

Complications

Complications of acute bacterial prostatitis may include ascending infection, infection-related stones, abscess, fistula, cysts, and acute urinary retention. In the case of acute urinary retention precipitated by prostatitis, a suprapubic catheter rather than a Foley catheter should be placed to avoid damage to the prostate.

Treatment

Treatment is determined by the severity of illness as well as local resistance rates. In cases of very ill patients, broad-spectrum parenteral antibiotics should be initiated. Typically, a penicillin or penicillin derivative and an aminoglycoside can be used. As the illness is treated, the patient can be transitioned to oral therapy with either a quinolone or trimethoprim-sulfamethoxazole for at least 3–4 weeks. Less ill patients can be started on oral therapy with a quinolone or trimethoprim-sulfamethoxazole, again for 3–4 weeks. An α-blocker can be considered for mild urinary retention. A urinary catheter should be considered for more severe retention.

Prognosis

The prognosis is very good for patients with acute uncomplicated bacterial prostatitis.

Table 22-4. Differential diagnosis of dysuria in men.

<table>
<thead>
<tr>
<th>If Patient Has</th>
<th>Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute, colicky flank pain or history of kidney stones</td>
<td>Kidney stone; complicated cystitis</td>
</tr>
<tr>
<td>Costovertebral angle tenderness, fevers</td>
<td>Pyelonephritis</td>
</tr>
<tr>
<td>Urethral discharge</td>
<td>Sexually transmitted disease</td>
</tr>
<tr>
<td>Diabetes/immunosuppression</td>
<td>Complicated cystitis, unusual pathogens</td>
</tr>
<tr>
<td>Testicular pain</td>
<td>Torsion; epididymoorchitis</td>
</tr>
<tr>
<td>Joint pains</td>
<td>Spondyloarthropathy (ie, Reiter or Behçet syndrome)</td>
</tr>
<tr>
<td>History of childhood UTI or urologic surgery</td>
<td>Abnormal anatomy; complicated cystitis</td>
</tr>
<tr>
<td>Recurrent symptoms after treatment</td>
<td>Abnormal anatomy; abscess; stone; chronic prostatitis; resistant organism; inadequate length of treatment; Munchausen syndrome; somatization disorder</td>
</tr>
</tbody>
</table>


CHRONIC BACTERIAL PROSTATITIS

ESSENTIALS OF DIAGNOSIS

- Dysuria, frequency, urgency.
- Symptoms lasting more than 3 months.
- Urine dipstick analysis positive for leukocyte esterase or nitrites, or both.
- Pyuria on microscopy.
- Positive four-glass or two-glass test for prostatic origin.

General Considerations

Chronic bacterial prostatitis, or NIH category II prostatitis, is quite rare, and consequently very few studies have examined it. Bacterial disease comprises only a small percentage of the cases of chronic prostatitis. It has been estimated that the percentage of both acute and chronic bacterial prostatitis is only 5%-10% of all prostatitis diagnoses, and of the bacterial cases the vast majority are acute.

Prevention

Early and sufficient treatment of acute bacterial prostatitis is felt by some authors to prevent chronic prostatitis.

Clinical Findings

A. Symptoms and Signs

Symptoms and signs include dysuria, frequency, and urgency; prostatic tenderness on examination; low back pain; and perineal, penile, or rectal pain. Symptoms are usually present for more than 3 months.

B. Laboratory and Imaging Findings

A urine dipstick analysis will be positive for leukocyte esterase or nitrites, or both. Additionally, a four-glass or two-glass test (discussed below) will be positive for prostatic origin. A transrectal prostatic ultrasound should be performed if an abscess or a stone is suspected.

C. Special Tests

1. Four-glass test—Not used by the majority of practitioners, this is a localization test for chronic prostatitis. The patient should not have been on antibiotics for a month, should not have ejaculated for 2 days, and needs a reasonably full bladder. Signs and symptoms of urethritis or cystitis should have been worked up previously and treated. To perform the test, the patient first cleans himself and carefully retracts the foreskin, then urinates the first 5-10 mL into a sterile container (VB_1). He then urinates 100-200 mL into the toilet, and a second 10-20 mL sample into a sterile container (VB_2). Prostatic massage is then done, milking secretions from the periphery to the center, and any expressed prostatic secretions (EPSs) are caught in a third sterile container. The patient then cleans himself again, and urinates a final 10-20 mL sample into a fourth container (VB_3).

All urine samples are examined microscopically and cultured. Expressed prostatic secretions are wet-mounted, examined, and cultured. The test is positive for prostatic localization if WBCs per high-power field (HPF) and colony counts in VB_3 are at least 10 times greater than in VB_1 or VB_2, or if there are 10 polymorphonuclear leukocytes (PMNL)/HPF in the wet mount. If there is a significant colony count in both VB_1 and VB_3, the patient should be treated for 3 days with nitrofurantoin, which does not penetrate the prostate, and the test should be repeated.

2. Two-glass test—A verified modification of the four-glass test, this test requires an initial clean-catch urine sample, prostatic massage, and a post-massage urine sample. It is functionally equivalent to the VB_2 and VB_3 portions of the four-glass test and more often used in clinical practice.

Differential Diagnosis

See Table 22-4.

Complications

Complications of chronic bacterial prostatitis may include ascending infection, infection-related stones, abscess, fistula, cysts, and acute urinary retention.

Treatment

Antibiotic treatment with quinolones have shown the best results. Therapy is with an oral quinolone for at least 4-6 weeks. Trimethoprim-sulfamethoxazole for 1-3 months can also be considered. α-Blockers may provide some benefit to treatment as well.

Prognosis

The prognosis for treatment of chronic bacterial prostatitis is not known. A clear differentiation of which patients will respond to antibiotics and which will not has not been made.

CHAPTER 22

CHRONIC ABACTERIAL PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME

ESSENTIALS OF DIAGNOSIS

Not very well characterized; most suggestive symptoms include:

- Perineal pain.
- Lower abdominal pain.
- Penile, especially penile tip, pain.
- Testicular pain.
- Ejaculatory discomfort or pain.
- STDs and UTI ruled out.

General Considerations

Chronic abacterial prostatitis was renamed by the NIH in 1995. It is now called chronic pelvic pain syndrome and can be further subclassified into inflammatory, meaning with inflammatory cells isolated in tests, or noninflammatory. This change was made in an attempt to recognize that the pain syndrome physicians have been referring to as “chronic abacterial prostatitis” or even “prostatodynia” in the absence of inflammatory cells on examination has never been proven to originate in the prostate.

The NIH further divided chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) into two categories. These are inflammatory (IIIA) and noninflammatory (IIIB). In the “inflammatory” case, leukocytes are found in semen, in expressed prostatic secretions, or in a post-prostatic massage urine sample. In “noninflammatory” prostatitis, no leukocytes are found in secretions. Recent evidence suggests cytokines may play a role in diagnosis in the future. Current research efforts include the Chronic Prostatitis Clinical Research Network, funded in 1997 by the NIH to investigate the chronic pelvic pain syndrome. Their work is ongoing and not definitive at this time.

The etiology of chronic prostatitis remains unknown. Current theories include infection with unusual or fastidious organisms, lower urinary tract obstruction or dysfunctional voiding, intraprostatic ductal reflux and subsequent chemical irritation with urea from urine forced into the gland, immunologic or autoimmune processes, or neuromuscular causes, such as reflex sympathetic dystrophy. Although none of these theories has been proven, continued research, it is hoped, will increase our understanding of this problem.

Prevention

Trials of preventive measures for chronic prostatitis or chronic pelvic pain syndrome are lacking, and risk factors for prostatitis or chronic pelvic pain have not been investigated.

Clinical Findings

A. Symptoms and Signs

Symptoms include dysuria, frequency, urgency, other irritative voiding symptoms, and pain in the perineal area for more than 3 of the last 6 months.

B. Laboratory Findings

Laboratory testing shows no evidence of current cystitis or demonstrable bacterial infection. Patients with inflammatory-type chronic pelvic pain syndrome have leukocytes in expressed prostatic secretions or post-prostatic massage urine.

C. Special Tests

If the patient has hematuria, urine cytology should be performed. The two-glass test (first part of a clean-catch urine sample in one bottle; prostatic massage milking from periphery to center; second urine sample into a sterile container) has been shown to be as reliable as the more complicated four-glass test (discussed earlier) at distinguishing chronic bacterial prostatitis and inflammatory and noninflammatory prostatitis.

Differential Diagnosis

See Table 22-4.

Treatment

There is no clear-cut prescription for the treatment of chronic prostatitis of either the inflammatory or noninflammatory type. This treatment discussion therefore groups inflammatory and noninflammatory prostatitis into one entity for discussion.

Although CP/CPPS does not have a bacterial etiology, antimicrobials do improve symptoms in up to 50% of patients. Patients with a shorter duration of symptoms are more likely to respond. The antimicrobials utilized most include fluoroquinolones and trimethoprim/sulfamethoxazole for 4-6 weeks. α-Blockers such as tamsulosin, terazosin, and doxazosin have shown some improvement in patients as well. Once again, the sooner treatment is started, the better the outcomes. At least 6 weeks of therapy are needed with α-blockers. A combination of antimicrobial and alpha-blocker shows slight improvement over monotherapy. Despite high use by providers, nonsteroidal anti-inflammatory drugs (NSAIDs) have only shown minimal effects. Unless the patient has concomitant benign prostatic hyperplasia (BPH), 5α-reductase inhibitors (eg finasteride) have only had minimal effects.

There are several other modalities of treatment that need further review. These include transurethral microwave thermotherapy (TUMT), cooled transurethral microwave thermotherapy (cTUMT), transurethral needle ablation (TUNA), Botulinum toxin A injections, and transurethral resection of the prostate (TURP), electromagnetic therapy,
electroacupuncture and application of capsaicin on the perineal area. Although none of these have been studied extensively, cTUMT and electromagnetic therapy show promising results.

Table 22-5 reviews controlled trials that have shown possible efficacy of treatments.

**Prognosis**

The prognosis for chronic prostatitis and chronic pelvic pain syndrome category III is not good. Prognosis appears to be worse for patients with previous episodes or more severe pain.


**PYELONEPHRITIS**

**ESSENTIALS OF DIAGNOSIS**

- Fever.
- Chills.
- Flank pain.
- More than 100,000 CFU on urine culture.

<table>
<thead>
<tr>
<th>Table 22-5. Effective therapies for chronic abacterial prostatitis/chronic pelvic pain syndrome.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
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<tr>
<td></td>
</tr>
<tr>
<td>α-Blockers</td>
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<tr>
<td>Finasteride</td>
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<tr>
<td>Pentosan polysulfate</td>
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<tr>
<td>Thermotherapy</td>
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</tbody>
</table>


**General Considerations**

Pyelonephritis is an infection of the kidney parenchyma. It has been estimated to result in more than 100,000 hospitalizations per year. Information on outpatient visits is not readily available, but because many cases are now managed on an outpatient basis, it is likely to be seen by most primary care providers. Pyelonephritis usually results from upward spread of cystitis but can also result from hematogenous seeding of the kidney from another infectious source. The infection can be complicated by stones or renal scarring if untreated but usually resolves without sequelae in young healthy people if treated promptly.

The most common bacteria involved are the same organisms that cause uncomplicated cystitis: *E coli*, *S saprophyticus*, *Klebsiella* species, and occasionally *Enterobacter*. As with simple cystitis, women with genetic predispositions are more commonly affected than other women.

**Prevention**

There are no recent studies on prevention of pyelonephritis. Prompt treatment of cystitis may prevent some cases of pyelonephritis, but this has not been demonstrated.

**Clinical Findings**

Symptoms and signs include fever, chills, malaise, dysuria, and flank pain. Nausea and vomiting may also occur.

Laboratory findings include a urine dipstick analysis that is positive for leukocyte esterase or nitrites and urine culture showing more than 100,000 CFU.

Imaging studies generally are not required unless the patient is diabetic or there is suspicion that stones are complicating the infection, in which case a CT scan is the test of choice.

**Differential Diagnosis**

See Table 22-6.

**Complications**

Diabetic patients can experience emphysematous pyelonephritis. It is a severe necrotizing renal infection characterized by gas production within the renal parenchyma. This is diagnosed by CT scan or other imaging study showing gas in the renal collecting system or around the kidney. In a diabetic patient with emphysematous pyelonephritis, the definitive treatment is percutaneous drainage. If there is extensive diffuse gas, nephrectomy is advised, as the mortality rate in diabetics approaches 75%. This condition may rarely occur in nondiabetic patients and is often related to obstruction. In some of these cases relief of the obstruction and antibiotics may suffice.

Stones can complicate pyelonephritis by causing a partial or complete obstruction. These stones can be spontaneous or “infection” stones of struvite, caused by urea-splitting organisms. Stones complicating pyelonephritis must be removed before the infection will completely resolve.

**Prognosis**

Prognosis after an acute episode of uncomplicated pyelonephritis in a previously healthy adult is excellent.

People with a history of childhood pyelonephritis can have renal scarring and recurrent infections. These scars are unusual in healthy adults with pyelonephritis. Young men with pyelonephritis should be investigated for a cause.

Patients who do not respond to 48 hours of appropriate antibiotics should be worked up for occult complicating factors or other diagnoses.

**Treatment**

The best drugs for treatment of pyelonephritis are bactericidal, with a broad spectrum to cover gram-positive and gram-negative bacteria, and concentrate well in urine and renal tissues. Aminoglycosides; aminopenicillins such as amoxicillin with clavulanic acid, ticarcillin, or pipericillin; cephalosporins; fluoroquinolones; or, in extreme cases, imipenem, are all appropriate. First-line outpatient treatment is usually a fluoroquinolone. Cure rates have been reported to approach 90% with a 10- to 14-day course of antibiotics.

Patients experiencing severe nausea and vomiting who are unable to tolerate oral agents may need to be hospitalized for parenteral therapy. Patients with severe illness, suspected bacteremia, or sepsis should also be admitted.

**Table 22-6. Differential diagnosis of pyelonephritis.**

<table>
<thead>
<tr>
<th>If Patient Has</th>
<th>Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative urine dipstick or culture</td>
<td>Pelvic inflammatory disease; stone obstructing ureter; lower-lobe pneumonia; herpes zoster</td>
</tr>
<tr>
<td>Guarding/rebound</td>
<td>Acute cholecystitis; acute appendicitis; perforated viscus</td>
</tr>
<tr>
<td>Recurrent infection</td>
<td>Kidney stone, spontaneous or infection related; anatomic abnormality; resistant organism; inadequate treatment</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Emphysematous pyelonephritis</td>
</tr>
<tr>
<td>History of childhood infections, urologic surgery</td>
<td>Abnormal anatomy</td>
</tr>
<tr>
<td>History of kidney stones</td>
<td>Pyelonephritis complicated by stones</td>
</tr>
</tbody>
</table>


Arthritis is a complaint and a disease afflicting many patients and accounting for upwards of 10% of appointments to a generalist practice. Arthritis is multifaceted and can be categorized in several different fashions. For simplicity, this chapter focuses on conditions affecting the anatomic joint composed of cartilage, synovium, and bone. Other discussions would include localized disorders of the periarticular region (eg, tendonitis and bursitis) and systemic disorders that have arthritic manifestations (eg, vasculitides, polymyalgia rheumatica, and fibromyalgia). The chapter discusses three prototypical types of arthritis: osteoarthritis, as an example of a cartilage disorder; gout, as an example of both a crystal-induced arthritis and an acute arthritis; and rheumatoid arthritis, as an example of an immune-mediated, systemic disease and a chronic deforming arthritis.

OSTEOARTHRITIS

ESSENTIALS OF DIAGNOSIS

- Degenerative changes in the knee, hip, thumb, ankle, foot, or spine.
- Pain with movement that improves with rest.
- Synovitis.
- Sclerosis, thickening, spurs formation, warmth, and effusion in the joints.

General Considerations

Arthritis is among the oldest identified conditions in humans. Anthropologists examining skeletal remains from antiquity deduce levels of physical activity and work by searching for the presence of osteoarthritis (OA). Similarly, OA is more prevalent among people in occupations characterized by steady, physically demanding activity such as farming, construction, and production-line work. Obesity is a significant risk factor for OA, especially of the knee. Heredity and gender play a role in a person’s likelihood of developing OA, regardless of work or recreational activity.

Pathogenesis

It is increasingly accepted that most “garden variety” OA results, at least in part, from altered mechanics within the joint. (Certain metabolic conditions such as hemochromatosis and Gaucher disease involve a genetic defect in collagen/cartilage.) Altered mechanics may occur from minor gait abnormalities or major trauma which, over a lifetime, result in repeated stress and trauma to cartilage. Repeated trauma may result in microfracture of cartilage, with incomplete healing due to continuation of the altered mechanics. Disruption of the otherwise smooth cartilage surface allows differential pressure on remaining cartilage, as well as stress on the underlying bone. Debris from fractured cartilage acts as a foreign body, causing low-level inflammation within the synovial fluid. These multiple influences combine to prevent intrinsic efforts at cartilage repair, leading to progressive cartilage destruction and bony joint change. Current thinking suggests the process is not immutable but any intervention would have to be made while the joint is still asymptomatic—an unlikely occurrence.

Prevention

It is difficult to advise patients on measures to prevent osteoarthritis. Obese persons should lose weight, but few occupational or recreational precautions can be expected to alter the natural history of OA. Altered mechanics may be an important precipitating cause of arthritis but recognizing minor changes, especially within the currently accepted range of normal, makes diagnosis and preventive steps unrealistic.

Clinical Findings

A. Symptoms and Signs

Symptomatic OA represents the culmination of damage to cartilage, usually over many years. OA usually progresses from symptomatic pain to physical findings to loss of function but actually any of these can be first to present. OA can occur at any joint, but the most commonly involved joints are the knee, hip, thumb (carpometacarpal), ankle, foot, and spine. The strongly inherited spur formation at the distal interphalangeal joint (Heberden nodes) and proximal interphalangeal joint (Bouchard nodes) is often classified as OA, yet, although deforming, only infrequently causes pain or disability (Figure 23-1).

Cartilage has no pain fibers, so the pain of OA arises from secondary effects. Osteoarthritic pain is typically associated with movement, meaning that at rest the patient may be relatively asymptomatic. Patient’s awareness that at rest the joint is less painful can be maladaptive. A protective role played by surrounding muscle of both a normal and arthritic joint is that as a “shock-absorber.” Well-maintained muscle can actually reduce mechanical stress on cartilage and bone. But, if patients learn to “favor” the involved joint, disuse of supporting muscle groups may result in relative muscle weakness. Such weakness may result in decrease of the shock-absorber effect, hastening joint damage when stress (eg, walking) resumes. This mechanism also may lead to the complaint that a joint “gives way,” resulting in dropped items (if at the wrist) or falls (if at the knee). In joints with mild OA, pain and instability may counterintuitively improve with exercise or activity.

Advanced OA is characterized by bony destruction and alteration of joint architecture. Secondary spur formation with deformity, instability, or restricted motion is a common finding. Fingers, wrist, knees, and ankles appear abnormal and asymmetric. Warmth and effusion is seen in joints with advanced OA. At this stage, pain may be exacerbated by any movement, weight bearing, or otherwise.

B. Laboratory Findings

There are few laboratory studies of relevance to the diagnosis of OA. Rarely, the erythrocyte sedimentation rate (ESR) will be raised, but only if an inflammatory effusion is present (and even then an elevated ESR or C-reactive protein is more likely to be misleading than helpful). If an effusion is present, arthrocentesis can be helpful in ruling out other conditions (see laboratory findings in gout, later).

OA can be secondary to other conditions, and these diseases have their own laboratory evaluation. Examples include OA secondary to hemochromatosis (elevated iron and ferritin, liver enzyme abnormalities), Wilson disease (elevated copper), acromegaly (elevated growth hormone), and Paget disease (elevated alkaline phosphatase).

C. Imaging Studies

Radiographs are usually not needed for the early diagnosis of OA. Indeed, radiographs may be misleading. Plain films of joints afflicted with OA show changes of sclerosis, thickening, spur formation, loss of cartilage with narrowing of the joint space, and malalignment (Figure 23-2). Such radiographic changes typically occur late in the disease process yet do not always correlate with symptoms. Patients may complain of significant pain despite a relatively normal appearance of the joint and, conversely, considerable radiographic damage to a joint may exist with only modest symptoms. In addition, plain film radiography does not provide good information about cartilage, tendons, ligaments, or any soft tissue. Such findings may be crucial to explaining a patient complaint, especially if there is loss of function.

To see cartilage, ligaments, and tendon, magnetic resonance imaging (MRI) is important and, in many instances,
essential. MRI can detect abnormalities of the meniscus or ligaments of the knee, cartilage or femoral head deterioration at the hip, misalignment at the elbow, rupture of muscle and fascia at the shoulder, and a host of other abnormalities. Any of these findings may be incorrectly diagnosed as “OA” before MRI scanning.

Computed tomography (CT) and ultrasonography have lesser, more specialized uses. CT, especially with contrast, can detect structural abnormalities of large joints such as the knee or shoulder. Ultrasonography is an inexpensive means of detecting joint or periarticular fluid, or unusual collections of fluid such as a popliteal (Baker) cyst at the knee.

### Differential Diagnosis

In practice, it should not be difficult to differentiate among the three prototypical arthritides discussed in this chapter. Nonetheless, Table 23-1 suggests some key differential findings.

A common source of confusion and misdiagnosis occurs when a bursitis-tendinitis syndrome mimics the pain of OA. A common example is anserine bursitis. This bursitis, located medially at the tibial plateau, presents in a fashion similar to OA of the knee, but can be differentiated by a few simple questions and directed physical findings.

### Treatment

Typically, the early development of OA is silent. When pain occurs, and pain is almost always the presenting complaint, the osteoarthritic process has already likely progressed to joint destruction. Cartilage is damaged, bone reaction occurs, and debris mixes with synovial fluid. Consequently, when a diagnosis of OA is established, goals of therapy become control of pain, restoration of function, and reduction of disease progression. Although control of the patient’s complaints is possible, and long periods of few or no symptoms may ensue, the patient permanently carries a diagnosis of OA.

Treatment of OA involves multiple modalities and is inadequate if only a prescription for anti-inflammatory drugs is written. Patient education, assessment for physical therapy and devices, and consideration of intra-articular injections are additional measures in the total management of the patient.

**A. Patient Education**

Patient education is a crucial step. The patient must be made aware of the role he or she plays in successful therapy. Many resources are available to assist the provider in patient education. Patient education pamphlets are widely available from government organizations, physician organizations (eg, American College of Rheumatology, American Academy of Family Physicians), insurance companies, pharmaceutical companies, or patient advocacy groups (eg, the Arthritis Foundation). Many communities have self-help or support groups that are rich sources of information, advice, and encouragement.

One of the most effective long-term measures to both improve symptoms and slow progression of disease is weight loss. Less weight carried by the hip, knee, ankle, or foot reduces stress on the involved arthritic joint, decreases the destructive processes, and probably slows progression of disease. Unfortunately, OA makes weight loss more difficult as pain in the joints limits exercise.

### Table 23-1. Essentials of diagnosis.

<table>
<thead>
<tr>
<th></th>
<th>Osteoarthritis</th>
<th>Gout</th>
<th>Rheumatoid Arthritis</th>
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</table>

MCP, metacarpophalangeal; MTP, metatarsophalangeal; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
On the other hand, exercise is a crucial modality that should not be overlooked. Evaluation for appropriate exercise focuses on two issues: overall fitness and correction of any joint-specific disuse atrophy. One must be flexible in the choice of exercise. Swimming is an excellent exercise that limits stress on the lower extremities. Many older persons are reluctant to learn to swim anew, yet they may be amenable to water aerobic exercises. These exercises encourage calorie expenditure, flexibility, and both upper and lower muscle strengthening in a supportive atmosphere. Stationary bicycle exercise is also accessible to most people, is easy to learn, and may be acceptable to those with arthritis of the hip, ankle, or foot. Advice from an occupational or recreational therapist can be most helpful.

**B. Physical Therapy and Assistive Devices**

The pain of OA can result in muscular disuse. The best example is quadriceps weakness resulting from OA of the knee. The patient who “favors” the involved joint loses quadriceps strength. This has two repercussions: both cushioning (shock-absorption) and stabilization are lost. The latter is usually the cause of the knee “giving way.” Sudden buckling at the knee, often when descending stairs, is not due to destruction of cartilage or bone but rather to inadequate strength in the quadriceps to handle the load required at the joint. Physical therapy with quadriceps strengthening is highly efficacious, resulting in improved mobility, increased patient confidence, and reduction in pain.

The physical therapist or physiatrist should also be consulted for advice regarding assistive devices. Advanced OA of lower extremity joints may cause instability and fear of falls that can be addressed by canes of various types. Altered posture or joint malalignment can be corrected by orthotics, which has the advantage, when used early, of slowing progression of OA. Braces can protect the truly unstable joint and permit continued ambulation.

**C. Pharmacotherapy**

The patient wants relief of pain. Despite the widespread promotion of nonsteroidal anti-inflammatory drugs (NSAIDs) for OA, there is no evidence that NSAIDs alter the course of the disease. That being the case, NSAIDs are used for their analgesic, rather than anti-inflammatory, effects. Although effective as analgesics, NSAIDs have significant side effects and are not necessarily first-line drugs.

Begin with adequate doses of acetaminophen. Acetaminophen should be prescribed in large doses, 3-4 g/d, and continued at this level until pain control is attained. Once pain is controlled, dosage can be reduced if possible. Maintenance of adequate blood levels is essential and because acetaminophen has a relatively short half-life, frequent dosing is necessary (three or four times a day). High doses of acetaminophen are generally well tolerated, although caution is important in patients with liver disease or in whom alcohol ingestion is heavy.

NSAIDs mixed as a cream or gel and rubbed onto joints have long been advocated for small and even large joint arthritis. There, undoubtedly is less GI upset when delivered in this manner but well-designed studies demonstrating prolonged effectiveness are lacking. There are two FDA-approved products on the US market (diclofenac, ketoprofen), although some compounding pharmacies apparently have more NSAIDs available.

NSAIDs come in two main classes largely based on half-life. NSAIDs with shorter half-lives (eg, diclofenac, etodolac, ibuprofen, and indomethacin) need more frequent dosing than longer acting agents. Several NSAIDs are available in generic or over-the-counter form, which reduces cost. Despite differing pharmacology, there is little difference in efficacy, so choice of medication should be based on individual patient issues such as dosing intervals, tolerance, toxicity, and cost. As with acetaminophen, adequate doses must be used for maximal effectiveness. For example, ibuprofen at doses up to 800 mg three or four times a day should be maintained (if tolerated) before concluding that a different agent is necessary. Examples of NSAID dosing are given in Table 23-2.

Since such a major thrust of OA management is pain control, one must recognize the role played by narcotics. Narcotics should be confined to the patient with severe disease incompletely controlled by non-pharmacologic and non-narcotic analgesics, and in whom joint replacement is not indicated. The narcotic medication should be additive to all other measures; for instance, full-dose acetaminophen or NSAIDs should be continued. The patient must be reminded of the fluctuating nature of OA symptoms and not expect complete elimination of pain. Once narcotics are started (in any patient for any cause), most generalist practices institute monitoring measures such as a “drug contract” or referral to a specialist pain management clinic.

**D. Intra-Articular Injections**

Hyaluronic acid (hyaluronan) is a constituent of both cartilage and synovial fluid. Injection of hyaluronic acid, usually in a series of several weekly intra-articular insertions, is purported to provide improvement in symptomatic OA for up to 6 months. It is unknown why hyaluronic acid helps; there is no evidence hyaluronic acid is incorporated into cartilage, and it apparently does not slow the progression of OA. It is expensive and the injection process is painful. Use of these agents (Synvisc, Artzal) is limited to patients who have failed other forms of OA therapy.
Intra-articular injection of corticosteroids has been both under- and overutilized in the past. There is little question that steroid injection rapidly reduces inflammation and eases symptoms. The best use is one in which the patient has an exacerbation of pain accompanied by signs of inflammation (warmth, effusion). The knee is most commonly implicated and is most easily approached. Most authorities recommend no more than two injections during one episode and limiting injections to no more than two or three episodes per year. Benefits of injection are often shorter in duration than similar injection for tendinitis or bursitis, but the symptomatic improvement buys time to reestablish therapy with oral agents.


E. Surgery

Until recently, orthopedic surgeons have performed arthroscopic surgery on osteoarthritic knees in an effort to remove accumulated debris and to polish or debride frayed cartilage. However, a clinical trial using a sham-procedure methodology demonstrated that benefit from this practice could be explained by the placebo effect. It remains to be seen if the numbers of these procedures will decline.

Joint replacement is a rapidly expanding option for treatment of OA, especially of the knee and hip. Pain is reduced or eliminated altogether. Mobility is improved, although infrequently to premorbid levels. Expenditures for total joint replacement are likely to increase dramatically as the baby-boomer generation reaches the age at which OA of large joints is more common. Indications for joint replacement (which also applies to other joints, including shoulder, elbow, and fingers) include pain poorly controlled with maximal therapy, malalignment, and decreased mobility. Improvement in pain relief and quality of life should be realized in about 90% of patients undergoing the procedure. Because complications of both the surgery and rehabilitation are increased by obesity, many orthopedic surgeons will not consider hip or knee replacement without at least an attempt by the patient to lose weight. Patients need to be in adequate medical condition to undergo the operation and even more so to endure the often lengthy rehabilitation process. Some surgeons refer patients for “prehabilitation” or physical training prior to the operation. Counseling of patients should include the fact that there often is a 4- to 6-month recovery period involving intensive rehabilitation.


F. Complementary and Alternative Therapies

Glucosamine, capsaicin, bee venom, and acupuncture have been promoted as alternative therapies for OA. Glucosamine and chondroitin sulfate are components of glycosaminoglycans, which make up cartilage, although there is no evidence that orally ingested glucosamine or chondroitin sulfate are actually incorporated into cartilage. Studies suggest these agents are superior to placebo in symptomatic relief of mild OA. The onset of action is delayed, sometimes by weeks, but the effect may be prolonged after treatment is stopped. Glucosamine-chondroitin sulfate combinations are available over the counter and are generally well tolerated by patients.
Capsaicin, a topically applied extract of the chili pepper relieves pain by depletion of substance P, a neuropeptide involved in pain sensation. Capsaicin is suggested for tendinitis or bursitis, but may be tried for OA of superficial joints such as the fingers. The cream should be applied three or four times a day for 2 weeks or more before making any conclusion regarding benefit.

Bee venom is promoted in complementary medicine circles. A mechanism for action in OA is unclear. Although anecdotal reports are available, comparison studies to other established treatments are difficult to find. Various vitamins (D, K) and minerals have been recommended, supported, if at all, by poorly controlled studies.

Acupuncture can be useful in managing pain and improving function. There are more comparisons between acupuncture and conventional treatment for OA of the back and knee than for other joints. Generally, acupuncture is equivalent to oral treatments for mild symptoms at these two sites.


Prognosis

Restoring and rebuilding damaged cartilage is theoretically intriguing but not possible at this point. Investigations into regeneration of cartilage, perhaps through pharmaceuticals in conjunction with aggressive orthotic assistive devices, are proceeding. Even so, reversal of the pathophysiologic process in OA is unlikely to be readily available anytime soon. With application of all modalities of treatment—adequate pain control, weight loss, appropriate exercise, orthotics and devices, and surgery—the successful management of osteoarthritis should be realized in most patients.

GOUT

ESSENTIALS OF DIAGNOSIS

- Podagra (intense inflammation of the first metatarsophalangeal joint).
- Inflammation of the overlying skin.
- Pain at rest and intense pain with movement.
- Swelling, warmth, redness, and effusion.
- Tophi.
- Elevated serum uric acid level.

General Considerations

Gout, first described by Hippocrates in the fourth century BCE, has a colorful history, characterized as a disease of excesses, primarily gluttony. An association with diet is germane, as gout has a lower incidence in countries in which obesity is uncommon and the diet is relatively devoid of alcohol and reliance on meat and abdominal organs (liver, spleen). Gout is strongly hereditary as well, affecting as many as 25% of the men in some families.

Prevention

Despite the previously noted associations, it is difficult with any assurance to advise patients on measures to prevent gout. Even thin vegetarians develop gout, although at a markedly lower rate than obese, alcohol-drinking men. Gout has multiple etiologies and no consistent preventive steps are available to patients.

Clinical Findings

A. Symptoms and Signs

Gout classically presents as an acute monoarthritis, perhaps best described by Thomas Sydenham in the 17th century. Podagra—abrupt, intense inflammation of the first metatarsophalangeal joint—remains the most common presentation (Figure 23-3). The first attack often occurs overnight, with intense pain awakening the patient. Any pressure, even a bed sheet on the toe, increases the agony. Walking is difficult. The overlying skin can be intensely inflamed. On questioning, an exacerbating event may be elicited. Common stories include an excess of alcohol, a heavy meal of abdominal organs, or a recent physiologic stress such as surgery or serious medical disease. Alcohol alters renal excretion of uric acid, allowing rapid buildup of serum uric acid levels. Foods such as liver, anchovies, sardines, asparagus, salmon, and legumes contain relatively large quantities of purines that, when broken down, become uric acid.

Acute gout is not limited to the great toe; any joint may be affected, although lower extremity joints are more common.

Figure 23-3. Classic podagra involving the first metatarsophalangeal joint. In this photo, the ankle is also involved and the intense erythema could be mistaken for cellulitis.
The abruptness of many gouty attacks and the single joint presentation (acute monoarthritis) at any joint other than the great toe may lead to diagnostic confusion (Table 23-3). Gout in joints other than the great toe is often misdiagnosed. Atypical gout is not uncommon in older women and in men who have already experienced multiple previous episodes of podagra. Foot pain simulating plantar fasciitis is seen in older women. Gout of the ankle (with a positive Homan sign) can be mistaken for phlebitis.

The intense inflammation at some joints, especially smaller joints such as the ankle, can be impressive. The inflammation may appear to be spreading, encompassing an area greater than that thought to be the joint. Such cases can be mistaken for cellulitis (see Figure 23-3) or superficial phlebitis. The subsequent lack of response to outpatient treatment of cellulitis can cascade to hospital admission and treatment with increasingly strong and expensive antibiotics.

Untreated, attacks of gout spontaneously resolve with the involved joint becoming progressively less symptomatic over 8-10 days. Long-standing gout is distinguished by the development of extra-articular manifestations. Tophi are deposits of urate crystals and are found in the ear helix or as nodules elsewhere; atypically placed tophi (eg, Heberden nodes, heart valves) serve as the source of colorful medical anecdotes. Chronic, untreated gout is a contributor to renal insufficiency (especially in association with heavy metal lead exposure).

Physiologic stress is a common precipitating factor for an acute attack. Monoarthritis within days of a surgical procedure raises concern of infection (which it should!) but is just as likely due to crystal-induced gout or pseudogout. In some circumstances, prophylaxis in a person with known gout can prevent these attacks.

About 10% of kidney stones include uric acid. A person with nephrolithiasis due to uric acid stones need not have attacks of gout, but patients with gout are at increased risk of developing uric acid stones. A prior history of nephrolithiasis is an important factor in choosing therapy in the patient with gout.

Gout is largely a disease of men, with a male-to-female ratio of 9:1. The first attack of podagra typically occurs in men in their thirties or forties. One attack need not necessarily predict future attacks. In fact, in up to 20% of men who have one attack of gout a second attack never follows. Even after a second attack, a sizable percentage (as many as 5%) do not progress to chronic, recurrent gout.

Premenopausal women rarely have gout; indeed, confirmed gout in a young woman might raise the question of an inborn error of metabolism. Diagnosis of gout in postmenopausal women is infrequent, less because it does not occur than because it is uncommonly suspected. Gout is also more likely to have an atypical presentation in joints other than the great toe in women. A high index of suspicion must be practiced.

### B. Laboratory Findings

The fundamental abnormality in gout is excess uric acid. In most first attacks of gout, serum uric acid is elevated. In long-standing disease, the uric acid value may be normal yet symptoms still occur. It is important to note, however, that mild hyperuricemia has a rather high prevalence in the general population. Indeed, fewer than 25% of persons with elevated uric acid will ever have gout.

During acute attacks of gout, the white blood cell count may be slightly elevated and ESR increased, reflecting acute inflammation. Gout is not uncommon in chronic kidney disease and measurement of blood urea nitrogen and creatinine is recommended following a first gout attack.

Gout usually results from either inappropriately low renal excretion of uric acid (implicated in 90% of patients) or abnormally high endogenous production of uric acid. Collecting a 24-hour urine sample for evaluation of uric acid and creatinine clearance can be useful in therapy (below).

A strong recommendation must be made to attempt arthrocentesis of the joint in suspected acute gout. First episodes of gout present as an acute monoarthritis, for which the differential diagnosis is noted in Table 23-3. Infectious arthritis is a medical emergency—the correct diagnosis must be made rapidly and appropriate antibiotic therapy begun to avoid destructive changes. Pseudogout is rarely distinguished from gout on the basis of symptoms alone. The settings of both pseudogout and gout can be similar (eg, immediately after

### Table 23-3. Inflammatory and noninflammatory causes of monoarthritis.

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Noninflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal-induced</td>
<td>Fracture or meniscal tear</td>
</tr>
<tr>
<td>Gout</td>
<td>Other trauma</td>
</tr>
<tr>
<td>Pseudogout (calcium pyrophosphate deposition disease)</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Apatite (and others)</td>
<td>Tumors</td>
</tr>
<tr>
<td>Infectious</td>
<td>Osteochondroma</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Osteoid osteema</td>
</tr>
<tr>
<td>Fungi</td>
<td>Pigmented villonodular synovitis</td>
</tr>
<tr>
<td>Lyme disease or other spirochetes</td>
<td>Cancerous</td>
</tr>
<tr>
<td>Tuberculosis and other mycobacteria</td>
<td>Osteonecrosis</td>
</tr>
<tr>
<td>Viruses (eg, HIV, hepatitis B)</td>
<td>Hemarthrosis</td>
</tr>
<tr>
<td>Systemic diseases</td>
<td>Cancers</td>
</tr>
<tr>
<td>Psoriatic or other spondyloarthopathies</td>
<td></td>
</tr>
<tr>
<td>Reactive (eg, inflammatory bowel,</td>
<td></td>
</tr>
<tr>
<td>Reiter syndrome)</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
</tr>
</tbody>
</table>

surgery). Clinical features of many of the monoarthritides are not characteristic enough to ensure a correct diagnosis. However, finding negatively birefringent needle-shaped crystals in synovial fluid is diagnostic of gout. Features of synovial fluid in selected disease settings are highlighted in Table 23-4.

**C. Imaging Studies**

Radiographs are not needed for the diagnosis of gout. Other means of diagnosing gout (eg, arthrocentesis) are more useful. Characteristic erosions occur with long-standing gout but are rarely seen in first attacks.

**Differential Diagnosis**

The first attack of gout must be distinguished from an acute monoarthritis. A review of Tables 23-1 and 23-3 is relevant.

**Treatment**

The inflammation of acute gout is effectively managed with anti-inflammatory medications. Once recognized, most cases of gout can be controlled within days, occasionally within hours. Remaining as a challenge is the decision regarding long-term treatment.

Standard therapy for acute gout is a short course of NSAIDs at adequate levels. As one of the first NSAIDs developed, indomethacin (50 mg three or four times a day) is occasionally thought to be somehow unique in the treatment of gout. In fact, all NSAIDs are probably equally effective, although many practitioners feel response is faster with short-acting agents such as naproxen (375-500 mg three times a day) or ibuprofen (800 mg three or four times a day). Pain often decreases on the first day, with treatment indicated for not much more than 3-5 days.

A classic medication for acute gout is colchicine. Typically given orally, the instructions to the patient can sound bizarre. The drug is prescribed as a 0.6-mg tablet every 1-2 hours “until relief of pain or uncontrollable diarrhea.” Most attacks actually respond to the first two or three pills, with a maximum of six pills in 24 hours, a prudent upper limit. Most patients develop diarrhea well before the sixth pill. Colchicine is dosed three times daily and, as with NSAIDs, is not often needed after 3-5 days.

On occasion, corticosteroids are used in acute gout. Oral prednisone (eg, up to 60 mg), methylprednisolone or triamcinolone (eg, 40-80 mg) intramuscularly, or intra-articular agents can be used. Indications include intense overlying skin involvement (mimicking cellulitis), polyarticular presentation of gout, and contraindication to NSAID or colchicine therapy. Intra-articular steroid use may be considered for ankle or knee gout, if infection is ruled out.

Decisions regarding long-term treatment of gout must take into account the natural history of attacks. The first attack, especially in young men with a clear precipitating event (such as an alcohol binge), may not be followed by a second attack for years, even decades. As stated earlier, as many as 20% of men will never have a second gouty attack. Data from the Framingham longitudinal study suggest that intervals up to 12 years are common between first and second attacks. This is not always the case for young women with gout (who tend to have a uric acid metabolic abnormality) or for either men or women who have polyarticular gout. But for many young men, a reasonable recommendation after a first episode is to watch expectantly but not necessarily to treat with uric acid–lowering drugs.

The physician and patient may even decide to withhold prophylactic medication after a second attack, but when episodes of gout become more frequent than one or two a year, both parties are usually ready to consider long-term medication. The primary medications used at this point are probenecid and the xanthine oxidase inhibitor allopurinol. Probenecid is a uric acid tubular reuptake inhibitor, which

<table>
<thead>
<tr>
<th>Fluid</th>
<th>WBC Count (in fluid)</th>
<th>Differential</th>
<th>Glucose</th>
<th>Crystals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gout</td>
<td>Clear/cloudy</td>
<td>10-100,000</td>
<td>&gt;50% PMNs</td>
<td>Normal</td>
</tr>
<tr>
<td>Pseudogout</td>
<td>Clear/cloudy</td>
<td>10-100,000</td>
<td>&gt;50% PMNs</td>
<td>Normal</td>
</tr>
<tr>
<td>Infectious</td>
<td>Cloudy</td>
<td>&gt;50,000</td>
<td>Often &gt;95% PMNs</td>
<td>Decreased</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>Clear</td>
<td>2-10,000</td>
<td>&lt;50% PMNs</td>
<td>Normal</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Clear</td>
<td>10-50,000</td>
<td>&gt;50% PMNs</td>
<td>Normal or decreased</td>
</tr>
</tbody>
</table>

WBC, white blood cells; PMNs, polymorphonuclear leukocytes.

*Debris in synovial fluid may be misleading on plain microscopy but only crystals respond to polarizing light.
results in increased excretion of uric acid in the urine. Allopurinol inhibits the uric acid synthesis pathway, blocking the step at which xanthine is converted to uric acid. Xanthine is much more soluble than uric acid and is not implicated in acute arthritis, nephrolithiasis, or renal insufficiency. Assessing 24-hour uric acid excretion can be helpful at this time. The patient with low excretion of uric acid (<600 mg/d) and normal renal function should respond to probenecid. A typical dose is 500-1000 mg/d, with infrequent rash the only side effect. Probenecid loses effectiveness when the creatinine clearance falls below 50 mL/min, so alternative therapy is necessary in patients with chronic kidney disease. If the patient has uric acid nephrolithiasis, probenecid is contraindicated to avoid increased delivery of uric acid to the stone-forming region.

Some “underexcretors” and virtually all “overproducers” of uric acid will require a xanthine oxidase inhibitor. Typical dosing of allopurinol begins at 100 mg/d; doses up to 300 mg/d may be used to lower serum uric acid levels and prevent gouty attacks. It is recommended to aim for a serum uric acid level of 6 g/dL or less. Allopurinol is a well-tolerated drug with only infrequent side effects of nausea, diarrhea, or headache. The side effect of concern is rash. Although rare, allopurinol-induced rash can progress to a toxic hypersensitivity with fever, leukocytosis, epidermal necrolysis, and renal failure. Patients should be cautioned, but not alarmed, about this complication. A new xanthine oxidase inhibitor, febuxostat (Uloric), was approved in 2009 by the Food and Drug Administration (FDA). Studies submitted for FDA approval suggest fewer side effects and less toxic hypersensitivity; long-term realization of this improved safety profile await post-marketing analysis.

Xanthine oxidase inhibitors are especially indicated for treatment of tophaceous gout and for uric acid nephrolithiasis. These agents should be drugs of choice for those with uric acid metabolic abnormalities (often young women) and polyarticular gout. Caution must be used, however, when starting any uric acid–lowering drug for the first time. Rapid lowering of the serum uric acid causes instability of uric acid crystals within the synovial fluid and can actually precipitate an attack of gout. Consequently, prior establishment of either NSAID or colchicine therapy is recommended to obviate this complication.

Patients are occasionally seen who have been prescribed long-term therapy with colchicine. There is some conceptual attraction to this choice. Between attacks of gout (the so-called “intercritical period”), examination of synovial fluid continues to show uric acid crystals. Using colchicine to prevent the spiral to inflammation seems appealing. But this choice is deceptive. Colchicine does nothing to lower uric acid levels. Long-term use allows deposition of uric acid into destructive tophi or contributes to renal disease and kidney stones. Colchicine can be an effective prophylactic agent, however, if started prior to a surgical procedure in a patient with known gout who is not using allopurinol or probenecid. But use of this drug as a solo agent courts significant complications.

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**Prognosis**

Gouty attacks can be both effectively treated and prevented. A clear diagnosis is important and arthrocentesis essential. Management is relatively straightforward and no patient should have to endure tophi or repeated acute attacks.


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**RHEUMATOID ARTHRITIS**

### ESSENTIALS OF DIAGNOSIS

- Arthritis of three or more joint areas.
- Arthritis in hands, feet, or both (bilateral joint involvement).
- Morning stiffness.
- Fatigue.
- Swelling, tenderness, warmth, and loss of function.
- Rheumatoid nodules.
- Elevated ESR and C-reactive protein.
- Positive test for rheumatoid factor.

### General Considerations

Bony changes consistent with rheumatoid arthritis (RA) have been found in the body of a Native American who lived 3000 years ago. Differentiation of RA from other types of arthritis is more recent, delineated only in the late 19th century. RA is more frequently seen in women, with the ratio of premenopausal women to age-matched men approximately 4:1; after the age of menopause, the ratio of incident RA is closer to 1:1.

### Pathogenesis

Although the etiology of RA is not known, the pathophysiology has been elucidated to a remarkable degree in recent decades. Important knowledge of all inflammatory processes has come from studies in RA. Early in the disease process, the synovium of joints is targeted by T cells (this is the feature that leads to the “autoimmune” moniker applied to RA). Release of interleukins, lymphokines, cytokines, tissue necrosis factor, and other messengers attracts additional inflammatory cells to the synovium. Intense inflammation ensues, experienced by the patient as pain, warmth, swelling, and loss of function. Reactive cells move to the inflammatory...
synovium, attempting to repair damaged tissue. Without treatment, this intense reaction develops into the pathologic tissue called *pannus*, an exuberant growth of tissue engulfing the joint space and causing destruction itself. Cartilage becomes swept into the pathologic process, resulting in breakdown, deterioration, and eventual destruction. Periarticular bone responds to inflammation with resorption, seen as erosions on radiographs. All these changes clearly are maladaptive and responsible for deformity and disability.

**Prevention**

It is difficult with any assurance to advise patients on measures to prevent arthritis. RA has multiple etiologies and no consistent preventive steps are available to patients.

**Clinical Findings**

**A. Symptoms and Signs**

RA is a systemic disease, causing fatigue, rash, nodules, and even clinical depression as joints become progressively more stiff and inflamed. Most, but by no means all, of the initial symptoms are in the joints. There is inflammation, so the presence of swelling, warmth, and loss of function is imperative to the diagnosis. Joints of the hands (Figure 23-4) and feet are typically affected first, although larger joints can be involved at any time. The disease is classically symmetric with symptoms present bilaterally in hands or feet, or both. This mirroring is almost unique to RA; systemic lupus erythematosus, which is often confused with RA in its early stages, is not so consistently symmetric.

Fingers and wrists are stiff and sore in the mornings, requiring heat, rubbing, and movement to be functional (“morning stiffness”). Stiffness after prolonged lack of movement (“gelling”) is not uncommon in many joint disorders, but the morning stiffness of RA is so prolonged and characteristic that queries regarding this symptom are one of the essentials of diagnosis.

The patient reports fatigue out of proportion to lack of sleep. Daytime naps are almost unavoidable, yet are not fully restorative. Anorexia, weight loss, or even low-grade fever can be present. Along with musculoskeletal complaints, these somatic concerns may lead to mistaken diagnoses of fibromyalgia or even depression.

RA can eventually involve almost any joint in the body. Selected important manifestations of RA in specific joints are listed in Table 23-5. The cause of any one manifestation may be unique to a particular joint and the surrounding periarticular structure. Common features include inflammation-induced stretching of tendons and ligaments resulting in joint laxity, subconscious restriction of movement resulting in “frozen” joints, and consequences of inflammatory synovitis with cartilage destruction and periarticular bone erosion. An objective sign of destruction includes the high-pitched, “crunchy” sound of crepitus.

Extra-articular manifestations of RA can be seen at any stage of disease. Most common are rheumatoid nodules, found at some point in up to 50% of all patients with RA.

These occur almost anywhere in the body especially along pressure points (the typical olecranon site), along tendons, or in bursae. Vasculitis is an uncommon initial presentation of RA. Dry eyes and mouth are seen in the RA-associated sicca syndrome. Dyspnea, cough, or even chest pain may signal respiratory interstitial disease. Cardiac, gastrointestinal, and renal involvement in RA is not common. Peripheral nervous system symptoms are seen as compression neuropathies (eg, carpal or tarsal tunnel syndrome) and reflect not so much direct attack on nerves as consequences of squeezing compression as nerves are forced into passages narrowed by nearby inflammation.
B. Laboratory Findings

In contrast to OA, the laboratory findings in RA can be significant and helpful. A normocytic anemia is common in active RA. This anemia is almost always the so-called anemia of chronic disease. The white blood cell count is normal or even slightly elevated; an exception is the rare Felty syndrome (leukopenia and splenomegaly in a patient with known RA).

RA does not typically affect electrolytes and renal function. There is no pathophysiologic reason why transaminases, bilirubin, alkaline phosphatase, or other liver, pancreatic, or bone enzymes should be altered. Similarly, calcium, magnesium, and phosphate values should be unchanged. Most hormone measurements are normal, particularly thyroid and the adrenal axis. Any chronic inflammatory disease may alter the menstrual cycle, but measurement of luteinizing hormone and follicle-stimulating hormone is of little help.

An elevated ESR is almost ubiquitous in RA. C-reactive protein (CRP) is considered by many rheumatologists to be a more sensitive indicator of inflammation and might be increased in settings in which the ESR is either “normal” or minimally elevated. Although ESR is quite reliable, in some circumstances a false value may be reported (Table 23-6). For this reason, evaluation of C-reactive protein, although more expensive, is increasingly used by specialists.

The test most associated with RA is the rheumatoid factor (RF) blood test. RF is actually a family of antibodies, the most common of which is an immunoglobulin M (IgM) antibody directed against the Fc portion of immunoglobulin G (IgG). There is no question this antibody is frequently present in RA, with RF-negative RA accounting for only about 5% of all patients with RA. The problem lies with the low specificity of the test. Surveys demonstrate that in a young population, 3%-5% of “normal” individuals have a high RF titer (positive test) whereas in an older cohort the

### Table 23-5. Manifestations of rheumatoid arthritis in specific joints.

<table>
<thead>
<tr>
<th>Joint</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand</td>
<td>Ulnar deviation (hand points toward ulnar side)</td>
</tr>
<tr>
<td></td>
<td>Swan-neck deformity (extension of PIP joint)</td>
</tr>
<tr>
<td></td>
<td>Boutonniere deformity (flexion at DIP)</td>
</tr>
<tr>
<td>Wrist</td>
<td>Swelling causing carpal tunnel syndrome</td>
</tr>
<tr>
<td>Elbow</td>
<td>Swelling causing compressive neuropathy</td>
</tr>
<tr>
<td></td>
<td>Deformity preventing complete extension, loss of</td>
</tr>
<tr>
<td></td>
<td>power</td>
</tr>
<tr>
<td>Shoulder</td>
<td>“Frozen shoulder” (loss of abduction, nighttime</td>
</tr>
<tr>
<td></td>
<td>pain)</td>
</tr>
<tr>
<td>Neck</td>
<td>Subluxation of C1-C2 joint with danger of</td>
</tr>
<tr>
<td></td>
<td>dislocation and spinal cord compression (“hangman’s</td>
</tr>
<tr>
<td></td>
<td>injury”)</td>
</tr>
<tr>
<td>Foot</td>
<td>“Cock-up” deformity and/or subluxation at MTP</td>
</tr>
<tr>
<td>Knee</td>
<td>Effusion leading to Baker cyst (evagination of</td>
</tr>
<tr>
<td></td>
<td>synovial lining and fluid into popliteal space</td>
</tr>
</tbody>
</table>

PIP, proximal interphalangeal; DIP, distal interphalangeal; MTP, metatarsophalangeal.

### Table 23-6. Nondisease factors that influence the ESR.

<table>
<thead>
<tr>
<th>Increase ESR</th>
<th>Decrease ESR</th>
<th>No Effect on ESR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>Leukocytosis (&gt;25,000)</td>
<td>Obesity</td>
</tr>
<tr>
<td>Female</td>
<td>Polycythemia (Hgb &gt;18)</td>
<td>Body temperature</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Red blood cell changes</td>
<td>Recent meal</td>
</tr>
<tr>
<td>Anemia</td>
<td>Sickle cell</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Macrocytosis</td>
<td>Anisocytosis</td>
<td>NSAID</td>
</tr>
<tr>
<td>Congenital hyper-fibrinogenemia</td>
<td>Microcytosis</td>
<td></td>
</tr>
<tr>
<td>Technical factors</td>
<td>Acanthocytosis</td>
<td></td>
</tr>
<tr>
<td>Dilutional</td>
<td>Protein abnormalities</td>
<td></td>
</tr>
<tr>
<td>Elevated specimen temperature</td>
<td>Dysproteinemia with hyperviscosity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypofibrinogenemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypogammaglobulin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Technical factors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dilutional</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inadequate mixing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vibration during test</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clotting of specimen</td>
<td></td>
</tr>
</tbody>
</table>

ESR, erythrocyte sedimentation rate; Hgb, hemoglobin; NSAID, nonsteroidal anti-inflammatory drug.

prevalence of positive RF reaches 25%. With the national prevalence of RA only 1%, it is clear that many people with an elevated RF titer do not have RA. In fact, a false-positive RF titer is a common reason for incorrect referral of patients to rheumatologists. Some of the conditions that are associated with a positive RF test are listed in Table 23-7.

A relatively new test useful for diagnosis of RA in the most early stages is the anti-cyclic citrullinated peptide (anti-CCP). This test is positive in most patients with RA, and may precede the onset of clinically diagnosed RA by months or even years. When combined with the RF test, this test will confirm the diagnosis even in confusing settings.


### Imaging Studies

Radiographs are no longer needed for the initial diagnosis of rheumatoid arthritis. Other means of diagnosing RA are more useful. Nonetheless, RA is a disease of synovial tissue and, because the synovium lies on and attaches to bone, inflammation can cause changes on plain film radiography. Small erosions, or lucencies, on the lateral portions of phalanges are early indications of significant inflammation and should prompt immediate suppressive treatment.

CT, MRI, or both, have limited but useful supporting roles. An undesired complication of treatment of RA, aseptic necrosis (eg, of the femoral head) has a characteristic appearance on MRI. Scintigraphy is useful in detecting aseptic necrosis but, along with MRI, is better employed to differentiate the intense synovitis of RA from infection such as septic arthritis, overlying cellulitis, or adjacent osteomyelitis.

### Differential Diagnosis

In practice, it is should not be difficult to differentiate among the three prototypical arthritides discussed in this chapter (see Table 23-1). Criteria developed by subspecialty organizations give valuable guidelines to making an accurate diagnosis of RA (Table 23-8). Because treatment started early is so generally successful, rheumatologists promote early referral—treating a new diagnosis of RA almost as a “medical emergency.”


### Complications

Serious extra-articular manifestations of RA are not infrequent. Some of these are life-threatening and require sophisticated management by physicians experienced in dealing with these crises. The responsibility often remains with the primary care physician to recognize these conditions and refer appropriately. Table 23-9 lists several of these complications with a brief description of the clinical presentation.

### Treatment

Therapy of RA has changed from managing inflammation to specific measures directed against the fundamental sources of the inflammation. In the past decades, treatment of RA has undergone perhaps the most wholesale shift of any of the rheumatologic conditions. Therapy is now directed at fundamental processes and begins with aggressive, potentially toxic disease-modifying drugs. The outlook can be hopeful, with preservation of joints, activity, and lifestyle a realistic goal.
Table 23-9. Extra-articular manifestations of rheumatoid arthritis.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Brief Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid nodules</td>
<td>Found over pressure points, classically olecranon. Typically fade with disease-modifying antirheumatic drug (DMARD) therapy. Also may be found in internal organs. If causing disability, may attempt intralesional steroids, or surgery.</td>
</tr>
<tr>
<td>Popliteal cyst</td>
<td>Usually asymptomatic unless ruptures; then mimics calf thrombophlebitis. Ultrasoundography (and high index of suspicion) useful.</td>
</tr>
<tr>
<td>Anemia</td>
<td>Usually “chronic disease” and, despite low measured iron, does not respond to oral iron therapy. Improves with control of inflammatory disease.</td>
</tr>
<tr>
<td>Scleritis/episcleritis</td>
<td>Inflammatory lesion of conjunctiva. More prolonged, intense, and uncomfortable than “simple” conjunctivitis. Requires ophthalmologic management.</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>Ranges from simple pleuritis and pleural effusion (noted for low glucose) to severe bronchiolitis, interstitial fibrosis, nodulosis, and pulmonary vasculitis. May require high-dose steroid therapy once diagnosis established by bronchoscopy or even open lung biopsy.</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>Often occurring with RA, includes sicca syndrome with thickened respiratory secretions, dysphagia, vaginal atrophy, hyperglobulinemia, and distal renal tubule defects. Treatment of sicca syndrome possible with muscarinic-receptor agonists; other manifestations more difficult.</td>
</tr>
<tr>
<td>Felty syndrome</td>
<td>Constellation of RA, leukenopienia, splenomegaly, and often anemia, thrombocytopenia. Control underlying RA with DMARDs; may need granulocyte colony-stimulating factor, especially if infectious complications are frequent.</td>
</tr>
<tr>
<td>Rheumatoid vasculitis</td>
<td>Spectrum from digital arteritis (with hemorrhage) to cutaneous ulceration to mononeuritis multiplex to severe, life-threatening multisystem arteritis involving heart, gastrointestinal tract, and other organs. Resembles polyarteritis nodosum.</td>
</tr>
</tbody>
</table>

RA need no longer be the “deforming arthritis” by which it was known just a short time ago.


A. Assessment of Prognostic Factors

One of the early steps in treating RA is to assess prognostic factors in the individual patient. Poor prognosis leads to the decision to start aggressive treatment earlier. Some prognostic features are demographic, such as female sex, age more than 50 years, low socioeconomic status, and a first-degree relative with RA. Clinical features associated with poor prognosis include a large number of affected joints, especially involvement of the flexor tendons of the wrist, with persistence of swelling at the fingers; rheumatoid nodules; high ESR or C-reactive protein and high titers of RF; presence of erosions on radiographs; and evidence of functional disability. Formal functional testing and disease activity questionnaires are frequently employed, not only in establishing stage of disease but also at interval visits. In practice, though, most rheumatologists urge their generalist colleagues to refer patients identified with new onset RA early. Despite certain prognostic factors noted above, most patients are indicated for, and respond to, early therapeutic intervention.

B. Patient Education

Therapy begins with patient education and again there are multiple sources of information from support and advocacy groups, professional organizations, government sources, and pharmaceutical companies. Patients should learn about the natural history of RA and the therapies available to interrupt the course. They should learn about joint protection and the likelihood that at least some activities need to be modified or discontinued. RA, especially before disease modification is established, is a fatiguing disorder. Patients should realize that rest is as important as appropriate types of activity. Of vital importance is the patient’s acknowledgment that drug regimens about to be started are complex but that compliance is critical to successful outcomes. The patient should frankly be told that the drugs are toxic and may have adverse effects.

C. Pharmacotherapy

1. Pain relief—Pain is caused by inflammation, and establishment of effective anti-inflammatory drugs is the first goal of medication. NSAIDs, at doses recommended earlier (see Table 23-2), give the patient early relief. NSAIDs are used throughout the course of treatment; it is not uncommon to switch from one to another as effectiveness falters. However, even adequate pain relief does not abdicate responsibility for appropriate disease modifying therapy.

2. Alternative and complementary therapies—If the patient is reluctant to start drugs, fish oil supplementation may provide symptomatic relief. Both omega-3 and omega-6 fatty acids in fish oil modulate synthesis of highly inflammatory prostaglandin E\(_2\) and leukotriene E\(_4\). The fish oil chosen must contain high concentrations of the relevant fatty acids. A large number of capsules need to be taken, and palatability, diarrhea, and halitosis are frequent adverse effects. γ-linolenic acid interrupts the pathway of arachidonic acid, another component of the inflammatory cascades. Extracted from the oils of plant seeds such as linseed, sunflower seed, and flaxseed, γ-linolenic acid...
demonstrates some efficacy in short-term studies using large doses of the extract. Similar to what was noted above with NSAIDs, alternative therapies are not a substitute for early intervention with disease-modifying drugs.

3. Disease-modifying antirheumatic drugs—Neither NSAIDs nor “natural” products are disease modifying. Disease-modifying antirheumatic drugs (DMARDS) are drugs that suppress the underlying factors that result in synovitis, tissue reactivity (eg, pannus), erosions, ligament and tendon laxity, subluxations, and all the other complications of RA. DMARDS are almost always used in combination, both to enhance efficacy and to decrease dosage and potential toxicity. Toxicity is a major concern with DMARDS and, in fact, the monitoring for adverse effects may account for almost as much cost and inconvenience as the drugs themselves.

A. Sulfasalazine and hydroxychloroquine—Both of these drugs were initially developed for other diseases (inflammatory bowel disease and malaria, respectively) and coincidentally noted to be effective in RA. They are weak DMARDS. Hydroxychloroquine, a common first choice, requires ophthalmologic examinations every 6-12 months to detect color change or deposition of drug in the retina. The eye complications of hydroxychloroquine are rare and typically are seen with doses higher than the recommended 200 mg twice a day. Sulfasalazine is remarkably well tolerated and safe when prescribed at doses up to 2-3 g/d. A few patients experience gastric intolerance; the unlikely occurrence of leukopenia requires hematologic monitoring with some regularity (as often as every 2 months). Some patients with mild RA experience control of symptoms and delay or even suppression of disease progression with a combination of NSAID and hydroxychloroquine or sulfasalazine.

B. Gold and penicillamine—Gold preparations, either oral (auranofin) or parenteral (thiomalate, aurothioglucose), had been a standard therapy with disease-modifying properties in both short-term and intermediate use. These drugs are not easy to use and have gastrointestinal, renal, and bone marrow complications.

Penicillamine is another drug that had been widely, although cautiously, employed. It has DMARD properties and is effective enough at low doses (eg, 250 mg/d). But it now is prescribed only in refractory cases of RA because the adverse effects, when they do occur, are complex and difficult to treat.

C. Antibiotics—Minocycline is included in many combination therapies in mild disease. This antibiotic is not used for its antibacterial effects. Rather, minocycline is an inhibitor of metalloproteinase, an enzyme involved in the production of pannus within joints. Several well-designed studies support the use of minocycline at a dose of 100 mg twice a day in mild to moderate RA, typically in combination regimens.

D. Methotrexate—The drug that has become standard in treatment of RA is methotrexate. Especially when used in combination with an antimalarial or sulfasalazine, methotrexate truly modifies the natural course of RA. Response is common and relatively rapid, providing symptom control within weeks. Early fears of liver toxicity and cirrhosis have largely been allayed, but frequent measurement of liver enzymes is required. At recommended doses, gastrointestinal, mucocutaneous, and hematologic adverse effects are infrequent. Methotrexate affects T cells. The pathologic process in RA is complex, but enhanced activity of T cells is central to the development of destructive pannus. The ability of methotrexate to alter this activity is the key to disease modification.

Although methotrexate is the most commonly used DMARD, it is not an easy drug to take. Patients who imbibe large quantities of alcohol must alter this habit as adverse liver effects with methotrexate are considerably heightened. Folic acid is usually prescribed with methotrexate and, in addition to preventing macrocytic anemia, seems to diminish gastrointestinal side effects. Dosing starts low, as little as 5-7.5 mg/wk, and is increased gradually to avoid mucositis or other gastrointestinal side effects. An early fear that long-term use of methotrexate would result in an increased incidence of infections or cancer has not been borne out. Nonetheless, awareness of infectious complications, including those from organisms such as Pneumocystis carinii, is necessary. Perhaps of even more concern is the development of a diffuse pulmonary alveolitis. Usually responsive to discontinuation of methotrexate and use of corticosteroids, this complication appears more likely to occur in patients with preexisting pulmonary disease.

Finally, an unfortunate side effect of methotrexate use is that disease flare is common (>75%) should methotrexate have to be stopped. The flare, which develops within 2-3 months, is occasionally resistant to reinduction therapy, either with methotrexate or other DMARDS. Even so, methotrexate is almost universally used in RA, has efficacy in most patients, and ranks as one of the most significant advances in disease treatment in the past decades.

E. Azathioprine and cyclophosphamide—Azathioprine and cyclophosphamide are two other chemotherapy drugs considered for RA drug regimens. These agents have neither the efficacy nor relatively benign side effect profile of methotrexate but may be chosen in circumstances in which an additional agent is needed to control symptoms or halt disease progression. Azathioprine use is limited to patients with moderate or severe RA unresponsive to other DMARDS. Gastrointestinal and hematologic adverse effects are most commonly experienced. Azathioprine has been used with success in treatment of serious extra-articular manifestations. Cyclophosphamide causes such frequent problems with bone marrow suppression, cystitis, bladder hemorrhage, and risk of cancer that its use is rare. However, used in combination with high-dose corticosteroids, cyclophosphamide is indicated in life-threatening rheumatoid vasculitis.

F. Leflunomide—Leflunomide (Arava) is a pyrimidine synthesis inhibitor with efficacy equivalent to methotrexate. Even when used in low doses (10-20 mg/d after a loading
dose), it causes considerable liver toxicity, and surveillance with blood tests for liver enzyme abnormalities is required. Leflunomide is not cleared from the body as rapidly as methotrexate, which is sometimes seen as an advantage (prompting the concept of a “drug holiday”). But similar to other chemotherapy agents, leflunomide is a teratogen, making the prolonged presence in body tissues a deceptive problem. Women of childbearing age must remain on effective contraception for as much as a year after stopping leflunomide. This drug is being investigated for use in moderate to severe RA, occasionally in combination with methotrexate.

G. CYCLOSPORINE—Cyclosporine was once promoted for RA treatment as a DMARD with unique properties. It suppresses immunologic processes at steps different than chemotherapeutic agents. It is effective, as demonstrated in several studies. But the toxicity of cyclosporine is considerable, including the development of a particularly resistant type of hypertension and reduction in renal clearance. Cyclosporine is currently limited to combinations with methotrexate in severe RA poorly responsive to other therapies. Generally replacing these latter drugs are newer, potent, but also potentially toxic agents.

H. TUMOR NECROSIS FACTOR INHIBITORS—A different approach to management of RA has followed the development of tumor necrosis factor (TNF) inhibitors. TNF is a messenger attracting other inflammatory cells to a site. TNF is also involved in production of interferon and interleukins. Blockade of these effects diminishes the inflammatory response, both decreasing patient symptoms and slowing disease progression. Etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira) are current examples of TNF inhibitors. These drugs require subcutaneous or intravenous injection, as often as every other week. Despite that, they are relatively well tolerated and any hematologic toxicity responds to discontinuation. Although TNF inhibitors carry FDA indication for moderate to severe RA, they are increasingly given as single agents and even as first-line drugs. Following the same physiologic idea, an interleukin-1 receptor antagonist, anakinra (Kineret), has also been introduced. This drug has modest benefit as both a single agent (for which it really is not recommended) and in combination with an agent such as methotrexate. Side effects are relatively common, with leukopenia and sepsis of most concern.

I. ABATACEPT—Abatacept (Orencia) inhibits T-cell activation. It may be used if methotrexate or TNF inhibitors fail, although some protocols use this drug in combination with methotrexate. Infectious complications and worsening of chronic obstructive pulmonary disease occurs more often than during treatment with TNF inhibitors.

J. RITUXIMAB—Already marketed for B-cell lymphoma, rituximab (Rituxan) now carries an indication for use with methotrexate in RA patients who have not responded to treatment with TNF inhibitors. Acute infusion reactions are unfortunately common. Serious infections seem to occur at twice the rate of methotrexate alone.

K. CORTICOSTEROIDS—Corticosteroid use in RA goes back to the earliest days of steroid development. It was the dramatic demonstration of symptom reduction in RA that propelled the use of corticosteroids in rheumatic diseases, resulting in a Nobel Prize in Medicine in 1950. But it was the use of high-dose steroids in RA that also led to the recognition of serious complications and the cautions physicians employ every day in decisions regarding use of steroids. Current recommendations suggest use of steroids in limited, but not infrequent, settings.

Corticosteroids suppress activity of RA while other DMARDs are being established. As initial therapy for a patient with moderate, active disease, steroids (eg, prednisone, 40-60 mg/d) can rapidly control symptoms, decrease inflammation, and provide time for DMARDs to have an effect. Similarly, if a patient has a disease flare and the decision is made to change DMARD therapy, steroids can provide “bridging” to the new therapy. If the patient has one or two joints that persist in inflammation and symptoms despite adequate overall control, intra-articular steroids provide an excellent intervention.

More controversial is the long-term use of corticosteroids at relatively low dose (eg, prednisone 5-10 mg/ day). Most studies acknowledge symptom control, and a few recent studies even suggest slowing of joint destruction. Concern about progressive long-term complications to bone, skin, and other connective tissues has not been allied with these recent reports.

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D. SURGERY

Joint instability and resultant disability are often due to a combination of joint destruction, a primary effect of synovial inflammation, and tendon or ligament laxity, a secondary effect or “innocent bystander.” The innocent bystander effect notes that these connective tissues are stretched, weakened, or malaligned due to inflammation of the joints over which they cross but not due to a direct attack on the tendon or ligament itself. Nonetheless, at some point joint destruction and connective tissue laxity combine to produce useless, and frequently painful, joints. At this point, the surgeon has much to offer. Joint stabilization, connective tissue reinsertion, and joint replacement of both small (interphalangeal) and large (hip, knee) joints provide return of function and reduction of pain. The timing of surgery is still an art and is most effective when close collaboration exists between the primary physician and surgeon.
Prognosis

Morbidity and mortality are increased in patients with RA over age-matched persons without RA. Correlated with active disease, there is a well-described increase in stroke and myocardial infarction. These manifestations may be due to a hypercoagulable state induced by the autoimmune process and circulating antibodies. There are suggestions that the increased rate of stroke and MI may be reduced by effective DMARD therapy. Even so, it is recommended that appropriate cardiovascular interventions be considered (eg, aspirin, lipid management, etc). Even under conscientious treatment, complications from infection, pulmonary and renal disease, and gastrointestinal bleeding occur at rates higher than those in the general population. Many of the latter complications are related as much to the drugs used to control the disease as to the disease itself.


Web Sites


Low Back Pain in Primary Care: An Evidence-Based Approach

Charles W. Webb, DO, FAAFP
Francis G. O’Connor, MD, MPH

General Considerations

Low back pain (LBP), discomfort, tension, or stiffness below the costal margin and above the inferior gluteal folds, is one of the most common conditions encountered in primary care, second only to the common cold. LBP has an annual incidence of 5%, and a lifetime prevalence of 60%-90%. It is the leading cause of disability in the United States for adults younger than 45 years of age, and is responsible for one-third of workers’ compensation costs and accounts for direct medical costs in excess of $38 billion per year. At any given time 1% of the US population is chronically disabled and another 1% temporarily disabled as a result of back pain. Numerous studies report a favorable natural history for acute and subacute LBP, with up to 90% of patients regaining function within 6-12 weeks with or without physician intervention. Recent studies, however, suggest that back pain is often recurrent and chronically disabling. Approximately 85% of back pain has no readily identifiable cause, and up to one-third of all patients will develop chronic low back pain. This chapter reviews a detailed evidence-based approach to the assessment, diagnosis, and management of the adult patient with acute, subacute, and chronic LBP.


Prevention

LBP is a heavy medical and financial burden to not only the patients who are experiencing the ailment, but also to society. The US Preventive Services Task Force recently produced a recommendation statement on primary care interventions to prevent low back pain in adults. Currently there is insufficient evidence to support or rebuke routine use of exercise as a preventive for low back pain. However, regular physical activity has been shown to be beneficial in the treatment and the limitation of recurrent episodes of chronic low back pain. Lumbar supports (back belts) have not been found effective in the prevention of low back pain. Work site interventions, including education on lifting techniques, have been shown to have some short-term effects on decreasing lost time from work for patients with back pain.

Risk factor modifications may be the only way to truly prevent LBP. These risk factors can be classified as individual, psychosocial, occupational, and anatomic. Table 24-1 lists the prominent risk factors for LBP.


Clinical Findings

The key elements in the correct diagnosis and management of the issues surrounding the causes of LBP include an evaluation for serious health problems, screening for red and yellow flags (Tables 24-2 and 24-3), symptom control for acute...
### Table 24-1. Risk factors associated with LBP.

<table>
<thead>
<tr>
<th>Individual</th>
<th>Psychosocial</th>
<th>Occupational</th>
<th>Anatomic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>Stress</td>
<td>Monotonous tasks</td>
<td>Disc space narrowing</td>
</tr>
<tr>
<td>Smoking</td>
<td>Depressed mood</td>
<td>Low control job</td>
<td>Facet joint arthritis</td>
</tr>
<tr>
<td>History</td>
<td>Decreased cognition</td>
<td>Manual handling of materials</td>
<td>Synovial cysts</td>
</tr>
<tr>
<td>Obesity</td>
<td>Somatization</td>
<td>Job dissatisfaction</td>
<td>Lumbo-sacral transitional vertebra</td>
</tr>
<tr>
<td>Education level</td>
<td>Long duration of pain</td>
<td>Night shift work</td>
<td>Schmoral nodes</td>
</tr>
<tr>
<td>Unemployment</td>
<td>Fear avoidance behavior</td>
<td>Bending, twisting, pulling, pushing,</td>
<td>Annular disruption</td>
</tr>
<tr>
<td>High birth weight</td>
<td></td>
<td>Whole-body vibration</td>
<td>Spondylolysis</td>
</tr>
<tr>
<td>High levels of pain</td>
<td></td>
<td>Lifting more than 3/4 of day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unavailability of light duty</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High pressure on time</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coworker socialization</td>
<td></td>
</tr>
</tbody>
</table>


### Table 24-2. Red flags and appropriate actions.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Red Flag</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>History of cancer Unexplained weight loss Age ≥50 Failure to improve with therapy Pain ≥4-6 wk Night/rest pain</td>
<td>If malignant disease of the spine is suspected, imaging is indicated and CBC and ESR should be considered. Identification of possible primary malignancy should be investigated, eg, PSA, mammogram, UPEP/SPEP/IPEP.</td>
</tr>
<tr>
<td>Infection</td>
<td>Fever History of intravenous drug use Recent bacterial infection: UTI, skin, pneumonia Immunocompromised states (steroid, organ transplants, diabetes, HIV) Rest pain</td>
<td>If infection in the spine is suspected, MRI, CBC, ESR and/or UA are indicated.</td>
</tr>
<tr>
<td>Cauda equina syndrome</td>
<td>Urinary retention or incontinence Saddle anesthesia Ana sphincter tone decrease/local incontinence Bilateral lower extremity weakness/numbness or progressive neurologic deficit</td>
<td>Request immediate surgical consultation.</td>
</tr>
<tr>
<td>Fracture</td>
<td>Use of corticosteroids Age ≥70 or history of osteoporosis Recent significant trauma</td>
<td>Appropriate imaging and surgical consultation.</td>
</tr>
<tr>
<td>Acute abdominal aneurysm</td>
<td>Abdominal pulsating mass Other atherosclerotic vascular disease Rest/night pain Age ≥ 60</td>
<td>Appropriate imaging (ultrasound) and surgical consultation.</td>
</tr>
<tr>
<td>Significant herniated nucleus pulposus (HNP)</td>
<td>Major muscle weakness</td>
<td>Appropriate imaging and surgical consultation.</td>
</tr>
</tbody>
</table>

CBC, complete blood count; ESR, erythrocyte sedimentation rate; PSA, prostate-specific antigen; UPEP, urine protein electrophoresis; SPEP, serum protein electrophoresis, IPEP, immunoprotein electrophoresis; UTI, urinary tract infection; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; UA, urinalysis.
Table 24-3. Yellow flags in low back pain.

<table>
<thead>
<tr>
<th>Belief Systems</th>
<th>Comorbid Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear</td>
<td>Lack of sleep secondary to pain</td>
</tr>
<tr>
<td>Avoidance</td>
<td>History of other disabling injuries or conditions</td>
</tr>
<tr>
<td>Expectation of pain with normal activity</td>
<td>Waddel Signs</td>
</tr>
<tr>
<td>Excessive focus on pain</td>
<td>Pain with axial loading of the spine</td>
</tr>
<tr>
<td>Feeling out of control</td>
<td>Superficial tenderness to palpation (light touch)</td>
</tr>
<tr>
<td>Passivity toward rehabilitation</td>
<td>Overreaction (pain out of proportion to physical findings)</td>
</tr>
<tr>
<td>Affective Factors</td>
<td>Straight leg raise test improves with distraction</td>
</tr>
<tr>
<td>Poor work history</td>
<td>Regional weakness</td>
</tr>
<tr>
<td>Poor compliance with exercise</td>
<td></td>
</tr>
<tr>
<td>Withdrawal from activities</td>
<td></td>
</tr>
<tr>
<td>History of substance abuse</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
</tr>
<tr>
<td>Lack of socialization</td>
<td></td>
</tr>
<tr>
<td>History of physical or psychological abuse</td>
<td></td>
</tr>
</tbody>
</table>


and subacute LBP, and follow-up evaluation of patients whose condition worsens or fails to improve. The first step is the accurate and timely identification of clinical conditions for which low back pain is a symptom.

A. Symptoms and Signs

A careful medical history and physical examination is critical in determining the presence of a more serious condition in the patient presenting with acute LBP. On examining the patient, the primary care provider must look for “red and yellow flags” that indicate the presence of a significant medical or psychological condition. If any red flags are identified, patients requiring emergent or urgent care should be given immediate consultation or referral to the appropriate specialist. Nonemergent patients with red flags should be scheduled for the appropriate diagnostic test to determine if they have a condition that requires a referral. If any yellow flags are identified it signifies the presence of psychological distress and strongly correlates to chronicity and poor patient outcomes in both pain control and disability. When yellow flags are identified early, an interdisciplinary approach should be considered.

1. History—The history should focus on the location of the pain, the mechanism of injury (what was the patient doing when he/she first noticed the pain), was it insidious or was there a specific trauma or activity), the character (mechanical, radicular, caldicitic, or nonspecific), and duration of the pain (acute: less than 6 weeks, subacute: between 6 and 12 weeks, or chronic: greater than 12 weeks). The provider must identify neurologic symptoms (bowel/bladder symptoms, weakness in the extremities, saddle anesthesia) suggestive of cauda equina syndrome (CES: a true neurosurgical emergency). The functional status of the patient should be noted as should any exacerbating or ameliorating factors. The presence of fever, weight loss, and night pain are particularly concerning as these could be pointing to a more serious disease, such as an underlying malignancy. The social history should include information about drug use/abuse, intravenous (IV) drug use, tobacco use, and the presence of physical demands at work, and the presence of psychosocial stressors. Past medical and surgical history should also be obtained, particularly a history of previous spinal surgery or immunosuppression (history of cancer, steroid use, HIV). A thorough history enables the primary care provider to identify any “red and/or yellow flags” that require a more extensive workup to rule out a potentially serious and disabling disease processes.

2. Physical examination—The physical examination supplements the information obtained in the history by helping to identify underlying serious medical conditions or possible serious neurologic compromise. The primary elements of the physical examination are inspection, palpation, observation (including range of motion testing), and a specialized neuromuscular evaluation. The examination should start with an evaluation of the spinal curvature, lumbar range of motion, noting the amount of pain free movement. Palpation should include the paraspinal muscles, the spinous processes, the sacroiliac joints, the piriformis muscles, and the position of the pelvic bones. Because the lumbar spine is kinetically linked to the pelvis, (particularly the sacroiliac area), pain from the pelvis is often referred to the lumbar spine. Hip flexors and hamstring flexibility should also be assessed as a potential cause for the pain.

3. Neurologic evaluation—The neurologic evaluation should include Achilles (S1) and patellar tendon (L2-L4) reflex testing, ankle and great toe dorsiflexion (L4-L5) and plantarflexion (S1) strength, as well as the location of sensory complaints (dermatomes involved). Light touch testing for sensation in the medial (L4), dorsal (L5), and lateral (S1) aspects of the foot should also be performed. In patients presenting with acute LBP and no specific limb complaints, a more elaborate neurologic examination is not usually necessary. A seated and supine straight leg raise test (SLR) evaluates for nerve root impingement. This abbreviated neurologic evaluation of the lower extremity allows detection of clinically significant nerve root compromise at the L4-L5 or L5-S1 levels. These two sites make up over 90% of all significant radiculopathy secondary to lumbar disc herniation. Because this abbreviated examination may fail to diagnose some of the less common causes of LBP, any patient who has not improved in 4-6 weeks should return for further evaluation.

4. Risk stratification—All patients, with acute LBP should be risk stratified with an initial assessment attempting to
identify red flags—responses or findings in the history and physical examination that indicate a potentially serious underlying condition, such as a fracture, tumor, infections, abdominal aneurysm, or CES that can lead to considerable patient morbidity and/or mortality. These clinical clues (red flags) include a history of major trauma, minor trauma in patients older than 50 years of age, persistent fever, history of cancer, metabolic disorder, major muscle weakness, bladder or bowel dysfunction, saddle anesthesia, decreased sphincter tone, and unrelenting night pain. Red flags risk stratify the patient to an increased risk and should prompt an earlier clinical action, such as imaging or laboratory work up. See Table 24-2 for a listing of red flags and their related conditions.

Psychosocial factors also significantly affect pain and function in LBP patients. These psychosocial factors are known as “yellow flags” and are better predictors of treatment outcomes than physical factors in some patients. These yellow flags are listed in Table 24-3.

B. Imaging Studies

Diagnostic imaging is rarely indicated in the acute setting of LBP. Even though some studies have indicated greater patient satisfaction with lumbar radiography, the evidence demonstrates it may not lead to greater improvement in outcomes. After the first 4-6 weeks of symptoms, the majority of patients will have regained function. However, if the patient is still limited by back symptoms diagnostic imaging should be considered to look for conditions that present as low back pain. Patients for whom diagnostic imaging should be considered include children, patients older than 50 years of age, trauma patients, or patients for whom back pain fails to improve despite appropriate conservative treatment. Imaging studies must always be interpreted carefully since disc degeneration and protrusion has been noted in 20%-25% of asymptomatic individuals. Therefore abnormal findings on diagnostic imaging may or may not represent the reason for the patient’s pain.

Plain films remain the most widely available modality for imaging the lumbar spine and are rarely useful in evaluating or guiding treatment of adults with acute LBP in the absence of red flags. Plain lumbar x-rays are helpful in detecting spinal fractures, and evaluating tumor and/or infection. Anteroposterior (AP) and lateral views allow assessment of lumbar alignment, the intervertebral disc space, bone density, and a limited evaluation of the soft tissue. Oblique views should only be used when spondylosis is suspected as they double the radiation exposure and add only minimal information. Sacroiliac views are used to evaluate ankylosing spondylitis, and again should only be used when this is suspected.

When the history or physical examination suggests an anatomic abnormality as a cause for the back pain with neurologic deficits, four imaging studies are commonly used: (1) plain myelography, (2) computed tomography (CT) scan, (3) magnetic resonance imaging (MRI) scan, and (4) CT myelography. These four tests are used in similar clinical situations and provide similar information. The objective of these studies is to define a medically or surgically remediable anatomic condition. These tests are not done routinely, and should only be used for patients who present with certain clinical findings, such as, radicular symptoms and clinically detectable nerve root compressive symptoms severe enough to consider surgical intervention (major muscle weakness, progressive motor deficit, intractable pain, and persistent radicular pain beyond 6 weeks). For a listing of these and other special tests and tier indications/recommendations, see Table 24-4.

Diagnostic imaging plays a central role in diagnosing spinal infections. Plain films should be obtained but are often only helpful in the advanced stages of the infection. MRI is the imaging modality of choice in evaluating spinal infection. When infection is identified or suspected, a spinal surgeon should be consulted immediately.

C. Laboratory Testing

Laboratory testing should be reserved for patients who are felt to have conditions masquerading as simple LBP such as cancer or infection (Table 24-5). Laboratory tests that are
recommended in the evaluating patients with a suspicious history for cancer include a complete blood count (CBC) with differential, and an erythrocyte sedimentation rate (ESR). An ESR over 50 mm/h is suggestive of malignancy, infection, or inflammatory disease. Blood urea nitrogen (BUN), creatinine (Cr), and urinalysis (UA) are helpful for identifying underlying renal or urinary tract disease. Serum calcium, phosphorus, and alkaline phosphatase should be checked in patients with osteopenia, osteolytic vertebral lesions, or vertebral body collapse. If prostate carcinoma is suspected, prostate specific antigen and acid phosphatase levels should be checked. If multiple myeloma is suspected a serum immunolectrophoresis can help guide treatment.

Table 24-4. Special tests and indications/recommendations.

<table>
<thead>
<tr>
<th>Special Test</th>
<th>Indication/Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain x-ray</td>
<td>Not recommended for routine evaluation of acute LBP unless red flags present</td>
</tr>
<tr>
<td></td>
<td>Recommended for ruling out fractures - Obliques are only recommended when findings are</td>
</tr>
<tr>
<td></td>
<td>suggestive of Spondylolisthesis or spondylytis</td>
</tr>
<tr>
<td>Electrophysiological tests</td>
<td>questionable nerve root dysfunction with leg symptoms ≥ 6 wk</td>
</tr>
<tr>
<td>(EMG and SPEP)</td>
<td>Not recommended if radiculopathy is obvious</td>
</tr>
<tr>
<td>MRI or CT-myelography</td>
<td>Back related leg symptoms and clinically detectable nerve root compromise</td>
</tr>
<tr>
<td></td>
<td>History of neurogenic claudication suspicious for spinal stenosis</td>
</tr>
<tr>
<td></td>
<td>Findings suggesting CES, fracture, infection, tumor</td>
</tr>
<tr>
<td>ESR</td>
<td>Suspected tumors, infection, inflammatory conditions, metabolic disorders</td>
</tr>
<tr>
<td>CBC</td>
<td>Suspected tumors, myelogenous conditions, infections</td>
</tr>
<tr>
<td>UA</td>
<td>Suspected UTI, pylonephritis, myeloma</td>
</tr>
<tr>
<td>IPEP</td>
<td>Suspected multiple myeloma</td>
</tr>
<tr>
<td>Chemistry profile to include</td>
<td>Suspected electrolyte disorders, thyroid dysfunction, metabolic dysfunction,</td>
</tr>
<tr>
<td>TSH, calcium, and alkaline</td>
<td></td>
</tr>
<tr>
<td>phosphatase</td>
<td></td>
</tr>
<tr>
<td>Bone scan</td>
<td>Suspected occult pars interarticularis fracture, or metastatic disease.</td>
</tr>
<tr>
<td></td>
<td>Contraindicated in pregnant patient</td>
</tr>
</tbody>
</table>

LBP: low back pain; EMG, electromyelogram; SPEP, serum protein electrophoresis; MRI, magnetic resonance imaging; CT, computed tomography; CES, cauda equina syndrome; ESR, erythrocyte sedimentation rate; CBC, complete blood count; UA, urinalysis; UTI, urinary tract infection; IPEP, immunoprotein electrophoresis; TSH, thyroid-stimulating hormone.

Table 24-5. Masqueraders of LBP.

<table>
<thead>
<tr>
<th>System</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Expanding aortic aneurysm</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Pancreatitis, Peptic ulcers, Cholecystitis, Colonic cancer</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Endometriosis, Tubal pregnancy, Kidney stones, Prostatitis, Chronic pelvic inflammatory disease, Perinephric abscess, Pylonephritis</td>
</tr>
<tr>
<td>Endocrinologic/Metabolic</td>
<td>Osteoporosis, Osteomalacia, Hyperparathyroidism, Paget disease, Acromegaly, Cushing disease, Ochronosis</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Hemoglobinopathy, Myelofibrosis, Mastocytosis</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>Spondyloarthropathies - Ankylosing Spondylitis, Reiter Syndrome, Psoriatic arthritis, Enteropathic arthritis, Bechet syndrome, Familial Mediterranean fever, Whipple disease, Diffuse idiopathic skeletal hyperostosis</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>Affective disorder, Conversion disorder, Somatization disorder, Malingering</td>
</tr>
<tr>
<td>Infection</td>
<td>Osteomyelitis, Epidural/paraspinal abscess, Disc space infection, Pyogenic sacroiliitis</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Skeletal metastases, Spinal cord tumors, Leukemia, Lymphoma, Retropertitoneal tumors, Primary lumbosacral tumors, Benign, Malignant</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Sarcoïdosis, Subacute endocarditis, Retropertitoneal fibrosis, Herpes zoster, Fat herniation of lumbar spine</td>
</tr>
</tbody>
</table>

Historical red flags such as IV drug abuse and immunocompromise, as well as fever, should raise concern for an underlying infection. An elevated white blood cell count (WBC) is a clue to an underlying infection, but can be within normal limits even in acute infection. The ESR and C-reactive protein (CRP) can be used to monitor the efficacy of treatment of spinal infections. Urinalysis and urine culture should be obtained because urinary tract infection (UTI) often precedes spinal infection. Blood cultures should be obtained as well. Though they are usually negative, positive cultures identify the infecting organism and provide antibiotic sensitivity to guide treatment.

| Harwood MI: What is the most effective treatment for acute low back pain. J Fam Prac 2002;51(2): 118. |

### Differential Diagnosis

After potential red flags have been ruled out, the differential diagnosis for LBP remains extensive. Table 24-5 presents a list of conditions that can present as simple LBP.

### Treatment

If the patient has no red flags and the history and physical examination do not suggest an underlying cause, the diagnosis of mechanical LBP can be made, and treatment may be initiated. Methods of symptom control should focus on providing comfort and keeping the patient as active as possible while awaiting spontaneous recovery. Evidence for the most common treatments currently used in the primary care setting flows. Depending on the patient, this treatment may include activity modification, bed rest (short duration), conservative medications, progressive range of motion and exercise, manipulative treatment, and patient education. This line of treatment should be used for 4-6 weeks before ordering additional diagnostic test unless the history and physical examination identify a more concerning diagnosis.

### A. Patient Education

Patient education is the cornerstone of effective treatment of LBP. Patients who present to the primary care clinic with acute LBP should be educated about expectations for recovery and the potential recurrence of symptoms. Management of the patient’s expectations of therapy and educating them about the management goals is an effective way to decrease apprehension and promote a quick recovery. Management goals focus on decreasing pain and improving overall function of the patient. Patients should be informed of safe and reasonable activity modifications, and be given information on how to limit the recurrence of low back problems through proper lifting techniques, treatment of obesity, and tobacco cessation. If medications are used, patients should be given information on their use and the potential side effects. Patients should be instructed to follow up in 1-3 weeks if they fail to improve with conservative treatment, develop bowel or bladder dysfunction, or worsening neurologic function.

### B. Activity Modification

Patients with acute LBP may be more comfortable if they are able to temporarily limit or avoid specific activities that are known to increase mechanical stress on the spine. Prolonged unsupported sitting and heavy lifting, especially while bending or twisting, should be avoided. Activity recommendations for the employed patient with acute LBP should consider the patient’s age, general health, and the physical demands of the job.

### C. Bed Rest

A gradual return to normal activities is more effective than prolonged bed rest for the treatment of LBP. Bed rest for longer than 4 days may lead to debilitating muscle atrophy and increased stiffness and therefore is not recommended. Most patients with acute and subacute LBP will not require bed rest. For patients with severe initial symptoms, however, limited bed rest for 2-4 days remains an option.

### D. Medications

Oral medications (acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], muscle relaxants, and opioids) and injection treatments are available for the treatment of LBP. Most patients with chronic low back pain will self medicate with an over-the-counter pain reliever (acetaminophen and ibuprofen). Also, most are prescribed at least one medication to control pain and improve function. Currently there is good evidence to use NSAIDs or skeletal muscle relaxants for the management of acute LBP, but are less effective when used as monotherapy. NSAIDs have both anti-inflammatory and analgesic properties, and are widely used for all kinds of LBP. However, they can cause gastrointestinal (GI), renal, and hepatic side effects, and the selective cyclooxygenase 2 (COX-2) inhibitors have been linked to increased risk of cardiovascular events. Therefore all of these medications should be used with caution and at the lowest possible dose for the shortest duration. Because opioids are only slightly more effective in relieving low back symptoms than other analgesics (aspirin, acetaminophen) and because of their potential for other complications (dependency), opioid analgesics, if used, should be used only over a time-limited course. Oral corticosteroids are not recommended for the treatment of acute LBP.

There is limited evidence supporting the use of herbal remedies, such as devil’s claw, willow bark, and capsicum for the treatment of acute episodes of chronic LBP.
Injection therapy for the treatment of low back symptoms includes trigger point, ligamentous, sclerosant, facet joint, and epidural injections. Injections are an invasive treatment option that exposes patients to potentially serious complications. No conclusive studies have proven the efficacy of trigger point, sclerosant, ligamentous, or facet joint injections in the treatment of acute LBP. However, epidural and facet joint injections may benefit patients who fail conservative treatment as a means of avoiding surgery. A series of one to three epidural steroid injections may be beneficial for patients who have radiculopathy that has not improved after 4-6 weeks of conservative therapy.

E. Spinal Manipulation

There is some evidence supporting the use of manipulative therapy in the treatment of acute LBP. Spinal manipulation techniques attempt to restore joint and soft tissue range of motion. Impaired motion of synovial joints has a detrimental effect on joint cartilage and vertebral disc metabolism leading to degenerative spinal changes. Manipulation is useful early after symptom onset for patients who have acute LBP without radiculopathy. If the patient’s physical findings suggest progressive or severe neurologic deficit, aggressive manipulation should be postponed pending an appropriate diagnostic assessment.

F. Physical Agents and Modalities

Physical agents include ice and moist heat treatments. There is good evidence to support the use of superficial heat for muscle relaxation and analgesia. The evidence supporting cryotherapy is limited at best. Self-administrated home programs using moist heat and cold are often used.

Transcutaneous electrical nerve stimulation (TENS) is thought to modify pain perception by counterstimulation of the nervous system. Currently there is insufficient evidence on the efficacy of the TENS to recommend its routine use.

Shoe insoles (or inserts) can vary from over the counter foam, rubber inserts to custom orthotics. These devices aim to reduce back pain due to leg length discrepancies, or abnormal foot mechanics. There is limited evidence that shoe orthotics (either over the counter or custom) may provide short-term benefit for patients with mild back pain, although there is no evidence supporting their long-term use. The role of leg length discrepancies in LBP has not been established, and differences of less than 2 cm are unlikely to produce symptoms.

Lumbar support devices for low back problems include corsets, support belts, various types of braces, and molded jackets, and back rests for chairs and car seats. Lumbar corsets and support belts may be beneficial in the preventing of low back pain and time lost from work for individuals whose jobs require frequent lifting, however, the evidence is lacking. Lumbar corsets have not been proven to be beneficial in the treatment of LBP.

A randomized control trial found that mattresses of medium firmness are beneficial in reducing pain symptoms and disability in patients with chronic low back pain.

Acupuncture and other dry needling techniques have not been found to be beneficial for treating acute and subacute LBP patients. However, recent evidence does suggest that traditional Chinese medical acupuncture and therapeutic massage is beneficial in the treatment of chronic low back pain. Acupuncture, when added to conventional therapies, improves function, sleep, and pain better than conventional therapy alone.

G. Exercise

Therapeutic exercises should be started early to control pain, avoid deconditioning, and restore function. Intensive therapeutic exercise can helped decrease pain and improve function in patients with chronic LBP. No single treatment or exercise program has proven effective for all patients with LBP. Poor endurance and abnormal firing of the hip muscles have been noted in patients with both acute and chronic LBP. Various studies have shown that the occurrence of LBP may be reduced by strengthening the back, legs, and abdomen (core muscle groups) and by improving muscular stabilization. Initial exercises should focus on strengthening and stabilizing the spine and stretching the hip flexors. Lower extremity muscle tightness is common with LBP and must be corrected to allow normal range of motion of the lumbar spine.

H. Behavioral Therapy

There have been a multitude of factors that play a role in the patients return to function and decreasing pain. Psychological stressors (yellow flags) have emerged as the strongest single baseline predictor of 4-year outcomes exceeding pain intensity. Fear avoidance beliefs also have a strong influence on recovery. These factors highlight the importance of exercise as a management tool for low back pain. Exercise reduces fear avoidance behavior and facilitates function despite ongoing pain. Graded behavior intervention reinforces that pain does not necessarily mean harm. A patient may still have pain, but be able to function, and thereby improve his/her prognosis over time. Cognitive intervention and exercises programs have demonstrated similar results for improving disability as lumbar fusion, in patients with chronic back pain and disc degeneration.

I. Reevaluation

For those patients with LBP, whose condition worsens during the time of symptoms control, reevaluation and consultation or referral to specialty care is recommended. Patients with LBP should always be reevaluated as indicated after 1-3 weeks to assess progress. This can be accomplished with either a follow-up phone call or office visit. This empowers the patient to take the initiative in their disease course. Patients must be advised to follow up sooner if their condition worsens. Any worsening of neurologic symptoms warrants a complete reevaluation.
Conservative treatment is warranted for 4-6 weeks from the initial evaluation. This follow-up visit is also the appropriate time to consider a work-related ergonomic evaluation. As the patient improves there should be a gradual return to normal activity and a weaning of the medications.

J. Referral

If a patient has LBP for more than 6 weeks despite an adequate course of conservative therapy, the patient should be reexamined in the office. A comprehensive reevaluation including a psychosocial assessment and physical examination should be performed. During follow-up visits, questions should be directed at identifying any detriments in the patient’s condition, including new neurologic symptoms, increased pain, or new radiation of the pain. If such problems are found, the patient should be reevaluated for other health problems and consultation or imaging modalities.

For patients with pain that radiates below the knee, especially with a positive tension sign the anatomy must be evaluated with an imaging study. If there are abnormal findings then consultation with a neurosurgeon or spine surgeon is appropriate. If, however, the imaging study does not reveal anatomic pathology then a nonsurgical back specialist may be necessary to help manage the patient. Table 24-6 lists these specialists and indications for their referral. Table 24-7 further identifies useful websites that can assist the provider in identifying resources for management and indications for referral.

If there are no abnormal findings on a comprehensive reassessment, including selected diagnostic tests, it is crucial to start patients on a program that will enable them to resume their usual activities. The management of the patient without structural pathology should be directed toward a physical conditioning program designed with exercise to progressively build activity tolerance and overcome individual limitations. This may include referral to behavior modification specialists, activity specific educators, or an organized multidisciplinary back rehabilitation program.


Henschke N, Ostelo RWJG, van Tulder MW, Vlaeyen JWS, Morley S, Assendelft WJJ, Main CJ: Behavioral treatment for chronic low-back pain. Cochrane Database of Systematic Reviews 2010 (7);Art.No.:CD002014;DOI:10.1002/14651858. CD002014; 3.


Table 24-7. Helpful Web sites.

<table>
<thead>
<tr>
<th>Address</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="http://www.ahcpr.gov/consumer">http://www.ahcpr.gov/consumer</a></td>
<td>Agency for Healthcare Research and Quality</td>
</tr>
<tr>
<td><a href="http://www.rheumatology.org/public/factsheets/backpain_new.asp?aud=pat">http://www.rheumatology.org/public/factsheets/backpain_new.asp?aud=pat</a></td>
<td>American College of Rheumatology, patient education on back pain</td>
</tr>
<tr>
<td><a href="http://orthoinfo.aaos.org">http://orthoinfo.aaos.org</a></td>
<td>American Academy of Orthopedic Surgeons Information page</td>
</tr>
<tr>
<td><a href="http://www.intelihealth.com/IH/iHTIH/WSAUS000/331/9519.html">http://www.intelihealth.com/IH/iHTIH/WSAUS000/331/9519.html</a></td>
<td>Intelihealth back pain page</td>
</tr>
<tr>
<td><a href="http://preventiveservices.ahrq.gov">http://preventiveservices.ahrq.gov</a></td>
<td>US Preventative Services Task Force</td>
</tr>
<tr>
<td><a href="http://www.icsi.org/knowledge/detail.asp?catID=296&amp;itemID=149">http://www.icsi.org/knowledge/detail.asp?catID=296&amp;itemID=149</a></td>
<td>Institute for Clinical Systems improvement, low back pain guideline</td>
</tr>
<tr>
<td><a href="http://www.medinfo.co.uk/conditions/lowbackpain.html">http://www.medinfo.co.uk/conditions/lowbackpain.html</a></td>
<td>European Clinical Practice Guideline on the Treatment of Low Back pain, including the pediatric population</td>
</tr>
<tr>
<td><a href="http://familydoctor.org/">http://familydoctor.org/</a></td>
<td>Patient Education Handouts</td>
</tr>
<tr>
<td><a href="http://www.aafp.org/cmebulletin/lbp">http://www.aafp.org/cmebulletin/lbp</a></td>
<td>CME bulletin, a peer-reviewed bulletin for the family physician The diagnosis and management of acute low back pain and caring for patients who have chronic low back pain</td>
</tr>
<tr>
<td><a href="http://www.aafp.org/cmebulletin/lbp/yellowflags">http://www.aafp.org/cmebulletin/lbp/yellowflags</a></td>
<td>CME bulletin, yellow flag listing</td>
</tr>
</tbody>
</table>


Prognosis

The long-term course of LBP is variable. One recent review discovered that a majority of patients continue to report pain 12 months after initial onset of symptoms. However, 90% of patients will regain function with decreasing pain after 6 weeks, despite physician intervention.
Harwood MI: What is the most effective treatment for acute low back pain. J Fam Pract 2002;51(2):118.

General Considerations

Neck pain is a common clinical problem experienced at some point in life by nearly two-thirds of people. In addition to being a common problem, neck pain is quite disabling, in some countries accounting for nearly as much disability as low back pain. The economic impact of whiplash injuries alone is estimated to be nearly $4 billion.

Neck pain is also quite similar to low back pain in that the etiology is poorly understood and the clinical diagnoses are quite vague. Compared to low back pain, however, which has been the subject of numerous clinical practice guidelines, neck pain has received limited study. The few randomized controlled studies available lack consistency in study design. A review of the National Guidelines Clearinghouse (http://www.ngc.gov) demonstrates eight published guidelines on neck pain, pertaining to the use of facet neurotomy, imaging, and selected rehabilitation and therapeutic interventions in neck pain. This chapter reviews the epidemiology and anatomy of neck pain and provides an evidenced-based assessment of the evaluation, diagnosis, and management of this challenging disorder.

Neck pain is most prevalent in middle-aged adults; however, prevalence tends to vary with different definitions of neck pain and with differing methodologies of neck pain surveys. One study, for example, found that the 1-year prevalence in adults ranged from 16.7% to 75.1% and rose with longer time periods. Almost 85% of neck pain may be attributed to chronic stress and strains or acute or repetitive injuries associated with poor posture, anxiety, depression, and occupational or sporting risks. The acceleration and deceleration of a whiplash injury may result in cervical sprains or strains, which, in turn, are common causes of neck pain. Radicular neck pain occurs later in life, with an estimated incidence of 10% among 25- to 29-year-olds, rising to 25%-40% in those older than 45 years.

Occupational neck pain is ubiquitous and not limited to any particular work setting. Predictors for occupational neck pain include little influence on the work situation, work-related psychosocial factors, and perceived general tension. Predictors of occupational neck pain include prolonged sitting at work (>95% of the workday), especially with the neck forward flexed 20 degrees or more for more than 70% of the work time.

Functional Anatomy

The cervical spine is a highly mobile column that supports the 6- to 8-lb (2.7-3.6 kg) head and provides protection for the cervical spinal cord. The cervical spine consists of 7 vertebrae, 5 intervertebral discs, 14 facet joints (zygapophyseal joints or Z-joints), 12 joints of Luschka (uncovertebral joints), and 14 paired anterior, lateral, and posterior muscles. The vertebrae can be grouped into three major groups: the atlas (C1), the axis (C2), and the others (C3–C7). The atlas is a ring-shaped vertebra with two lateral masses, each with superior and inferior facets to articulate with the occiput and C2 respectively, as well as an anterior portion of the ring to articulate with the odontoid process (dens) of C2. The axis consists of a large vertebral body (the largest in the cervical spine) with the anterior odontoid process articulating with C1 and inferior and superior facet joints. This odontoid...
process has a precarious blood supply, placing it at risk for nonunion and malunion when fractured. The atlantooccipital articulation accounts for 50% of the flexion and extension range of motion (ROM) of the neck and the alantoaxial joint accounts for 50% of the rotational ROM of the neck.

Each of the remaining cervical vertebrae consists of an anterior body with a posterior projecting ring of the transverse and spinous processes that form the vertebral foramen for the spinal cord. The most prominent spinous processes that can be palpated are C2 and C7 (vertebral prominens). The spinous and transverse processes are the origin and insertion of the multiple interspinous and intervertebral ligaments and muscles. Between each vertebral body are intervertebral discs, each consisting of a gelatinous center (nucleus pulposus) with a tougher, multilayered (onion skin–like) surrounding annulus fibrosis. Each vertebral body from C3 to C7 articulates with the others through a bony lip (uncus) off the lateral margins called the joints of Luschka. These are not considered true diarthrodial joints (because they have no synovium); however, they may develop degenerative spurs, limiting motion. The facet joints are part of the transverse process and are paired superiorly and inferiorly. The facet joints have articular cartilage and a synovium that can be involved in degenerative and inflammatory processes. Among the multiple interspinous and intervertebral ligaments, the most important are the anterior and posterior longitudinal ligaments along the vertebral bodies, the ligamentum nuchae along the spinous process, and the ligamentum flavum along the anterior surfaces of the laminae. The weaker posterior longitudinal ligaments help stabilize the intervertebral discs posteriorly and are often damaged in disc herniation. Hypertrophy of the ligamentum flavum may contribute to spinal stenosis or nerve root impingement. Eight cervical nerve roots exit posterolaterally through the neuroforamina. Given that there are seven vertebrae, each cervical root emerges through a neuroforamen above the vertebra of its number (ie, the C6 root arises between C5 and C6, with C8 exiting between C7 and T1. The cervical cord gives rise to the nerves that innervate the neck, upper extremity, and diaphragm. In the evaluation of problems related to the cervical spine, the physician should have a basic understanding of the motor and sensory innervations of the upper extremity (Table 25-1).

The musculature of the cervical spine includes flexors, extensors, lateral flexors, and rotators. Major flexors include the sternocleidomastoid, scalenes, and prevertebrals. Extensors include the posterior paravertebral muscles (splenius, semispinalis, capitis) and trapezius. Lateral flexors include the sternocleidomastoid, scalenes, and interspinous (between the transverse processes) muscles, and the rotators include the sternocleidomastoid and the interspinous muscles. The ability of the cervical spine to absorb and diffuse the energy from acute injuries is related to its lordotic curvature and the energy absorption of the paraspinal muscles and intervertebral discs. The paraspinal muscles can be strained and become spastic. Occasionally, so-called trigger points—hypermotable myo-nodules and taut muscle fiber bands—may develop.

The combined motion of all the preceding joints gives a significant ROM of the neck, allowing the head to scan the environment with the eyes and ears. Normal ROM includes extension of 70 degrees (chin straight up to the ceiling), flexion of 60 degrees (chin on chest, or within 3 cm of chest), lateral flexion of approximately 45 degrees (ear to shoulder), and rotation of approximately 80 degrees (looking right and left). The center of motion for flexion is C5-C6 and for extension, C6-C7; hence, degeneration and injury often occurs at these levels. ROM can be reduced by injury to muscles, vertebrae, or discs, or by degenerative processes causing spondylosis and spinal stenosis.

Table 25-1. Upper extremity motor and sensory innervations.

<table>
<thead>
<tr>
<th>Spinal Level</th>
<th>Motor</th>
<th>Reflex</th>
<th>Sensory</th>
<th>Peripheral Nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5</td>
<td>Deltoid (shoulder abduction)</td>
<td>Biceps</td>
<td>Lateral shoulder</td>
<td>Axillary</td>
</tr>
<tr>
<td></td>
<td>Biceps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C6</td>
<td>Biceps (elbow flexion)</td>
<td>Brachioradialis</td>
<td>Lateral forearm</td>
<td>Musculocutaneous</td>
</tr>
<tr>
<td></td>
<td>Wrist extensors</td>
<td></td>
<td>Dorsal first web space</td>
<td>Radial</td>
</tr>
<tr>
<td>C7</td>
<td>Triceps (elbow extension)</td>
<td>Triceps</td>
<td>Dorsal middle finger</td>
<td>Median</td>
</tr>
<tr>
<td></td>
<td>Wrist flexion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Finger extension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C8</td>
<td>Finger flexors</td>
<td>None</td>
<td>Ring finger</td>
<td>Ulnar</td>
</tr>
<tr>
<td></td>
<td>Thumb flexion/opposition</td>
<td></td>
<td>Small finger</td>
<td>Medial antebrachial cutaneous</td>
</tr>
<tr>
<td>T1</td>
<td>Hand intrinsics (finger</td>
<td>None</td>
<td>Medial arm axilla</td>
<td>Medial brachial cutaneous</td>
</tr>
<tr>
<td></td>
<td>abduction/adduction)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prevention strategies for high-risk groups have been employed for both neck and lower back pain. A review of 27 investigations into educational efforts, exercises, ergonomics, and risk factor modification found sufficient evidence for only strengthening exercises as an effective prevention strategy. A more recent randomized controlled trial showed that specific resistance and all-round exercise programs were more effective than general health counseling in preventing occupation-related neck pain.

Clinal Findings

A. Symptoms and Signs

The mechanism of injury of the cervical spine, like that of other injuries, can be classified in multiple ways: acute injuries—including a fall, blow to the head, or the whiplash injury—or chronic-repetitive injury—associated with recreational or occupational activities. Other classifications can include the direction of the stress or force generating the injury: flexion, extension-hyperextension, axial load, lateral flexion, or rotation. At 30 degrees of forward flexion, the cervical spine is straight and most vulnerable to axial load-type injuries. Most chronic neck pain is associated with poor posture and ergonomics, anxiety or depression, neck strain, or occupational and sport-related injuries.

In the evaluation of cervical spine problems the most important first step is to obtain a thorough history, ascertaining the mechanism of injury. In many cases, the mechanism of injury may identify the injury or guide the physical examination. The examiner should identify any history of prior injuries or problems with the cervical spine (e.g., a history of prior surgery or degenerative arthritis). Radicular or radiating symptoms in the upper extremity should be identified. This includes radiating pain, motor weakness, numbness, or paresthesias of the upper or lower extremities. Determining both the apparent origin and source of radiating symptoms is important. Occasionally, a myofascial trigger point may exhibit referral patterns that may mimic those of radiculopathy, and may often play a role in chronic neck pain. Conversely, musculoskeletal neck pain can also refer to the head and play a large role in cervicogenic headaches. Additionally, the examiner should ask about any symptoms related to upper motor neuron pathology. This includes bowel or bladder dysfunction or gait disturbance.

Additional information gathered should include the duration and course of symptoms, aggravating and alleviating motions or activities, and attempted prior treatments initiated by patients on their own or by other providers.

Comorbid diseases such as inflammatory spondyloarthropathies, cardiac disease, or gastrointestinal problems should be identified, as well as a history of tobacco or alcohol abuse. Current occupational and recreational activities and requirements should be identified, as they may contribute to the underlying problem and identify the desired end point for recovery and return to activity.

B. Cervical Spine Examination

The cervical spine is examined in an organized and systematic way that includes adequate exposure of the neck, upper back, and shoulders for observation; palpation of bony and soft tissues; evaluation of ROM; a Spurling test for nerve root irritation; assessment of Lhermitte sign for cervical radiculopathy; upper extremity motor and sensory examination; and evaluation for upper motor neuron symptoms.

1. Observation—Observation should begin as the patient walks into the examination room, looking for the presence or absence of normal fluid motion of the neck and arm swing with walking. After exposure, the examiner may note the posture (many patients have a poor head-forward with rounded-shoulder posture that contributes to chronic cervical muscular strain), shoulder position (looking for elevation from muscle spasm), and evidence of atrophy. The examiner should also observe for head tilt or rotation.

2. Palpation—Palpation of major bony prominences and the soft tissues should be performed. The spinous processes and the facet joints (about 1 cm lateral and deep to the spinous process) should be gently palpated, noting tenderness. (Caveat: If enough pressure is applied to the spinous process, pain can be produced in virtually any patient.) Palpation of the prevertebral and paravertebral muscles should be performed, noting hypertonicity, pain, or the presence of tender or trigger points. Common sites for trigger points include the levator scapulae (off the superior, medial margin of the scapula), upper trapezius, rhomboids, and upper paraspinals near the insertion into the occiput. Palpation of trigger points may elicit tenderness, referred pain (which may mimic radicular symptoms), or a local twitch response.

3. Range of motion—Active ROM should be tested first with judicious use of passive motion as pain permits. Motion should be tested in the six prime directions: forward flexion, extension, left and right lateral flexion, and left and right rotation. ROM can be recorded in degrees from the erect (neutral) position or as a percentage of the expected norm of chin on chest, chin to sky, ear to each shoulder, and rotation to each shoulder.

4. Spurling test—This test assesses for evidence of nerve root irritation, which can be related to spondylotic compression, discogenic compression, or the Stinger-Burner syndrome (a compression or stretch injury of the brachial plexus, commonly seen in football). To perform the Spurling test, the physician extends, side bends, and partially rotates the neck.
patient’s head toward the side being tested. An axial load is then gently applied to the top of the head. A positive test is indicated by radiation of pain, generally into the posterior shoulder or arm on the ipsilateral side. Although generally considered to be a reliable test of root irritation, one study of both normal and symptomatic patients—confirmed by electromyography (EMG)—found a sensitivity of 30% and a specificity of 93% for the Spurling test. It is therefore not a definitive screening test, but is useful in helping to confirm cervical radiculopathy.

5. Lhermitte sign—The Lhermitte sign may also be used to test for cervical radiculopathy. Forward flexion of the neck that causes paraesthesias down the spine or extremities suggests cervical radiculopathy, spondylosis, myelopathy, or multiple sclerosis. Manual cervical distraction may reduce neck and limb symptoms in cervical radiculopathy.

6. Upper extremity motor examination—This examination includes manual muscle testing and deep tendon reflexes (DTRs; see Table 25-1). A quick mnemonic to keep the upper extremity motor findings in order is *blocker, beggar, kisser, grabber, Spock* (Figure 25-1). By assuming these positions, the examiner can remember the motor innervation of the cervical roots in the upper extremity. The examiner can quickly check arm abduction (blocking position) for deltoid function, then resisted elbow flexion and extension (biceps and triceps), wrist extension and flexion, grip, and finger abduction (spread fingers). DTRs should be checked for the biceps (C5), triceps (C7), and brachioradialis (C6). Sensory testing should focus on the dermatomes for the cervical roots, with focus on the lateral deltoid area (C5), dorsal first web space (C6), dorsal middle finger (C7), small finger (C8), and inner arm (T1). Upper extremity testing for upper motor neuron findings can be accomplished by looking for a Hoffman sign: With the third proximal interphalangeal joint immobilized, the patient extends the third distal interphalangeal joint with a quick flexion-flick; an abnormal flexion reflex in the thumb or other fingers is a positive test (positive Hoffman sign).

Testing for thoracic outlet syndrome can be accomplished with the Adson test and Roo test. In the Adson test, the patient’s neck is extended, with the head rotated toward the

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**Figure 25-1.** Upper extremity motor evaluation.
affected side and lungs in deep inspiration, while the examiner palpates the ipsilateral radial pulse. Decrease in the amplitude of the radial pulse with this maneuver is a positive test. The Roo test (also called the elevated arm stress test) is performed with both the patient’s arms (shoulders) in an abducted and externally rotated position (90 degrees each), and the elbow flexed to 90 degrees. The patient then opens and closes both hands for 3 minutes. Inability to continue this maneuver for 3 minutes due to reproduction of symptoms suggests thoracic outlet syndrome. Reasonably low false-positive rates make the Roo test the preferred test.

7. Upper motor neuron symptoms—Lower extremity testing for upper motor neuron findings should be performed, including DTRs (looking for hyperreflexia), assessment for clonus in the ankle, and testing for the Babinski reflex. The Babinski reflex may be elicited by firmly stroking the sole (plantar surface) of the foot. The reflex is present if the great toe dorsiflexes and the other toes fan out (abduct). This is normal in younger children, but abnormal after the age of 2 years. If the examiner has not queried about bowel and bladder function, it can be done at this time.

C. Laboratory Findings

In patients whose upper extremity weakness is not improving with therapy, electromyography (EMG) and nerve conduction studies (NCS) should be considered. EMG and NCS are useful in evaluating upper extremity neurologic disorders and help to distinguish between peripheral (including brachial plexus) and nerve root injuries. EMG and NCS also distinguish between stable and active denervating and recovery processes. Testing may not be diagnostic until 3-4 weeks after an acute nerve injury, so this study should not be ordered in the acute setting. In general, however, routine follow-up EMG and NCS in patients with whiplash injuries may not contribute useful information to clinical and imaging findings.

Other laboratory studies—including complete blood count, sedimentation rate, rheumatoid factor, and others—should be reserved for the evaluation of spondylarthropathies and play little role in the evaluation of most cases of isolated neck pain.

D. Imaging Studies

Potential imaging studies of the cervical spine can include plain radiographs, magnetic resonance imaging (MRI), computed tomography (CT), bone scan, and myelography. Bone scan does not significantly contribute to the evaluation of neck pain in most acute or chronic settings. Plain films include the basic three-view series (anteroposterior, lateral, open mouth), oblique, and lateral flexion-extension views. Recommendations about the use of imaging studies in the evaluation of neck pain can be divided into recommendations for acute (traumatic) or chronic neck pain.

In the acute trauma situation, the three-view radiograph is the basic study of choice. In one study of 34,000 blunt trauma patients, the three-view radiograph was abnormal and diagnostic in 498 of 818 patients, nondiagnostic in 320, and failed to note abnormality in 23. CT or lateral flexion and extension views can be used to further evaluate nondiagnostic radiographs or cases of high clinical suspicion for injury.

Cervical fractures may be ruled out on a clinical basis if the patient does not complain of neck pain when asked; does not have a history of loss of consciousness; does not have mental status change from trauma, drugs, or alcohol; does not have symptoms referable to the neck (paralysis or sensory change—present or resolved); does not have midline cervical tenderness to palpation; and does not have other distracting painful injuries.

The American College of Radiology (ACR) published the ACR appropriateness criteria for imaging of suspected cervical spine trauma in 1995 and updated the criteria in 1999, 2002, and again in 2007 (http://acr.org). It concluded that cervical imaging is not required in patients who are alert; asymptomatic; without cervical tenderness, neurologic findings, or distracting injury; with or without a cervical collar; and with or without a history of unconsciousness. In 2007, the panel concluded that thin-section CT, and not plain radiography, is the screening study of choice for suspected cervical spine injury. If CT scanning is not readily available, those with cervical tenderness should have, at a minimum, the basic three-view series. Patients with upper or lower extremity paraesthesias (or other neurologic findings) should have a CT scan of the cervical spine; MRI of the cervical spine may be considered, depending on the CT findings or in cases where myelopathy is suspected. Patients with femur fractures should be evaluated for imaging (eg, three-view series), as previously discussed. Those who are unconscious at the time of evaluation or are in an altered mental state (due to alcohol or drugs) should receive both the three-view series and a CT scan of the cervical spine. Patients with neck pain and clinical findings suggestive of ligamentous injury, with normal radiographic and CT findings, may be considered for MRI of the cervical spine and flexion-extension radiographs.

The ACR appropriateness criteria for imaging of chronic neck pain were published in 1998, and updated in 2005, and 2008. It was concluded that there are no existing evidence-based guidelines for the radiological evaluation of the patient with chronic neck pain. The initial imaging study should be the three-view series. The most common findings include a loss of lordosis (straight cervical spine) or disc space narrowing with degenerative change at the C5-C6 and C4-C5 levels. Oblique and flexion-extension views should be ordered at the discretion of the attending physician. When patients have chronic neck pain after hyperextension or flexion injury with normal radiographs and persistent pain or evidence of neurologic injury, lateral flexion-extension views should be considered to rule out instability. Abnormal findings include more than 3.5-mm horizontal displacement or more than 11 degrees of rotational difference to that of the adjacent vertebrae on resting or flexion-extension lateral radiographs. Oblique radiographs may be helpful to look for
bony encroachment of the neuroforamina in the evaluation of radicular neck pain. MRI should be performed on all patients who have chronic neck pain with neurologic signs or symptoms, or both. If there is a contraindication to MRI (ie, pacemaker, nonavailability, claustrophobia, or interfering hardware in the neck), CT myelography is recommended.


Differential Diagnosis

See Table 25-2.

Treatment

Multiple treatment options are available for the patient and practitioner, although there is limited evidence-based support for the efficacy of most treatment options used for such patients. Early management focuses on proper initial evaluation, use of over-the-counter analgesics, early return to motion, and judicious use of physical modalities. Acupuncture and manual therapy may help reduce pain early after injury or presentation. Chronic neck pain can be related to psychosocial factors at home and in the workplace and may be tied to litigation in whiplash-type injuries. Specialty consultation beyond physical therapy is rarely needed.

A. Initial Care

Initial management should include avoidance of aggravating factors at work or with recreational activities, as well as pain management, recognizing that most pain is self-limiting. Subsequent management should focus on early return to motion, isometric strengthening, and modification of occupational or recreational aggravating factors with return to activity—observing good ergonomics.

Absolute rest should be limited to a very short period of time (ie, <1-2 days). This includes the use of cervical collars. Early motion should be encouraged as soon as severe pain allows. Early mobilization after whiplash-type injury is associated with better pain relief and return of motion. Patients should focus on proper posture (neck centered and back over the shoulders) and gentle motion of the neck in the six major motions mentioned earlier under testing for ROM. Each position should be held for 15-20 seconds. Proprioceptive neuromuscular facilitation or muscle energy techniques may be employed in a structured program with physical therapy or in a home program with the goal to improve motion. This is done by having patients move the head in a direction to the point of pain. Next, they attempt to move in the opposite direction against the resistance of their own hand on the chin for a count of 5, contracting the rehabilitating muscle

<table>
<thead>
<tr>
<th>Acute Injury</th>
<th>Noninflammatory Disease</th>
<th>Inflammatory Disease</th>
<th>Infectious Causes</th>
<th>Neoplasm</th>
<th>Referred Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical sprain, strain,</td>
<td>Cervical osteoarthritis (spondylosis)</td>
<td>Rheumatoid arthritis</td>
<td>Meningitis</td>
<td>Primary</td>
<td>Temporomandibular joint</td>
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<tr>
<td>spasm, whiplash</td>
<td>Discogenic neck pain</td>
<td>Spondyloarthropathies</td>
<td>Osteomyelitis</td>
<td>Myeloma</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Cervical tendonitis,</td>
<td>Cervical spinal stenosis</td>
<td>Juvenile rheumatoid arthritis</td>
<td>Infectious discitis</td>
<td>Cord tumor</td>
<td>Diaphragmatic irritation</td>
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<td>tendinosis</td>
<td>Cervical myelopathy</td>
<td>Arthritis</td>
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<td>Metastatic</td>
<td>Gastrointestinal irritation</td>
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<td>Cervical instability</td>
<td>Myofascial pain</td>
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<td>Gastric ulcer</td>
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<td>Fractures</td>
<td>Trigger points</td>
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<td>Gall bladder</td>
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<td>Vertebral body</td>
<td>Fibromyalgia</td>
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<td>Pancreas</td>
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<td>Tear drop</td>
<td>Reflex sympathetic dystrophy/complex regional pain syndrome</td>
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<td>Thoracic outlet syndrome</td>
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<td>Burst</td>
<td>Migraines (or variants)</td>
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<td>Shoulder disorders</td>
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<tr>
<td>Chance</td>
<td>Torticollis</td>
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<td>Brachial plexus injuries</td>
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<td>Compression</td>
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<td>Peripheral nerve injury</td>
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<td>Transverse process</td>
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<td>Facet</td>
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<td>Odontoid (C2)</td>
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<tr>
<td>Hangman (C2)</td>
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<td>Jefferson (C1)</td>
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<td>Stinger or Burner</td>
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Table 25-2. Differential diagnosis of neck pain.
B. Pain Management

Pain management may take the form of ice, medications, physical modalities, or manual therapy techniques. Application of ice (15 minutes every 2 hours) is effective for acute pain after injury or for post-activity pain during the recovery process. Medications used in the management of acute and chronic neck pain include salicylates (aspirin, 500 mg four times daily, or salsalate, 500 mg three times daily), non-steroidal anti-inflammatory drugs (NSAIDs; ibuprofen, 600 mg four times daily or 800 mg three times daily; naproxen, 500 mg twice daily; indomethacin, 25-50 mg three times daily; piroxicam, 20 mg/d; or cyclooxygenase-2 inhibitors, eg, celecoxib, 200 mg/d), acetaminophen (500-1000 mg four times daily), muscle relaxants (diazepam, 5 mg three times daily; methocarbamol, 1000-1500 mg four times daily; and cyclobenzaprine, 10 mg three times daily), narcotic medications (acetaminophen with codeine, acetaminophen with oxycodone, acetylmethadol with hydrocodone, meperidine), and corticosteroids. For acute radicular symptoms, a short course of corticosteroids may be considered (prednisone, 40-60 mg/d for 5-7 days) to reduce inflammation associated with a herniated nucleus pulposus. Although there is no literature to support the use of ice or systemic steroids, anecdotal evidence suggests that they may be helpful in the acute setting.

For pain that is becoming more chronic (eg, >30 days), tricyclic antidepressants (TCAs; nortriptyline, 25-50 mg, or amitriptyline, 10-50 mg) or selective serotonin reuptake inhibitors (SSRIs; fluoxetine, 10-60 mg, or sertraline, 25-100 mg at bedtime) may be used at night for chronic pain management and management of sleep disturbance that often accompanies chronic pain of any source. Side effects of TCAs include excessive drowsiness, dry mouth, urinary retention, and potential cardiac conduction problems. Side effects of SSRIs include insomnia, drowsiness, dry mouth, nausea, headache, and anorexia. The combination of SSRIs and TCAs may result in increased serum levels of the TCA and toxicity. Randomized controlled studies support the use of simple analgesics and NSAIDs in the management of acute pain but do not support the other treatment options.

C. Physical Modalities

Multiple physical modalities are available for the management of pain and to improve motion, although there is little clinical evidence of their effectiveness and few well-designed randomized controlled studies that support their use in management of acute or chronic neck pain. These modalities include the application of heat, ultrasound, cervical traction, acupuncture, and electrical stimulation (including transcutaneous electrical nerve stimulation [TENS]). Cervical traction can be effective for relief of spasm or in the management of radicular pain from a herniated nucleus pulposus or spondylosis. Traction may be performed in a controlled setting at physical therapy or with the use of home traction units. Typical sessions in physical therapy are 2-3 days per week for 30 minutes per session. A typical home cervical traction regimen would start at 10 lb of longitudinal traction and titrate up by 5 lb every 1-2 days until a goal of 20-30 lb is reached. Home traction is used on a daily or every-other-day basis. Heat, ultrasound, and electric stimulation may be effective in local pain management, allowing early return to normal motion.

D. Acupuncture, Acupressure, and Needling

Acupuncture has been shown to be effective in the treatment of neck pain—although literature supporting its effectiveness beyond five treatment sessions for acute neck pain or four weeks of treatment for chronic neck pain—is limited. A home program of ischemic pressure (acupressure) with stretching has also been shown to be effective in the management of myofascial neck pain and trigger points. Although much of the evidence on trigger point injections has been conflicting, a recent systematic review reported that trigger point injections may be useful in relieving trigger point–related pain in chronic conditions lasting longer than 3 months. Outcomes were not significantly different in regards to the injectant used, including dry needling. However, the injection of a local anesthetic does seem to decrease discomfort related to the needling process.

E. Manual Therapy

Manual therapy (eg, osteopathic and chiropractic manipulation, or manual therapy techniques applied by a physical therapist) is commonly used in the management of chronic neck and lower back pain, although there is limited evidence supporting its use. For acute neck injuries, however, there is some evidence supporting the use of manual techniques involving passive neck motion aimed at restoring normal spinal ROM and function, excluding spinal manipulations. A study on the use of manual therapy in the treatment of neck and low back pain showed an average improvement of 53.8% in acute pain and 48.4% in chronic pain with 12 treatments over a 4-week period of time. A case report of a patient with persistent neck and arm pain—after failed cervical disc surgery with resolution after a program of manual therapy and rehabilitative exercises—further supports the use of manual therapy in the management of both myofascial and radicular neck pain. However, caution should be exercised, as one study reported that 30% of patients undergoing spinal manipulation had adverse effects, especially in those with severe neck pain or severe headache prior to treatment.

F. Therapeutic Exercise

There is some evidence to support the effectiveness of active ROM exercises for acute mechanical neck disorders. As throughought the entire maneuver. Then they attempt to further move in the original direction, usually with improved motion. This should be done in the six major directions.
patients recover, a program of strengthening should be instituted. Simple isometric exercises focusing on resisted forward flexion, extension, and right and left lateral flexion will improve pain and strength, contributing to recovery and long-term resistance to further injury. Attention to posture and an ergonomic survey are also important and can help in customizing a complete therapeutic exercise program for both treatment and prevention of neck pain.

G. Referral

Specialty referral may be considered at multiple points in the recovery process to aid in diagnosis or treatment of acute or chronic neck pain. Physical therapy may be used early in the process to incorporate physical modalities and initiate a strengthening program. However, evidence supporting the use of electrotherapy in neck disorders is lacking, limited, or conflicting. Typical consults involve two to three sessions per week for 4-6 weeks, with follow-up evaluation by the primary provider. Physical Medicine and Rehabilitation (PM&R) involvement may be considered for comanagement of chronic pain of any source and to obtain EMGs. The input of a neurologist may be considered to obtain EMGs or for consultation in patients with confusing neurologic conditions. Neurosurgery or orthopedic-spinal surgery should be considered for patients requiring operative management. Early referral should be considered for severe muscle weakness, fractures, and evidence of myelopathy (long-track signs). Success rates for surgery have been reported to be as high as 80%-90% for radicular pain and 60%-70% for myelopathy. There is insufficient evidence to compare conservative treatment with surgical management of patients who have neck pain and radiculopathy. Referral for chronic pain management should be considered for patients who have chronic radiating pain after 9-12 weeks of conservative management. Referral for anesthesia or to a pain clinic should be considered for comanagement of patients with chronic pain or consideration of epidural steroid (ESI) or facet joint injections. Two randomized controlled studies provided limited evidence to support the use of ESI in chronic neck pain. Intramuscular injections of lidocaine, similar to those used in trigger-point injections, may be effective in patients with chronic mechanical neck pain. Intramuscular injections of botulinum toxin type A have been found to be no more efficacious than saline.


Prognosis

Neck pain usually resolves in days to weeks, but like low back pain can become recurrent. The incidence of chronic neck pain is about 10%, and about 5% of people will experience severe disability. Patients who experience symptoms for at least 6 months have a less than 50% chance of recovering even with aggressive therapy. Predictors of chronic neck pain include a prior history of neck pain or injury, female gender, number of children, poor self-assessed health, poor psychological status (eg, excessive concerns about symptoms, unrealistic expectations of treatment, and psychosocial concerns), and history of low back pain.

Up to 40% of patients with whiplash injuries report symptoms for up to 15 years post injury. These patients have a three times higher risk of neck pain in the next 7 years. A Swedish study showed that 55% of an exposed group and 29% of a control group had residual symptoms up to 17 years post injury. Initial signs and symptoms that are predictive of slower recovery from whiplash-type injuries include mode of...
motor vehicle collision, age more than 60 years, female gender, neck pain on palpation, muscle pain, headache, and pain or numbness radiating to the arms, hands, or shoulders. High initial pain intensity is an important predictor of delayed functional recovery. The single best estimation of handicap due to whiplash injury was return of normal cervical ROM.


Web Sites
Useful sites for patient education on topics such as home rehabilitation, correction of occupational and postural risk factors:

http://familydoctor.org/x2557.xml
http://www.nismat.org/orthocor/programs/neck/neckex.html
http://www.nismat.org/ptcor/neck
Cancer Screening in Women
Breast Cancer

Nicole Powell-Dunford, MD

General Considerations

Breast cancer is the second most common cancer in women after skin cancer, with cancer related mortality only exceeded by lung cancer. Breast cancer is most often caused by a number of various genetic insults leading to dysplastic cellular changes; only a small minority is clearly linked to heritable mutations in the BRCA1 and BRCA2 tumor suppressor genes. However BRCA positivity is a strong risk factor for cancer development, with both BRCA1- and BRCA2-positive individuals at significantly increased risk for breast cancer. Other risk factors for breast cancer include earlier age of menarche, later age of menopause, nulliparity, and late age of first birth, all of which determine the cumulative number of ovarian cycles. Obesity, alcohol use, older age, decreased physical activity, other genetic and environmental factors as well as hormone replacement therapy (HRT) have also been linked to risk for breast cancer. The Breast Cancer Risk Assessment Tool, based on the Gail model, is an interactive tool designed by scientists at the National Cancer Institute (NCI) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) to estimate a woman’s risk of developing invasive breast cancer. Available online, this tool calculates a 5-year breast cancer risk in women ages 35 and older based on ethnicity, current age, age of menarche, age of first live birth, and history of breast biopsy or history of any breast cancer or of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS).

Primary and Secondary Prevention

Breast cancer in the general population is often discovered on examination and/or mammography. While these techniques have clearly reduced the risk of breast cancer death through earlier detection, neither technique is perfect. False-positive results are a source of considerable anxiety, cost, and morbidity—especially in younger populations who are much more likely to have benign breast disease. Computer-aided detection (CAD) and enhanced digital technologies may improve accuracy of mammography. However, screen film mammography is the gold standard for breast cancer screening. As a result of emerging evidence about the potential harms of early screening, controversy surrounds the ideal age of initiation of mammogram surveillance and appropriate screening intervals for breast cancer in the general population, as well as the efficacy of breast self examination. Previously, there had been a relatively broad consensus among multiple professional organizations that 40 years of age was the ideal age to institute screening mammography. In 2009, however, US Preventive Services Task Force (USPSTF) endorsed 50 rather than 40 years as the recommended age for initiation of mammogram screening in the general population, revising an earlier recommendation. A summary of current recommendations from the American Cancer Society, American College of Gynecologist and Obstetricians, as well as the USPSTF is found in Table 26-1. Recommendations for breast self-examination, once generally accepted, have also evolved and are outlined in Table 26-1.

Identification of BCRA genetic mutation as a critical factor in the development of breast cancer in some women has revolutionized breast cancer prevention methods, which were previously limited to clinical and self examination, radiological screening and biopsies (Table 26-2). Women positive for this heritable mutation may also benefit from prophylactic medication, enhanced surveillance techniques as well as prophylactic surgery. Tamoxifen prophylaxis in high-risk women has significantly reduced breast cancer incidence in this group. Further research is required to establish the efficacy of raloxifene and the aromatase inhibitors. Prophylactic medication is not prescribed for use in the general population given the risks of deep vein thrombosis (DVT) and endometrial cancer. Both MRI and ultrasound


have been used to augment standard mammography in high risk women. Although it is clear that MRI-guided biopsy should be available at the referral diagnostic center in order to avoid requirement for a repeat MRI, the efficacy of ultrasound and MRI screening is not presently clear. Prophylactic bilateral total mastectomy however has been found to be extremely effective in reducing the incidence of breast cancer in BRCA-positive women.

Table 26-1. Current mammogram and examination recommendations.

<table>
<thead>
<tr>
<th></th>
<th>Mammogram 40-49</th>
<th>Mammogram 50+</th>
<th>Examinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOG</td>
<td>Women aged 40-49 y should have screening mammography every 1-2 y.</td>
<td>Women aged ≥50 y should have annual screening mammography.</td>
<td>Despite a lack of definitive data for or against breast self-examination, breast self-examination has the potential to detect palpable breast cancer and can be recommended. All women should have clinical breast examinations annually as part of the physical examination.</td>
</tr>
<tr>
<td>ACS</td>
<td>Women aged ≥40 y should have a screening mammogram every year and should continue to do so for as long as they are in good health.</td>
<td>Women aged ≥40 should have a screening mammogram every year and should continue to do so for as long as they are in good health.</td>
<td>Women in their 20s and 30s should have a clinical breast exam (CBE) as part of a periodic (regular) health exam by a health professional, at least every 3 years. After age 40, women should have a breast exam by a health professional every year. Breast self exam (BSE) is an option for women starting in their 20s. Women should be told about the benefits and limitations of BSE. Women should report any breast changes to their health professional right away.</td>
</tr>
<tr>
<td>USPSTF</td>
<td>USPSTF recommends against routine screening mammography in women aged 40-49 y. The decision to start regular, biennial screening mammography before the age of 50 y should be an individual one and should take patient context into account, including the patient’s values regarding specific benefits and harms. (Grade C recommendation)</td>
<td>The USPSTF recommends biennial screening mammography for women aged 50-74 y. (Grade: B recommendation)</td>
<td>The USPSTF recommends against teaching breast self-examination (BSE). (Grade D recommendation)</td>
</tr>
<tr>
<td>WHO</td>
<td>Mammography every 1-2 y for women aged 50-69 y,</td>
<td>Mammography every 1-2 y for women aged 50-69 y,</td>
<td>CBE/BSE not recommended</td>
</tr>
</tbody>
</table>

ACOG, American College of Obstetricians and Gynecologists; ACS, American Cancer Society; USPSTF: United States Preventative Services Task Force; WHO, World Health Organization.

Table 26-2. Indications for genetic referral for BCRA testing.

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<table>
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<tbody>
<tr>
<td>A first-degree relative with breast cancer before age 40</td>
</tr>
<tr>
<td>Two or more relatives with breast or ovarian cancer at any age</td>
</tr>
<tr>
<td>Three or more relatives with breast, ovarian, or colon cancer at any age</td>
</tr>
</tbody>
</table>


Assessment and Diagnosis

Breast cancer most commonly presents as a painless, irregularly bordered mass. Other presentations may include local swelling, dimpling, breast pain, skin and nipple changes as well as nipple discharge. Rarely, a breast cancer may present as axillary lymphadenopathy before localized breast changes are appreciated. Markedly delayed clinical presentations, such as those associated with denial of diagnosis, may include pain and/or fracture from bony metastasis. A concerning breast mass can be further evaluated through diagnostic mammography, ultrasound with or without fine needle aspiration, and/or ductal lavage and/or ductogram. Food and Drug Administration (FDA) approved adjuncts to mammography include scintimammography, positron emission tomography, and electrical impedance imaging. MRI may afford very high sensitivity in detecting small masses, but are expensive, associated with IV contrast risks, and are not widely available with guided biopsy. Cumulative radiation doses from screening mammograms may contribute to significant overall radiation risks. Pathological
specimens may be obtained for diagnosis through fine needle aspiration, large (core) needle biopsy, and/or open surgical biopsy, each technique providing specific advantages and disadvantages. Disparities exist in breast cancer screening, diagnosis, and survival. Although deaths caused by breast cancer have decreased among white women, African American women continue to have higher rates of mortality from breast and cervical cancer, potentially as a result of reduced screening. Table 26-3 illustrates recommended screening for high-risk women.

### Table 26-3. Screening recommendations for high-risk women.

<table>
<thead>
<tr>
<th></th>
<th>BCRA Testing</th>
<th>Imaging</th>
<th>Prophylactic Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOG</td>
<td>Evaluating a patient’s risk of hereditary breast and ovarian cancer syndrome is an important first step in cancer prevention and early detection and should be a routine part of ob-gyn practice. Those who are likely to have the syndrome should be referred for further assessment to a clinician with expertise in genetics.</td>
<td>No specific recommendation for imaging in high risk women.</td>
<td>Any decision to use tamoxifen be made on an individual basis after consideration of the patient’s medical history, risk assessment, and preferences, and with attention to the ability to manage complications of therapy. Women with BRCA1 or BRCA2 mutations should be offered risk-reducing salpingo-oophorectomy by age 40 y or when childbearing is complete.</td>
</tr>
<tr>
<td>ACS</td>
<td>No specific recommendation for or against genetic testing.</td>
<td>Women at high risk (&gt;20% lifetime risk) should get an MRI and a mammogram every year. Women at moderately increased risk (15%-20% lifetime risk) should talk with their doctors about the benefits and limitations of adding MRI screening to their yearly mammogram. Yearly MRI screening is not recommended for women whose lifetime risk of breast cancer is &lt;15%.</td>
<td>American Cancer Society (ACS) recommends that women taking tamoxifen learn about their testing options for endometrial cancer but do not recommend routine testing for these women.</td>
</tr>
<tr>
<td>USPSTF</td>
<td>The US Preventive Services Task Force (USPSTF) recommends against routine referral for genetic counseling or routine breast cancer susceptibility gene (BRCA) testing for women whose family history is not associated with an increased risk for deleterious mutations in breast cancer susceptibility gene 1 (BRCA1) or breast cancer susceptibility gene 2 (BRCA2). (Grade D recommendation) The USPSTF recommends that women whose family history is associated with an increased risk for deleterious mutations in BRCA1 or BRCA2 genes be referred for genetic counseling and evaluation for BRCA testing. (Grade B recommendation)</td>
<td>The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of either digital mammography or magnetic resonance imaging (MRI) instead of film mammography as screening modalities for breast cancer. (Grade I recommendation)</td>
<td>The U.S. Preventive Services Task Force (USPSTF) recommends against routine use of tamoxifen or raloxifene for the primary prevention of breast cancer in women at low or average risk for breast cancer. (Grade D recommendation) The USPSTF recommends that clinicians discuss chemoprevention with women at high risk for breast cancer and at low risk for adverse effects of chemoprevention. Clinicians should inform patients of the potential benefits and harms of chemoprevention. (Grade B recommendation)</td>
</tr>
</tbody>
</table>

*Definition of high risk: known BRCA1 or BRCA2 gene mutation, a first-degree relative (parent, brother, sister, or child) with a BRCA1 or BRCA2 gene mutation without a personal history of genetic testing, a lifetime risk of breast cancer of 20%-25% or greater, according to risk assessment tools that are based mainly on family history, a history of radiation therapy to the chest between the ages of 10 and 30 years, and/or Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome, or have first-degree relatives with one of these syndromes.*
Cervical Cancer

General Considerations

Although cervical cancer kills thousands of women each year in the United States, mortality from this disease is largely preventable through effective primary and secondary strategies. A preponderance of evidence has established high-risk HPV serotype infection as the primary and necessary cause of cervical cancer. Factors such as smoking, long-term OCP (oral contraceptive pills) use, immunosuppression, and parity influence either human papillomavirus (HPV) acquisition or natural history of disease progression, with smoking being an important modifiable risk factor for cancers in general. Safe sexual practices as well as immunization with FDA-approved Gardisil can prevent oncogenic viral transmission, with Papanicolaou (Pap) smear screening capable of remarkable reductions in cancer mortality linked to HPV infection.

The human papillomavirus quadrivalent (types 6, 11, 16, 18) recombinant vaccine (Gardisil) is derived from noninfectious highly purified virus-like particles (VLPs); this immunization induces good immunogenicity against high-risk types of HPV and reduces cervical as well as external genital lesions associated with HPV. This immunization is administered intramuscularly in three doses at intervals of 0, 2, and 6 months. As with any immunization, Gardisil can be associated with pain as well as syncope with occasional syncpe-related tonic-clonic movement. FDA has granted approval for use of Gardisil in males and females between 9 and 26 years of age, and the Advisory Committee on Immunization Practices recommends immunization of females in the appropriate age group, but does not yet recommend universal immunization of males. Preliminary studies of immunogenicity of Gardisil in boys and men are promising. Universal immunization strategies may further reduce cervical cancer burden in women through decreased transmission rates. Abstinence, monogamy, and use of barrier devices such as condoms clearly have the potential to reduce oncogenic viral transmission. However, abstinence-only programs may not reduce behaviors associated with HPV transmission while simultaneously withholding preventative information about barrier methods. In terms of secondary prevention, cervical cancer screening through Pap smears is highly effective in reducing the incidence and mortality associated with cervical cancer. HPV cytological testing can augment traditional Pap smear screening and has been incorporated into recent practice guidelines. Certain diagnostic procedures such as biopsy and LEEP (loop electrosurgical excision procedure) may be simultaneously diagnostic and therapeutic.

Assessment and Diagnosis

Invasive cervical cancer which has not been identified at an earlier stage through screening may present clinically or through an abnormal Pap smear. In these cases of late diagnosis of invasive disease, most present with abnormal bleeding or discharge, while a minority will present with an abnormal Pap screening, pain, or other symptoms. Invasive cervical cancer that presents with clinical symptoms rather than being identified through a Pap smear abnormality is associated with significantly increased tumor size and worsened prognosis. Short-term disease-free survival is significantly shortened in women presenting with abnormal bleeding and/or pain. In contrast, the vast majority of invasive cancers identified through Pap smear screening are limited to nonmetastatic disease, with significantly increased rates of disease-free survival. Other manifestations of invasive cervical cancer aside from abnormal bleeding, abnormal vaginal discharge, and localized pain may include symptoms of metastatic disease within the pelvic region.
Diagnosis and appropriate follow up of precancerous cervical cytology and histology serve as the basis for effective secondary prevention programs. Pap smears and newer cytological technologies provide cytological specimens from the high-risk cervical transformation zone in which cervical cancer typically arises. Cytological results vary from normal and nonspecific abnormalities to frank carcinoma. Colposcopic examination and cervical biopsy are subsequently used to evaluate concerning cytological abnormalities. A biopsy result of CIN I (carcinoma in situ) is considered the histological equivalent of a recent HPV infection and is usually associated with spontaneous disease remission, especially in younger populations; CIN II and CIN III are precursors to invasive cancer which entail closer follow-up.

In terms of initial secondary screening techniques, spatula with cytobrush is more effective in obtaining endocervical cells than a spatula alone, making their combined use a superior practice technique. Newer screening technologies such as thin layer cytology (ThinPrep, AutoCyte PREP), computerized rescreening (PapNet), and algorithm-based screening (AutoPap) are more costly than traditional methods but have not yet proven to be more effective in preventing invasive cervical cancer. An advantage of liquid-based cytology is the ability for reflex HPV DNA testing. Letters and other invitations for screening are effective in increasing numbers of women presenting for Pap smear screening. However continued disparities exist in women from disadvantaged socioeconomic backgrounds as well as within ethnic minority populations. In particular, cervical cancer is diagnosed at an early stage more often in whites than in African Americans and relative survival in whites continues to exceed that for African Americans.

**Clinical Practice Guidelines**

Guidelines for screening have evolved with increased understanding of the disease process and diagnostic technologies. Various organizations have established recommendations for initiation and discontinuance of screening efforts, along with intervals for continued surveillance. More detailed practice guidelines developed by various professional organizations outline specific surveillance recommendations of Pap, HPV DNA, and colposcopic abnormalities as they relate to patient age, and menopausal and pregnancy status. Likelihood of individual patient compliance as well as specific state laws governing management of the adolescent are important considerations when using any clinical practice guideline.

Recommendations for initiation, interval, and discontinuance of cervical cancer screening are detailed in Table 26-4. Detailed clinical practice guidelines for management of abnormal Pap smear and HPV DNA results have been set forth by the American Colposcopic Society for Colposcopy and Cervical Pathology as well as the American College of Gynecologists and Obstetricians. In general, adolescents have greater likelihood of disease remission; early disease is therefore managed less aggressively than in older women, in whom HPV infection is more likely to progress to cancer. Definitive follow-up of cytological abnormalities of pregnancy is typically reserved until post partum except in cases of frank malignancy with postpartum regression of disease being common; endocervical curettage is never acceptable in pregnancy. Given HPV immunization and advances in HPV DNA technologies, it is anticipated that these practice guidelines will continue to evolve. Figure 26-1 shows the management of women with ASC-US. Management of adolescent women with either ASCUS or LSIL can be seen in Figure 26-2. Management of women with ASC-H is explained in Figure 26-3. Figure 26-4 gives the management of women with LSIL. Figures 26-5 and 26-6 show the management of women and adolescent women with HSIL, and initial workup of women with AGC, respectively. Progress is still required to maximize cervical cancer screening in the primary care population. Table 26-5 compares cervical cancer screening and primary/secondary prevention goals as outlined by Healthy People 2010.

**Other Cancer Screening in Women**

*(For a review of colorectal cancer screening in women and men, see Chapter 65.)*

Given the high mortality rates associated with late presenting cancers such as lung and ovarian carcinoma, a screening test capable of early disease identification would be of tremendous value. However no adequate screening tests are available for a number of cancers. False-positive reports resulting from unproven screening tests can result in morbidity and mortality associated with unwarranted surgical exploration as well as needless anxiety. Furthermore, limited resources may be diverted away from screening programs which have proven effectiveness. Although aggressive testing may be warranted in certain high-risk populations in conjunction with genetic consultation, the use of improper screening tests must be strongly discouraged against. As good patient advocates, it is important for the family physician to...
educate patients who may be targeted for direct to consumer marketing. Engaging in healthy behaviors, smoking cessation, and daily physical activity are preventative against a number of cancers.

**LUNG CANCER**

Lung cancer has become an increasingly important cancer in women given dramatic increases in tobacco use in this population. Lung cancer has finally surpassed breast cancer as the number one cause of cancer mortality in US women. The USPSTF found fair evidence that screening with CT, CXR, or sputum cytology can detect lung cancer at an earlier stage than lung cancer would be detected in an unscreened population; however, the USPSTF found poor evidence that any screening strategy for lung cancer decreases mortality. Because of the invasive nature of diagnostic testing and the possibility of a high number of false-positive tests in certain populations, the USPSTF issued a Grade I “inconclusive” recommendation for lung cancer screening through these methods and is not advocated by a number of professional organizations. Smoking cessation however has clearly been linked with definitive reduction in lung cancer mortality. Physician counseling is effective in increasing smoking cessation rates and augmentation of counseling with pulmonary function testing further enhances tobacco cessation rates. Pregnancy is often an ideal time to address tobacco use, given additional risks to the fetus which often leads to increased maternal motivation for cessation. The USPSTF has issued a strong recommendation based on Grade A evidence for

<table>
<thead>
<tr>
<th>Table 26-4. Screening recommendations for cervical cancer.</th>
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<tbody>
<tr>
<td><strong>Initiation</strong></td>
</tr>
<tr>
<td>ACOG</td>
</tr>
<tr>
<td>ACS</td>
</tr>
<tr>
<td>USPSTF</td>
</tr>
</tbody>
</table>

ACOG, American College of Obstetricians and Gynecologists; ACS, American Cancer Society; USPSTF, United States Preventative Services Task Force.
screening all adults for tobacco use, providing tobacco cessation interventions for those who use tobacco products and providing augmented pregnancy-tailed counseling to those who women who smoke; only inconclusive evidence supports screening for tobacco use in children and adolescents REF.


Management of adolescent women with either atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL).

Figure 26-1. Management of adolescent women with either atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL). (Reprinted from The Journal of Lower Genital Tract Disease. Vol. 11 Issue 4, with the permission of ASCCP © American Society of Colposcopy of Cervical Pathology 2007. No copies of the algorithm with be made without the prior consent of ASCCP.)
OVARIAN CANCER

Nonspecific symptoms such as bloating, pelvic pain, anorexia, and urinary symptoms make ovarian cancer a difficult diagnosis. Frequently, disease is advanced at the time of diagnosis, making mortality high. Serum CA-125 levels are elevated in the setting of recurrent ovarian cancer and are used to monitor for disease recurrence. Use of this blood test has been explored as a potential tool for early diagnosis of primary disease. However, primary ovarian cancers are not always associated with elevated levels of CA-125, and CA-125 elevations may occur independently of ovarian pathology. Studies of fair quality involving the use of CEA as well as transvaginal ultrasound monitoring have resulted in earlier diagnosis of early ovarian cancer.

Management of women with atypical squamous cells: cannot exclude high-grade SIL (ASC-H).

Management of women with high-grade squamous intraepithelial lesion (HSIL)∗.

▲ Figure 26-3. Management of women with atypical squamous cells: cannot exclude high-grade SIL (ASC-H). (Reprinted from The Journal of Lower Genital Tract Disease. Vol. 11 Issue 4, with the permission of ASCCP © American Society of Colposcopy of Cervical Pathology 2007. No copies of the algorithm with be made without the prior consent of ASCCP.)

▲ Figure 26-4. Management of women with high-grade squamous intraepithelial lesion (HSIL). (Reprinted from The Journal of Lower Genital Tract Disease. Vol. 11 Issue 4, with the permission of ASCCP © American Society of Colposcopy of Cervical Pathology 2007. No copies of the algorithm with be made without the prior consent of ASCCP.)
Management of adolescent women (≤20 Years) with high-grade squamous intraepithelial lesion (HSIL).

**Figure 26-5.** Management of adolescent women (20 years and younger) with high-grade squamous intraepithelial lesion (HSIL). (Reprinted from The Journal of Lower Genital Tract Disease. Vol. 11 Issue 4, with the permission of ASCCP © American Society of Colposcopy of Cervical Pathology 2007. No copies of the algorithm with be made without the prior consent of ASCCP.)

**Figure 26-6.** Subsequent management of women with atypical glandular cells (AGC). (Reprinted from The Journal of Lower Genital Tract Disease. Vol. 11 Issue 4, with the permission of ASCCP © American Society of Colposcopy of Cervical Pathology 2007. No copies of the algorithm with be made without the prior consent of ASCCP.)
**ENDOMETRIAL CANCER**

Endometrial cancer is more common in older women and typically presents with abnormal vaginal bleeding. The American Cancer Society does not recommend routine screening for endometrial cancer, however women who may be at risk due to history of unopposed estrogen therapy, late menopause, tamoxifen therapy, nulliparity, infertility or failure to ovulate, obesity, diabetes, or hypertension should be encouraged to report and seek evaluation for abnormal bleeding. Additionally women at high risk of endometrial cancer due to known or suspected hereditary nonpolyposis colorectal cancer (HNPCC) associated genetic mutations should be routinely screened with endometrial biopsy beginning at age 35.

**CANCER SURVIVORS**

Survivors of childhood, adolescents, and young adult cancers are at increased risk for cancer recurrence as well as new primary cancers. Screening recommendations are available for this population through the American Cancer Society (Table 26-8).

---

**Table 26-5. National screening and prevention goals for cervical cancer.**

<table>
<thead>
<tr>
<th>Objective</th>
<th>1998</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women aged ≥18 y who have ever received a Pap test</td>
<td>92%</td>
<td>97%</td>
</tr>
<tr>
<td>Women aged ≥18 y who received a Pap test within the preceding 3 y</td>
<td>79%</td>
<td>90%</td>
</tr>
<tr>
<td>Primary care providers who counsel about Pap tests</td>
<td>55%</td>
<td>85%</td>
</tr>
<tr>
<td>Family Physicians who counsel about smoking cessation</td>
<td>43%</td>
<td>85%</td>
</tr>
</tbody>
</table>

*Healthy People 2010 is a comprehensive set of disease prevention and health promotion objectives for the nation to achieve over the first decade of the new century. Reductions in overall cancer mortality as well as specific cancer mortality from cervical, colorectal, breast, and lung cancer are among the current Healthy People 2010 Objectives with elimination of disparity in health outcomes an overarching goal. Source: Healthy People 2010. Office of Disease Prevention and Health Promotion U.S. Department of Health and Human Services. Available at: http://www.healthypeople.gov/About/hpfact.htm.*

**Table 26-6. Ovarian cancer screening recommendations.**

<table>
<thead>
<tr>
<th>Source</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOG</td>
<td>Providers should remain vigilant for the early signs and symptoms of ovarian cancer, such as abdominal or pelvic pain and unexplained weight loss, these symptoms should be evaluated by pelvic examination, CA-125, or ultrasound.</td>
</tr>
<tr>
<td>ACS</td>
<td>Women with a strong family history of this disease may be screened, but transvaginal ultrasound and CA-125 are not recommended for screening women without known strong risk factors for ovarian cancer.</td>
</tr>
<tr>
<td>USPSTF</td>
<td>Potential harms of transvaginal ultrasound and CA-125 screening outweigh the potential benefits and is not recommended.(Grade D recommendation).</td>
</tr>
</tbody>
</table>

Table 26-7. Other cancer screening recommendations.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Recommendation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>Microscopic urinalysis, urine dipstick, urine cytology, or such new tests as bladder tumor antigen (BTA) or nuclear matrix protein (NMP22) immunoassay can detect bladder cancers that are clinically unapparent. However, because of the low prevalence of bladder cancer, the positive predictive value of these tests is low, routine screening is not recommended.</td>
<td>U.S. Preventive Services Task Force (USPSTF): Screening for bladder cancer in adults: Recommendation statement. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2004 Jun. 5</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Recommend against routine screening for pancreatic cancer in asymptomatic adults using abdominal palpation, ultrasonography, or serologic markers (Grade D recommendation)</td>
<td>U.S. Preventive Services Task Force (USPSTF): Screening for pancreatic cancer: recommendation statement. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2004 Feb. 3</td>
</tr>
</tbody>
</table>

Table 26-8. American Cancer Society recommendations for cancer prevention.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain a healthy weight throughout life. Balance caloric intake with physical activity. Avoid excessive weight gain throughout the life cycle. Achieve and maintain a healthy weight if currently overweight or obese.</td>
<td>Consume a healthy diet, with an emphasis on plant sources. Choose foods and beverages in amounts that help achieve and maintain a healthy weight. Eat five or more servings of a variety of vegetables and fruits each day. Choose whole grains in preference to processed (refined) grains. Limit consumption of processed and red meats. Limit alcohol consumption; no more than one drink per day for women or two per day for men.</td>
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<table>
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<tr>
<th>Activity</th>
<th>Community</th>
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<tbody>
<tr>
<td>Adopt a physically active lifestyle. Adults: engage in at least 30 min of moderate to vigorous physical activity, above usual activities, on 5 or more days of the week. Forty-five to 60 minutes of intentional physical activity are preferable. Children and adolescents: engage in at least 60 min per day of moderate to vigorous physical activity at least 5 d per week.</td>
<td>Public, private, and community organizations should work to create social and physical environments that support the adoption and maintenance of healthful nutrition and physical activity behaviors. Increase access to healthful foods in schools, worksites, and communities. Provide safe, enjoyable, and accessible environments for physical activity in schools, and for transportation and recreation in communities.</td>
</tr>
</tbody>
</table>

Respiratory infections and chronic lung diseases are among the most common reasons that patients consult primary care physicians. Most of the respiratory problems encountered by primary care physicians are acute, with the majority comprising respiratory infections, exacerbations of asthma, chronic obstructive pulmonary diseases (COPDs), and pulmonary embolism (PE).

**UPPER RESPIRATORY TRACT INFECTIONS**

**COMMON Colds/UppEr Respiratory Tract Infections**

**Essentials of Diagnosis**

- Sore throat, congestion, low-grade fever, mild myalgias, and fatigue.
- Symptoms lasting for 12-14 days.

**General Considerations**

Although colds are mild, tend to get better on their own, and are of short duration, they are a leading cause of sickness and of industrial and school absenteeism. Each year, colds account for 170 million days of restricted activity, 23 million days of school absence, and 18 million days of work absence.

Most colds are caused by viruses. Rhinoviruses are the most common type of virus and are found in slightly more than half of all patients. Coronavirus are the second most common cause. In rare instances (0.05% of all cases), bacteria can be cultured from individuals with cold symptoms. It is not clear if these bacteria cause the cold, are secondary infectious agents, or are simply colonizers. Bacterial pathogens that have been identified include *Chlamydia pneumoniae, Haemophilus influenzae, Streptococcus pneumoniae*, and *Mycoplasma pneumoniae*.

**Prevention**

The mechanisms of transmission suggest that colds can be spread through contact with inanimate surfaces, but the primary transmission appears to be via hand-to-hand contact. The beneficial effects of removing viruses from the hands are supported by observations that absences due to colds among children in day-care or school settings have been reduced through the use of antiseptic hand wipes throughout the day.

**Clinical Findings**

Colds generally last 12-14 days. Telling patients that colds last no longer than a week underestimates the actual natural history of an uncomplicated viral respiratory tract infection and leads patients to believe that symptoms that persist beyond a week are not normal. When the symptoms of congestion persist longer than 2 weeks, consideration should be given to other causes of chronic congestion (Table 27-1).

Symptoms of colds include sore throat, congestion, low-grade fever, and mild myalgias and fatigue. In general, early in the development of a cold the discharge is clear. As more inflammation develops, the discharge takes on some coloration. A yellow, green, or brown-tinted nasal discharge is an indicator of inflammation, not secondary bacterial infection. Discolored nasal discharge raises the likelihood of sinusitis, but only if other predictors of sinusitis are present. In addition, several studies have shown that patients with discolored discharge respond to antibiotics no better than they respond to placebos.

**Complications**

Primary complications from upper respiratory tract infection are otitis media and sinusitis. These complications develop from obstruction of the eustachian tube or sinus ostia from nasal passage edema. Although treatment of these infections with antibiotics is common, the vast majority of infections clear without antibiotic therapy.
One misconception is that using antibiotics during the acute phase of a cold can prevent these complications. Evidence shows that taking antibiotics during a cold does not reduce the incidence of sinusitis or otitis media.

**Differential Diagnosis**

The differential diagnosis of colds includes complications of the cold such as sinusitis or otitis media, acute bronchitis, and noninfectious rhinitis. Influenza shares many of the symptoms of a common cold, but generally patients have a much higher fever, myalgias, and more intense fatigue.

**Treatment**

Despite the widespread recognition that viruses cause common colds, several studies have shown that patients with the common cold who are seen in physicians’ offices are often treated with antibiotics. The prescribing of antibiotics for colds occurs more often in adults than children. Although this practice appears to have declined in adults, the use of broad-spectrum antibiotics for colds is still common in children. The need to reduce the use of antibiotics for viral conditions has important ramifications on community-wide drug resistance; in areas in which prescribing antibiotics for respiratory infections has been curtailed, reversals in antibiotic drug resistance have been observed.

Currently, the most effective symptomatic treatments are over-the-counter decongestants, the most popular of which include pseudoephedrine hydrochloride and topically applied vasoconstrictors. These agents produce short-term symptomatic relief. However, patients must be warned to use topical agents cautiously because prolonged use is associated with rebound edema of the nasal mucosa (rhinitis medicamentosa).

Several over-the-counter medications contain a mix of decongestants, cough suppressants, and pain relievers. Again, the use of these preparations will not cure the common cold but will provide symptomatic relief.

Antihistamines, with a few exceptions, have not been shown to be effective treatments. Zinc gluconate lozenges are available without a prescription, but a meta-analysis of 15 previous studies on zinc concluded that zinc lozenges were not effective in reducing the duration of cold symptoms.

Some herbal remedies are useful for treatment of the common cold. Echinacea, also known as the American coneflower, has been purported to reduce the duration of the common cold by stimulating the immune system; however, evidence for its efficacy is mixed. Echinacea should be used only for 2-3 weeks to avoid liver damage and other possible side effects that have been reported during long-term use of this herb. Ephedra, also known as ma huang, has decongestant properties that make it similar to pseudoephedrine. Ephedra is more likely than pseudoephedrine to cause increased blood pressure tachyarrhythmia. This is especially true if used in conjunction with caffeine.

Other herbal preparations that have been touted as remedies for the common cold include goldenseal, yarrow, eyebright, and elderflower. However, no systematic evidence supports the use of these herbs in treating the common cold.


**SINUSITIS**

**ESSENTIALS OF DIAGNOSIS**

- “Double-sickening” phenomenon.
- Maxillary toothache and purulent nasal discharge.
- Poor response to decongestants.
- History of discolored nasal discharge.

**General Considerations**

Sinusitis is most often a complication of upper respiratory viral infections, so the incidence peaks in the winter cold season. Medical conditions that may increase the risk for sinusitis include cystic fibrosis, asthma, immunosuppression, and allergic rhinitis. Cigarette smoking may also increase the risk of bacterial sinusitis during a cold because of reduced mucociliary clearance.

Most cases of acute sinusitis are caused by viral infection. The inflammation associated with viral infection clears without additional therapy. Bacterial superinfection of upper respiratory infections (URIs) is rare and occurs in only 0.5%-1% of colds. Fungal sinusitis is very rare and usually occurs in immunosuppressed individuals or those with diabetes mellitus.
**Clinical Findings**

Acute sinusitis has considerable overlap in its constellation of signs and symptoms with URIs. One-half to two-thirds of patients with sinus symptoms seen in primary care are unlikely to have sinusitis. URIs are often precursors of sinusitis and at some point symptoms from each condition may overlap. Sinus inflammation from a URI without bacterial infection is also common.

The signs and symptoms that increase the likelihood that the patient has acute sinusitis are a “double-sickening” phenomenon (whereby the patient seems to improve following the URI and then deteriorates), maxillary toothache, purulent nasal discharge, poor response to decongestants, and a history of discolored nasal discharge.

**Treatment**

Antibiotics are commonly prescribed for adult patients who present with complaints consistent with acute sinusitis. The effectiveness of antibiotics is unclear. If an antibiotic is used, evidence with trimethoprim-sulfamethoxazole suggests that short-duration treatment (eg, 3 days) is as effective as longer treatment. Further, a meta-analysis indicates that narrow-spectrum agents are as effective as broad-spectrum agents.


Williams JW Jr, Simel DL: Does this patient have sinusitis: diagnosing acute sinusitis by history and physical examination. JAMA 1993;270:1242. [PMID: 8355389]


**INFLUENZA (ADULTS)**

**ESSENTIALS OF DIAGNOSIS**

- High Fever.
- Extreme fatigue.
- Myalgias.

Diagnosis, treatment, and prevention of influenza in children are reviewed extensively in Chap. 5.

**General Considerations**

Although most cases of the flu are mild and usually resolve without medical treatment within 2 weeks, some will develop complications. Currently, three types of viruses causing influenza have been identified in the United States: A, B, and C. Seasonal epidemics from influenza A and B are seen every winter. Type C influenza usually causes a mild respiratory illness and is not responsible for epidemics. If a new strain emerges and infects a population, an influenza pandemic can result.

Influenza A is identified by two proteins on the virus surface: a hemagglutinin (H) and a neuraminidase (N). These proteins result in 16 different H subtypes and 9 different N subtypes. The A form of influenza can be further divided into strains. The two subtypes of influenza A found in humans currently are A(H1N1) and A(H3N2). In 2009, an influenza pandemic occurred when a very different strain of influenza A(N1H1) developed in humans. The influenza B is broken down by different strain, but not by subtypes.

**Prevention**

The most effective prevention is vaccination against influenza. The seasonal flu vaccination contains the regular influenza A’s (H1N1/H3N2) and influenza B and is based on the previous year experience of the viruses seen during that season. However, new strains would not be included in the already manufactured vaccine. With the emergence of the 2009 H1N1 virus, a new vaccination was developed for the new strain. People were encouraged to receive both influenza vaccinations. Influenza vaccinations require annual dosing. A complete listing of who should be immunized can be found on the Centers for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP) web site and others.

The spread of influenza is from person to person by sneezing or coughing. Therefore, everyday care to stay healthy can help prevent contracting the flu and/or spreading the flu to others. Simple steps, such as covering nose and mouth when sneezing or coughing with a tissue; avoiding touching mouth, nose, and eyes if sick; washing hands frequently with soap or germicide solution; and staying home if sick to avoid others, may help prevent the spread of influenza.

**Clinical Findings**

The flu can last from 3 days to 2 weeks. Mild cases may be thought to have the common cold and receive no medical treatment. Symptoms include high fever, extreme fatigue, and myalgias. Other symptoms associated with the flu include sore throat, rhinorrhea, cough, headache, and chills. Some people experience nausea, vomiting, and diarrhea.

**Complications**

Complications can lead to hospitalization and even death. These complications include, but are not limited to, otitis media, sinusitis, acute bronchitis, and pneumonia. Exacerbations of chronic illnesses such as asthma, congestive heart failure, and chronic obstructive lung disease are further complications of the flu.

**Differential Diagnosis**

One must consider other viruses, such as the common cold viruses which have many of the same symptoms in less severity.
Treatment

People who develop symptoms of the flu should seek medical treatment as soon as possible, especially those in the high-risk group, as shown in Table 27-2. If treatment with antivirals is begun within 48 hours of becoming ill, the patient gets the greatest benefit. These benefits include shortening the illness by at least 24 hours, preventing serious complications, and decreasing the likelihood of spreading the disease to others. Treatment with oseltamivir or zanamivir is effective against all forms of human influenza, including A(H1N1)/(H3N2), 2009 A(H1N1), and B. Two older medications, amantadine and rimantadine, remain susceptible to influenza A but not to B. The CDC recommends the use of oseltamivir or zanamivir at this time, due to the emergence of the new strain of A(N1H1). Treatment guidelines differ for age groups and high-risk groups. Therefore, it is important when considering treatment options to refer to the Physician’s Desk Reference (PDR) to ensure appropriate treatment is given. Symptomatic treatment can be given with antipyretic for the fever and anti-inflammatory for pain and myalgias.


LOWER RESPIRATORY TRACT INFECTIONS

ACUTE BRONCHITIS

ESSENTIALS OF DIAGNOSIS

- Cough lasting more than 3 weeks.
- Fever, constitutional symptoms, and a productive cough.

General Considerations

Viral infection is the primary cause of most episodes of acute bronchitis. A wide variety of viruses has been shown to cause acute bronchitis, including influenza, rhinovirus, adenovirus, coronavirus, parainfluenza, and respiratory syncytial virus. Nonviral pathogens, including M pneumoniae and C pneumoniae (TWAR), have also been identified as causes. The etiologic role of bacteria such as H influenzae and S pneumoniae in acute bronchitis is unclear because these bacteria are common upper respiratory tract flora. Sputum cultures for acute bronchitis are therefore difficult to evaluate because it is unclear whether the sputum has been contaminated by pathogens colonizing the nasopharynx.

Clinical Findings

Patients with acute bronchitis may have a cough for a significant time. Although the duration of the condition is variable, one study showed that 50% of patients had a cough for more than 3 weeks and 25% for more than 4 weeks. Other causes of chronic cough are shown in Table 27-3.

Both acute bronchitis and pneumonia can present with fever, constitutional symptoms, and a productive cough. Although patients with pneumonia often have rales, this finding is neither sensitive nor specific for the illness. When pneumonia is suspected on the basis of the presence of a high fever, constitutional symptoms, severe dyspnea, and certain physical findings or risk factors, a chest radiograph should be obtained to confirm the diagnosis.

Differential Diagnosis

Asthma and allergic bronchospastic disorders can mimic the productive cough of acute bronchitis. When obstructive symptoms are not obvious, mild asthma may be diagnosed as acute bronchitis. Further, because respiratory infections can

<table>
<thead>
<tr>
<th>Table 27-2. High-risk populations for flu-related complications.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Children &lt;5 years of age</td>
</tr>
<tr>
<td>- Adults &gt;64 years of age</td>
</tr>
<tr>
<td>- Pregnant women</td>
</tr>
<tr>
<td>- Heart disease (heart failure, coronary artery disease, congenital heart disease, and others)</td>
</tr>
<tr>
<td>- Asthma</td>
</tr>
<tr>
<td>- Neurologic disorders (cerebral palsy, intellectual disability, developmental delay, spinal cord injury, epilepsy, muscular dystrophy, stroke, and others)</td>
</tr>
<tr>
<td>- Kidney diseases</td>
</tr>
<tr>
<td>- Liver diseases</td>
</tr>
<tr>
<td>- Blood disorders (sickle cell disease and others)</td>
</tr>
<tr>
<td>- Chronic lung disease (COPD, cystic fibrosis, and others)</td>
</tr>
<tr>
<td>- Endocrine diseases (diabetes mellitus and others)</td>
</tr>
<tr>
<td>- Metabolic disorders</td>
</tr>
<tr>
<td>- Immune deficiencies (people with cancer, HIV or AIDS, chronic steroid use, and others)</td>
</tr>
<tr>
<td>- Younger than 19 years on chronic aspirin therapy</td>
</tr>
</tbody>
</table>
trigger bronchospasm in asthma, patients with asthma that occurs only in the presence of respiratory infections resemble patients with acute bronchitis.

Finally, nonpulmonary causes of cough should enter the differential diagnosis. In older patients, congestive heart failure may cause cough, shortness of breath, and wheezing. Reflux esophagitis with chronic aspiration can cause bronchial inflammation with cough and wheezing. Bronchogenic tumors may produce a cough and obstructive symptoms.

**Treatment**

Clinical trials of the effectiveness of antibiotics in treating acute bronchitis have had mixed results. Meta-analyses indicated that the benefits of antibiotics in a general population are marginal and should be weighed against the impact of excessive use of antibiotics on the development of antibiotic resistance.

Data from clinical trials suggest that bronchodilators may provide effective symptomatic relief to patients with acute bronchitis. Treatment with bronchodilators demonstrated significant relief of symptoms, including faster resolution of cough and return to work. The effect of albuterol in a population of patients with undifferentiated cough was evaluated and no beneficial effect was found. Because a variety of conditions presents with cough, there may have been some misclassification in generalizing this finding to acute bronchitis.

**Table 27-3. Causes of chronic cough.**

<table>
<thead>
<tr>
<th>Pulmonary causes</th>
<th>Infectious</th>
<th>Postobstructive pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tuberculosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Pneumocystis jiroveci</em> (formerly, <em>Pneumocystis carinii</em>)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bronchiectasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung abscess</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Noninfectious</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic bronchitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allergic aspergillosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bronchogenic neoplasms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemical or smoke inhalation</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular causes</td>
<td>Congestive heart failure/pulmonary edema</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enlargement of left atrium</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Reflux esophagitis</td>
<td></td>
</tr>
<tr>
<td>Other causes</td>
<td>Medications, especially angiotensin-converting enzyme (ACE) inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psychogenic cough</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Foreign body aspiration</td>
<td></td>
</tr>
</tbody>
</table>

**COMMUNITY-ACQUIRED PNEUMONIA**

**ESSENTIALS OF DIAGNOSIS**

- Fever and cough (productive or nonproductive).
- Tachypnea.
- Rales or crackles.
- Positive chest radiograph.

**General Considerations**

Pneumonia is the cause of over 10 million visits to physicians annually, accounts for 3% of all hospitalizations, and is the sixth leading cause of death in the United States. A variety of factors, including increasing age, increase the risk of pneumonia. Among the elderly, institutionalization and debilitation further increase the risk for acquiring pneumonia. Patients aged 55 years or older, smokers, and patients with chronic respiratory diseases are more likely to require hospitalization for pneumonia. Those with congestive heart failure, cerebrovascular diseases, cancer, diabetes mellitus, and poor nutritional status are more likely to die. Thus, age and comorbidities are important factors to consider when deciding whether to hospitalize a patient with pneumonia. These risk factors are summarized in Table 27-4.

**Prevention**

Pneumococcal pneumonia may be prevented through immunization with multivalent pneumococcal vaccine. The 23-valent pneumococcal polysaccharide vaccine is indicated for individuals older than 65 years, and for those 2 years of age or older with diabetes mellitus, chronic pulmonary or cardiac disease, or without a spleen. Additionally, anyone who lives in a long-term care facility should be vaccinated. CDC states to immunize all patients with the following medical conditions: immunosuppressed patients, including those with human immunodeficiency virus (HIV) infection, alcoholism, cirrhosis, chronic renal failure, nephritic syndrome, functional or anatomic asplenia (eg, sickle cell disease or splenectomy), cochlear implants, cerebrospinal fluid leaks, or multiple myeloma.

In addition to initial vaccination, clinicians should advise patients that the duration of protection is uncertain. For
those at particularly high risk of mortality from pneumococcal pneumonia, such as patients with chronic pulmonary disease, lacking a spleen, chronic renal disease or nephrotic disease, functional or anatomic asplenia, and patients with immunocompromising conditions, should receive a one-time revaccination after 5 years from their first vaccination. For patients who are older than 65 years, a one-time revaccination is also recommended if their last vaccination was earlier than 5 years ago or if they were younger than 65 when they received their first vaccination.

A conjugated pneumococcal vaccination is effective for children younger than 2 years. Current recommendations are to immunize all children younger than 2 years and high-risk children younger than 5 years.

### Clinical Findings

The most common presenting complaints for patients with pneumonia are fever and a cough that may be either productive or nonproductive. As an example, in one study, 80% of patients with pneumonia had a fever. Other symptoms that may be suggestive of pneumonia include dyspnea and pleuritic chest pain. However, none of these symptoms is specific for pneumonia.

Symptoms of pneumonia may be nonspecific in older patients. Elderly individuals who suffer a general decline in their function, become confused or have worsening dementia, or experience more frequent falls should receive a chest x-ray even if no pulmonary symptoms or physical findings are present. Elderly patients who have preexisting cognitive impairment or depend on someone else for support of their daily activities are at highest risk for not exhibiting typical symptoms of pneumonia.

The most consistent sign of pneumonia is tachypnea. In one study of elderly patients, tachypnea was observed to be present 3-4 days before the appearance of other physical findings of pneumonia. Rales or crackles are often considered the hallmark of pneumonia, but these may be heard in only 75%-80% of patients. Other signs of pneumonia such as dullness to percussion or egophony, which are usually believed to be indicative of consolidation, occur in less than a third of patients with pneumonia.

Chest radiography is the standard for diagnosing pneumonia. In rare cases, the chest x-ray may be falsely negative. This generally occurs in patients exhibiting profound dehydration, early pneumonia (first 24 hours), infection with *Pneumocystis*, and severe neutropenia.

Microbiological testing for pneumonia is not very useful in relatively healthy patients with nonsevere pneumonia. Blood and sputum cultures are most likely to be beneficial in patients with risk factors for unusual organisms or who are very ill.

### Differential Diagnosis

Other conditions such as postobstructive pneumonitis, pulmonary infarction from an embolism, radiation pneumonitis, and interstitial edema from congestive heart failure all may produce infiltrates that are indistinguishable from an infectious process.

### Treatment

With the emergence of other pathogens causing pneumonia and the development of resistance to penicillin and other drugs in *S. pneumoniae*, treatment decisions have become more complex. The 2003 update to the Infectious Disease Society of America (ISDA) and American Thoracic Society (ATS) guidelines for the treatment of community-acquired pneumonia differ depending on the health and age of patients (ie, 65 years or older), whether they have recently been treated with an antibiotic, and whether they are at risk for an aspiration pneumonia or influenza superinfection (Table 27-5). For patients with no serious comorbidities, the ISDA/ATS recommends a respiratory quinolone or an advanced macrolide plus high-dose amoxicillin (or amoxicillin-clavulanic acid) as first-line therapy. If an antibiotic has been used recently, then either a respiratory quinolone or an advanced macrolide plus a second- or third-generation cephalosporin are recommended options. If aspiration is suspected, the ISDA/ATS guidelines include a choice of amoxicillin-clavulanic acid or clindamycin as initial treatment.
Suitable empiric antimicrobial regimens for inpatient pneumonia include an intravenous β-lactam antibiotic, such as cefuroxime, ceftriaxone sodium, or cefotaxime sodium, or a combination of ampicillin sodium and sulbactam sodium plus a macrolide. New fluoroquinolones with improved activity against *S pneumoniae* can also be used to treat adults with community-acquired pneumonia. Vancomycin hydrochloride is not routinely indicated for the treatment of community-acquired pneumonia or pneumonia caused by drug-resistant *S pneumoniae*.

**Ebell MH:** Outpatient vs. inpatient treatment of community-acquired pneumonia. Am Fam Physician 2006;73:1425. [PMID: 16669565]


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**NONINFECTIOUS RESPIRATORY PROBLEMS**

### ASTHMA

#### ESSENTIALS OF DIAGNOSIS

- Recurrent wheezing, shortness of breath, or cough.
- Histories of allergies in children.
- Increase in airway secretions.
- Airway constriction, obstruction, or both.
- Bronchospasm documented on spirometry.
- Dyspnea.

#### General Considerations

Asthma is one of the most common illnesses in childhood. Risk factors for the development of asthma include living in poverty and being in a nonwhite racial group. Part of the difference in asthma rates noted among different races may be related to increased exposure to allergens and other irritants such as air pollution, cigarette smoke, dust mites, and cockroaches in less affluent families, but racial differences persist even after adjusting for socioeconomic status.

Allergy is an important factor in asthma development in children but does not appear to be as significant a factor in adults. Although as many as 80% of children with asthma also are atopic, 70% of adults younger than 30 and fewer than half of all adults older than 30 have any evidence of allergy. Therefore, although an allergic component should be sought in adults, it is less commonly found than in children with asthma.

#### Clinical Findings

In most cases, asthma is diagnosed based on symptoms of recurrent wheezing, shortness of breath, or cough. Children with recurrent cases of "bronchitis" who experience night cough or have difficulty with exercise tolerance should be suspected of having asthma. An additional history of allergies is useful, because 80% of childhood asthma is associated with atopy.

Formal spirometry testing can usually be accomplished in children as young as 5 years of age and can confirm the diagnosis of asthma. Both the forced expiratory volume in 1 second (FEV₁) and FEV₁/FVC ratio are useful in documenting obstruction to airway flow. Further confirmation is provided by improvement of the FEV₁ by 12% or more following the use of a short-acting bronchodilator.
For a valid test, though, children should avoid using a long-acting β-agonist in the previous 24 hours or a short-acting β-agonist in the previous 6 hours.

In some patients with asthma, spirometry may be normal. When there is a high index of suspicion that asthma may still be present, provocative testing with methacholine may be necessary to make the diagnosis.

It is useful to stratify patients with asthma by the severity of their illness. The severity of asthma is based on the frequency, intensity, and duration of baseline symptoms, level of airflow obstruction, and the extent to which asthma interferes with daily activities. Stages of severity range from severe persistent (step 4), in which symptoms are chronic and limit activity, to mild intermittent (step 1), in which symptoms are present no more than twice a week and pulmonary function studies are normal between exacerbations (Table 27-6). Patients are classified as to severity based on their worst symptom and frequency, not upon having met all or the majority of the criteria in any category.

### Treatment

The approach to managing asthma relies on acute management of exacerbations, treatment of chronic airway inflammation, monitoring of respiratory function, and control of the factors that precipitate wheezing episodes. For all of these, patient and family education is vital.

Treatment of persistent asthma requires daily medication to prevent long-term airway remodeling. Mild, intermittent asthma may require therapy only during wheezing episodes.

Guidelines for the management of asthma are based on the child’s age (≤6 years) and are stratified by severity of illness. Guidelines for older children, adults, and younger children are provided in Table 27-7.

The treatment of exacerbations of asthma relies on fast-acting bronchodilators to produce rapid changes in airway resistance along with management of the late-phase changes that occur several hours after the initial symptoms are manifested. The failure to recognize the late-phase component of an acute exacerbation may lead to a rebound of symptoms several hours after the patient has left the office or emergency department. Corticosteroids are the mainstay for preventing the late-phase response.

For patients with persistent symptoms (step 2 and higher), chronic therapy is required. The management of persistent asthma may include long-acting bronchodilators to control intermittent symptoms and nighttime cough, but also should provide chronic anti-inflammatory therapy to prevent long-term remodeling. Both inhaled steroids and nonsteroidal anti-inflammatory medications (ie, cromoglycates) can provide anti-inflammatory therapy. When symptoms are recurrent or large doses of anti-inflammatory agents are required, treatment with a leukotriene inhibitor can provide additional anti-inflammatory therapy and may allow a reduction in the dose of other anti-inflammatory agents such as steroids.

When drugs are selected for the treatment of asthma, the potential side effects of each agent need to be weighed against the potential benefits. For children, chronic use of inhaled steroids has been associated with a small decrease in

<table>
<thead>
<tr>
<th>Step</th>
<th>Symptoms</th>
<th>Nighttime Symptoms</th>
<th>Lung Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 4</td>
<td>Severe persistent</td>
<td>Continual symptoms Limited physical activity Frequent exacerbations</td>
<td>Frequent</td>
</tr>
<tr>
<td>Step 3</td>
<td>Moderate persistent</td>
<td>Daily symptoms Daily use of inhaled short-acting β2-agonist Exacerbations affect activity Exacerbations ≥2 times a week; may last days</td>
<td>&gt;1 time a week</td>
</tr>
<tr>
<td>Step 2</td>
<td>Mild persistent</td>
<td>Symptoms &gt;2 times a week but &lt;1 time a day Exacerbations may affect activity</td>
<td>&gt;2 times a month</td>
</tr>
<tr>
<td>Step 1</td>
<td>Mild intermittent</td>
<td>Symptoms &lt;2 times a week Asymptomatic and normal PEF between exacerbations Exacerbations are brief; variable intensity</td>
<td>≤2 times a month</td>
</tr>
</tbody>
</table>
### Table 27-7. Asthma drug therapy based on severity.

<table>
<thead>
<tr>
<th>Step</th>
<th>Ages 6 Years Through Adulthood</th>
<th>Quick Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 4</strong></td>
<td><strong>Severe persistent</strong></td>
<td>Choose all needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-dose inhaled corticosteroid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-acting bronchodilator</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A leukotriene modifier</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral corticosteroid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short-acting bronchodilator</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily or increasing use of short-acting inhaled ( \beta_2 )-agonist indicates need for additional long-term control therapy</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td><strong>Moderate persistent</strong></td>
<td>Usually need two</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Either low- or medium-dose inhaled corticosteroid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-acting bronchodilator</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short-acting bronchodilator</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily or increasing use of short-acting inhaled ( \beta_2 )-agonist indicates need for additional long-term control therapy</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td><strong>Mild persistent</strong></td>
<td>Choose one</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low-dose inhaled corticosteroid cromolyn</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sustained-release theophylline (to serum concentration of 5-15 ( \mu )g/mL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A leukotriene modifier</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short-acting bronchodilator</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily or increasing use of short-acting inhaled ( \beta_2 )-agonist indicates need for additional long-term control therapy</td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
<td><strong>Intermittent</strong></td>
<td>No daily medication needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short-acting bronchodilator</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of short-acting inhaled ( \beta_2 )-agonist ( \geq 2 ) times per week indicates need for additional long-term control therapy</td>
</tr>
</tbody>
</table>

Review treatment every 1-6 mo; a gradual stepwise reduction in treatment may be possible

If control is not maintained, consider step up; first, review patient medication technique, adherence, and environmental control (avoidance of allergens and/or other factors that contribute to asthma severity)

<table>
<thead>
<tr>
<th>Step</th>
<th>Daily Anti-inflammatory Medications</th>
<th>Quick Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 4</strong></td>
<td><strong>Severe persistent</strong></td>
<td>High-dose inhaled corticosteroid with spacer/holding chamber and facemask and, if needed, add systemic corticosteroids 2 mg/kg/d and reduce to lowest daily or alternate-day dose that stabilizes symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short-acting bronchodilator as needed for symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>By nebulizer or metered dose inhaler (MDI) with spacer/holding chamber and facemask or oral ( \beta_2 )-agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily or increasing use of short-acting inhaled ( \beta_2 )-agonist indicates need for additional long-term control therapy</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td><strong>Moderate persistent</strong></td>
<td>Either medium-dose inhaled corticosteroid with spacer/holding chamber and facemask or low- to medium-dose inhaled corticosteroid and long-acting bronchodilator (theophylline)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short-acting bronchodilator as needed for symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>By nebulizer or MDI with spacer/holding chamber and facemask or oral ( \beta_2 )-agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily or increasing use of short-acting inhaled ( \beta_2 )-agonist indicates need for additional long-term control therapy</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td><strong>Mild</strong></td>
<td>Young children usually begin with a trial of cromolyn or low-dose inhaled corticosteroid with spacer/holding chamber and facemask</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short-acting bronchodilator as needed for symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>By nebulizer or MDI with spacer/holding chamber and facemask or oral ( \beta_2 )-agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily or increasing use of short-acting inhaled ( \beta_2 )-agonist indicates need for additional long-term control therapy</td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
<td><strong>Intermittent</strong></td>
<td>No daily medication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short-acting bronchodilator as needed for symptoms ( &lt;2 ) times a week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>By nebulizer or MDI with spacer/holding chamber and facemask or oral ( \beta_2 )-agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Two times weekly or increasing use of short-acting inhaled ( \beta_2 )-agonist indicates need for additional long-term control therapy</td>
</tr>
</tbody>
</table>

Review treatment every 1-6 mo; a gradual stepwise reduction in treatment may be possible

If control is not maintained, consider step up; first, review patient medication technique, adherence, and environmental control (avoidance of allergens and/or other factors that contribute to asthma severity)
total height attained. Although the difference in height attainment is small, it might be preferable to use nonsteroidal anti-inflammatory agents such as cromolyn and nedocromil in children.

In addition to pharmacologic management, patients with asthma should avoid known and possible airway irritants. These include cigarette smoke (including second-hand inhalation of smoke), environmental pollutants, suspected or known allergens, and cold air. Children who have difficulty participating in sports may benefit from the use of a short-acting β-agonist such as albuterol before participating in exertion to prevent wheezing or cough.

The monitoring of pulmonary function is an important component of asthma management for all patients with persistent disease. Children and adults should be provided with a peak flow meter and instructed on how to use the device reliably. The use of a peak flow meter can determine subtle changes in respiratory function that may not cause symptoms for several days. To use a peak flow meter, patients must establish a “personal best,” which represents the best reading that they can obtain when they are as asymptomatic as possible. Daily or periodic recordings of peak flows are compared with this personal best to gauge the current pulmonary function. Readings between 80% and 100% of the personal best indicate that the patient is doing well. Peak flows between 50% and 80% of an individual’s personal best are cause for concern even if symptoms are mild. Patients should be instructed beforehand how to respond in these instances. If a repeat of the peak flow later in the day after appropriate measures have been taken does not show improvement, patients should seek further medical attention. Patients should be told that severe decreases in peak flow to less than 50% are cause for immediate medical attention.

For patients with allergic symptoms, the use of immunotherapy should be considered. However, although immunotherapy usually results in improvements in symptoms of allergic rhinitis, it often does not improve asthma symptoms.


**General Considerations**

Chronic airway disease is the second leading cause of disability in the United States after coronary artery disease. It is also fourth in the list of leading causes of death in the United States. For the last 7 years, more women died secondary to chronic obstructive pulmonary disease (COPD) than men. Symptoms of chronic bronchitis first develop when patients are between 30 and 40 years of age and progressively become more common as patients reach their 50s and 60s. The development of chronic bronchitis is associated with heavier cigarette use; those smoking over 25 cigarettes per day have a risk of chronic bronchitis that is 30 times higher than nonsmokers. Although chronic bronchitis affects both genders and all socioeconomic strata, it is more commonly observed in men and in those of lower socioeconomic classes. It is presumed that these populations may be at higher risk due to higher consumption of cigarettes observed in these groups.

In addition to smoking, air pollution may play a role in the development and exacerbation of symptoms in patients with chronic bronchitis. Patients with COPD who live in industrialized areas with heavy levels of particulate air pollution may be at increased risk of recurrent disease and death.

Only 10%-15% of smokers will develop COPD, so other factors must also play a role in the progression from acute to chronic lung damage. The development of chronic bronchitis is thought to include both a predisposition to inflammatory damage plus exposure to the proper stimuli that cause inflammation, such as cigarette smoke or pollutants. Genetic factors, prolonged heavy exposure to other inflammatory mediators such as environmental pollutants, preexisting lung impairment from other inflammatory processes such as recurrent infection or childhood passive smoke exposure, and other mechanisms may all predispose individuals to the development of chronic bronchitis from smoking.

α₁-Antitrypsin deficiency is a rare genetic abnormality that causes panlobular emphysema in adults and is responsible for approximately 2%-3% of cases of COPD. This trait is inherited in an autosomal-recessive pattern. Nonsmokers with this genetic defect develop emphysema at young ages. Those with this trait who smoke develop progressive emphysema at very early ages. Emphysema related to α₁-antitrypsin deficiency rarely shows up below age 25 and rarely in nonsmokers.

**Clinical Findings**

COPD includes both chronic bronchitis and emphysema, and these two often coexist. Chronic bronchitis is characterized by a productive cough featuring sputum production for at least 3 months for 2 consecutive years. Emphysema causes chronic dyspnea due to destruction of lung tissue, resulting in enlargement of air space and reduced compliance. In most cases, chronic bronchitis and emphysema can be differentiated based on whether the predominant symptom is a chronic cough or dyspnea. In contrast to asthma, changes in COPD are relatively fixed and only partially reversible with bronchodilator use.
When suspected clinically, COPD can be confirmed with chest radiography and spirometry. Although chest radiographic findings occur much later in the course of the disease than alterations in pulmonary function testing, a chest x-ray may be useful in patients suspected of having COPD because it can detect several other clinical conditions often found in these patients.

Spirometry is usually used to diagnose COPD because it can detect small changes in lung function and is easy to quantify. Changes in the FEV\textsubscript{1} and the FVC can provide an estimate of the degree of airway obstruction in these patients. Symptoms of COPD usually develop when FEV\textsubscript{1} falls below 80% of the predicted rate. In addition, a peak expiratory flow rate (PEFR) less than 350 L/min in adults is a sign that COPD is likely to be present.

Spirometry also is useful in gauging the severity of COPD. Decreases in FEV\textsubscript{1} on serial testing are associated with increased mortality rates (ie, patients with a faster decline in FEV\textsubscript{1} have a higher rate of death). The major risk factor associated with an accelerated rate of decline of FEV\textsubscript{1} is continued cigarette smoking. Smoking cessation in patients with early COPD improves lung function initially and slows the annual loss of FEV\textsubscript{1}. Once FEV\textsubscript{1} falls below 1 L, 5-year survival is approximately 30%.

The United States Preventive Services Task Force (USPSTF) has recommended against the use of spirometry to screen asymptomatic adult patients for COPD which carries a D recommendation.

**Treatment**

A. Nonpharmacologic Therapy

The first step in treating the patient with chronic bronchitis or COPD is promoting a healthy lifestyle. Regular exercise and weight control should be started and smoking stopped to maximize the patient’s therapeutic options.

Smoking cessation is the first and most important treatment option in the management of chronic bronchitis or COPD. Several interventions to assist patients in smoking cessation are available. These include behavioral modification techniques as well as pharmacotherapy (see the next section). A combination of behavioral and pharmacologic approaches such as nicotine replacement appears to yield the best results. Even minimal counseling from the provider improves the effectiveness of the nicotine patch.

Once patients have stopped smoking, those who are hypoxemic with a PaO\textsubscript{2} of 55 mm Hg or less or an O\textsubscript{2} saturation of 88% or less while sleeping should receive supplemental oxygen. Along with smoking cessation, home oxygen is the only therapy shown to reduce mortality in COPD. Continuous long-term oxygen therapy (LTOT) should be considered in those patients with stable chronic pulmonary disease with PaO\textsubscript{2} less than 55 mm Hg on room air, at rest, and awake. The presence of polycythemia, pulmonary hypertension, right heart failure, or hypercapnia (PaO\textsubscript{2} >45 mm Hg) is also an indication for use of continuous LTOT.

Exercise and pulmonary rehabilitation may also be beneficial as adjunct therapies for patients whose symptoms are not adequately controlled with appropriate pharmacotherapy. Exercise and pulmonary rehabilitation are most useful for patients who are restricted in their activities and have decreased quality of life.

B. Pharmacotherapy

1. **Smoking cessation pharmacotherapy**—Multiple medications are available to assist with smoking cessation. Nicotine can be substituted 1 mg (1 cigarette) per milligram with the use of the patch, gum, or inhaler to help with symptoms of nicotine withdrawal. Patches and gum are both available over the counter as well as by prescription. Some evidence suggests that use of the patch and gum simultaneously enhances quit rates, but use of both is not approved by the Food and Drug Administration. Although all these products state that patients must not smoke while using nicotine replacement because of early case reports of myocardial infarction, more recent studies show that smoking is relatively safe when using nicotine replacement and may help reduce smoking before a patient actually quits. However, even at best, the cessation rate is only about 20%-30% at 1 year.

Bupropion also is approved for smoking cessation as an adjunct to behavior modification. The main effect of bupropion is to reduce symptoms of nicotine withdrawal. Bupropion should be instituted for 2 weeks before the quitting target date. Then a nicotine substitute can be used in combination to maximize alleviation of symptoms of nicotine withdrawal. Because many patients with chronic bronchitis are already taking multiple medications, potential drug interactions and adverse effects must be taken into consideration before instituting therapy with bupropion.

A third agent to assist in smoking cessation is varenicline tartrate. Varenicline is a selective nicotine receptor partial agonist. The drug stimulates nicotine receptors to produce a nicotine-replacement type effect but also blocks the receptors from additional exogenous nicotine stimulation. Use of varenicline has been reported to achieve quit rates of 40% at 12 weeks and continuous quit rates of about 22% after 1 year, which was significantly more than either bupropion or nicotine replacement alone. Adverse effects of varenicline occur in 20%-30% of patients and include nausea, insomnia, headache, and abnormal dreams but necessitated discontinuation of the drug in 2%-3% of patients in clinical trials.

2. **Bronchodilators**—An anticholinergic agent such as ipratropium bromide is the drug of choice for patients with persistent symptoms of chronic bronchitis. Anticholinergic agents such as ipratropium bromide or tiotropium have fewer side effects and a better response than intermittent β-agonists. Although both of these agents have a delayed onset of action compared with short-acting β-agonists, the beneficial effects...
are prolonged. Ipratropium requires dosing several times a day; in contrast, tiotropium can be used once a day.

For patients with mild to moderately severe symptoms, intermittent use of a β-agonist inhaler such as albuterol is sometimes beneficial even without significant changes in their FEV₁. Adverse effects of β-agonist agents include tachycardia, nervousness, and tremor. Short-acting β-agonists may not last through the night; when nighttime symptoms develop, long-acting β-agonists such as salmeterol may be more useful. Levalbuterol, the active agent of racemic albuterol, has recently been studied and appears to have greater efficacy than albuterol with fewer side effects.

Combination inhalers of ipratropium bromide and albuterol have also been used in the treatment of patients with chronic bronchitis but have demonstrated only minimal changes in outcomes compared with single agents.

3. Antibiotics—Patients with acute exacerbations of chronic bronchitis pose a more difficult therapeutic dilemma. Many of these exacerbations are probably due to viral infections. However, a meta-analysis of studies using a wide range of antibiotics (ampicillin, sulfamethoxazole-trimethoprim, and tetracyclines) demonstrated some benefit from empiric use of antibiotics for exacerbations of chronic bronchitis.

4. Other agents—As symptoms increase, addition of inhaled β-agonists, theophylline, and corticosteroids may provide symptomatic relief of symptoms of chronic bronchitis. In a multicenter randomized placebo-controlled trial, patients who used inhaled fluticasone had improved peak expiratory flows, FEV₁, FVC, and midexpiratory flow. At the end of treatment, patients also showed increased exercise tolerance compared with the placebo group. Corticosteroids at a therapeutic dose of 60 mg/d for 5 days have been shown to provide some symptomatic relief for severe exacerbations.

Mucolytics have not been shown to be beneficial. Iodinated glycerol has not been shown to improve any objective outcome measurements.

Newer agents such as aerosolized surfactant also have been used to treat stable chronic bronchitis. A prospective randomized controlled trial showed a minimal but statistically significant improvement in spirometry and sputum clearance. However, the cost of such a treatment regimen is high and may not add any advantage to the underlying treatment.

For the treatment of cough, agents that may be of benefit for patients with chronic bronchitis include ipratropium bromide, guaimesal, dextromethorphan, and viminol.

Anabolic steroids have recently been used for patients who have severe malnutrition and in those in whom weight loss is a concern. These agents show some beneficial effects.


Horsley L: Practice guidelines. ACCP guideline recommends diagnosis and management strategies for COPD. Am Fam Physician August 1, 2008;78(3).


EMBOLIC DISEASE

ESSENTIALS OF DIAGNOSIS

- Dyspnea.
- Hypoxia.
- Pleuritic pain.

General Considerations

Pulmonary embolism (PE) usually results from the mobilization of blood clots from thromboses in the lower extremities or pelvis. However, embolization of other materials, including air, fat, and amniotic fluid, also can obstruct the pulmonary vasculature. The symptoms of pulmonary embolism range from mild, intermittent shortness of breath or pleuritic chest pain to complete circulatory collapse and death.

The most common source of embolism is the disruption of blood clots from thromboses in the lower extremities or pelvis. However, embolization of other materials, including air, fat, and amniotic fluid, also can obstruct the pulmonary vasculature. The symptoms of pulmonary embolism range from mild, intermittent shortness of breath or pleuritic chest pain to complete circulatory collapse and death.

The most common source of embolism is the disruption of thrombi formed in the deep veins. Mortality in untreated cases is 30% but can be reduced to 2% with prompt recognition and appropriate management. Recurrent pulmonary embolism carries a very high mortality in the range of 45%-50%.

Strong risk factors for pulmonary embolism are leg or hip fracture, major general surgery, knee or hip replacement, spinal cord injury, and major trauma. Other risk factors include venous stasis, trauma, abnormalities in the deep veins, and hypercoagulable states. Hypercoagulability occurs with some cancers as well as with inherited conditions such as factor V Leiden mutation that results in resistance to the anticoagulant effects of protein C. Other congenital hypercoagulation disorders include protein C deficiency, protein S deficiency, and antithrombin III deficiency.

Hypercoagulation states also exist with the use of certain medications. Use of estrogens either as part of hormone
replacement therapy or for contraception increases the risk by a factor of three. The effects of these drugs are compounded in patients with factor V Leiden mutation. Pregnancy and postpartum states increase the risk of pulmonary embolism.

In addition, smoking appears to be an independent risk factor for deep vein thrombosis (DVT) and pulmonary embolism. The presence of more than two of these risk factors places the patient at a synergistic increased risk for the development of venous thromboembolism.

**Prevention**

Because pulmonary emboli usually arise from lower extremity thromboses, prophylactic anticoagulation can be used to reduce the incidence of these thrombi in high-risk individuals. Both low-molecular-weight heparin products and unfractionated heparin are effective in preventing DVT. Selection of the agent and the dose is based on the risk factor and other characteristics of the patient as shown in Table 27-8.

In addition to preventing initial thrombi, the pulmonary embolism can be reduced through the use of a venacaval filter in patients with known thrombi and contraindications to long-term anticoagulation. The long-term impact of intravacaval (IVC) filters has not been studied extensively. One study showed a complication rate, such as thrombi trapped in the filter or the filter tilting, malpositioning, or migrating, in nearly 50% of those who survived 3 years. However, given the high mortality rates from recurrent pulmonary embolism, the complication rates from long-term IVC filter insertion appear to be a worthwhile trade-off in high-risk patients.

**Clinical Findings**

Patients with pulmonary emboli usually exhibit dyspnea and hypoxia, and often have pleuritic chest pain. However, other than hypoxia, most routine studies including chest radiographs may be normal. The clinical assessment of the patient should include the criteria in the Wells score looking at signs and symptoms consistent with DVT, different diagnosis less likely, a heart rate greater than 100 beats/min, previous PE or DVT; surgery within the last 4 weeks or immobilization, current malignancy, and presence of hemoptysis. Scores placed patients in either a low, intermediate or high probability of having a PE. The Christopher Study (modified Wells) further divided the scoring into PE likely or unlikely. Suspicious signs of embolism on a chest radiograph include a wedge-shaped infiltrate resulting from lobar infarction, new pleural effusion, or both. Confirmation

<table>
<thead>
<tr>
<th>Table 27-8. Strategies to prevent venous thromboembolism.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Condition or Procedure</strong></td>
</tr>
</tbody>
</table>
| General surgery | Unfractionated heparin, 5000 units two or three times a day  
Enoxaparin, 40 mg/d subcutaneously  
Daltaparin, 2500 or 5000 U/day subcutaneously  
Nadroparin, 3100 U/d subcutaneously  
Tinzaparin, 3500 U/d subcutaneously, with or without graduated-compression stockings |
| Total hip replacement | Warfarin (target INR, 2.5)  
Intermittent pneumatic compression  
Enoxaparin, 30 mg subcutaneously twice daily  
Danaparoid, 750 units subcutaneously twice daily |
| Total knee replacement | Enoxaparin, 30 mg subcutaneously twice daily  
Ardeparin, 50 U/kg subcutaneously twice daily |
| General medical condition requiring hospitalization | Graduated-compression stockings, intermittent pneumatic compression, or unfractionated heparin, 5000 units two or three times daily |
| Condition requiring hospitalization in the intensive care unit | Graduated-compression stockings and intermittent pneumatic compression, with or without unfractionated heparin, 5000 units two or three times daily |
| Pregnancy in high-risk patient* | Daltaparin, 5000 U/d subcutaneously  
Enoxaparin, 40 mg/d subcutaneously |

of a pulmonary embolism is based on either demonstrating obstruction of vascular flow through pulmonary angiography, finding a mismatch of perfusion and ventilation, or visualization of a clot on spiral (helical) computed tomography (CT) scanning. Although pulmonary angiography is considered the gold standard, because of its invasiveness, spiral CT and ventilation-perfusion scan are usually employed to make the diagnosis. Of the noninvasive tests available, spiral CT has the best sensitivity for detecting pulmonary artery thrombi (95%-100%), although it is not as useful in identifying subsegmental emboli.

D-Dimer testing has been evaluated as a serum marker for pulmonary embolism or DVT. The presence of D-dimer is not specific for thrombotic disease because D-dimer also rises in other conditions such as recent surgery, congestive heart failure, myocardial infarction, and pneumonia. Although the presence of D-dimer is not useful in diagnosing thrombosis or embolism, the negative predictive value of the absence of D-dimer is very high (97%-99%), so this test can be useful in ruling out embolism. Clinically predictive rules, such as the modified Wells, can be used together with the D-dimer test to identify those in the “PE unlikely” group who would not require further study. Using these two tools, clinical assessment and laboratory test, those that fall into the “PE likely” category can be further evaluated with CT angiography or spiral CT.

### Treatment

Options for management of the patients with an acute pulmonary embolism include anticoagulation to prevent further embolism from occurring, clot lysis with thrombolytic agents, or surgical removal of the clot.

Patients without life-threatening embolism can be managed with acute anticoagulation with heparin followed by long-term maintenance on warfarin. Heparin may be administered either as unfractionated heparin or as low-molecular-weight heparin. Unfractionated heparin is generally administered intravenously with the dosage rate titrated to produce a suitable anticoagulation state. The use of a weight-based nomogram for loading and maintenance dosing can improve the time to achieve adequate anticoagulation and reduce the risks of bleeding. The drawbacks of unfractionated heparin include the need for hospitalization to monitor coagulation status and administer the intravenous drug plus the possibility of thrombocytopenia associated with the use of this agent. Should bleeding occur as a complication of treatment with unfractionated heparin, stopping the heparin is the first step to stop further anticoagulation. If bleeding continues after stopping the heparin, protamine can be given to reverse the anticoagulation.

In contrast, low-molecular-weight heparin can be administered as a daily intramuscular dose without titration or frequent anticoagulation monitoring. As a result, low-molecular-weight heparin therapy usually can be provided in the patient’s home.

To achieve long-term anticoagulation, warfarin should be started promptly at a dose of 5 mg/d. Starting with a higher dose of warfarin does not appear to achieve oral anticoagulation any faster or reduce the days that heparin is needed. Heparin can be discontinued when a prothrombin time indicates that the international normalized ratio (INR) has reached 2.0-3.0. Should excessive anticoagulation occur from administering warfarin and bleeding occurs, vitamin K can be given to reverse the effect of warfarin.

The duration of anticoagulation for pulmonary embolism depends on whether the precipitating event is known and reversible or whether the cause is unknown. In situations in which the thrombosis and embolism are the result of an acute event such as an injury or surgery, treatment for 6 months is recommended. If the risk factor associated with the embolic event is not reversible, such as cancer or coagulation disorder, then lifetime anticoagulation is advisable. When a risk factor or event causing the embolism is not known, so-called idiopathic embolism, treatment with anticoagulants for 6 months is indicated.

The use of thrombolytic agents for pulmonary embolism is usually reserved for patients with extensive embolism who show hemodynamic instability. Thrombolytic agents available for use in this situation include urokinase, streptokinase, tissue plasminogen activator (tPA), and reteplase. Embolectomy is rarely performed and is reserved for patients in whom embolism is rapidly diagnosed and a very large embolism is suspected that completely occludes the pulmonary arteries. In most situations, this is treated as a “last ditch” effort to save the patient.

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ESSENTIALS OF DIAGNOSIS

- Migraine.
  - Headache lasting 4-72 hours.
  - Unilateral onset often spreading bilaterally.
  - Pulsating quality and moderate or severe intensity of pain.
  - Aggravated by or inhibiting physical activity.
  - Nausea and photophobia.
  - May present with an aura.
- Cluster headache.
  - Strictly unilateral orbital, supraorbital, or temporal pain lasting 15-180 minutes.
  - Explosive excruciating pain.
  - One attack every other day to eight attacks per day.
- Tension-type headache.
  - Pressing or tightening (nonpulsating) pain.
  - Bilateral band-like distribution of pain.
  - Not aggravated by routine physical activity.

General Considerations

Headache is among the most common pain syndromes presenting in primary care with a lifetime prevalence of over 90% among adults. The prevalence of migraine is approximately 18% in women and 6% in men; the prevalence among both genders is 38.3% for episodic and 2.2% for chronic tension-type headache. The main task before the primary care provider is to determine if the patient has a potentially life-threatening headache disorder and, if not, to provide appropriate management to limit disability from headache.

A distinction between primary headaches (benign, recurrent headaches having no organic disease as their cause) and secondary headaches (those caused by an underlying, organic disease) is practical in primary care. Over 90% of patients presenting to primary care providers have a primary headache disorder (Table 28-1). These disorders include migraine (with and without aura), tension-type headache, and cluster headache. Secondary headache disorders comprise the minority of presentations; however, given that their underlying etiology may range from sinusitis to subarachnoid hemorrhage, these headache disorders often present the greatest diagnostic challenge to the practicing clinician (Table 28-2).


Clinical Findings

A. Symptoms and Signs

1. History—The majority of patients presenting with headache have a normal neurologic and general physical examination; for this reason, the headache history is of utmost importance (Table 28-3). A key issue in the headache history is identifying patients presenting with “red flags”—diagnostic alarms that prompt greater concern for the presence of a secondary headache disorder and a greater potential need for additional laboratory evaluation and neuroimaging (Table 28-4).

The onset of primary headache disorders is usually between 20 and 40 years of age; however, they may occur at any age. Patients without a history of headaches who present
with a new-onset headache outside of this age range should be considered at higher risk for a secondary headache disorder. Serious consideration should be given to performing additional testing or neuroimaging in these patients or those complaining of their "first or worst" headache. Temporal (giant cell) arteritis should be a consideration in any patient 50 years of age or older with a new complaint of head, facial, or scalp pain, diplopia, or jaw claudication.

Symptoms suggesting a recurring, transient neurologic event, typically lasting 30-60 minutes and preceding headache onset, strongly suggest the presence of an aura and an associated migraine headache disorder. Migraine without aura, the most common form of migraine (formerly called common migraine), may present with unilateral pain in the head (cephalalgia) with subsequent generalization of pain to the entire head. Bilateral cephalalgia is present in a small percentage of migraineurs at the onset of their headache. Nausea accompanying a migraine may be debilitating and warrant specific treatment. After excluding secondary headache disorders, the combination of disability, nausea, and sensitivity to light has a positive predictive value of 0.93 for migraine headache among primary care patients.

Cluster headaches are strictly unilateral in location and are typically described as an explosive, deep, excruciating pain. They are associated with ipsilateral autonomic signs and symptoms, and have a much greater prevalence in men.

Tension-type headaches, the most prevalent form of primary headache disorder, often present with pericranial muscle tenderness and a description of a bilateral band-like distribution of the pain.

Patients with chronic medical conditions have a greater possibility of having an organic cause of their headache (see Table 28-4). Patients with cancer, hypertension (with diastolic pressures >110 mm Hg), or human immunodeficiency...
virus (HIV) infection may present with central nervous system (CNS) metastases, lymphoma, toxoplasmosis, or meningitis as the etiology of their headache. Numerous medications have headache as a reported adverse effect, and medication-overuse headache (formerly drug-induced headache) may occur following frequent use of analgesics or any antiheadache medication, including the triptans (ie, sumatriptan, others). The duration and severity of withdrawal headache following discontinuation of the medication varies depending on the medication itself; withdrawal is shortest for triptans (4.1 days) compared with ergots (6.7 days) or analgesics (9.5 days), respectively. Medical or dental procedures (lumbar punctures, rhinoscopy, tooth extraction, etc) may be associated with post-procedure headaches. Any history of head trauma or loss of consciousness should prompt concern for an intracranial hemorrhage in addition to a postconcussive disorder.

2. Physical examination—Physical examination is performed to attempt to identify a secondary, organic cause for the patient’s headache. Additionally, special attention should be paid to any red flags identified during the headache history (see Table 28-4). A general physical examination should be

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**Table 28-3. Questions to ask when obtaining a headache history.**

<table>
<thead>
<tr>
<th>H:</th>
<th>How severe is your headache on a scale of 1-10 (1 = minimal pain, 10 = severe pain)?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>How did this headache start (gradually, suddenly, other)?</td>
</tr>
<tr>
<td></td>
<td>How long have you had this headache?</td>
</tr>
<tr>
<td>E:</td>
<td>Ever had headaches before?</td>
</tr>
<tr>
<td></td>
<td>Ever had a headache this bad before (first or worst headache)?</td>
</tr>
<tr>
<td></td>
<td>Ever have headaches just like this one in the past?</td>
</tr>
<tr>
<td>A:</td>
<td>Any other symptoms noted before or during your headache?</td>
</tr>
<tr>
<td></td>
<td>Any symptoms right now?</td>
</tr>
<tr>
<td>D:</td>
<td>Describe the quality of your pain (throbbing, stabbing, dull, other).</td>
</tr>
<tr>
<td></td>
<td>Describe the location of your pain.</td>
</tr>
<tr>
<td></td>
<td>Describe where your pain radiates.</td>
</tr>
<tr>
<td></td>
<td>Describe any other medical problems you may have.</td>
</tr>
<tr>
<td></td>
<td>Describe your use of medications (prescription and over-the-counter products).</td>
</tr>
<tr>
<td></td>
<td>Describe any history of recent trauma or any medical or dental procedures.</td>
</tr>
</tbody>
</table>

---

**Table 28-4. Red flags in the evaluation of acute headaches in adults.**

<table>
<thead>
<tr>
<th>Red Flag</th>
<th>Differential Diagnosis</th>
<th>Possible Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache beginning after 50 y of age</td>
<td>Temporal arteritis, mass lesion</td>
<td>Erythrocyte sedimentation rate, neuroimaging</td>
</tr>
<tr>
<td>Very sudden onset of headache</td>
<td>Subarachnoid hemorrhage, pituitary apoplexy, hemorrhage into a mass lesion or vascular malformation, mass lesion (especially posterior fossa mass)</td>
<td>Neuroimaging, lumbar puncture if computed tomography is negative</td>
</tr>
<tr>
<td>Heads increasing in frequency and severity</td>
<td>Mass lesion, subdural hematoma, medication overuse</td>
<td>Neuroimaging, drug screen</td>
</tr>
<tr>
<td>New-onset headache in patient with risk factors for HIV infection or cancer</td>
<td>Meningitis (chronic or carcinomatous), brain abscess (including toxoplasmosis), metastasis</td>
<td>Neuroimaging, lumbar puncture if neuroimaging is negative</td>
</tr>
<tr>
<td>Headache with signs of systemic illness (eg, fever, still neck, rash)</td>
<td>Meningitis, encephalitis, Lyme disease, systemic infection, collagen vascular disease</td>
<td>Neuroimaging, lumbar puncture, serology</td>
</tr>
<tr>
<td>Focal neurologic signs or symptoms of disease (other than typical aura)</td>
<td>Mass lesion, vascular malformation, stroke, collagen vascular disease</td>
<td>Neuroimaging, collagen vascular evaluation (including antiphospholipid antibodies)</td>
</tr>
<tr>
<td>Papilledema</td>
<td>Mass lesion, benign intracranial hypertension (pseudotumor cerebri), meningitis</td>
<td>Neuroimaging, lumbar puncture</td>
</tr>
<tr>
<td>Headache following head trauma</td>
<td>Intracranial hemorrhage, subdural hematoma, epidural hematoma, post-traumatic headache</td>
<td>Neuroimaging of brain, skull, and, possibly, cervical spine</td>
</tr>
</tbody>
</table>

performed, including vital signs; general appearance; and examinations of the head, eyes (including a funduscopic examination), ears, nose, throat, teeth, neck, and cardiovascular regions. Particular attention should be given to palpation of the head, face, and neck.

A detailed neurologic examination should be performed and the findings well documented. Assessment includes mental status testing; level of consciousness; pupillary responses; gait; coordination and cerebellar function; motor strength; sensory, deep tendon, and pathologic reflex testing; and cranial nerve tests. The presence or absence of meningeal irritation should be sought. Examinations such as evaluation for Kernig and Brudzinski signs should be documented; both signs may be absent, however, even in the presence of subarachnoid hemorrhage.

B. Laboratory Findings and Imaging Studies

Additional laboratory investigations should be driven by the history and by any red flags that have been identified (see Table 28-4). The routine use of electroencephalography is not warranted in the evaluation of the patient with headache. Although there are different characteristics that may lead to choosing either computed tomography (CT) or magnetic resonance imaging (MRI) (Table 28-5), routine use of neuroimaging is not cost-effective.

The US Headache Consortium has provided evidence-based guidelines on neuroimaging in the patient with nonacute headache. They revealed the prevalence of patients with a normal neurologic examination, and migraine having a significant abnormality (acute cerebral infarct, neoplastic disease, hydrocephalus, or vascular abnormalities, eg, aneurysm or arteriovenous malformation) on a neuroimaging test is 0.2%. Their recommendations are as follows:

- Neuroimaging should be considered in patients with nonacute headache and an unexplained abnormal finding on neurologic examination.
- Evidence is insufficient to make specific recommendations in the presence or absence of neurologic symptoms.

Table 28-5. Computerized tomographic scans versus magnetic resonance imaging in patients with headaches.

<table>
<thead>
<tr>
<th>CT Scan</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need to identify an acute hemorrhage</td>
<td>Need to evaluate the posterior fossa</td>
</tr>
<tr>
<td>Generally more readily available at most medical centers</td>
<td>More sensitive at identifying pathologic intracranial processesa</td>
</tr>
<tr>
<td>Generally less expensive at most medical centers</td>
<td></td>
</tr>
</tbody>
</table>

*aIncreased sensitivity may not correlate with an improved health outcome and may be associated with identifying more clinically insignificant findings.

- Neuroimaging is not usually warranted for patients with migraine and normal neurologic examination. For patients with atypical headache features or patients who do not fulfill the strict definition of migraine (or have some additional risk factor), a lower threshold for neuroimaging may be applied.
- Data were insufficient to make an evidence-based recommendation regarding the use of neuroimaging for tension-type headache.
- Data were insufficient to make any evidence-based recommendations regarding the relative sensitivity of MRI compared with CT in the evaluation of migraine or other nonacute headache.

Although the US Headache Consortium based the preceding recommendations on a review of the best available evidence, clinicians must individualize management plans to meet a variety of needs, including addressing patient fears and medicolegal concerns.

Within the first 48 hours of acute headache, CT scanning without contrast medium followed, if negative, by lumbar puncture and cerebrospinal fluid (CSF) analysis is the preferred approach to attempt to diagnose subarachnoid hemorrhage. Xanthochromia, a yellow discoloration detectable on spectrophotometry, may aid in diagnosis if the CT scan and CSF analysis are normal yet suspicion of subarachnoid hemorrhage remains high. Xanthochromia may persist for up to a week following a subarachnoid hemorrhage.

In addition to CSF analysis, lumbar puncture is useful for documenting abnormalities of CSF pressure in the setting of headache. Headaches are associated with low CSF pressure (<90 mm H2O as measured by a manometer) and elevated CSF pressure (>200-250 mm H2O). Headaches related to CSF hypotension include those caused by post-traumatic leakage of CSF (ie, after lumbar puncture or CNS trauma). Headaches related to CSF hypertension include those associated with idiopathic intracranial hypertension and CNS space-occupying lesions (ie, tumor, infectious, mass, hemorrhage).

Detsky ME et al: Does this patient with headache have a migraine or need neuroimaging? JAMA 2006;296:1274. [PMID: 16968852]
Differential Diagnosis

In addition to migraine, tension-type, and cluster headaches, the differential diagnosis for acute headaches in adults is presented in Table 28-2.

Treatment

Treatment of headache is best individualized based on a thorough history, physical examination, and the interpretation of appropriate ancillary testing. Secondary headaches require accurate diagnosis and therapy directed at the underlying etiology (see Tables 28-2 and 28-4). Nonpharmacologic measures and cognitive-behavioral therapy (CBT) are worth consideration in most patients with primary headache disorders. CBT may have a prophylactic effect in migraine similar to propranolol (an approximate 50% reduction). Cluster headache, chronic tension-type headache, and medication-overuse headache respond poorly to CBT as monotherapy. The evidence for a benefit of acupuncture in acute and preventive headache treatment is contradictory; no clear recommendation can be derived from the literature. A systematic review (six total randomized controlled trials [RCTs]) revealed no positive effect of various manual therapies in the treatment of tension-type headache.

A. Migraine

The US Headache Consortium lists the following general management guidelines for treatment of migraine patients:

- Educate migraine sufferers about their condition and its treatment, and encourage them to participate in their own management.
- Use migraine-specific agents (triptans, dihydroergotamine [DHE], ergotamine, etc) in patients with more severe migraine and in those whose headaches respond poorly to nonsteroidal anti-inflammatory drugs (NSAIDs) or combination analgesics such as aspirin plus acetaminophen plus caffeine.
- Select a nonoral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex.
- Consider a self-administered rescue medication for patients with severe migraine who do not respond well to (or fail) other treatments.
- Guard against medication-overuse headache (the terms rebound headache and drug-induced headache are sometimes used interchangeably with medication-overuse headache; however, the latter is the currently recommended terminology).

Pharmacologic treatment options are numerous in the management of migraine headache. Effective acute/abortive treatment options include an oral, intranasal, or subcutaneous triptan (eg, sumatriptan, others), intravenous (D.H.E. 45) or intranasal (Migranal) DHE, and intravenous antiemetics (ie, prochlorperazine, metoclopramide, promethazine). Based upon the available evidence, first-line use of these agents is preferred over the commonly used meperidine (or other narcotic analgesics) or ketorolac in abortive migraine treatment. A meta-analysis of seven RCTs (pooled data on 742 patients) of the addition of dexamethasone to standard acute migraine treatment in the emergency department (ED) setting revealed a moderate benefit (RR = 0.87, 95% CI = 0.80-0.95) to reducing the risk of having a moderate or severe migraine headache at 24-72 hours after ED evaluation.

The goal of therapy in migraine prophylaxis is a reduction in the severity and frequency of headache by 50% or more. The strongest evidence surrounds the use of amitriptyline, propranolol, timolol, and divalproex sodium for migraine prevention. Topiramate also has proven prophylactic effects in migraine treatment. Botulinum toxin A was found to have no significant clinical or statistical effect as a migraine-preventive treatment when compared to placebo in a meta-analysis of eight RCTs.

B. Tension-Type Headache

Initial medical therapy of episodic tension-type headache often includes aspirin, acetaminophen, or NSAIDs. Avoidance of habituating, caffeine-containing over-the-counter or prescription drugs as well as butalbital-, codeine-, or ergotamine-containing preparations (including combination products) is recommended given the significant risk of developing drug dependency or medication-overuse headache.

Similar general management principles for treatment of migraine headaches can be applied to the treatment of chronic tension-type headaches. In a randomized placebo-controlled trial of tricyclic antidepressant use (amitriptyline hydrochloride, up to 100 mg/d, or nortriptyline hydrochloride up to 75 mg/d) and stress management (eg, relaxation, cognitive coping) therapy, combined therapy produced a statistically and clinically greater reduction (≥50%) in headache activity. A meta-analysis of antidepressant treatment (eg, tricyclic antidepressants, serotonin antagonists, and selective serotonin reuptake inhibitors) of chronic headache (eg, migraine, tension-type, or both) revealed that treated study participants were twice as likely to report headache improvement and consumed less analgesic medication than nontreated patients. Other considerations for prophylaxis of chronic tension-type headaches include calcium channel blockers and β-blockers. The American Academy of Neurology’s evidence-based review of botulinum toxin concludes that it is “probably ineffective” in the treatment of chronic tension-type headache.
C. Cluster Headache

Acute management of cluster headache includes the use of sumatriptan in either its subcutaneous (FDA-approved indication), intranasal, or oral forms (the latter two being less effective), intranasal zolmitriptan, 100% oxygen at 7-10 L/min via face mask, and intranasal lidocaine. Verapamil, lithium, divalproex sodium, gabapentin, lithium, melatonin (possibly), topiramate (possibly), methysergide, and prednisone may be considered for prophylaxis. Because of side effects related to chronic use, methysergide and prednisone should be used with caution.

D. Referral

Referral to a headache specialist should be considered for patients whose findings are difficult to classify into a primary or secondary headache disorder. Additionally, referral is often warranted in cases of daily or intractable headache, drug-rebound, habituation, or medication-overuse headache, or in any scenario in which the primary care provider feels uncomfortable in making a diagnosis or offering appropriate treatment. Patients who request referral, who do not respond to treatment, or whose condition continues to worsen should be considered for referral.


Holroyd KA et al: Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. JAMA 2001;285:2208. [PMID: 11325322]
General Considerations

Osteoporosis is a public health problem affecting more than 40 million people, one-third of postmenopausal women and a substantial portion of the elderly in the United States and almost as many in Europe and Japan. An additional 54% of postmenopausal women have low bone density measured at the hip, spine, or wrist. Osteoporosis results in more than 1,500,000 fractures annually in the United States alone. At least 90% of all hip and spine fractures among elderly women are a consequence of osteoporosis. The direct expenditures for osteoporotic fractures have increased during the past decade from $5 billion to almost $15 billion per year. Thus, family physicians and other primary care providers will (1) frequently care for patients with subclinical osteoporosis, (2) recognize the implications of those who present with osteoporosis-related fractures, and (3) determine when to implement prevention for younger people.

Of the 25 million women in the United States thought to have osteoporosis, 8 million have a documented fracture. The female-to-male fracture ratios are reported to be 7:1 for vertebral fractures, 1.5:1 for distal forearm fractures, and 2:1 for hip fractures. Approximately 30% of hip fractures in persons aged 65 years and older occur in men. Osteoporosis-related fractures in older men are associated with lower femoral neck bone mineral density (BMD), quadriceps weakness, higher body sway, lower body weight, and decreased stature. Osteoporotic fractures are more common in whites and Asians than in African Americans and Hispanics, and more common in women than in men. Little is known regarding the influence of ethnicity on bone turnover as a possible cause of the variance in bone density and fracture rates among different ethnic groups. Significant differences in bone turnover in premenopausal and early perimenopausal women can be documented. The bone turnover differences do not appear to parallel the patterns of BMD. Other factors, such as differences in bone accretion, are likely responsible for much of the ethnic variation in adult BMD.

Pathogenesis

Osteoporosis is characterized by microarchitectural deterioration of bone tissue that leads to decreased bone mass and bone fragility. The major processes responsible for osteoporosis are poor bone mass acquisition during adolescence and accelerated bone loss during the perimenopausal period (mid-50s to the sixth decade in women and the seventh decade in men) and beyond. Both processes are regulated by genetic and environmental factors. Reduced bone mass, in turn, is the result of varying combinations of hormone deficiencies, inadequate nutrition, decreased physical activity, comorbidity, and the effects of drugs used to treat various medical conditions.

Primary osteoporosis—deterioration of bone mass not associated with other chronic illness—is related to increasing age and decreasing gonadal function. Therefore, early menopause or premenopausal estrogen deficiency states may hasten its development. Prolonged periods of inadequate calcium intake, a sedentary lifestyle, and tobacco and alcohol abuse also contribute to primary osteoporosis.

Secondary osteoporosis results from chronic conditions that contribute significantly to accelerated bone loss. These include endogenous and exogenous thyroxine excess, hyperparathyroidism, cancer, gastrointestinal diseases, medications, renal failure, and connective tissue diseases. Secondary forms of osteoporosis are listed in Table 29-1. If secondary osteoporosis is suspected, appropriate diagnostic workup may identify a different management course.
Prevention

A. Nutrition

Bone mineralization is dependent on adequate nutritional status in childhood and adolescence. Therefore, measures to prevent osteoporosis should begin with increasing the milk intake of adolescents to improve bone mineralization. Nutrients other than calcium are also essential for bone health. Adolescents must, therefore, maintain a balance in calcium intake, protein intake, other calorie sources, and phosphorus. Substituting phosphorus-laden soft drinks for calcium-rich dairy products and juices compromises calcium uptake by bone and promotes decreased bone mass.

Eating disorders are nutritional conditions that affect BMD. Inability to maintain normal body mass promotes bone loss. The body weight history of women with anorexia nervosa has been found to be the most important predictor of the presence of osteoporosis as well as the likelihood of recovery. The BMD of these patients does not increase to a normal range, even several years after recovery from the disorder, and all persons with a history of an eating disorder remain at high risk for osteoporosis in the future.

Major demands for calcium are placed on the mother by the fetus during pregnancy and lactation. The axial spine and hip show losses of BMD during the first 6 months of lactation, but this bone mineral loss appears to be completely restored 6-12 months after weaning. Risk factors for osteoporosis are summarized in Table 29-2.

Endocrine or Metabolic Causes

- Acromegaly
- Anorexia nervosa
- Athletic amenorrhea
- Type 1 diabetes mellitus
- Hemochromatosis
- Hyperadrenocorticism
- Hyperparathyroidism
- Hyperprolactinemia
- Thyrotoxicosis

Collagen/Genetic Disorders

- Ehlers-Danlos syndrome
- Glycogen storage disease
- Marfan syndrome
- Osteogenesis imperfecta
- Homocystinuria
- Hypophosphatasia

Drugs

- Cyclosporine
- Excess thyroid medication
- Glucocorticoids
- Prolonged heparin Rx
- Phenytoin
- Methotrexate
- Phenobarbital
- Gonadotropin-releasing hormone agonists
- Phenothiazines

Nutritional

- Alcoholism
- Calcium deficiency
- Chronic liver disease
- Gastric operations
- Malabsorptive syndromes
- Vitamin D deficiency

B. Lifestyle

Sedentary lifestyle or immobility (being confined to bed or a wheelchair) increases the incidence of osteoporosis. Low body weight and cigarette smoking negatively influence bone mass. Excessive alcohol consumption has been shown to depress osteoblast function and, thus, to decrease bone formation. Those at risk for low BMD should avoid drugs that negatively affect BMD (see Table 29-1).

C. Behavioral Measures

Behavioral measures that decrease the risk of bone loss include eliminating tobacco use and excessive consumption of alcohol and caffeine. A balanced diet with adequate calcium and vitamin D intake and a regular exercise program (see below) retard bone loss. Medications, such as glucocorticoids, that decrease bone mass should be avoided if possible. The importance of maintaining estrogen levels in women should be emphasized.

Measurement of bone density should be considered in the patient who presents with risk factors, but additional evidence is needed before instituting preventive measures.

D. Exercise

Regular physical exercise can reduce the risk of osteoporosis and delay the physiologic decrease of BMD. Short- and long-term exercise training (measured up to 12 months; eg, walking, jogging, stair climbing) in healthy, sedentary, postmenopausal women results in improved bone mineral content. Bone mineral content increases more than 5% above baseline after short-term, weight-bearing exercise training. With reduced weight-bearing exercise, bone mass reverts to baseline levels. Similar increases in BMD have been seen in women who participate in strength training. In the elderly, progressive strength training has been demonstrated to be a safe and effective form of exercise that reduces risk factors for falling and may also enhance BMD.

Table 29-1. Secondary forms of osteoporosis.

<table>
<thead>
<tr>
<th>Endocrine or Metabolic Causes</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acromegaly</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>Excess thyroid medication</td>
</tr>
<tr>
<td>Athletic amenorrhea</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>Prolonged heparin Rx</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Hyperadrenocorticism</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Gonadotropin-releasing hormone agonists</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>Phenothiazines</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Collagen/Genetic Disorders</th>
<th>Nutritional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ehlers-Danlos syndrome</td>
<td>Alcoholism</td>
</tr>
<tr>
<td>Glycogen storage disease</td>
<td>Calcium deficiency</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>Chronic liver disease</td>
</tr>
<tr>
<td>Osteogenesis imperfecta</td>
<td>Gastric operations</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>Malabsorptive syndromes</td>
</tr>
<tr>
<td>Hypophosphatasia</td>
<td>Vitamin D deficiency</td>
</tr>
</tbody>
</table>

Table 29-2. Risk factors for osteoporosis.

<table>
<thead>
<tr>
<th>Female gender</th>
<th>Petite body frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>White or Asian race</td>
<td>Sedentary life-style/immobilization</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>Increasing age</td>
</tr>
<tr>
<td>High caffeine intake</td>
<td>Renal disease</td>
</tr>
<tr>
<td>Lifelong low calcium intake</td>
<td>Smoking</td>
</tr>
<tr>
<td>Excessive alcohol use</td>
<td>Long-term use of certain drugs</td>
</tr>
<tr>
<td>Postmenopausal status</td>
<td>Low body weight</td>
</tr>
<tr>
<td>Impaired calcium absorption</td>
<td></td>
</tr>
</tbody>
</table>


Estrogen deficiency results in diminished bone density in younger women as well as in older women. Athletes who exercise much more intensely and consistently than the average person usually have above-average bone mass. However, the positive effect of exercise on the bones of young women is dependent on normal levels of endogenous estrogen. The low estrogen state of exercise-induced amenorrhea outweighs the positive effects of exercise and results in diminished bone density. When mechanical stress or gravitational force on the skeleton is removed, as in bed rest, space flight, immobilization of limbs, or paralysis, bone loss is rapid and extensive. Weight-bearing exercise can significantly increase the BMD of menopausal women. Furthermore, weight-bearing exercise and estrogen replacement therapy have independent and additive effects on the BMD of the limb, spine, and Ward triangle (hip).

There have been no randomized prospective studies systematically comparing the effect of various activities on bone mass. Recommended activities include walking and jogging, weight training, aerobics, stair climbing, field sports, racquet sports, court sports, and dancing. Swimming is of questionable value to bone density (because it is not a weight-bearing activity) and there are no data on cycling, skating, or skiing. It should be kept in mind that any increase in physical activity may have a positive effect on bone mass for women who have been very sedentary. To be beneficial, the duration of exercise should be between 30 and 60 minutes and the frequency should be three times per week.

Clinical Findings

A. Symptoms and Signs

The history and physical examination are neither sensitive enough nor sufficient for diagnosing primary osteoporosis. However, they are important in screening for secondary forms of osteoporosis and directing the evaluation. The goals of the evaluation should be (1) to establish the diagnosis of osteoporosis by assessing bone mass, (2) to determine fracture risk, and (3) to determine whether intervention is needed. A medical history provides valuable clues to the presence of chronic conditions, behaviors, physical fitness, and the use of long-term medications that could influence bone density. Those already affected by complications of osteoporosis may complain of upper or midthoracic back pain associated with activity, aggravated by long periods of sitting or standing, and easily relieved by rest in a recumbent position. The history should also assess the likelihood of fracture. Other indicators of increased fracture risk are low bone density, a propensity to fall, taller stature, and the presence of prior fractures.

The physical examination should be thorough for the same reasons. For example, lid lag and enlargement or nodularity of the thyroid suggest hyperthyroidism. Moon facies, thin skin, and a buffalo hump suggest hypercortisolism. Cachexia mandates screening for an eating disorder or cancer. A pelvic examination is one aspect of the total evaluation of hormonal status in women and a necessary part of the physical examination in women. Osteoporotic fractures are a late physical manifestation. Common fracture sites are the vertebrae, forearm, femoral neck, and proximal humerus. The presence of a “Dowager hump” in elderly patients indicates multiple vertebral fractures and decreased bone volume.

Because the true value of an assessment of bone density is to prevent injury, recent studies completed under the auspices of the World Health Organization Collaborating Centre for Metabolic Bone Diseases used a 10-year probability model to develop a more accurate assessment of fracture risk. A fracture risk assessment tool (FRAX) was developed to identify and account for clinical risk factors for fracture—age, low body mass index, parental history of hip fracture, current smoking, alcohol intake greater than 3 units daily, rheumatoid arthritis or other secondary causes of osteoporosis, oral glucocorticoids, and previous fragility fracture—Primary data were used from nine large patient cohorts in North America, Europe, Asia, and Australia representing over 1 million patient-years. The primary data are used to accurately evaluate the interaction of each risk factor, rather than being limited to the potential bias of published data. Additional secondary causes of osteoporosis include untreated hypogonadism, inflammatory bowel disease, prolonged immobility, organ transplantation, type 1 diabetes, thyroid disorders, and chronic obstructive pulmonary disease. This tool estimates the 10-year, patient-specific absolute risk of hip or major osteoporotic fracture (hip, spine, shoulder, or wrist), taking account of death from all causes and death hazards (eg, smoking). The tool may be used alone using individual clinical risk factors, with or without BMD.

B. Laboratory Findings

Basic chemical analysis of serum is indicated when the history suggests other clinical conditions influencing bone density. The tests presented in Tables 29-3 and 29-4 are appropriate for excluding secondary causes of osteoporosis. These tests provide clues to serious illnesses that may otherwise have gone undetected and that, if treated, could result in resolution or modification of the bone loss. Specific biochemical markers (human osteocalcin, bone alkaline phosphatase, immunoassays for pyridinoline cross-links and type 1 collagen-related peptides in urine) that reflect the overall rate of bone formation and bone resorption are now available.
These markers are primarily of research interest and are not recommended as part of the basic workup for osteoporosis. They suffer from substantial biological variability and diurnal variation and do not differentiate causes of altered bone metabolism. For example, measures of bone turnover increase and remain elevated after menopause but do not necessarily provide information that can direct management.

C. Imaging Studies

Plain radiographs are not sensitive enough to diagnose osteoporosis until total bone density has decreased by 50%, but bone densitometry is useful for measuring bone density and monitoring the course of therapy (see Table 29-5). Single or dual photon absorptiometry (SPA, DPA) has been used in the past but provides poorer resolution, less accurate analysis, and more radiation exposure than x-ray absorptiometry. The most widely used techniques for assessing BMD are dual-energy x-ray absorptiometry (DXA) and quantitative computerized tomography (CT). These methods have errors in precision of 0.5%-2%. Quantitative CT is most sensitive, but results in substantially greater radiation exposure than DXA. For this reason, DXA is the diagnostic measure of choice.

Smaller, less-expensive systems for assessing the peripheral skeleton are now available. These include DXA scans of the distal forearm and the middle phalanx of the non-dominant hand and a variety of devices for performing quantitative ultrasound (QUS) measurements on bone. Prospective studies using QUS of the heel have predicted hip fracture and all nonvertebral fractures nearly as well as DXA at the femoral neck. Both of these methods provide information regarding fracture risk and predict hip fracture better than DXA at the lumbar spine. Clinical trials of pharmacologic agents have used DXA rather than QUS, so it is unclear whether the results of these trials can be generalized to patients identified by QUS to have high risk of fracture.

### Table 29-3. Abnormalities in routine laboratory studies and suggested pathology.

<table>
<thead>
<tr>
<th>Abnormal Study</th>
<th>Suggested Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑Creatinine</td>
<td>Renal disease</td>
</tr>
<tr>
<td>↑Hepatic transaminases</td>
<td>Hepatic disease</td>
</tr>
<tr>
<td>↑Calcium</td>
<td>Primary HPT or malignancy</td>
</tr>
<tr>
<td>↓Calcium</td>
<td>Malabsorption, vitamin D deficiency</td>
</tr>
<tr>
<td>↑Phosphorus</td>
<td>Osteomalacia</td>
</tr>
<tr>
<td>↑Alkaline phosphatase</td>
<td>Liver disease, Paget disease, fracture, other bone pathology</td>
</tr>
<tr>
<td>↓Albumin</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>↑TSH</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>↑ESR</td>
<td>Myeloma</td>
</tr>
<tr>
<td>↑24 h calcium excretion</td>
<td>Malabsorption, vitamin D deficiency</td>
</tr>
</tbody>
</table>


### Table 29-4. Directed laboratory assessment for secondary osteoporosis.

<table>
<thead>
<tr>
<th>Hypogonadism</th>
<th>↓Testosterone in men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↓Estrogen in women</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>↑TSH</td>
</tr>
<tr>
<td></td>
<td>↑T&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>↑PTH</td>
</tr>
<tr>
<td></td>
<td>↑Serum calcium</td>
</tr>
<tr>
<td></td>
<td>↑1,25(OH)D</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>↓25-Hydroxycholcalciferol</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Serum iron</td>
</tr>
<tr>
<td></td>
<td>Ferritin</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>24-h urine free cortisol excretion</td>
</tr>
<tr>
<td></td>
<td>Overnight dexamethasone suppression test</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Serum protein electrophoresis–spike and Bence–Jones proteinuria</td>
</tr>
<tr>
<td></td>
<td>↑ESR</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>↓PTH</td>
</tr>
</tbody>
</table>


### Table 29-5. Indications for measuring bone density.

| Concerned perimenopausal women willing to start therapy |
| Radiographic evidence of bone loss |
| Patient on long-term glucocorticoid therapy (more than 1 mo at 7.5 mg of prednisone/day) |
| Asymptomatic hyperparathyroidism where osteoporosis would suggest parathyroidectomy |
| Monitoring therapeutic response in women undergoing treatment for osteoporosis if the result of the test would affect the clinical decision |
Bone densitometry reports provide a T score (the number of standard deviations above or below the mean BMD for sex and race) or Z score (comparing the patient with a population adjusted for age as well as for sex and race). The BMD result enables the classification of patients into three categories: normal, osteopenic, and osteoporotic. Normal patients receive no further therapy; osteopenic patients are counseled, treated, and followed so that no further bone loss develops; osteoporotic patients receive active therapy aimed at increasing bone density and decreasing fracture risk. Osteoporosis is indicated by a T score of more than 2.5 standard deviations below the sex-adjusted mean for normal young adults at peak bone mass. Z scores are of little value to the practicing clinician.

There is little evidence from controlled trials that women who receive bone density screening have better outcomes (improved bone density or fewer falls) than women who are not screened. The US Preventive Services Task Force suggests the primary argument for screening is that postmenopausal women with low bone density are at increased risk for subsequent fractures of the hip, vertebrae, and wrist, and that interventions can slow the decline in bone density after menopause. The presence of multiple risk factors (age ≥80 years, poor health, limited physical activity, poor vision, prior postmenopausal fracture, psychotropic drug use, and others) seems to be a stronger predictor of hip fracture than low bone density. The patient who is not asymptomatic but may have only one or two risk factors can benefit from BMD screening. Indications for BMD screening are outlined in Table 29-5.


## Differential Diagnosis & Screening

The approach to the patient is governed by the presentation. The greatest challenge for clinicians is to identify which asymptomatic patients would benefit from screening for osteoporosis, rather than determining a treatment regimen for those with known disease (see Table 29-2). All women and girls should be counseled about appropriate calcium intake and physical activity. Assessment of osteoporosis risk is also important when following a patient for a chronic disease known to cause secondary osteoporosis (see Table 29-1). Figure 29-1 presents an algorithm to assist in the evaluation. Preventive measures are always the first step in therapy.

Should there be a suspicion of osteoporosis in a man or evidence of a pathologic fracture in a man or a woman, assessment of risk via medical history and determination of BMD should be completed. BMD measurement and laboratory evaluation are necessary to document the extent of bone loss and to rule out secondary causes of osteoporosis. Should there be clinical evidence of a particular condition, the evaluation can focus on the suspected condition once the basic laboratory work has been completed as described in Table 29-3 and Figure 29-1.

Recognizing the variety of conditions conferring risk of osteoporosis, the National Osteoporosis Foundation makes the following recommendations to physicians:

1. Counsel all women on the risk factors for osteoporosis. Osteoporosis is a “silent” risk factor for fracture just as hypertension is for stroke; one of two white women will experience an osteoporotic fracture at some point in her lifetime.
2. Perform evaluation for osteoporosis on all postmenopausal women who present with fractures, using BMD testing to confirm the diagnosis and determine the disease severity.
3. Recommend BMD testing to postmenopausal women younger than 65 years who have one or more additional risk factors for osteoporosis in addition to menopause.
4. Recommend BMD testing to all women aged 65 years and older regardless of additional risk factors.
5. Advise all patients to obtain an adequate intake of dietary calcium (at least 1200 mg/d, including supplements if necessary).
6. Recommend regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures.
7. Advise patients to avoid tobacco smoking and to keep alcohol intake moderate.
8. Consider all postmenopausal women who present with vertebral or hip fractures candidates for treatment of osteoporosis.
9. Initiate therapy to reduce fracture risk in women with BMD T scores below −2 in the absence of risk factors and in women with T scores below −1.5 if other risk factors are present.
10. Pharmacologic options for prevention and treatment of osteoporosis include hormone replacement therapy, alendronate, raloxifene, and ibandronate (prevention), and calcitonin (treatment).

## Treatment

Decisions to intervene when osteoporosis is diagnosed reflect a desire to prevent early or continuing bone loss, a belief that there can be an immediate impact on the patient’s well-being, and a willingness to comply with the patient’s desires. Bone densitometry can assist in the decision-making process if the patient’s age confers risk, there are no manifestations of disease, and the decision point is prevention rather than treatment. BMD measurements can also assist in therapy when
Symptomatic patient
- Fracture
- Possible osteoporotic pain
Asymptomatic female patient

**Risk Factor Assessment**
- Background (age, family history, habits)
- Ongoing conditions/medications
- Nutrition
- Exercise
- Surgical history

**Physical Examination**

- No signs of chronic disease
- Signs of secondary osteoporosis (Table 28–1)
  - No risks (Table 28–2)
  - Risks (Table 28–2)
    - Bone mineral density (BMD) study
      - Negative results
      - Positive results
        - Laboratory evaluation (Tables 28–3 and 28–4)
          - Negative results
          - Positive results
            - Repeat evaluation in 6 mo
            - Institute prevention
            - Treat specific diagnosis

**Prevention**
- Habits (No tobacco or alcohol)
- Exercise
- Calcium

**Treat Osteoporosis: select treatment**
- Calcium + Vitamin D
- Exercise
- No tobacco or alcohol
- Bisphosphonates (risedronate, alendronate or ibandronate)
- Calcitonin
- Selective estrogen receptor modulators
- Postmenopausal hormone replacement therapy
- BMD every 12–24 mo to monitor therapy

▲Figure 29-1. Protocol for approaching osteoporosis.
there are relative contraindications to a specific agent and demonstrating efficacy could encourage continuation of therapy. Medicare currently reimburses costs of bone densitometry according to the conditions outlined in Table 29-6. The decision to intervene with pharmacologic therapy involves clinical judgment based on a global assessment, rather than BMD measurement alone. All currently approved therapeutic agents for the prevention and treatment of osteoporosis work by inhibiting or decreasing bone resorption.

A. Estrogen

Adequate estrogen levels remain the single most important therapy for maintaining adequate bone density in women. Prior to 2003, estrogen replacement therapy was considered for all women with decreased bone density, absent contraindications. However, in July 2002, the Women's Health Initiative randomized controlled primary prevention trial was stopped at a mean 5.2 years of follow-up by the data and safety monitoring board because the test statistic for invasive breast cancer exceeded the stopping boundary for the adverse effect of estrogen and progesterone versus placebo. Estimated hazard ratios were excessive for coronary heart disease, breast cancer, and strokes, but were less than 1.0 for colorectal cancer, endometrial cancer, and hip fracture. Therefore, careful risk assessment is needed for each patient to determine whether the improvement of risk for hip fracture (0.66) balances the risk for cardiovascular and breast disease. Contraindications to estrogen replacement therapy are listed in Table 29-7.

Studies have been done to determine the effect of the timing of initiation and the duration of postmenopausal estrogen therapy on BMD. Current users who started estrogen therapy at menopause had the highest BMD levels, which were significantly higher than those of women who never used estrogen therapy or past users who started at menopause (with a duration of use of at least 10 years). BMD was similar for women using unopposed estrogen or estrogen plus progestin, and for current smokers or nonsmokers. Current users who started estrogen within 5 years of menopause had a decreased risk of hip, wrist, and all nonspinal fractures compared with those who never used estrogen. Long-term users who initiated therapy 5 years after menopause had no significant reduction in risk for all nonspinal fractures, despite an average duration of use of 16 years. Therefore, early initiation of estrogen with respect to menopause may be more important than the total duration of use. Estrogen initiated early in the menopausal period and continued into late life appears to be associated with the highest bone density.

As more and more women utilize estrogen therapy, there has been increasing concern regarding its impact on breast cancer risk. The relation between the use of hormones and the risk of breast cancer in postmenopausal women was assessed in a follow-up survey of participants in the Nurses’ Health Study in 1992. The risk of breast cancer was significantly increased among women who were currently using estrogen alone or estrogen plus progestin, as compared with postmenopausal women who had never used hormones. Women currently taking hormones who had used such therapy for 5-9 years had an adjusted relative risk (RR) of breast cancer of 1.46, as did those currently using hormones who had done so for a total of 10 or more years (RR = 1.46). The addition of progestins to estrogen therapy does not reduce the risk of breast cancer among postmenopausal women.

The only randomized trial of estrogen-progesterone therapy describes secondary prevention of coronary heart disease in postmenopausal women (Heart and Estrogen/progesterin Replacement Study [HERS]) and included only women who had a prior history of cardiovascular disease. Women received either estrogen or estrogen and progesterone. There was an excess of deaths from coronary heart disease and a threefold excess risk of venous thrombosis during the first year of the trial in women on estrogen and a small risk of stroke in women on estrogen and progesterone. Recommendations at the conclusion of the trial included not starting women who

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### Table 29-6. Conditions qualifying for Medicare coverage of densitometry.

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen-deficient woman at clinical risk for osteoporosis</td>
</tr>
<tr>
<td>Individual with vertebral abnormalities (eg, osteopenia, vertebral fractures, osteoporosis)</td>
</tr>
<tr>
<td>Individual receiving long-term (more than 3 mo) glucocorticoid therapy</td>
</tr>
<tr>
<td>Primary hyperparathyroidism</td>
</tr>
<tr>
<td>Individual being monitored to assess response to osteoporosis drug therapy</td>
</tr>
</tbody>
</table>

### Table 29-7. Contraindications to estrogen replacement therapy.

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
<td>History of breast cancer</td>
</tr>
<tr>
<td></td>
<td>Estrogen-dependent neoplasia</td>
</tr>
<tr>
<td></td>
<td>Undiagnosed or abnormal genital bleeding</td>
</tr>
<tr>
<td></td>
<td>History of or active thromboembolic disorder</td>
</tr>
<tr>
<td>Relative</td>
<td>Migraine</td>
</tr>
<tr>
<td></td>
<td>History of thromboembolism</td>
</tr>
<tr>
<td></td>
<td>Familial hypertriglyceridemia</td>
</tr>
<tr>
<td></td>
<td>Uterine leiomyomas</td>
</tr>
<tr>
<td></td>
<td>Uterine cancer</td>
</tr>
<tr>
<td></td>
<td>Gallbladder disease</td>
</tr>
<tr>
<td></td>
<td>Strong family history of breast cancer</td>
</tr>
<tr>
<td></td>
<td>Chronic hepatic dysfunction</td>
</tr>
<tr>
<td></td>
<td>Endometriosis</td>
</tr>
</tbody>
</table>

already have clinical cardiovascular disease on estrogen and progesterone therapy (ie, secondary prevention).

B. Calcium and Vitamin D

Calcium supplementation produces small beneficial effects on bone mass throughout postmenopausal life and may reduce fracture rates by more than the change in BMD would predict—possibly as much as 50%. Postmenopausal women receiving supplemental calcium over a 3-year period in a placebo-controlled, randomized clinical trial had stable total body calcium and BMD in the lumbar spine, femoral neck, and trochanter compared with the placebo group.

Vitamin D increases calcium absorption in the gastrointestinal tract, so that more calcium is available in the circulation and is subsequently reabsorbed in the renal proximal tubules. There is now evidence of significant reductions in nonvertebral fracture rates from physiologic replacement of vitamin D in the elderly. Vitamin D supplementation is important in those of all ages with limited exposure to sunlight.

Dietary calcium augmentation should be recommended to maintain lifetime calcium levels and to help prevent early postmenopausal bone loss (Table 29-8). Adults should ingest 1000 mg of elemental calcium per day for optimal bone health. Teenagers, pregnant or lactating women, women older than 50 years taking estrogen replacement therapy, and everyone older than 65 years should ingest 1500 mg of elemental calcium per day for optimal bone health. If this cannot be achieved by diet alone, calcium supplementation is recommended. Calcium preparations should be compared relative to elemental calcium content. Therefore, attention to which form the patient is ingesting is important.

C. Calcitonin

Calcitonin, a hormone directly inhibiting osteoclastic bone resorption, is an alternative for patients with established osteoporosis in whom estrogen replacement therapy is not recommended. A unique characteristic of calcitonin is that it produces an analgesic effect with respect to bone pain and, thus, is often prescribed for patients who have suffered an acute osteoporotic fracture. The American College of Rheumatology recommends treatment until the pain is controlled, followed by tapering of medication over 4-6 weeks. Calcitonin decreases further bone loss at vertebral and femoral sites in patients with documented osteoporosis but has a questionable effect on fracture frequency. Calcitonin has been shown to prevent trabecular bone loss during the first few years of menopause, but it is unclear whether it has any impact on cortical bone. Calcitonin is also thought to be effective in decreasing the fracture rate of vertebral and peripheral bones.

The PROOF (Prevent Recurrence of Osteoporotic Fractures) trial—a 5-year double-blind study that randomized 1255 postmenopausal women with osteoporosis to receive placebo or one of three dosages of intranasal calcitonin (100, 200, or 400 IU/d)—demonstrated a 36% reduction in the relative risk of new vertebral fractures compared with placebo. There was no effect with 100 IU/d and no significant change in the reduction seen with 400 IU/d.

For reasons that are poorly understood, the increase in BMD associated with administration of calcitonin may be transient or there may be the development of resistance. Calcitonin can be provided in two forms. Nasal congestion and rhinitis are the most significant side effects of the nasal formulation. The injectable formulation has gastrointestinal side effects and is less convenient than the nasal preparation. The increase in bone density observed by this therapy is significantly less than that achieved by bisphosphonates or estrogen and may be limited to the spine, but it still has recognized value in reducing risk of fracture.

D. Bisphosphonates

Bisphosphonates are antiresorptive agents and effective for preventing bone loss associated with estrogen deficiency, glucocorticoid treatment, and immobilization. Antiresorptive agents improve the quality of bone by preserving trabecular architecture. They may increase bone strength by methods other than by increasing BMD. All bisphosphonates act similarly on bone in binding permanently to mineralized bone surfaces and inhibiting osteoclastic activity. Thus, less bone is degraded during the remodeling cycle. First-, second-, and third-generation bisphosphonates are now available (etidronate, alendronate, risedronate, and ibandronate). Because food and liquids can reduce the absorption of bisphosphonates, they should be given with a glass of plain water 30 minutes before the first meal or beverage of the day. Patients should not lie down for at least 30 minutes to lessen the chance of esophageal irritation. In addition, patients should consider taking supplemental calcium and vitamin D if their dietary intake is inadequate.

Bisphosphonates are of comparable efficacy to hormone replacement therapy in preventing bone loss and have a demonstrated positive effect on symptomatic and asymptomatic vertebral fracture rate as well as on nonvertebral fracture rate (forearm and hip). More than 4 years of treatment

---

Table 29-8. Calcium-rich foods.

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk (skim, lowfat, or whole)</td>
<td>8 oz</td>
</tr>
<tr>
<td>Plain yogurt</td>
<td>8 oz</td>
</tr>
<tr>
<td>Frozen yogurt, fruit</td>
<td>8 oz</td>
</tr>
<tr>
<td>Swiss cheese</td>
<td>1 oz</td>
</tr>
<tr>
<td>Ricotta cheese, part skim</td>
<td>4 oz</td>
</tr>
<tr>
<td>Sardines, canned</td>
<td>3 oz</td>
</tr>
<tr>
<td>Cooked greens, collards, or mustard</td>
<td>8 oz</td>
</tr>
<tr>
<td>Firm cheeses (Edam, Brick, Cheddar, Gouda, Colby, Mozzarella)</td>
<td>1 oz</td>
</tr>
<tr>
<td>Calcium-fortified orange juice</td>
<td>8 oz</td>
</tr>
</tbody>
</table>

*Approximately 300 mg.
would be needed in women with low bone density ($T$ score $\geq -2.0$), but without preexisting fractures, to substantially reduce the risk of clinical fracture.

In clinical trials, alendronate was generally well tolerated and no significant clinical or biological adverse experiences were observed. Alendronate appears to be effective at doses of 5 mg daily in preventing osteoporosis induced by long-term glucocorticoid therapy. In placebo-controlled studies of men and women (aged 17-83) who were receiving glucocorticoid therapy, femoral neck bone density and the bone density of the trochanter and total body increased significantly in patients treated with alendronate.

Alendronate appears to be a safe and well-tolerated agent for the treatment of osteoporosis. Some small studies suggest an additional benefit of adding alendronate to hormone replacement therapy, and ongoing studies should provide additional information. However, all of the bisphosphonates accumulate over time in bone, and further research is needed to determine their long-term impact as well as their potential for use in premenopausal women and men.

Risedronate is a pyridinyl bisphosphonate approved as treatment for several metabolic bone diseases in 2000. In doses of 5 mg daily, risedronate reduces the incidence of vertebral fractures in women with two or more fractures by rapidly increasing BMD at sites of cortical and trabecular bone. In a randomized trial of 2458 postmenopausal women with diagnosed osteoporosis, participants were treated with either 2.5 mg or 5 mg of risedronate or placebo as well as calcium supplementation and cholecalciferol if they had low baseline 25-hydroxyvitamin D levels. The 2.5-mg dose was found to be ineffective in other trials and was discontinued. After 3 years of treatment, the 5-mg risedronate group showed a 41% reduction in risk of new vertebral fractures and a 39% reduction in incidence of nonvertebral fractures.

In a large, prospective, hip fracture prevention trial of elderly women, risedronate was shown to significantly reduce the risk of hip fracture in women with osteoporosis. Bisphosphonates should be prescribed for 3-4 years in women with osteoporosis and low bone density.

Ibandronate is currently approved by the Food and Drug Administration (FDA) for the treatment and prevention of osteoporosis in postmenopausal women. Over a 3-year period, ibandronate was shown to decrease the incidence of new vertebral fractures by 52% and to increase BMD at the spine by 5%. It can be administered daily or once a month.

**E. Selective Estrogen Receptor Modulators**

Raloxifene is the first drug to be studied from a new class of drugs termed selective estrogen receptor modulators. This drug has a mixed agonist-antagonist action on estrogen receptors; estrogen agonist effects on bone and antagonist effects on breast and endometrium. Its discovery evolved from a structural rearrangement of the antiestrogen tamoxifen, although it is structurally very different. It blocks estrogen in a manner similar to tamoxifen, while also binding and stimulating other tissue receptors to act like estrogen. Raloxifene inhibits trabecular and vertebral bone loss in a manner similar, but not identical, to estrogen (ie, by blocking the activity of cytokines that stimulate bone resorption).

Raloxifene therapy results in decreased serum total and low-density lipoprotein (LDL) cholesterol without any beneficial effects on serum total high-density lipoprotein (HDL) cholesterol or triglycerides. Reported side effects of raloxifene are vaginitis and hot flashes. Investigators in the Multiple Outcomes of Raloxifene (MORE) trial of more than 7000 postmenopausal, osteoporotic women over 3 years showed a decreased risk of breast cancer in those already at low risk for the disease. The study results were analyzed separately for women presenting with preexisting fracture. Although treatment effectiveness was similar in both groups, the absolute risk of fractures in the group with preexisting fractures was 4.5 times greater than in the group with osteoporosis, but no preexisting fracture (21% vs 4.5%). Thus, it is important to identify and treat patients at higher risk. Studies of women at higher risk for breast cancer are currently underway.

A summary of overall treatment strategies is given in Table 29-9 and guidelines for dosing the pharmacologic agents are given in Table 29-10. Table 29-11 summarizes the risks and benefits of osteoporosis therapy.

### Table 29-9. Treatment strategies.

<table>
<thead>
<tr>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium-rich diet ± vitamin D supplements</td>
</tr>
<tr>
<td>Weight-bearing exercise</td>
</tr>
<tr>
<td>Avoidance of alcohol, tobacco products, excess caffeine, and drugs</td>
</tr>
<tr>
<td>Estrogen replacement within 5 y of menopause, and used for 10+ y</td>
</tr>
<tr>
<td>Alendronate</td>
</tr>
<tr>
<td>Raloxifene</td>
</tr>
<tr>
<td>Calcitonin</td>
</tr>
</tbody>
</table>

**For Patients on Glucocorticoids**

- Lowest dose of a short-acting glucocorticoid or topical preparations whenever possible
- Maintain a well-balanced, 2- to 3-g sodium diet
- Weight-bearing and isometric exercise to prevent proximal muscle weakness
- Calcium intake of 1500 mg/day and vitamin D intake of 400-800 IU/day after hypercalcemia is controlled
- Gonadal hormones in all postmenopausal women, premenopausal women with low levels of estradiol, and men who have low levels of testosterone (unless contraindicated)
- Thiazide diuretic to control hypercalcemia
- Measure bone mineral density at baseline and every 6-12 mo during the first 2 y of therapy to assess treatment efficacy
- If bone loss occurs during treatment or hormone replacement therapy is contraindicated, treat with calcitonin or bisphosphonate

F. Other Modalities

Fluoride increases bone formation by stimulating osteoblasts and increasing cancellous bone formation in patients with osteoporosis. However, the bone is formed only in the spine and is abnormal—irregularly fibrous and woven with lacunae of low mineral density. Cessation of therapy resulted in rapid loss of much of the bone formed during treatment. The major side effect of fluoride therapy is gastric distress, an effect that is thought to be related to the direct effect of hydrofluoric acid on the gastric mucosa. Fluoride is also associated with joint pain and swelling. For these reasons, sodium fluoride is not routinely used for treatment of osteoporosis and does not have FDA labeling for this indication.

Anabolic therapy produces some increase in bone mass. Teriparatide (PTH 1-34), marketed under the trade name Forteo or recombinant parathyroid hormone, is FDA approved for the treatment of osteoporosis in perimenopausal women who are at high risk for fracture. Teriparatide also has FDA labeling for increasing bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. Unlike antiresorptive agents, teriparatide stimulates new bone formation. There are some concerns regarding extended use of teriparatide because of the long-term effects on multiple organ systems (ie, significant hepatotoxicity, reduced HDL, and elevated LDL cholesterol).

Teriparatide is the first approved agent for the treatment of osteoporosis that stimulates new bone formation. It is administered once a day by injection (20 μg/d) in the thigh or abdomen. Patients treated with 20 μg/d of teriparatide, along with calcium and vitamin D supplementation, had statistically significant increases in BMD at the spine and hip when compared with patients receiving only calcium and vitamin D supplementation. Clinical trials also demonstrated that teriparatide reduced the risk of vertebral and nonvertebral fractures in postmenopausal women. The effects of teriparatide on fracture risk have not been studied in men.

Of note, osteosarcoma developed in animals in early studies, and the possibility that humans treated with teriparatide may face an increased risk of developing this cancer cannot be ruled out. This safety issue is highlighted in a black box warning in the drug label for health professionals and explained in a brochure for patients. Children and adolescents with growing bones and patients with Paget disease of the bone have a higher risk for developing osteosarcoma and should not be treated with this agent. Because the effects of long-term treatment with teriparatide are not known, therapy for more than 2 years is not recommended.

Testosterone replacement is acceptable therapy for many of the causes of hypogonadism in men (eg, Klinefelter syndrome, isolated gonadotropin deficiency [Kallmann syndrome]).

G. Complementary and Alternative Therapies

Evidence from animal studies suggests a beneficial effect of phytoestrogens on bone, but long-term human studies are lacking. Epidemiologic evidence that Asian women have a lower fracture rate than white women even though the bone density of Asian women is less than that of African-American women promotes consideration of the impact of nutrition. It is possible that high soy intake contributes to improved bone quality in Asian women. A comparison study of a soy protein and high isoflavone diet versus a milk protein diet or

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol patch</td>
<td>0.05 mg every wk</td>
<td>Topical</td>
</tr>
<tr>
<td>Conjugated estrogens</td>
<td>0.625-1.25 mg/d</td>
<td>Oral</td>
</tr>
<tr>
<td>Elemental calcium</td>
<td>1000-1500 mg/d</td>
<td>Oral</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>200 IU/d</td>
<td>Intranasal</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>50-100 IU/d</td>
<td>Subcutaneous or intramuscular</td>
</tr>
<tr>
<td></td>
<td>800 IU/d-800 IU/d</td>
<td>Orally three times per wk for 8 wks, then return to maintenance</td>
</tr>
<tr>
<td>Alendronate</td>
<td>5 mg/d (prevention) 10 mg/d (Rx)</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>5 mg/d or 35 mg every wk</td>
<td>Oral</td>
</tr>
<tr>
<td>Risedronate</td>
<td>2.5 mg/d or 150 mg every mo</td>
<td>Oral</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>60 mg/d</td>
<td>Oral</td>
</tr>
</tbody>
</table>

Table 29-10. Pharmacologic doses.
medium isoflavone and soy protein diet demonstrated that only those receiving the higher isoflavone preparation were protected against trabecular (vertebral) bone loss. A topical form of natural progesterone derived from diosgenin in either soybeans or Mexican wild yam has been promoted as a treatment for osteoporosis, hot flashes, and premenstrual syndrome, and a prophylactic against breast cancer. However, eating or applying wild yam extract or diosgenin does not produce increased progesterone levels in humans because humans cannot convert diosgenin to progesterone.

### H. Glucocorticoid-Induced Osteoporosis

Glucocorticoids are widely used in the treatment of many chronic diseases, particularly asthma, chronic lung disease, and inflammatory and rheumatologic disorders, and in those who have undergone organ transplantation. The risk oral steroid therapy poses to bone mineral density, among other side effects, has been known for some time. As a result clinicians have eagerly substituted inhaled steroids in an endeavor to protect the patient from unwanted negative steroid effects. Recent evaluations of the effects of inhaled glucocorticoids on bone density in premenopausal women demonstrated a dose-related decline in bone density at both the total hip and the trochanter. Women with asthma were enrolled and were divided into three groups: those using no inhaled steroids; those using four to eight puffs per day; and those using more than eight puffs per day at 100 μg per puff. No dose-related effect was noted at the femoral neck or the spine. Serum and urinary markers of bone turnover or adrenal function did not predict the degree of bone loss. To achieve the best possible outcome for the patient, given the potentially devastating effects of systemic steroids, therapy to combat the steroids should begin as soon as the steroids are begun. See Table 29-9 for specific guidelines.

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**Table 29-11.** Risks and benefits of osteoporosis therapy.

<table>
<thead>
<tr>
<th></th>
<th>Estrogen</th>
<th>Raloxifene</th>
<th>Calcitonin</th>
<th>Alendronate</th>
<th>Risedronate</th>
<th>Ibandronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of vertebral fracture</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reduction of non-vertebral fracture</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Experience with long-term use</td>
<td>Large epidemiologic studies over decades</td>
<td>RCT 3 y in length</td>
<td>RCT 5 y in length</td>
<td>RCT 4 y in length</td>
<td>RCT 3 y in length</td>
<td>RCT 3 y in length</td>
</tr>
<tr>
<td>Administration</td>
<td>Orally: once daily any time</td>
<td>Orally: once daily any time</td>
<td>Intranasally: once daily any time</td>
<td>Once daily in morning, 30 min before eating, with water while upright; or weekly</td>
<td>Once daily (or weekly) in morning, 30–60 min before eating, with water, while upright</td>
<td>Orally: once monthly in morning, 30–60 min before eating, with water, while upright, or intravenously every 3 mo</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Breast tender-ness, vaginal bleeding, thromboembolic disorders</td>
<td>Increased risk of venous thrombosis, hot flashes, leg cramps</td>
<td>Nasal irritation</td>
<td>Dyspepsia; esophagitis; avoid in patients with esophagheal disorders</td>
<td>Dyspepsia</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td>Effect on CV mortality</td>
<td>Increased in those with preexisting CV disease</td>
<td>No final out-come data</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Increased</td>
<td>Possibly decreased risk of estrogen receptor-positive breast cancer</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>Increased if unopposed estrogen used</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

RCT, randomized clinical trial; CV, cardiovascular.
Col NF et al: Patient-specific decisions about hormone replacement therapy in postmenopausal women. JAMA 1997; 277:1140. [PMID: 9087469]


Web Sites

The National Osteoporosis Foundation:http://www.nof.org
**General Considerations**

Abdominal pain is the chief complaint in 5%-10% of patients presenting to emergency departments and one of the top 10 outpatient complaints. Accurate diagnosis can be difficult, because the array of possible problems associated with abdominal pain is wide. For this reason, a detailed history, thorough physical examination, and laboratory and radiologic evaluations are necessary.

**Clinical Findings**

**A. History**

- **ESSENTIALS OF DIAGNOSIS**

  - Determine acute versus chronic.
  - Quality, location, and radiation of pain.
  - Associated symptoms.

The history is one of the most important components in the evaluation of abdominal pain and can help direct the subsequent workup. The first priority is to determine whether the pain is acute or chronic. The sudden or severe onset of abdominal pain, particularly pain associated with peritoneal irritation as from appendicitis, or ruptured abdominal organ. Many of these problems require emergency management and consultation with a surgeon. In the family medicine office, many other issues present with a more gradual onset of abdominal pain and by abdominal pain that is chronic in nature (Table 30-1).

2. **Quality of pain**—The patient’s description of the quality of the pain provides clues to the etiology of the problem. Pain can be sharp, stabbing, burning, dull, gnawing, colicky, crampy, gasey, focal, migrating, or radiating. A pressure-like description (“there’s an elephant sitting on me”) suggests cardiac ischemia. The more focal these symptoms are, the more helpful the location can be to determining the diagnosis.

3. **Location**—The location of the pain coupled with any radiation can be helpful. The abdomen can be separated into four quadrants: right upper (RUQ), left upper (LUQ), right lower (RLQ), and left lower (LLQ). Location can further be identified, including mid-epigastric or suprapubic. From the location of the pain, the differential of causes can be narrowed. Several causes of abdominal pain have classic patterns of location and radiation even to areas outside the abdomen. For example, pain from the lower esophagus may be referred higher in the chest and is often confused with pain associated with cardiac conditions, such as an acute myocardial infarction.

4. **Frequency/Timing**—The frequency and pattern of the pain are particularly useful in identifying abdominal pain that is gradual in onset. Pain timing may be related to eating, defecation, body position, or movement. The type of meal which seems to cause pain gives more diagnostic clues. Peritoneal irritation is eased by lack of movement, while visceral pain tends to cause patient to keep moving to try to find a comfortable position. Many pains may peak and then be relieved by defecation. This finding is suggestive of colonic pathology.
5. Other diagnostic clues/Associated symptoms—

Physicians need to determine if other associated symptoms are present. Patient should be asked specifically about presence and quality of nausea, vomiting, diarrhea, or constipation. The presence of blood, melena, hematochezia, or mucus is important in assessing vomitous or bowel movements. Fever and chills suggest an infectious etiology. Feculent emesis is correlated with bowel obstruction. The presence of blood or melena in the stool requires further evaluation due to the possibility of gastrointestinal (GI) bleeding. Emotional stress can exacerbate functional bowel disease. However, it should not be used as a primary diagnostic discriminator between functional and organic disease because many organic diseases can be accentuated by emotional stress.

Past medical history can provide important clues to the etiology of abdominal pain. A history of previous episodes can help direct further evaluation. Previous abdominal surgery increases the risk for bowel obstruction secondary to adhesions, strangulation, or hernia. Patients with a history of cardiovascular disease are at greater risk for bowel infarction. A history of tobacco or alcohol use is associated with an increased incidence of gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD). Alcohol abuse is also a common cause of pancreatitis. Multiparity, obesity, and diabetes mellitus all increase the risk of gallbladder disease. Tubal ligation or a history of pelvic inflammatory disease (PID) indicates a greater risk for an ectopic pregnancy.

No medical history is complete without a medication history that also includes both over-the-counter drugs and herbal supplements. Aspirin and other platelet aggregation inhibitors, steroids and nonsteroidal anti-inflammatory drugs (NSAIDs), and antidepressants increase the risk of GI bleeding. Antibiotics can be associated with nausea, diarrhea, or both.

Advancing age can change the patient’s presentation and perception of abdominal pain. There is a 10%-20% reduction in intensity of pain per decade of age over 60 years. This fact should be considered when elderly patients present with only vague or mild abdominal pain. The elderly are significantly less likely to present with a classic symptom pattern for things like appendicitis or PUD.

B. Physical Examination

Table 30–1. Common causes of abdominal pain by location.

<table>
<thead>
<tr>
<th>Localized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midepigastric</td>
</tr>
<tr>
<td>Dyspepsia</td>
</tr>
<tr>
<td>GERD</td>
</tr>
<tr>
<td>Pancreatitis</td>
</tr>
<tr>
<td>PUD</td>
</tr>
<tr>
<td>RUQ</td>
</tr>
<tr>
<td>Gallbladder diseases</td>
</tr>
<tr>
<td>Hepatitis</td>
</tr>
<tr>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>RLQ</td>
</tr>
<tr>
<td>Appendicitis</td>
</tr>
<tr>
<td>Crohn disease</td>
</tr>
<tr>
<td>GYN-related diseases</td>
</tr>
<tr>
<td>Ruptured ovarian cyst</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
</tr>
<tr>
<td>PID</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Meckel diverticulitis</td>
</tr>
<tr>
<td>LUQ</td>
</tr>
<tr>
<td>MI</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Sickle cell crisis</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td>Splenomegaly—EBV</td>
</tr>
<tr>
<td>Gastritis</td>
</tr>
<tr>
<td>LLQ</td>
</tr>
<tr>
<td>Diverticulitis</td>
</tr>
<tr>
<td>Bowel obstruction</td>
</tr>
<tr>
<td>Ischemic colitis</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Urinary calculi</td>
</tr>
<tr>
<td>Suprapubic</td>
</tr>
<tr>
<td>Cystitis</td>
</tr>
<tr>
<td>Prostatitis</td>
</tr>
<tr>
<td>Urinary retention</td>
</tr>
<tr>
<td>Generalized</td>
</tr>
<tr>
<td>Abdominal wall pain—multiple causes</td>
</tr>
<tr>
<td>Celiac disease</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Chronic diarrhea</td>
</tr>
<tr>
<td>IBS</td>
</tr>
<tr>
<td>Gastroenteritis/infectious diarrhea</td>
</tr>
<tr>
<td>Mesenteric lymphadenitis</td>
</tr>
<tr>
<td>Perforated colon</td>
</tr>
<tr>
<td>Ruptured aortic aneurysm</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
</tbody>
</table>

GERD, gastroesophageal reflux disease; PUD, peptic ulcer disease; GYN, gynecologic; PID, pelvic inflammatory disease; MI, myocardial infarction; EBV, Epstein–Barr virus; IBS, inflammatory bowel disease; RUQ, right upper quadrant; RLQ, right lower quadrant; LUQ, left upper quadrant; LLQ, left lower quadrant.

▶ Inspect, auscultate, palpate, and percuss abdomen.

▶ Assess for tenderness on palpation as well as rebound tenderness.

▶ Listen for infrequent bowel sounds

The history obtained dictates the focus of the abdominal examination. In addition to the abdominal examination, a pelvic examination is frequently indicated in female patients presenting with abdominal pain. An effective physical
examination of the abdomen has many steps that flow intuitively. The physician should begin by positioning the patient supine with the knees slightly bent then proceed with the steps listed as follows:

1. **Inspection**—An inspection for distention, discoloration, scars, and striae should be conducted. Distention suggests ascites, obstruction, or other masses increasing the abdominal contents. Discoloration may include bruising as in the case of hemoperitoneum, found in the central portion of the abdomen, especially following abdominal trauma. The presence and location of scars help clarify and confirm the history previously obtained. Striae suggest rapid growth of the abdomen. Old striae tend to be white, whereas new striae or those related to endocrine abnormalities tend to be purplish or dark pink. In persons of color, this may appear to be a darkening of the skin. The abdomen should also be inspected when the patient is in a supine position.

2. **Auscultation**—Auscultation should be performed prior to palpation. The physician should listen for the quality of bowel sounds: normal, hypoactive, hyperactive, or high pitched. Hypoactive and hyperactive bowel sounds can both be present in the case of total or partial bowel obstruction, or ileus. It is also necessary to listen for bruits over the aorta, renal arteries, and femoral arteries when auscultating. Bruits may be suggestive of aneurysms in those areas. Palpating gently while auscultating decreases the likelihood of guarding, embellishment, or symptom magnification on the part of the patient.

3. **Palpation**—Palpation of the abdomen should be done in several steps, beginning with the lightest of touches away from the area of greatest pain and moving closer to the tender area as the examination progresses. There are several aspects to palpation, including consistency, tenderness, masses, and organ size. Consistency can range from soft to rigid; increased rigidity is indicative of an acute abdomen needing more emergent intervention.

   Tenderness can be separated by location, radiation, and associated rebound or guarding. Murphy sign, sudden cessation of the patient’s inspiratory effort during deep palpation of the RUQ, is suggestive of acute cholecystitis. Pain stemming from visceral organs may appear to radiate secondary to other areas being innervated by the same nerve. For example, the pain caused by pancreatitis often radiates to the back. Kehr sign, abdominal pain radiating to the left shoulder, is indicative of splenic rupture, renal calculi, or ectopic pregnancy. Radiation of pain can also be caused by inflammation of surrounding tissues.

   It is difficult to palpate the deep muscles of the abdomen, but the same effect can be obtained by examining pain with motion of muscles. For example, the iliopsoas muscle test can assess for inflammation within the psoas muscle or inflammation of overlying structures such as the appendix. The test is performed by having the patient lie supine, then lift the right leg while flexing at the hip. Resistance is applied to the leg. Pain with this maneuver is suggestive of appendicitis or retroperitoneal dissection.

   Rebound tenderness indicates peritoneal irritation, which can come from perforation along the GI tract or from the non-GI sources such as a ruptured ovarian cyst or PID. When there is peritoneal irritation, the patient will often demonstrate guarding. Guarding can be voluntary or involuntary. Voluntary guarding can occur when the patient anticipates the pain. The “closed eye” sign has been shown to help differentiate the etiology of the pain. Patients whose pain has an organic etiology will keep their eyes open and watch as the examiner approaches the abdomen. Patients who close their eyes are more likely to have psychosocial factors contributing to their abdominal pain.

   Involuntary guarding is caused by flexion of the abdominal wall muscle as the body attempts to protect the internal organs. This protective reflex can be used to differentiate visceral pain from abdominal wall or psychogenic pain, demonstrated with the Carnett test. Once the area of greatest tenderness is located, the patient then flexes the abdominal wall and the point is palpated again. Pain that is less severe with palpation of the flexed abdomen wall has a high probability of being visceral. Pain that remains the same or is worsened with this maneuver likely stems from the abdominal wall or from nonorganic causes.

   Palpation of the abdomen of a ticklish patient can be difficult. Two approaches can help the physician palpate these patients more thoroughly. One method is to first use the stethoscope for light palpation and then curl the fingers past the edge of the stethoscope to create a less sensitive touch. In an alternative technique, the patient places his or her hands on the abdomen and the examiner palpates through the patient’s hands and just over the edge of the patient’s fingers. This permits deep palpation without contraction of the abdominal muscles from laughing.

   In addition to feeling for tenderness with palpation, the physician should examine the abdomen for masses and organ size. Palpable masses include colon cancer masses, kidney abnormalities, non-GI tumors, aneurysms, or other organ abnormalities. Most are found on deep palpation. This palpation can be facilitated by having the patient in the supine position with the knees slightly bent, to allow for relaxation of the abdominal muscles. If a mass is palpated, it should be examined for location, size, shape, consistency, pulsations, mobility, and movement with respiration.

   When palpating for organ size, the liver and spleen should be examined. Before trying to palpate the lower border of the liver or spleen, the examiner should ask the patient take a deep breath and then exhale while he or she palpates deeper. The normal liver span at the midclavicular line is 6-12 cm. The liver in men and taller individuals tends to be larger than that in women and shorter individuals. Additionally, the liver span in the midclavicular line can be helpful. This span is normally 4-8 cm. Anything larger than 8 cm should be considered enlarged. The size of the liver may better be appreciated
by percussing along the midclavicular line. The examiner should start in an area of tympany and progress to an area of dullness, both from above the liver and below the liver. The upper border generally sits at the fifth to seventh intercostal space. Inferior displacement is suggestive of emphysema or other pulmonary disease.

The spleen may not be palpable or just a tip of the spleen may be palpable. Both of these findings are normal. The actual span of the spleen can be determined by percussion. The area of dullness related to the spleen is generally from the sixth to the tenth rib. It should be percussed in the left midaxillary line.

**4. Percussion**—Percussion can be helpful to determine both the size of the organs and other information about the abdomen. Percussion over the liver or spleen should be slightly dull. A change in the character of the sound can indicate that the edge of the organ is reached. This can also be determined by the scratch test, a gentle form of percussion. It is performed by placing the stethoscope over the liver, gently scratching the surface of the skin beginning above the upper border of the liver and progressing down below the lower border of the liver. The quality of the sound changes as the examiner’s scratch travels from the lung field to the liver and then to the abdomen. These changes in sound help to identify the borders of the liver.

After the size of organs is determined, the rest of the abdomen can be examined for other abnormalities. Tympany should be present over the stomach bubble because of the air present. Tympany related to the stomach should be found in the area of the left lower border of the rib cage and left epigastrium. However, any increased tympany throughout the rest of the abdomen suggests dilation or perforation of the bowel. Dullness can be stationary, as with solid masses, or shifting as with mobile fluid. Shifting dullness is generally present with significant ascites.

### C. Laboratory Findings

- CBC, electrolytes, BUN, creatinine, glucose for most patients.
- All women of childbearing age should have pregnancy test.
- Iron studies for adults older than 50 years.

There are many laboratory tests available to clarify diagnosis in patients with abdominal pain. Most patients should have basic testing to include complete blood cell count (CBC), electrolytes, blood urea nitrogen (BUN), creatinine, and glucose. Alkaline phosphatase and liver function tests can be helpful. Other tests should be ordered for specific concerns or locations of pain. The CBC in the acute setting can be misleading. A normal hemoglobin and hematocrit in the setting of acute rapid blood loss can be reassuring, but should be rechecked as patient is fluid-resuscitated. With increased fluid volume, anemia is often apparent. The presence of anemia, especially in those older than 50, should prompt iron studies including ferritin level. Older patients may present with vague abdominal pain in the setting of hypothyroidism, and so a thyroid-stimulating hormone level can be useful.

RUQ pain should be evaluated with bilirubin, lase, amylase, trypsin, and liver function tests. There are settings where hepatitis panels are useful as well. Amylase is elevated in most cases of pancreatitis, but also many other abdominal problems. Therefore, a lipase and trypsin level can help clarify diagnosis, as these tests are more specific for pancreatitis.

Abdominal pain associated with diarrhea may need stool studies depending on the timing and type of diarrhea present. The acute setting rarely needs laboratory testing except in the setting of severe dehydration, blood in stool, or the immunocompromised patient. Stool studies, including white blood cell count (WBC), hemoccult testing, ova and parasite, culture for enteric pathogens, and *Clostridium difficile* toxin level, can be done for chronic diarrhea or bloody diarrhea. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) should be checked if there is concern for inflammatory bowel disease, especially if WBCs are found in stool. Intermittent symptoms suggestive of celiac disease may warrant laboratory tests for antiendomysial antibody.

Some populations should have other tests done as well. Women of childbearing age should have pregnancy test done regardless of tubal ligation. Lower abdominal pain patients may need a urinalysis (U/A), although many intra-abdominal problems can cause changes in U/A that may appear similar to urinary tract infection. Other lower abdominal pain causes warrant vaginal cultures for gonorrhea and *Chlamydia*. Cardiac pain can cause abdominal complaints and necessitates its own set of laboratory studies. Generalized complaints may warrant further studies such as magnesium level, calcium level, or vitamin D panel.

### D. Imaging Studies

- CT scan is test of choice for acute abdominal pain.
- U/S is test of choice for RUQ pain.
- Colonoscopy should be considered in abdominal pain in all patients older than 50.

Plain films of the abdomen can be a fast effective first test in the evaluation of the patient with abdominal pain, both acute and chronic. Upright and lateral decubitus films of the abdomen can show dilated small bowel loops (suggestive of obstruction), free air (perforated organ), mass (tumor or other obstructing cause), or stones (biliary or renal). Small
bowel follow-through shows abnormalities of ileum such as ulcer or mass. Barium enema can be useful for evaluation of constipation. The advantages of plain radiographs include the speed of availability, low cost, and low radiation exposure. Despite these advantages, sometimes it is more useful to bypass this first step and start with more specific testing, especially in the setting of an acute abdomen.

Computerized tomography (CT) of the abdomen and pelvis is the test of choice for many acute (and some nonacute) causes of abdominal pain. Protocols for specific problems can limit radiation exposure and time of examinations while providing more accurate information. Spiral CT for either appendicitis or renal calculus has been shown to be fast, safe, effective, and cost efficient. Other problems well visualized by CT scan include diverticulitis, bowel obstruction, pancreatitis, abdominal aortic aneurysm, and pneumoperitoneum. Most soft tissue tumors are well visualized. Renal and biliary stones can be seen on CT scan, although many are not radio opaque and are more easily visualized with ultrasound.

Ultrasonography (US) is the test of choice for most RUQ pain. It is a low-cost, low-risk imaging technique. Ultrasound is the most reliable imaging of the biliary system and pelvic organs. Hernias can sometimes be identified with ultrasound. It is useful for pregnant patients because there is no radiation exposure or contrast material. Children may tolerate US better than CT scan for certain problems like appendicitis due to a shorter time and lesser need to remain completely still for the examination. Obesity limits the usefulness of this testing modality. US is very operator dependent in its accuracy.

In the setting of chronic pain, direct visualization of the internal structures of the GI tract is often needed. Upper endoscopy is used for evaluation of dyspepsia, ulcers, and other upper gastric abnormalities. This imaging modality allows for direct visualization of the mucosal as well as for biopsy of mucosa or lesions and treatment of bleeding sources. Colonoscopy or sigmoidoscopy is indicated for most patients older than 50 years or with other risk factors for cancer. Colonoscopy or sigmoidoscopy allows for direct visualization of the mucosal as well as for biopsy of mucosa or lesions and treatment of bleeding sources. Colonoscopy or sigmoidoscopy is indicated for most patients older than 50 years or with other risk factors for cancer.

Other modalities are available for imaging of the abdomen, including magnetic resonance imaging (MRI). MRI is useful for further evaluation of lesions seen on other tests. There are many other imaging modalities for problems related to the urinary system as well. Further discussion of specific imaging is discussed in each section focused on problems.

**DYSPEPSIA**

**General Considerations**

The word *dyspepsia* was first used in the early 18th century to describe a person’s ill humor, indigestion, or disgruntlement. The modern family practitioner uses the term to describe a set of symptoms that can encompass several different diseases and the etiology associated with them. Chronic or recurrent discomfort centered in the upper abdomen is the description most commonly used by clinicians for dyspepsia. Dyspepsia can be associated with heartburn, belching, bloating, nausea, or vomiting. Common etiologies include PUD and GERD. Rare causes include gastric and pancreatic cancers.

Although dyspepsia is reported to affect 40% of the world's adult population and accounts for 2%-3% of all visits to primary care providers, only about 10% of affected adults seek medical advice. Approximately 15%-25% of dyspepsia is caused by PUD and 5%-15% by GERD.

No specific etiology is found for approximately 50%-60% of patients who present with epigastric pain. When a patient has suffered at least 3 months of dyspepsia without a definitive structural or biochemical explanation, the clinical term applied is *nonulcer dyspepsia* or *functional dyspepsia*. Other etiologies that occur infrequently include gastric or esophageal cancer, biliary tract disease, gastroparesis, pancreatitis, carbohydrate malabsorption, medication-induced symptoms, non-GI diseases affecting the stomach (sarcoidosis, diabetes, and thyroid and parathyroid diseases), metabolic disturbances (hypercalcemia and hyperkalemia), hepatoma, intestinal parasites, and other cancers, particularly pancreatic cancer.

The history is often similar, whether the symptoms are from PUD, GERD, or nonulcer dyspepsia. Studies have shown that the symptoms and the degree of symptoms do not correlate with the findings on endoscopy.

The physical examination is also similar. There may be tenderness in the midepigastric area. Unless an ulcer has perforated, causing signs of peritonitis, the rest of the abdominal examination is unremarkable.

The treatment for dyspepsia depends on the etiology and will be discussed in the different sections on PUD, GERD, and nonulcer dyspepsia.


1. Peptic Ulcer Disease

**General Considerations**

The four major causes of ulcers include *Helicobacter pylori*-induced ulcers, NSAIDs, acid hypersecretory conditions, and idiopathic ulcers.

There is clear evidence to support the eradication of *H pylori* in patients who have documented ulcers. Over the past 20 years, the association of *H pylori* with peptic ulcers has decreased from 90% to as low as 15%-20% in some countries. This decrease is related to increased treatment of *H pylori* infections. *H pylori* infections have been commonly associated with low income, low educational levels, and
overcrowded living conditions. African Americans and Hispanics have about a one-third higher rate of infection than white Americans. In the United States, 40% of all adults are infected with *H pylori* by the time they reach 50 years of age, compared with only 5% of all children aged 6-12 years. In developing countries, children are more commonly infected at a younger age and there is a higher incidence of infection throughout the entire population.

**Pathogenesis**

Infection with *H pylori* used to be the leading cause of peptic ulcers and use of NSAIDs was the second leading cause. Now NSAID use and idiopathic ulcers are the most common cause. In the United States, one in seven individuals uses NSAIDs. Of long-term NSAID users who undergo an upper endoscopy, 5%-20% are found to have an ulcer. Risk factors for developing an ulcer due to NSAID use are a personal history of ulcer, age older than 65 years, current steroid use, use of anticoagulants or a history of cardiovascular disease, and the impairment of another major organ. NSAIDs are prescribed to nearly 40% of all persons older than 65 years. Elderly patients who commence a course of treatment with NSAIDs have a 1%-8% chance of being hospitalized within the first year of therapy for GI complications caused by NSAIDs. Patients who are *H pylori* positive and who are taking NSAIDs have a higher risk of complications.

**Prevention**

Eradication of *H pylori* infection before starting a course of treatment with NSAIDs reduced the risk of developing an ulcer early in the treatment.

**Clinical Findings**

As with most cases of abdominal pain, the history obtained provides the majority of information used to focus the differential diagnosis. Factors pointing toward PUD include a gnawing pain with the sensation of hunger, a prior personal or family history of ulcers, tobacco use, and a report of melena.

The most accurate diagnostic test is esophagogastroduodenoscopy (EGD), which allows both visualization and biopsy of the ulcer as well as testing for *H pylori*. There is good evidence to support the “test and treat” approach to evaluate *H pylori*. The most cost-effective noninvasive test is the monoclonal stool antigen test. Breath urea testing is also noninvasive but more expensive and, in some studies, not as accurate. Currently, serology testing is used mainly for research or surveillance testing. Serology may also be indicated in an actively bleeding ulcer that complicates the performance of an EGD.

**Complications**

In the elderly (aged ≥80 years) who have ulcers, the incidence of complications is much higher in patients who are taking aspirin and are *H pylori* infected. A hypersecretory condition, such as Zollinger-Ellison syndrome, is suspected in patients who have multiple ulcers and is caused by a gastrin-producing tumor. The incidence of GI bleeding from the upper GI tract has decreased (possibly related to the increased treatment of *H pylori*), so the relative frequency of lower GI bleeding has increased.

**Treatment**

Treatment of PUD requires the initial eradication of *H pylori* if present, stopping or reducing the dose of NSAIDs, and treatment with an H2 blocker or a proton pump inhibitor (PPI). Many Food and Drug Administration (FDA)–approved treatment regimens exist to eradicate *H pylori*. They usually include two or three antibiotics plus a PPI or an H2 blocker for 10-14 days. Because antibiotic resistance changes and subsequently recommended treatment options change, it is necessary to refer to current guidelines either locally or from the Centers for Disease Control and Prevention (CDC). Treatment of the *H pylori* infection facilitates the healing of the ulcer and decreases the rate of recurrence in the first year from 75% to only 10%. Medical treatment of peptic ulcer has become very effective and surgical intervention needs to occur less frequently. When surgery is performed, it is more commonly done with a laparoscopic repair.


2. Gastroesophageal Reflux Disease

**Clinical Findings**

Heartburn is the single most common symptom of GERD. Ten percent of the US population experience heartburn at least once per day and almost 50% experience symptoms at least once per month. Other common symptoms include regurgitation, belching, and dysphagia. GERD can also be associated with multiple extraesophageal symptoms and conditions. Pulmonary conditions that can be caused by GERD include asthma, chronic bronchitis, aspiration pneumonia, sleep apnea, atelectasis, and interstitial pulmonary fibrosis. Ear, nose, and throat manifestations of GERD include chronic cough, sore throat, hoarseness, halitosis, enamel erosion, subglottic stenosis, vocal cord inflammation, granuloma, and, possibly, cancer. Noncardiac chest pain, chronic hiccups, and nausea are also associated with GERD.
Changes in body position tend to exacerbate the symptoms of GERD, particularly lying down or bending forward. Complications include Barrett esophagus, esophageal strictures, ulceration, hemorrhage, and, rarely, perforation. Of all patients who undergo an upper endoscopy for GERD, 8%-20% are found to have Barrett esophagus.

The esophagus has three mechanisms in place to try to prevent mucosal injury. The lower esophageal sphincter (LES) creates a barrier to acid reflux. Peristalsis, gravity, and saliva provide acid clearance mechanisms. The third defense mechanism is epithelial resistance.

Diagnosis is made using the medical history and treatment with H₂ receptor antagonists, protonkinetic agents, or PPIs. Symptomatic improvement following treatment can be indicative of GERD. Other methods to assist with the diagnosis include symptom questionnaires, catheter and wireless pH-metry, and impedance-pH monitoring. Upper endoscopy fails to reveal 36%-50% of all patients who have been diagnosed via esophageal pH monitoring. Patients who have typical symptoms and respond to PPIs do not need further evaluation. Endoscopy should always be performed if alarming symptoms are present such as bleeding, weight loss, or dysphagia, especially if the alarm symptoms occur in an elderly patient.

Treatment of GERD involves lifestyle modification and medication. Lifestyle modifications that have the greatest impact in reducing symptoms of GERD and that also provide positive health benefits include cessation of smoking, moderation in the consumption of alcohol, weight loss in the case of overweight patients, and reduction in dietary fat intake. Certain foods that decrease LES pressure (chocolate), stimulate acid secretion (coffee, tea, and cola beverages), or produce symptoms by their acidity (orange or tomato juice) should be avoided. In addition, elevating the head of the bed by 6 in, avoiding bedtime snacks, and reducing meal size, particularly the evening meal, can all help ameliorate symptoms of GERD.

Medication treatment options are designed to decrease the acid or increase the defense mechanisms. Commonly used over-the-counter medications include antacids, Simethicon (Gaviscon), and H₂ blockers. Prescription medicines include prescription strength H₂ blockers, PPIs, protonkinetic agents (Reglan), bethanechol, and sucralfate. Agents that can irritate the mucosa (eg, aspirin and NSAIDs) should be avoided or used only sparingly. Other agents to avoid if possible include α-adrenergic antagonists, anticholinergics, β-adrenergic agonists, calcium channel blockers, diazepam, narcotics, progesterone, and theophylline.

If the patient’s symptoms have resolved or significantly improved with the preceding treatment measures, then no further evaluation is needed. If the symptoms have not improved, usually within 1-2 weeks, then endoscopy is the next step. Symptoms do not always correlate with the pathologic findings seen at the time of endoscopy. Even as symptoms improve over time, there still may be a risk of developing long-term complications. Patients who have developed Barrett esophagus need closer follow-up and monitoring because they have a 50- to 100-fold increased risk of developing esophageal cancer.

3. Nonulcer Dyspepsia

ESSENTIALS OF DIAGNOSIS

- Persistent or recurrent dyspepsia that has been present during the past 3 months with onset at least 6 months prior to diagnosis, without evidence of organic disease.
- Diagnosis is made by excluding other causes of dyspepsia.
- No diagnostic gold standard; consider EGD to rule out other causes if no response to PPIs and “test and treat” for H pylori.

General Considerations

Nonulcer dyspepsia, also referred to as idiopathic or functional dyspepsia, is defined as persistent or recurrent dyspepsia without evidence of organic disease that has been present for the past 3 months with onset more than 6 months prior to diagnosis, not relieved by defecation, and not associated with the onset of change in stool frequency or form (which would indicate irritable bowel syndrome [IBS]). Nonulcer dyspepsia is divided into at least two distinct subgroups: the postprandial distress syndrome, which features postprandial fullness and early satiety; and the epigastric pain syndrome, which features a more constant and less meal-related pain syndrome.

Nonerosive reflux disease (NERD) is defined as having typical symptoms of GERD, in the absence of visible esophageal mucosal injury when EGD is performed. Nonulcer dyspepsia and NERD may represent different aspects of the same disease entity. It has been suggested that separating the functional GI symptoms of dyspepsia and IBS may be inappropriate.

Pathogenesis

The pathophysiology of nonulcer dyspepsia is not entirely clear and is probably multifactorial. Suggested causes include changes in gastric physiology, nociception, motor dysfunction, central nervous system dysfunction, and psychological...
and environmental factors (see the discussion of IBS, later). *H pylori* and its effects on nonulcer dyspepsia are highly controversial. A percentage of patients with nonulcer dyspepsia and *H pylori* have significant improvement in their symptoms after using eradication therapy, yet improvement cannot be guaranteed. Approximately 50% of patients with nonulcer dyspepsia are *H pylori* positive.

**Clinical Findings**

Nonulcer dyspepsia is diagnosed by excluding other causes of dyspepsia. A negative endoscopy is needed to diagnose NERD. Endoscopy is also negative with nonulcer dyspepsia. A therapeutic trial of PPI’s and/or “test and treat” for *H pylori* are common practices and supported in the literature. Cost-effectiveness data indicate that testing for *H pylori* and treating the patients with positive results decreases the number of EGDs performed by approximately one-third.

**Treatment**

Management of nonulcer dyspepsia is multifactorial and includes making a diagnosis early and explaining as much of the relevant physiology as possible to the patient. It is important for the physician neither to investigate excessively nor to investigate the presenting symptoms alone. New investigation in a patient who has been previously diagnosed with nonulcer dyspepsia should be done whenever alarm symptoms are present or if a new objective symptom arises. (Alarm symptoms are highlighted by the mnemonic VBAD: Vomiting, evidence of Bleeding or anaemia, presence of Abdominal mass or weight loss, and Dysphagia.) The prevalence of *H pylori* in the community may also factor into the decision to “test and treat” or perform other investigations. It is important for the physician to determine why the patient has chronic symptoms presented at this particular time.

Psychosocial factors can exacerbate symptoms, so it is important for physicians to address these issues and offer counseling. A mainstay of management is postevaluation reassurance of the patient concerning the diagnosis and the absence of alarm symptoms. Patients should avoid any food or substance that tends to exacerbate symptoms (NSAIDs, alcohol, tobacco, and certain foods). Not all patients want or need to take prescription medicine. For these patients other treatment options should be explored. If symptoms of bloating or postprandial fullness are present, the patient should eat six small meals per day, which may help ameliorate symptoms.

A remarkable number of different medicines have been used in studies of nonulcer dyspepsia. The results are confounded by the fact that the studies do not use the same definition for the disorder and do not differentiate among the different symptom types. For example, PPIs appear to have some benefit in ulcer-like dyspepsia whereas patients with dysmotility-like dyspepsia do not respond. Medicines that decrease gastric dysrhythmias. Promethazine has been used to treat mild nausea. Of the antidepressants, tricyclic antidepressants have been most extensively studied in functional dyspepsia. Selective serotonin reuptake inhibitors have had some promising results with other functional bowel diseases (IBS).

Other approaches that are being used include acupuncture, acupressure, and gastric electrical stimulation. However, no randomized, double-blind controlled trials have been performed to evaluate their effectiveness. After discussing whether medications are needed and writing a prescription if necessary, physicians should schedule a follow-up appointment to assess the patient’s function and to determine any responses to the treatment.


**DISEASES OF THE GALLBLADDER & PANCREAS**

The three main causes of abdominal pain related to the gallbladder and pancreas are biliary colic, gallstones, cholecystitis, and pancreatitis. Gallbladder-related pain is usually located in the midepigastric region and may radiate to the right shoulder, right scapula, right clavicular area, or back. Pancreatitis tends to produce pain throughout the entire upper abdomen with frequent radiation to the back. For detailed discussion of these and other diseases of the biliary tract and pancreas, see Chapter 32.

**IRRITABLE BOWEL SYNDROME**

**General Considerations**

Estimates indicate that symptoms consistent with a diagnosis of IBS are present in from 3% to 20% of adults in the Western world. Although IBS occurs worldwide, cultural and
social factors affect its presentation. In Western countries, women have a higher incidence of the condition and are more likely to consult a physician. In India and Sri Lanka men have a higher incidence of IBS. In black South Africans, IBS symptoms are common in people who live in urban zones and are unusual in people who live in rural areas. In the United States, prevalence is similar between blacks and whites and some studies show a lower prevalence in Hispanics from Texas and Asians from California.

A large percentage of individuals (up to 50%) with symptoms consistent with a diagnosis of IBS never seek a physician’s care. Those who do seek care have often had a major life event (eg, a death in the family or loss of job) before presenting with GI complaints. Primary care providers see a larger percentage of these patients than do GI specialists.

Pathogenesis

Physiologic alterations contributing to symptoms of IBS have not been elucidated. Many theories exist, including disturbance in motility, postinfectious changes, altered perception either locally in the GI tract or in the central nervous system, visceral hypersensitivity, mucosal inflammation, autonomic nerve dysfunction, and psychological disturbance, but no theory is applicable to every patient who has symptoms of IBS. In one study a positron emission tomography (PET) scan was used to examine the activity of the brain when GI symptoms were induced. Patients with IBS did not activate the anterior cingulate cortex that is associated with opiate binding but did activate the prefrontal cortex that is associated with hypervigilance and anxiety. Studies to determine whether patients with IBS have a lower threshold of pain with colonic distention are inconclusive. All that can be stated with reasonable certainty is that studies have not clarified whether symptoms of IBS are a normal perception of an abnormal function or an abnormal perception of a normal function.

Clinical Findings

A. Symptoms and Signs

IBS belongs to a group of functional bowel disorders (ie, no organic cause can be identified) in which abdominal discomfort or pain is associated with defecation or a change in bowel habits and with features of disordered defecation. Diagnostic criteria developed by the Rome Consensus Committee for IBS are at least 3 days per month for the past 3 months with onset at least 6 months prior to diagnosis of abdominal discomfort or pain that is characterized by two of the following three features: (1) it is relieved with defecation, (2) its onset is associated with a change in frequency of stool, and (3) its onset is associated with a change in the form or appearance of the stool.

The Bristol Stool Form Scale (Figure 30-1 and Table 30-2) is used as a standard description for seven types of stool forms. Other symptoms that support the diagnosis of IBS include abnormal stool frequency (more than three per day or fewer than three per week), abnormal stool form (lumpy/hard or loose/watery), abnormal stool passage (straining, urgency, or a feeling of incomplete evacuation), passage of mucus, and a sensation of bloating or feeling of abdominal distention.

Stool form has been demonstrated to be reflective of GI transit time. Using the Bristol Stool Form Scale and frequency of bowel movements is more diagnostically precise and useful than using the imprecise terms diarrhea and constipation, which can have different meanings to different patients. Patients may complain of feeling constipated, attributable to a feeling of incomplete evacuation despite having just passed soft or watery stool.

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Separate hard lumps like nuts (difficult to pass)</td>
</tr>
<tr>
<td>2</td>
<td>Sausage shaped but lumpy</td>
</tr>
<tr>
<td>3</td>
<td>Like a sausage but with cracks on its surface</td>
</tr>
<tr>
<td>4</td>
<td>Like a sausage or snake, smooth and soft</td>
</tr>
<tr>
<td>5</td>
<td>Soft blobs with clear-cut edges (passed easily)</td>
</tr>
<tr>
<td>6</td>
<td>Fluffy pieces with ragged edges, a mushy stool</td>
</tr>
<tr>
<td>7</td>
<td>Watery, no solid pieces, entirely liquid</td>
</tr>
</tbody>
</table>

Figure 30-1. Bristol Stool Form Scale. See Table 30-2 for standard description for each of the seven types.
B. History

The patient history is the single most useful tool in diagnosing IBS. Continuity of care and a well-established rapport contribute significantly to obtaining an accurate and exhaustive history. A positive physician–patient interaction, including a psychosocial history, precipitating factors, and a discussion of diagnosis and treatment with patients, results in fewer return visits for IBS and lower utilization of health care resources. Chronic or recurrent abdominal pain indicates a need to assess quality of life. In one study undergraduate students with IBS had quality-of-life scores that were similar to patients with congestive heart failure, indicating a significant impact by IBS symptoms.

A history of abuse should be sought in patients with chronic abdominal pain. A study at a tertiary care gastroenterology clinic reported that 60% of the overall study population, all females, reported a history of physical or sexual abuse. The self-reported history of abuse was highest for those with functional bowel disease (up to 84%) and lowest for those with organic bowel disease, such as ulcerative colitis (38%). It is therefore worthwhile to overtly assess a patient’s psychosocial stressors as they can affect the success of the course of treatment. A physician should always assess for abuse when considering referral to a gastroenterologist. Family physicians are uniquely positioned to assess and address issues associated with abuse.

Patients with IBS have not been demonstrated to have a higher incidence of psychiatric diagnosis such as depression, anxiety, somatization, stress, lack of social support, or abnormal illness behavior compared with other patients presenting with abdominal pain of organic origin. However, patients presenting with abdominal pain do have more psychosocial abnormalities than control subjects without abdominal pain. Psychosocial factors have not been shown to be helpful in differentiating between organic and functional abdominal disease, but they have been helpful in understanding some of the health-seeking behavior.

Stressful life events such as the death of a family member or loss of a job often precede the onset of symptoms of IBS. Although such stressful life events may not be the cause of IBS, they might factor into the decision by patients to seek care for their symptoms. In women who have symptoms of IBS, the decision to seek care has been shown to have a significant and positive correlation between daily stress levels and daily symptoms of IBS.

In gathering the history of a patient with IBS, signs or symptoms of an anatomic disease should be absent. These include fever, GI bleeding, unintentional weight loss, anemia, and abdominal mass. Physicians should assess for laxative use, as laxatives could be a significant cause of IBS-like symptoms.

Patients with IBS may have had surgery, particularly appendectomy, or women may have had a hysterectomy or ovarian surgery. The most common discharge diagnosis of patients admitted to the hospital for abdominal pain is “nonspecific abdominal pain.” A study of patients discharged with this diagnosis showed that 37% of women and 19% of men met the criteria for IBS 1–2 years after discharge. Of such patients 70% had other prior attacks of abdominal pain and at the initial admission only 6% of patient charts listed IBS in the differential diagnosis. Of patients presenting with acute pain of less than 1 week’s duration, 50% had symptoms of IBS at the time of admission. It appears that assessing for diagnostic criteria of IBS symptoms can reduce the length of hospitalization, reduce the extent of testing, and thus decrease the cost of treatment of patients presenting with acute abdominal pain who do not need immediate surgical intervention.

C. Physical Examination

The physical examination is usually fairly unremarkable, except for some abdominal tenderness and an increased likelihood of abdominal scars.

D. Special Tests

No specific testing is required for diagnosis of IBS, although some physicians would be reassured by a normal CBC and ESR. Patients who meet the criteria to screen for colon cancer (>50 years or a family history of colon cancer) should be examined using either flexible sigmoidoscopy or colonoscopy. A colonoscopy should always be performed if there is a family history of colon cancer. Other tests to consider are C difficile toxin if the patient has recently taken antibiotics, stool evaluation for giardiasis in endemic areas (eg, Rocky Mountains), evaluation for lactose intolerance, and serologic testing or gluten elimination diet for evaluation for celiac disease.

▶ Treatment

A. Therapeutic Relationship

A therapeutic relationship is critical to the effective management of IBS. The therapeutic relationship is achieved by obtaining the history through a nondirective, patient-centered interview, being nonjudgmental, eliciting the patient’s understanding of the illness and his or her concerns, identifying and responding realistically to the patient’s expectation for improvement, setting consistent limits, and involving the patient in the treatment approach. The most effective treatment option is explanation and reassurance. A confident diagnosis based on the previously outlined clinical criteria helps convey that symptoms of IBS are not associated with a higher risk of other diseases (eg, cancer or GI bleeding) and that these symptoms are chronic in nature, are very likely to wax and wane over time, and may not ever completely go away. Patients’ reasons for seeking care at the time they did and the possibility that psychosocial issues are contributing to the symptoms should be assessed. Counseling regarding psychosocial stressors in patients’ lives may not resolve all the symptoms of IBS, but it may help patients to better cope with the symptoms.
B. Diet

Many different dietary approaches have been tried. Patients in whom gas-forming vegetables, lactose, caffeine, or alcohol exacerbate symptoms should be counseled to minimize their exposure to the offending substance. Food intolerance and elimination diets have not been proven to be effective. Dietary fiber has been shown to improve symptoms of constipation, hard stools, and straining, particularly if 30 g of soluble fiber is consumed each day. Patients often need to gradually increase the amount of fiber to improve adherence, as a sudden increase can lead to increased symptoms of bloating and gas. The most common reason for failure of a high-fiber diet is insufficient dose. Fiber is safe and inexpensive and should be routinely recommended, particularly to patients for whom constipation is a component of their IBS symptoms. Probiotics are live organisms that, when ingested, exert a significant health benefit to the host. Probiotics have been found to provide global improvement in IBS symptoms and abdominal pain. The exact mechanism contributing to the improvement in symptoms is not completely understood and can vary between strains and dose used. There is insufficient evidence to recommend the use of one strain or dose over another. Patients should be encouraged to consume probiotic-rich fermented foods such as yogurt, kefir, miso, tempeh, and sauerkraut.

C. Complementary and Alternative Therapies

A meta-analysis of five double-blind, placebo-controlled randomized trials suggested a significant (P < .001) positive effect of peppermint oil compared with placebo. Peppermint oil was given as a monopreparation in a dosage range of 0.2-0.4 mL. Randomized controlled trials of Chinese herbal medicine indicated that both a standardized herbal formulation (Tong Xie Yao Fang is a commonly used formula) as well as individualized Chinese herbal medicine treatment improved symptoms of IBS compared with placebo. Padma Lax, a Tibetan herbal digestive formula, has been used and studied in Europe and shown global improvement in symptoms. Acupuncture and moxibustion have been shown to be helpful compared to placebo treatments.

D. Psychological Therapies

Various psychological therapies have been studied in randomized, controlled trials compared with either control therapy or a physician's “usual management.” Some of the varied psychological therapies that have been studied include hypnotherapy, relaxation training, multicomponent psychological therapy, dynamic psychotherapy, cognitive-behavioral therapy (CBT), stress management, and self-administered CBT. Hypnotherapy has been studied regarding its effectiveness in treating patients with symptoms of IBS. Dramatic improvements in a high proportion of patients with poorly controlled IBS symptoms were seen for both individual and group hypnotherapy. Therapeutic audiotapes are easy to use and low cost, although somewhat inferior to hypnotherapy.

Psychotherapy relies on the relationship between the therapist and the patient and can vary according to that relationship, which makes these approaches difficult to evaluate in a randomized, controlled fashion. The quality of the data is not as strong as compared to that of some of the pharmacotherapy interventions, but the evidence does support that the number needed to treat with psychological therapies to prevent IBS symptoms persisting in one patient is 4. The number need to treat with antidepressants to prevent IBS symptoms persisting is also 4. Since patients with IBS are more likely to have coexisting mood disorders and anxiety than healthy control or patients with identifiable organic pathology as well as to report a lower quality of life, psychological interventions should be considered for most patients with IBS.

E. Pharmacotherapy

Drugs have been used for the treatment of IBS without proven benefit and with some troublesome side effects. A meta-analysis that concluded that smooth muscle relaxants and anticholinergics were better than placebo has been criticized for methodologic inadequacies. The most frequently used drugs and most common complaints that they are used to treat include the following:

- **Constipation:** psyllium, methylcellulose, calcium poly-carbophil, lactulose; 70% sorbitol and polyethylene glycol (PEG) solution, partial 5-HT₄ agonists (tegaserod) for female patients with constipation-predominant IBS symptoms.
- **Diarrhea:** loperamide, cholestyramine, Alosetron for female patients with diarrhea-predominant IBS symptoms.
- **Gas, bloating, or flatus:** simethicone, alpha-galactosidase (Beano), antibiotics (rifaximin), probiotics.
- **Abdominal pain:** anticholinergics and antispasmodics.
- **Chronic pain:** tricyclic antidepressants, selective serotonin reuptake inhibitors.

Encouraging patients to see their family physician on a consistent and regular basis for the purpose of reassurance, reinforcement, and explanation, combined with communication in a positive therapeutic relationship, can prevent the continual quest by patients for a “miracle” cure for IBS.


History of periumbilical pain migrating to RLQ with anorexia, nausea, and vomiting is often diagnostic.

CT scan is test of choice for most suspected cases that need confirmation.

Urgent surgical consult is needed.

Left shift of elevated WBC count 7000-19,000 is helpful in diagnosis.

General Considerations

Appendicitis occurs in more than 250,000 people per year in the United States alone. Appendicitis can occur in people of any age, but is most common in later childhood through young adulthood. When appendicitis occurs in young children or in the elderly, the presentation is often not classic. There does not seem to be any race or gender predilection, although diagnosis in female patients can be more difficult while males are more likely to have a perforation of the appendix.

Pathogenesis

The appendix is a long diverticulum that extends from the cecum. When its long lumen is occluded, appendicitis results. Proliferation of lymphoid tissue—often associated with viral infections, Epstein-Barr virus, upper respiratory infection, or gastroenteritis—is the most common cause of obstruction of the lumen and subsequent appendicitis in young adults. Other causes of occlusion include tumors, foreign bodies, fecaliths, parasites, or complications of Crohn disease.

Clinical Findings

A. Symptoms and Signs

The most important component in the diagnosis of appendicitis is the history. It is a critical component, because a missed diagnosis of appendicitis can have severe sequelae. The presence of the following historical indicators should be elicited: (1) abdominal pain, usually RLQ pain often preceded by periumbilical pain (~ 100% of patients); (2) anorexia (~ 100%); (3) nausea (90%), with vomiting (75%); (4) progression of abdominal pain from periumbilical to RLQ (50%); and (5) the classic progression from vague abdominal pain to anorexia, nausea, vomiting to RLQ pain to low-grade fever (50%).

B. Physical Examination

Careful examination of the abdomen—inspection followed by palpation and then percussion—can often identify the cause of abdominal pain. Peritoneal signs, rigidity, rebound tenderness, guarding, and low-grade fever (38°C [100.4°F]) are characteristic findings in appendicitis. In appendicitis, rebound tenderness and sharp pain upon palpation of McBurney point is usually elicited 2 in from the anterior superior iliac spine on a line drawn from this process through the umbilicus. However, the size of the appendix (and therefore the location of pain with palpation) varies, and pain may occur some distance from the classic McBurney point.

A pelvic examination should be performed in all women who present with RLQ pain to rule out multiple gynecologic causes. A thorough respiratory and genitourinary examination is often helpful as well. A rectal examination is useful only when the diagnosis remains unclear, and thus should not be performed unless necessary.

There is some debate about the use of analgesics during the evaluation of possible appendicitis. Traditional practice suggested that pain medication may mask important signs or symptoms. There are mixed results of studies of the use of analgesic in the setting of possible appendicitis. Many studies have now shown that the use of opiate medications can help alleviate some pain, while not compromising the ability for physical examination to identify a patient with acute appendicitis. It may enhance the examination. Some recent work has shown some increase in delay in treatment for acute appendicitis when nonsteroidal anti-inflammatory pain medication is used. This is in contrast to prior studies. Additional studies suggest that informed consent is compromised by not using adequate pain medication. An observational unit can be helpful as well to examine the progression of signs and symptoms.

C. Laboratory Findings

Although many laboratory studies are performed routinely on patients with abdominal pain, few, if any, are truly helpful in the diagnosis and management of the patient with possible appendicitis. In fact, laboratory studies can often be misleading and delay diagnosis in cases of appendicitis. The WBC count has classically been used, but studies suggest it is seldom helpful diagnostically. If the WBC count is less than 7000/mm³, it is unlikely that the patient has appendicitis. If it is greater than 19,000/mm³, the patient has a more than 80% chance of having appendicitis. The presence of neutrophilia makes the diagnosis of appendicitis more likely but is not
diagnostic. The presence of increased WBCs with neutropenia is generally accompanied by increased C-reactive protein levels. The presence of all three is not diagnostic, but the absence of all three rules out appendicitis.

The routine use of a chemistry examination is helpful only to determine the level of dehydration. Urinalysis commonly shows some leukocytosis and some increased red blood cells. Despite these common findings, it is more often misleading than helpful. The most important use of urinalysis is as a screening test for urinary tract infection. All women of childbearing age should have a pregnancy test.

D. Imaging Studies

Imaging studies are not always needed and can delay treatment, increase cost, and increase radiation exposure. In cases where the diagnosis seems clear from history and physical alone, rapid surgical consult should be obtained prior to imaging studies. If there is delay in available surgical consult, imaging studies can be helpful to confirm diagnosis. Studies have been helpful in less clear cases and may decrease the rate of removal of normal appendices. Current rate of negative pathology is around 3%. The CT scan is the single best test for diagnosing appendicitis. It is cost efficient, and can be fast and low radiation exposure when specific protocols are used. Plain radiographs can be misleading, are not diagnostic in most cases, and the cost of a complete abdominal series is about the same as that of a CT. Ultrasound is less invasive than CT, is cost efficient, and can be useful in situations in which CT is not possible. Findings can be considered “normal” only if a normal appendix is seen. If the appendix is located retroperitoneally or in the pelvis, it can be difficult to visualize. Ultrasound is most helpful in women in whom other pathologies can be identified, and it can be used in the evaluation of pregnant patients. It is also a good choice in children because of the lack of contrast and easier patient compliance with the test. However, CT is more sensitive, more specific, and provides visualization of many other possible problems. If the diagnosis of appendicitis is suspected, a focused spiral CT without contrast can be performed in less than an hour and can be very specific for appendicitis. Many different protocols for CT scan of appendix are currently being researched with various contrast options, including with IV or oral contrast. The use of contrast can increase risk and delay time of diagnosis, but may be helpful in certain cases, especially in thin patients, older patients, and those with unclear etiology of pain after history and physical examination.

**Treatment**

Treatment consists of surgical removal of the inflamed appendix using either laparotomy or laparoscopic-assisted technique. Laparotomy is faster, simpler, and less expensive, with a lower rate of complications, but laparoscopy allows visualization of other possible causes. Recent advances in surgical technology have shown other benefits of laparoscopic procedures: faster recovery, shorter hospital stay, and decreased postoperative pain. Both techniques are useful. Choice of surgical options should be done on an individual basis and based on surgical experience and opinion at time of surgery. There are a few small studies that suggest that treatment with antibiotics and observation can result in resolution of symptoms temporarily, but generally result in high reoccurrence rates. This may be an option in patients medically unstable for surgery or where surgery is not readily available.


**ESSENTIALS OF DIAGNOSIS**

- Inflammatory bowel disease should be considered in patients with abdominal pain associated with blood in stool or elevated sedimentation rate.
- CT scan remains helpful; colonoscopy is essential only after control of acute attack.
- Current medical management is changing rapidly.

**General Considerations**

Inflammatory bowel disease (IBD) is a broad category that encompasses several disease subtypes, the most common of which are ulcerative colitis (UC) and Crohn disease (CD). Other inflammatory bowel conditions such as acute infectious colitis and gastroenteritis can cause acute abdominal pain. They are not addressed further in this chapter. Please see either infectious disease—or gastrointestinal
disorder–specific texts for further recommendations. The role of genetics in both CD and UC has become clearer as the human genome project has advanced, and there is now clear evidence of a genetic predisposition to both UC and CD. Prevalence of CD is much higher in Caucasians, especially in those of Jewish descent. Specific gene loci have been identified that show a correlation with susceptibility to either CD or UC. This susceptibility seems to be affected by environmental factors such as smoking and microflora of the gut.

Environmental factors may make IBD more prevalent in people who work indoors and less prevalent in manual laborers who work outdoors. There is a 20%-50% increase in the prevalence of IBD in first-degree relatives and a 50- to 100-fold increase in the offspring of patients with IBD.

Risk factors seem to include work environment and diet, but there is a difference among the subtypes of IBD. Smoking appears to decrease the risk of UC but to increase the risk of CD. Birth control pills seem to increase the risk of CD.

Pathogenesis

As more is known about which genes create susceptibility, more is understood about pathogenesis of these disease processes. Environmental factors seem to allow for an altered immunologic response to normal intestinal flora, causing destruction within the mucosa of the GI tract. CD appears to be related to altered macrophage function; whereas UC more likely represents a pathologic inflammatory response to normal intestinal microflora. Decreases in bifidobacteria and lactobacilli are noted in patients with active CD when compared with healthy controls and in those with CD in remission. *Fusobacterium varium* may be a factor in pathogenesis of UC. Changes within the microflora, combined with the immune response, result in altered mucosal barriers, luminal antigens, and macrophage function.

Clinical Findings

A. Symptoms and Signs

Although both UC and CD can present with abdominal pain, this finding is more common in patients with CD. Patients with UC almost always present with perirectal pain and bloody diarrhea and have abdominal pain only during acute exacerbations of disease such as toxic megacolon. CD can be more difficult to differentiate from other diseases based on history and physical examination alone. RLQ pain is present in most patients with CD, reflecting involvement of the terminal ileum in 85% of cases.

B. Physical Examination

Physical examination findings are not very specific. Evaluation of the rectum for evidence of fissures, ulceration, or abscess can be helpful. Fullness or a palpable mass can suggest associated abscess. But generally, the examination reveals nonspecific generalized tenderness, with focal findings depending on the extent and activity of the disease. Skin examination may be useful because CD is associated with erythema nodosa and aphthous stomatitis, whereas UC is associated with pyoderma gangrenosum. Growth retardation and delayed sexual maturation can occur both from the disease process and from the medications used to treat the disease.

C. Laboratory Findings

Recommended laboratory tests include ESR, C-reactive protein, CBC, LFTs, albumen, electrolytes, vitamin B<sub>12</sub> level, folate level, and stool studies. The ESR is elevated in 80% of patients with CD and 40% of patients with UC. In 95% of cases, patients with symptomatic CD have an elevated C-reactive protein. Anemia is common as a result of iron deficiency and blood loss. Leukocytosis with increased eosinophilia is often noted. LFTs can identify liver involvement in patients with CD (eg, sclerosing cholangitis, autoimmune hepatitis, and cirrhosis). Albumen is an indicator of malnutrition associated with malabsorption. Stool studies are important to rule out infectious etiologies of colitis. Additionally, a perinuclear antineutrophil antibody (pANCA) titer is useful to differentiate between CD and UC. Approximately 6% of patients with CD have pANCA, in contrast to 70% of patients with UC. *Saccharomyces cervisiae* (ASCA) is found in about 50% of individuals with CD and correlates closely with involvement of the small bowel, stenosing lesions, and perforating disease.

D. Imaging Studies

There are many imaging options for IBD. The most accurate test is the colonoscopy, which allows direct visualization of the mucosa and biopsy. Use of colonoscopy is not recommended in the setting of acute active disease due to the risk of perforation. Plain films can be most helpful when looking for toxic megacolon, or if “thumb-printing” is seen, as with bowel wall edema. The classic string sign can be seen on barium enema. Abdominal CT can be useful for diagnosis and management of IBD. CT is most helpful in identifying abscesses, fistulas, bowel wall thickening, and fat stranding. In patients undergoing CD, plain films can be helpful to identify strictures, skip lesions (areas of the mucosa not affected by the disease process), or perforation. The use of video capsule endoscopy is controversial due to the high risk of impaction behind strictures.

Treatment

Management of IBD includes medical therapy, nutritional support, psychological support, and surveillance for cancer. Medications include aminosalicylates, corticosteroids, immunomodulators, antibiotics, probiotics, and biological therapy. Patients with severe disease require hospital admission with bowel rest, parenteral nutritional support, and corticosteroids. Immunomodulators have been used with
Increasing frequency, allowing for less use of systemic steroids. Infliximab is a biological agent that is used in refractory CD.

Nutritional therapy is helpful to maintain remission and decrease likelihood of nutritional deficiency due to malabsorption. It can be as effective as medications, especially in children.

Surgical therapy is often required. Approximately 85% of patients with persistent elevation of C-reactive protein and frequent liquid stools require total colectomy. Strictures and abscess formation in CD may necessitate surgical excision of small segments of bowel or strictureplasty.

The risk of adenocarcinoma is increased in any patient with chronic colon disease. The risk of development of cancer in UC is equivalent to that of CD with colon involvement. Therefore, current guidelines recommend colonoscopy with biopsy biannually after disease is present 10 or more years. The risk of other types of cancer, such as adenocarcinoma of the jejunum and ileum (when involved in disease), lymphoma, and squamous cell carcinoma of the vulva and rectum, is increased in CD.

Familial counseling is important to help family members cope with exacerbations of the disease. Genetic counseling is needed because of the strong inheritance factor in this disease.

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**DIVERTICULITIS**

**ESSENTIALS OF DIAGNOSIS**

- More than 3 days of abdominal pain with low-grade fever.
- Commonly left-sided pain, (right sided more common in people of Asian descent).
- CT scan test of choice.
- Early antibiotic treatment, bowel rest, hydration.

**General Considerations**

Diverticulitis occurs in 10%-25% of patients with diverticulosis. In the 20th century, the incidence of diverticulosis increased as fiber intake decreased. In addition to insufficient fiber, age is the single greatest risk factor contributing to diverticulosis. Typically, diverticulosis is seen in patients 60 years of age and older. It is uncommon before age 40 and is present in 50% of people older than 90 years. There is an increased prevalence of left-sided diverticula in patients of western European descent and an increased prevalence of right-sided diverticula in people of Asian descent.

**Pathogenesis**

The pathology of diverticulitis is directly related to the anatomy of the bowel wall. A true diverticulum consists of an outpouching of all three layers of the wall: mucosa, submucosa, and muscular layer. Most cases of diverticulitis, however, involve only pseudodiverticula. These consist of a herniation of the mucosa and submucosa through the muscular layer. The diverticula tend to form in rows between the mesenteric and lateral teniae. The area of penetration of the vasa recta has the greatest muscular weakness. This area is therefore the most common site of herniation. Lack of dietary fiber contributes to development of diverticula. As fiber content of the stool decreases, the colonic pressure increases and the transit time decreases. As we age, there is increased cross fibers within the collagen and elastin, causing the bowel wall to be less compliant. These changes result in high pressure in the colon, which essentially blows out areas of weakness in the colon wall.

Diverticulitis occurs when there is infection associated with one or more of these diverticula. Micro- or macroperforations of diverticula may occur, resulting in bowel contents contacting the peritoneum and infecting the pericolonic fat, mesentery, and associated organs. This process can be localized and can result in the development of an abscess, peritonitis, or a fistula. The most common fistula is a colovesical fistula, connecting the colon and the urinary bladder, and fistulae can form between the colon and any abdominal organ.

**Clinical Findings**

**A. Symptoms and Signs**

Left lower quadrant (LLQ) pain occurs in 93%-100% of patients. However, pain can be right sided, especially in patients of Asian descent. When RLQ pain occurs, a duration of 3 or more days is suggestive of diverticulitis rather than appendicitis. Commonly, patients have nausea, vomiting, constipation, or diarrhea. Dysuria and urinary frequency may also be present. Complicated diverticulitis, as with a colovesical fistula, can present with recurrent urinary tract infections. In macroperforation, diffuse abdominal pain is present.

Vital signs give some evidence supportive of the diagnosis of diverticulitis. Temperature at or greater than 38.1°C (100.7°F) and the presence of tachycardia are consistent with diverticulitis. Fever is present in most patients.
**B. Physical Examination**

The examination should include a complete abdominal examination. Signs suggestive of diverticulitis include tender LLQ (or RLQ in more infrequent right-sided cases), signs of peritoneal irritation such as guarding or tenderness to percussion, and occasionally the presence of a tender mass, which is suggestive of abscess. The rectal examination may demonstrate rectal tenderness or occasionally a tender rectal mass.

**C. Laboratory Findings**

Patients suspected of having diverticulitis should have a CBC and urinalysis. The WBC count is often increased, with a high prevalence of polymorphonuclear leukocytes; leukocytosis is present in more than two-thirds of patients. Anemia may be noted if there is associated diverticular bleeding. Urinalysis can show evidence of inflammation if there is irritation of the peritoneum surrounding the bladder or evidence of infection if a fistula is present.

**D. Imaging Studies**

Flat and upright abdominal films, or CT of the abdomen and pelvis if the diagnosis is less clear, should be obtained. The abdominal films can show evidence of free air, ileus, or mass. If the diagnosis is in doubt, a CT scan of the abdomen and pelvis can help clarify the cause of pain. In cases of diverticulitis, CT shows a thickened colonic wall and can show an abscess if present. With the abilities of interventional radiology, the use of CT has increased. Areas of abscess can be identified and percutaneous drainage can be done allowing for delay in any surgical intervention. These same findings can be seen on ultrasound, but CT best confirms diverticulitis because it reveals the presence and location of an abscess more easily as well as allows for identification of other pathologic processes such as cancer, Crohn disease, and appendicitis. Ureteral obstruction, fistula, or air in the bladder can also be seen. Colonoscopy should be reserved for evaluation 4-6 weeks after resolution of diverticulitis to evaluate for concomitant cancerous lesions. Colonoscopy has a role if diagnosis is not clear from CT scan and IBD is suspected.

**Treatment**

Treatment depends on the severity of the disease and the health of the patient. Outpatient treatment includes a clear liquid diet and oral broad-spectrum antibiotics. Current recommendations include ciprofloxacin and metronidazole for 7-10 days. Because of the ever-changing nature of antibiotic treatment and variations of resistance in different areas, the CDC guidelines or Sanford antibiotic recommendations should be followed. Pain medications such as morphine should be avoided as they increase colonic pressure and contribute to the problem. Meperidine is the best choice for pain control as it has been shown to decrease colonic pressure. Steroids and NSAIDs should be avoided due to the increased risk of GI bleeding and perforation associated with these medications.

Patients who have signs and symptoms of inflammation, such as fever and leukocytosis, require hospitalization. Patients should have complete bowel rest, intravenous fluids, and intravenous broad-spectrum antibiotics. A nasogastric tube is not needed unless there is significant ileus or obstruction. Most patients should improve in 48-72 hours, at which time they can resume diet, change to oral antibiotics, and be discharged home with close follow-up. A high-fiber diet is recommended for all patients. Surgical resection is recommended for some.

Surgery usually is not recommended after the first attack because the recurrence rate is only 20%-30%; however, this rate increases with each subsequent attack, as does the risk of morbidity associated with each attack. Therefore, surgery should be considered after the second or third attack. Surgical intervention can be considered with a first attack in patients who are immunocompromised due to the high risk of morbidity and mortality associated with an attack. Surgical intervention is done on a case-by-case basis in cases of complicated diverticulitis. If initial complicated attack can be treated with percutaneous drainage and antibiotic treatment, outcomes are improved by allowing decreased inflammation of the bowel wall prior to attempted anastomosis after resection. Morbidity and mortality rates are improved when primary anastomosis can be performed, rather than two-stage approach with colostomy. Patients younger than 40 at first attack have an increased lifelong risk due to the increased life expectancy, although the risk with each attack is not increased. These cases are determined on an individual bases looking at frequency and severity of attacks.

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**Meckel Diverticulum**

Meckel diverticulum is a congenital anomaly of the GI tract in which an outpouching portion of the intestine, derived from the fetal yolk stalk, contains gastric or pancreatic tissue. Patients can present with abdominal pain, nausea, vomiting, or intestinal bleeding. Meckel diverticulum can cause complications that include diverticulitis, intussusception, perforation, and obstruction. The best test for diagnosis is the technetium-99m pertechnetate scan, and treatment is surgical.


ABDOMINAL WALL PAIN

There are many presentations of abdominal wall pain because there are many different causes of abdominal wall pain. Several examination findings might suggest the abdominal wall as the source of pain. The lack of evidence for an intra-abdominal process is a good first indicator. When visceral problems have been ruled out, the physician should look for abdominal wall abnormalities. The pain is usually not related to meals or bowel function, but is related to posture. Often a trigger point can be found. Most of the time there is a positive Carnett sign.

Carnett sign is elicited by having the patient tense the abdominal muscles and then examining the patient’s abdomen. Places that are tender prior to tensing the abdomen and that are still tender afterward are considered positive and are suggestive of the abdominal wall as the source of pain. Most visceral pain will decrease with this maneuver. Causes of abdominal wall pain include hernias, herpes zoster, neuromas, hematomas of the abdominal wall or rectus sheath, desmoid tumor, endometriosis, myofascial tears, intra-abdominal adhesions, neuropathies, slipping rib syndrome, and general myofascial pain.

**Hernias**

Types of hernias include inguinal, femoral, umbilical, epigastric, spigelian, and Richter hernias. These are more commonly identified on examination rather than from the history. The history can be suggestive of many types of hernias, although it can be confusing if there is herniation of the bowel wall or omentum. Bowel herniation will cause visceral pain and obstruction, whereas omentum herniation will cause visceral pain with no signs of obstruction. A history of prior surgery, especially laparoscopic surgery, increases the likelihood that a hernia is present.

Certain hernias are more common in certain patients. Men more typically develop inguinal hernias, whereas women tend to develop femoral hernias. Umbilical and epigastric hernias are more common in obese or gravid patients. The spigelian hernia, a hernia along the border of the arcuate ligament, is most common in athletes.

Richter hernia is defined by the pathology rather than the location of the hernia. The side of the bowel wall herniates rather than the entire bowel segment. Often the hernia produces a slight bulge that may be confused with adenopathy or fat tissue. Because this type of hernia results in subtle findings, there is often a delay in diagnosis and therefore a higher fatality rate. Richter hernia is generally found in women older than 50 years, but it is increasing in frequency in young men, primarily due to the increased frequency of laparoscopic procedures. Because the size of the instruments used for laparoscopy is small, the abdominal wall defect left after surgery may allow only a portion of the bowel wall to herniate. The resultant tight hernia causes strangulation of the tissue that passes through. On examination, prior surgical sites must be examined. Erythema at these sites can be a sign of local infection, fistula formation, or an inflammatory process at an area of scarring.

Although a CT scan can identify hernias, they are often overlooked unless the radiologist is focused on thorough examination of the abdominal wall.

Hernias are best treated surgically. If surgery is contraindicated, hernias that cause pain or pose a risk of bowel obstruction can be treated with a truss or other restrictive garment.

**Rectus Sheath Hematoma**

Rectus sheath hematoma can be equally difficult to diagnose. They tend to occur more commonly in elderly or pregnant patients. The epigastric vessels are sheared, resulting in intramuscular bleeding. The shearing can occur from trauma or twisting motions. Again, the history is the most important factor in helping to direct the clinician. A history of unilateral midabdominal pain, use of anticoagulants such as aspirin or warfarin, and abdominal trauma are all important risk factors for hematoma. The pain is unilateral and is worse when patients tense their abdominal muscles. There is often a palpable mass within the rectus sheath.

Coagulation studies and blood count are the most useful laboratory studies. Helpful imaging studies include CT, ultrasound, and MRI. Ultrasound is the cheapest and most useful study if the diagnosis is highly suspected. CT is more useful for identifying other possible causes. MRI is sometimes helpful if the diagnosis remains unclear. Treatment is generally expectant, but severe cases may warrant reversal of coagulation abnormalities, administration of fluids, or even surgical evacuation and ligation or coagulation of vessels.

**Herpes Zoster**

Any time there is an abrupt onset of severe abdominal wall pain, herpes zoster should be suspected. The pain associated with zoster can precede the rash by more than 1 week, although commonly it is only 2-4 days. Zoster occurs most frequently in patients older than 50 years. Postherpetic neuralgia (PHN) can cause similar pain in patients with a history of zoster—most often patients older than 60 years. A thorough history and close follow-up are the best measures to establish this diagnosis. Prophylactic treatment includes the varicella vaccine. Treatment of acute herpes zoster with acyclovir, valacyclovir, or famciclovir in combination with a prednisone taper seems to decrease the incidence and severity of PHN. Treatment of PHN has proven difficult, and many modalities have been tried with only minor success. These include analgesics, narcotics, nerve stimulation, antidepressants, capsaicin, biofeedback, and nerve blocks.

**Other Causes of Abdominal Wall Pain**

Surgical scars are the location of many causes of abdominal wall pain. Hernias are frequently present at the site of scars, as previously discussed. Endometriosis can recur at the site of surgical scars, and neuromas often form at the border of scars. Other unusual causes include desmoid tumors,
myofascial tears, and intra-abdominal adhesions. The desmoid tumor is a dysplastic tumor of the connective tissue that tends to form in young adults and can be identified only after surgical removal. Myofascial tears and intra-abdominal adhesions occur most frequently in athletes.

**Treatment**

Most abdominal wall pain has a trigger point that reproduces the pain. Finding this point can help in both diagnosis and treatment. These trigger points are often found along the lateral border of the rectus abdominis muscle where nerve roots can become stretched, compressed, and irritated. These points are also found at areas of tight-fitting clothing or at insertion points of muscles. The Carnett sign, described earlier, is useful for diagnosis of trigger points.

Management of this type of pain can be difficult. Patient education and reassurance are both very important. Preventing further unnecessary testing can be helpful to patients by decreasing their concerns about the pain. Explaining the nature of the pain and its origins helps patients deal with the pain. Tricyclic antidepressants can be useful at low doses.

Treatment of many causes of abdominal wall pain can be achieved by injection of lidocaine or its equivalent. This treatment can be both diagnostic and therapeutic. It is necessary to find the point of greatest tenderness, usually an area less than 2 cm. Insertion of the needle into the correct point should elicit intense pain, but the pain should improve dramatically with injection. For areas that require more than one injection, a small amount of steroid can be used as well. Steroids should be avoided in areas near hernias or into fascia, as they can cause hernia formation. Dry needling has been shown to be as useful, but the initial treatment is followed by more pain at first. For patients with severe needle aversion, a therapeutic trial of a transcutaneous lidocaine patch can be considered. Pain clinics can help patients with more difficult cases.

**Gynecologic Causes of Abdominal Pain**

Gynecologic causes of abdominal pain can be separated into three categories: acute causes in the nonpregnant patient, chronic problems in the nonpregnant patient, and acute causes in the pregnant patient. Acute causes include PID, adnexal torsion, ruptured ovarian cyst, hemorrhagic corpus luteum cyst, endometriosis, and tuboovarian abscess. Chronic causes in the nonpregnant patient include dysmenorrhea, mittelschmerz, endometriosis, obstructive m\&uuml;llerian duct abnormalities, leiomyomas, cancer, and pelvic congestion syndrome. In the pregnant patient causes include ectopic pregnancy, retained products of conception, septic abortion, and ovarian torsion. Psychological factors can greatly contribute to pain related to the abdomen and pelvis. Patients can present with acute pain after a sexual assault.

Because of the wide differential, a careful history and a pregnancy test are both very important when evaluating women and girls with abdominal pain. The history should include the last menstrual period, a detailed menstrual history, a sexual history including possible assault, and a family history. The physical examination should include careful abdominal, pelvic, and rectovaginal examinations. Laboratory evaluation is based on specific findings from the physical examination. In evaluating PID, LFTs can identify possible Fitz-Hughes and Curtis syndrome, especially in the presence of RUQ pain.

PID occurs in 11% of US women of reproductive age, although it is rare in pregnancy. Numerous biological factors contribute to a higher incidence of PID in adolescents, including a lower prevalence of protective chlamydial antibodies, more penetrable cervical mucus, and larger zones of cervical ectopy with more columnar cells that are more vulnerable to bacterial and viral agents. Other risk factors that increase the likelihood of PID include early age at first sexual intercourse, a higher number of lifetime partners, or a new partner within the last 30-60 days. Diagnosis of PID requires the presence of abdominal pain, adnexal pain, cervical motion tenderness, and at least one of the following: temperature greater than 38.3°C (101°F), vaginal discharge, leukocytosis greater than 10,500/mm³, positive cervical cultures, intracellular diplococci, or WBCs on vaginal smear. Treatment varies, depending on whether the patient requires inpatient or outpatient treatment. Inpatient treatment is required in the following cases: surgical emergency, pregnancy, no response to outpatient therapy in 72 hours, nausea and vomiting, or immunodeficiency.

Endometriosis is found in 15%-32% of women undergoing laparoscopy for evaluation of abdominopelvic pain. This type of pain is generally cyclical but can present acutely with rupture of an ovarian endometrioma. On physical examination, a retroverted, fixed uterus with ash spots on the cervix suggests endometriosis. Conservative treatment includes the use of NSAIDs and oral contraceptive pills.

Most gynecologic causes of abdominal pain are best evaluated with pelvic ultrasound. Sometimes laparoscopy is needed, which is often therapeutic as well, as in the case of ovarian torsion. CT can help delineate unclear findings seen on ultrasound. Consultation or follow-up with a gynecologist is often warranted.

General Considerations

A. Adults

Anemia is defined as an abnormally low circulating red blood cell (RBC) mass, reflected by low serum hemoglobin (Hb). However, the normal range of Hb varies among different populations. For menstruating women, anemia is present if the Hb level is at or below 11.6-12.3 g/dL. In men and postmenopausal women, anemia is present if the Hb level is at or below 13.0-14.0 g/dL. Other factors, such as age, race, altitude, and exposure to tobacco smoke, can also alter Hb levels.

Anemia is usually classified by cell size (Table 31-1). Microcytic anemias, or those with mean corpuscular volume (MCV) below 80 fL, are usually due to iron deficiency, chronic inflammation, or thalassemia. Macrocytic anemias, those with MCV above 100 fL, are classified as megaloblastic or nonmegaloblastic. Megaloblasts, which are large, immature, nucleated precursors to RBCs, are seen with vitamin B₁₂ deficiency and folate acid deficiency. Nonmegaloblastic causes of macrocytosis include alcoholism, hypothyroidism, and chronic liver disease. Normocytic anemia (MCV between 80 and 100 fL) can be due to hemolytic or nonhemolytic causes. Hemolysis can result from hereditary abnormalities of the cell contents or cell membrane. Hemolysis can also result from acquired insults caused by autoantibodies, alloantibodies (in, eg, transfusion reactions), or a nonimmune process such as malaria or hypersplenism. Important nonhemolytic causes of normocytic anemia include poor production of RBCs due to aplastic anemia, renal insufficiency, and bone marrow infiltration.

B. Children

Normal Hb levels vary with age. At birth, mean Hb is about 16.5 g/dL. This level increases to 18.5 g/dL during the first week of life, followed by a drop to 11.5 g/dL by 1-2 months of age. This physiologic anemia of infancy is mediated by changes in erythropoietin levels. By 1-2 years of age, the Hb level begins to rise, to 14 g/dL in adolescent girls and 15 g/dL in adolescent boys. Other relevant laboratory values also vary in children. The median MCV, for example, can be as high as 120 fL in premature infants and as low as 78 fL in 1-year-old infants. Thus, laboratory values in children should always be compared with age-appropriate norms.

Many inherited causes of anemia are discovered in infancy and childhood. It is therefore important to obtain a careful family history in an anemic child, especially if the episodes of anemia are intermittent. Sickle cell anemia, thalassemia, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and spherocytosis are examples of inherited forms of anemia. When only male members of a family are affected, G6PD deficiency, which is X-linked, should be particularly considered.

Other elements of the history are also important when evaluating a child for anemia. Because infants with anemia can exhibit poor feeding, irritability, and tachycardia rather than classic adult symptoms and signs, these atypical features should be explored with the family. Nutrition should be evaluated carefully, with attention to dietary sources of vitamin B₁₂, folate acid, and iron. Potential sources of lead poisoning must also be considered. Finally, adolescents often require additional support and explanation. For instance, adolescent girls may not know what constitutes a normal menstrual period, so the specific number of tampons and pads used should be obtained.

Table 31-1. Anemia classification by cell size.

<table>
<thead>
<tr>
<th>Microcytic</th>
<th>Macrocytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>Megaloblastic</td>
</tr>
<tr>
<td>Anemia of chronic disease</td>
<td>Vitamin B₁₂ deficiency</td>
</tr>
<tr>
<td>Thalassemias</td>
<td>Folic acid deficiency</td>
</tr>
<tr>
<td>Sideroblastic anemia</td>
<td>Drug related</td>
</tr>
<tr>
<td></td>
<td>Nonmegaloblastic</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Liver disease</td>
</tr>
<tr>
<td></td>
<td>Alcoholism</td>
</tr>
<tr>
<td></td>
<td>Myelodysplastic syndromes</td>
</tr>
<tr>
<td>Normocytic</td>
<td></td>
</tr>
<tr>
<td>Hemolytic</td>
<td></td>
</tr>
<tr>
<td>Intrinsic</td>
<td>Acute blood loss</td>
</tr>
<tr>
<td>Membrane defects (spherocytosis)</td>
<td>Aplastic anemia</td>
</tr>
<tr>
<td>Enzyme deficiencies (G6PD deficiency)</td>
<td>Anemia of chronic disease</td>
</tr>
<tr>
<td>Hemoglobinopathies (sickle cell disease)</td>
<td>Chronic renal insufficiency</td>
</tr>
<tr>
<td>Extrinsic</td>
<td>Myelophthis</td>
</tr>
<tr>
<td>Autoimmune</td>
<td></td>
</tr>
<tr>
<td>Warm antibody mediated (chronic lymphocytic leukemia, systemic lupus erythematosus, idiopathic)</td>
<td></td>
</tr>
<tr>
<td>Cold antibody mediated (Mycoplasma, idiopathic)</td>
<td></td>
</tr>
<tr>
<td>Alloimmune</td>
<td></td>
</tr>
<tr>
<td>Nonimmune</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td></td>
</tr>
<tr>
<td>Physical trauma (thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, burns)</td>
<td></td>
</tr>
<tr>
<td>Infections (malaria)</td>
<td></td>
</tr>
</tbody>
</table>

G6PD, glucose-6-phosphate dehydrogenase.


Onega T: Sorting out the common anemias. JAAPA 2000;13:30. [PMID: 11521621]


IRON DEFICIENCY ANEMIA

**ESSENTIALS OF DIAGNOSIS**

- Low iron and serum ferritin levels, and elevated total iron-binding capacity (TIBC).
- Response to therapeutic trial of iron.
- In adults, nearly always due to blood loss.
- Can also be due to poor iron intake or poor absorption.

**General Considerations**

Iron deficiency is the most common cause of anemia. Up to 11% of women and 4% of men have iron deficiency; however, only about 2% of women and 1% of men develop anemia due to the deficiency.

The average adult has 2-4 g of stored iron. About 65% of this reserve is located in the RBCs, with the remainder in the bone marrow, liver, spleen, and other body tissues. Iron deficiency occurs when there is a net imbalance resulting from either excessive loss or poor intake.

Toddlers aged 1-3 years are vulnerable to iron deficiency anemia. National surveys report rates as high as 15% in this age group.

**Pathogenesis**

Extracorporeal blood loss is the most common cause of iron deficiency anemia. When RBCs are destroyed within the body, the reticuloendothelial system usually adequately recycles iron into the next generation of RBCs. Poor iron uptake, due either to poor nutrition or inadequate absorption, is a less common cause of iron deficiency anemia.

Women develop iron deficiency more readily than men because of increased potential for iron loss. On average, women lose an additional 1 mg of iron each day due to menstruation. Pregnancy, lactation, and delivery additionally cost a woman an average of 1000 mg of iron each.

In infancy, risk factors for iron deficiency are primarily dietary and include exclusive breast-feeding beyond 6 months without iron supplementation, prolonged bottle-feeding, and excessive cow’s milk consumption. However, other risk factors for iron deficiency in childhood include Hispanic ethnicity, poverty, and being overweight.

**Prevention**

The US Preventive Services Task Force (USPSTF) recommends primary prevention of iron deficiency anemia by encouraging parents to breast-feed their infants and to include iron-enriched foods in the diet of infants and young children.
Although there is insufficient evidence to recommend for or against the routine use of iron supplements for healthy infants or pregnant women, the USPSTF does currently recommend screening for iron deficiency anemia—using Hb or hematocrit—for both asymptomatic pregnant women and high-risk infants (B Recommendation).

Finally, the USPSTF suggests that although there is insufficient evidence to recommend for or against routine screening for iron deficiency anemia in other asymptomatic persons, screening may be indicated based on other clinical information.

Clinical Findings

A. Symptoms and Signs

Iron deficiency can be asymptomatic, especially in the early stages. However, patients can present with varying degrees of any of the common symptoms associated with anemia, such as weakness, fatigue, dizziness, headaches, exercise intolerance, or palpitations. Possible signs on physical examination include tachycardia, tachypnea, and pallor, especially of the palpebral conjunctivae.

One symptom associated with iron deficiency in particular is pica—the craving for ice, clay, or other unusual substances that may or may not contain iron. Rare symptoms include koilonychia (spoon nails), blue sclerae, and atrophic glossitis. Esophageal webs, dysphagia, and iron deficiency characterize the Plummer-Vinson syndrome, a disease of unknown pathophysiology that can increase the risk of squamous cell carcinoma of the pharynx and esophagus.

In childhood, iron deficiency anemia has been associated with cognitive and motor delays.

B. Laboratory Findings

Hb levels can be normal in early iron deficiency. Mild deficiency yields Hb levels of 9–11 g/dL, whereas in severe deficiency levels can fall as low as 5 g/dL.

Serum iron levels below 60 μg/dL indicate iron deficiency. As iron stores are depleted, serum ferritin falls below 30 ng/dL. TIBC therefore rises above 400 μg/dL. Percent iron saturation, which is inversely proportional to TIBC, falls below about 15%.

Although serum ferritin levels are often useful in differentiating iron deficiency from other forms of microcytic anemia, it should be noted that ferritin is an acute-phase reactant that can be elevated during acute illnesses, chronic inflammatory states, or cancer.

The peripheral blood smear is also a useful test. Iron-deficient RBCs manifest varying degrees of hypochromia and microcytosis. However, the gold standard of iron deficiency is bone marrow examination, which shows absent iron reserves in affected patients. A Prussian blue stain is used to examine marrow iron stores.

Another method of diagnosis involves measuring a patient’s response to oral iron therapy. Increased reticulocytosis several days after institution of oral iron treatment can be diagnostic.

Treatment

Iron can be increased in the diet. Foods particularly rich in iron include meats (especially liver) and fish. Whole grains, green leafy vegetables, nuts, seeds, and dried fruit also contain iron. Toddlers’ multivitamins commonly contain iron. Cooking with iron pots and pans also increases iron intake.

Oral iron therapy is available in the form of iron salts. One 300-mg tablet of iron sulfate, for example, delivers 60 mg of elemental iron. One 300-mg tablet of iron gluconate delivers 34 mg of elemental iron and may be better tolerated by some patients. Up to 180 mg of elemental iron can be given each day, depending on the degree of deficiency. Absorption of oral iron is dependent on many environmental factors. An acidic environment increases absorption; thus iron tablets are often given with ascorbic acid. For this same reason, antacids should be avoided within several hours of iron ingestion. Other substances that impair the absorption of iron include calcium, soy protein, tannins (found in tea), and phytate (found in bran). Side effects of oral iron therapy include gastrointestinal distress and constipation. For this reason, some physicians routinely prescribe an as-needed stool softener along with each iron prescription.

Iron can be given intramuscularly or intravenously to patients who cannot tolerate oral iron due to gastrointestinal upset. This route may also be convenient for patients who have concurrent gastrointestinal malabsorption or ongoing blood loss, such as those with severe inflammatory bowel disease. Phlebitis, muscle breakdown, anaphylaxis, and fever are possible side effects of parenteral iron.

ANEMIA OF CHRONIC DISEASE

ESSENTIALS OF DIAGNOSIS

- Presence of a chronic disease or chronic inflammation.
- Shortened RBC survival but poor compensatory erythropoiesis.
- High or normal serum ferritin level and low TIBC.
CHAPTER 31

General Considerations

Many chronic diseases—such as cancer, collagen vascular disease, chronic infections, diabetes mellitus, and coronary artery disease—can be associated with anemia (Table 31-2).

Pathogenesis

In spite of shortened RBC survival, bone marrow RBC production is low. This is thought to be due to (1) trapping of iron stores in the reticuloendothelial system, (2) a mild decrease in erythropoietin production, and (3) impaired response of the bone marrow to erythropoietin.

Clinical Findings

A. Symptoms and Signs

The anemia of chronic disease (ACD) is often mild and therefore general anemic symptoms, such as fatigue, dizziness, and palpitations, can be mild or nonexistent. Signs such as pallor of the palpebral conjunctivae are only sometimes present. The condition must therefore be suspected and investigated in patients known to have underlying conditions such as collagen vascular diseases, cancers, or chronic infections. The condition is often diagnosed incidentally on laboratory reports.

B. Laboratory Findings

Hb levels are generally mildly decreased (10–11 g/dL), but levels can occasionally be below 8 g/dL. RBCs are often hypochromic. MCV can be either normal (80-100 fl) or low (<80 fl). Because RBC production is poor, the absolute reticulocyte count is often low (<25,000/μL). Acute-phase reactants such as erythrocyte sedimentation rate (ESR), platelets, and fibrinogen can be elevated.

Because ACD is associated with decreased production of transferrin, serum iron level and TIBC are often both low. Calculated percent saturation, however, remains normal. This is to be distinguished from iron deficiency anemia, in which TIBC is often high, resulting in low-percent saturation. Serum ferritin level is high or normal in ACD but low in iron deficiency anemia.

Treatment

Treatment of ACD should be aimed at the underlying condition. Symptomatic patients or heart patients often require packed transfusions of RBCs, especially if the HBG count is below 10 mg/dL. Erythropoietin is also used to correct anemia associated with certain chronic diseases, especially cancer.


Table 31-2. Selected causes of anemia of chronic disease.

<table>
<thead>
<tr>
<th>Chronic infections</th>
<th>Abscesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subacute bacterial endocarditis</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
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<tr>
<td>Collagen vascular disease</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td></td>
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<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
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<tr>
<td>Temporal arteritis</td>
<td></td>
</tr>
<tr>
<td>Neoplasia</td>
<td></td>
</tr>
<tr>
<td>Hodgkin and non-Hodgkin lymphomas</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td></td>
</tr>
</tbody>
</table>

Thalassemia

ESSENTIALS OF DIAGNOSIS

- Elevated RBC count despite decreased Hb level.
- Exaggerated microcytosis.
- Positive family history.
- Mediterranean or African heritage.
- Pattern of inheritance.

General Considerations

One normal adult Hb molecule, also known as HbA, consists of a heme moiety, two α Hb chains, and two β Hb chains. The thalassemias are the diverse group of genetic diseases resulting from abnormal Hb due to defective α or β chains.

Other Hb chains exist, such as γ and δ chains. Fetal Hb consists of two α chains and two γ chains (α2γ2), and HbA2 consists of two α chains and two δ chains (α2δ2). Although ordinarily these lesser types of Hb comprise no more than 5% of the total amount of Hb, the thalassemias are characterized by increased proportions of non-A Hb because of defective α or β chains. These disorders are classified as α-thalassemias or β-thalassemias, based on the abnormal gene.

Thalassemia traits are more common in those with Mediterranean, African, and South Asian ancestry. This is at least in part because these parts of the world are inhabited by Plasmodium species, and heterozygous thalassemic traits confer survival advantage to those afflicted with malaria.
Pathogenesis

Because there are four α Hb genes per individual (two on each copy of chromosome 16), there are four major types of α-thalassemia. If only one α Hb gene is damaged, the result is called α-thalassemia minima, an essentially asymptomatic condition. Damage to two different α Hb genes results in α-thalassemia minor, which has only mild clinical significance. Three damaged α Hb genes can lead to a relative abundance of α Hb, causing an abundance of Hb β, also known as HbH. This disorder, also called hemoglobin H disease, is characterized by severe clinical manifestations of chronic hemolysis, hospitalizations, and decreased lifespan. Absence of normal α Hb chains causes Hb Barts disease and is fatal in utero.

The two β Hb genes are found on chromosome 11. If one is damaged, β-thalassemia minor results, with few clinical effects. Infants with two damaged copies of β Hb will be phenotypically normal at birth due to the predominance of fetal Hb (α2γ2). Affected infants become severely symptomatic in the first year of life, however, and often die before age 5.

Clinical Findings

A. Symptoms and Signs

α-Thalassemia minima is almost always asymptomatic. α-Thalassemia minor can be accompanied by occasional mild symptoms of anemia, including headaches, fatigue, and dizziness. Patients with HbH disease, however, often exhibit severe clinical manifestations of chronic hemolytic anemia, including hepatosplenomegaly and cholelithiasis (due to bilirubin gallstones). These patients often require chronic transfusions, usually beginning in late childhood and adolescence. Patients with no normal α Hb develop tetramers of γ Hb in utero, known as Hb Barts, which are inefficient at delivering oxygen to the tissues. The accompanying hypoxia results in high-output congestive heart failure, severe edema, and hydrops fetalis.

The clinical appearance of β-thalassemia minor often mimics that of mild or moderate iron deficiency, and often laboratory findings are necessary to distinguish the two. β-Thalassemia major, however, results in a severe phenotype. Widespread hemolysis in these patients causes pallor, irritability, jaundice, and hepatosplenomegaly. Eighty percent of patients die in the first 5 years of life due to severe anemia, high-output congestive heart failure, or infection.

B. Laboratory Findings

As with iron deficiency, Hb levels and MCV are often low with the thalassemias. In contrast to iron deficiency, however, thalassemias are usually characterized by an elevated RBC count. Furthermore, the decrease in MCV is often more exaggerated in the thalassemias; levels as low as 50-60 fL are not unusual. The red cell distribution width (RDW) can also be used to distinguish the two conditions. With iron deficiency, the RDW is elevated due to a variety of cell sizes, whereas the RDW is usually normal in thalassemic patients because RBCs are uniformly small.

Hb electrophoresis should be conducted on any patient with suspected thalassemia. Although some patients with α-thalassemia minima or media can have normal electrophoresis patterns, abnormalities are often seen in other thalassemic patients. In β-thalassemia minor, for example, relative proportions of fetal Hb (α2γ2) and HbA2 are increased.

Treatment

Patients with α-thalassemia minor, α-thalassemia minima, and β-thalassemia minor are generally asymptomatic and should be treated only if necessary. These patients may require blood transfusions under certain conditions, such as after vaginal delivery or surgery.

Patients with β-thalassemia major and HbH disease, however, require the care of a hematologist. These patients may require frequent transfusions, splenectomy, or both. Iron overload is a frequent complication in these patients, both those with and without transfusion therapy. Chelation therapy is often required to avoid end-organ damage in the heart, endocrine organs, and liver. Patients with a personal or family history of thalassemia should be offered genetic counseling when planning a family.

Macrocytic Anemia

Vitamin B₁₂ Deficiency

Essentials of Diagnosis

Macrocytosis.

Serum vitamin B₁₂ level below 100 pg/mL.

Hypersegmented neutrophils.

General Considerations

Vitamin B₁₂ (cobalamin) is involved in two important enzymatic reactions: the conversion of methylmalonylcoenzyme A (CoA) to succinyl-CoA and the methylation of homocysteine to methionine. This latter reaction is required for synthesis of thymidine, a component of DNA.

Because vitamin B₁₂ is present in all animal products, only people with unusual diets (vegans, fad dieters) receive inadequate intake. These individuals should receive vitamin B₁₂ supplementation. Some special populations, such as pregnant women and those who have had bariatric surgery, may require increased levels of vitamin B₁₂.
Clinical Findings

A. Symptoms and Signs

Many clinical features are common to all megaloblastic anemias: anemia, pallor, weight loss, fatigue, glossitis, lightheadedness, jaundice, and abdominal symptoms. Neurologic symptoms are specific to vitamin B<sub>12</sub> deficiency, however, beginning with paresthesias in the hands and feet. Disturbances in vision, taste, smell, proprioception, and vibratory sense can also occur. Untreated, vitamin B<sub>12</sub> deficiency can lead to posterior spinal column demyelination, resulting in spastic ataxia and dementia mimicking that of Alzheimer disease. These changes are often irreversible. Vitamin B<sub>12</sub> deficiency can also lead to psychotic depression and paranoid schizophrenia.

B. Laboratory Findings

The MCV is usually above 100 fl, and vitamin B<sub>12</sub> levels are usually below 100 pg/mL. The higher the MCV, the more likely the diagnosis. Lactate dehydrogenase and indirect bilirubin can be modestly elevated because of increased RBC destruction. The reticulocyte count can be depressed. Because DNA synthesis affects all cell lines, pancytopenia can occur. Peripheral blood smear affects all cell lines, pancytopenia can occur. Peripheral blood smear can show markedly abnormal RBCs along with hypersegmented neutrophils, which are pathognomonic for megaloblastic anemia.

The presence of anti-intrinsic factor (IF) antibodies confirms the diagnosis of pernicious anemia, with a sensitivity of 50%-70% and a specificity approaching 100%. There is evidence suggesting that early vitamin B<sub>12</sub> deficiency can be diagnosed by elevated levels of homocysteine or methylmalonic acid. These metabolite levels are most useful in cases where diagnosis is suspect but not supported by other laboratory values. Increased levels of methylmalonic acid confirm B<sub>12</sub> deficiency.

Although examination of the bone marrow is usually unnecessary for diagnosis, if performed, it shows erythroid hyperplasia and marked asynchrony in maturation between cytoplasmic components and nuclear material.

The Schilling test, although not often used today, has historically been used to confirm the diagnosis of pernicious anemia. In the first stage, a large dose of intramuscular vitamin B<sub>12</sub> is given, followed by oral ingestion of radiolabeled vitamin B<sub>12</sub>. Patients with intact vitamin B<sub>12</sub> absorption will have at least 7% of the oral dose present in urine. In the second stage, radiolabeled vitamin B<sub>12</sub> is administered with intrinsic factor. If pernicious anemia is the cause of vitamin B<sub>12</sub> deficiency, a poor absorption rate in the first stage will be corrected by the combination of vitamin B<sub>12</sub> and intrinsic factor in the second stage.

Treatment

Treatment requires monthly parenteral treatment of vitamin B<sub>12</sub> in doses of 100-1000 μg, usually administered daily or every other day for the first few weeks, followed by maintenance doses every 1-3 months. Once vitamin B<sub>12</sub> levels have been reestablished, oral therapy (1 mg/d) can then be substituted. Oral therapy alone may be sufficient. Treatment often also consists of concurrent administration of folate, 1-5 mg each day.

Folic Acid Deficiency

Pathogenesis

Folic acid deficiency can occur as a result of decreased intake. In spite of supplementation of US wheat products with folate, nutritional deficiencies still occur, especially in alcoholics and patients with atypical diets. Malabsorption can also affect intake of folate. Because small intestine microvilli convert the ingested complex folic acid molecule into an absorbable one, diseases of the small intestine, such as gluten enteropathy and Crohn disease, can cause deficiency. Drugs such as anticonvulsants and oral contraceptives also predispose to folate malabsorption. Other medications (e.g., antineoplastic agents, trimethoprim, and certain antimalarial drugs) inhibit the enzyme necessary for the replenishment of intracellular folate and can affect folate levels.
Folate deficiency can also result if increased requirements are not met. Pregnancy, for instance, increases folate requirements 5- to 10-fold by the third trimester. Patients with hemolytic anemia and exfoliative skin diseases also have increased requirements and should receive supplementation. Because folate is dialyzable, patients on dialysis can suffer from folate deficiency if they do not receive supplementation.

Folate deficiency is common among alcoholics for several reasons. First, although some folic acid is present in beer, alcoholics tend to consume less of other foods rich in folic acid, such as leafy green vegetables. Alcohol can also adversely affect intracellular processing of folate. Finally, alcohol may suppress bone marrow function. Although alcoholics commonly present with macrocytosis, only those who are folate or vitamin B₉ deficient will have accompanying megaloblastic anemia with its associated clinical features.

### Clinical Findings

**A. Symptoms and Signs**

Patients with mild folate deficiency often present with anemia on a routine blood screening. Those with more severe disease can present with pallor, weight loss, fatigue, glossitis, lightheadedness, jaundice, or abdominal symptoms, as in vitamin B₁₂ deficiency. In contrast to vitamin B₁₂ deficiency, however, neurologic symptoms are absent.

**B. Laboratory Findings**

Many laboratory findings are similar to those of vitamin B₁₂ deficiency: Hb levels can be variably depressed, pancytopenia can occur, and hypersegmented neutrophils can be seen on the peripheral blood smear. Also as with vitamin B₁₂ deficiency, examination of the bone marrow can show erythroid hyperplasia and marked asynchrony in maturation between cytoplasmic components and nuclear material.

With folate deficiency, however, serum and RBC folate levels are low, whereas vitamin B₁₂ levels are normal. RBC folate—which is low at less than 150 pg/L—is thought to be a more precise indicator of chronic folate deficiency than serum folate. The latter is thought to reflect more recent dietary intake. In cases where diagnosis remains in doubt, an elevated homocysteine level, in spite of a normal methylmalonic acid level, suggests folate deficiency.

### Treatment

Foods rich in folic acid should be consumed, which include leafy green vegetables, fruits, nuts, beans, wheat germ, and liver. Supplementation with oral folic acid—from 1 to 5 mg daily—is used to treat deficiency. Total correction often occurs within 6-8 weeks. Patients with increased folate requirements, such as pregnant women, should receive supplementation. Some authorities recommend treating all patients with macrocytic anemia, regardless of cause, with empirical addition of folic acid.

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**ESSENTIALS OF DIAGNOSIS**

- **Autosomal-dominant inheritance pattern** (in most cases).
- **Spherocytes on peripheral blood smear.**
- **Hemolysis.**

**General Considerations & Pathogenesis**

Hereditary spherocytosis (HS) is the most common inherited defect of the RBC membrane. Patients with this condition inherit one of a series of mutations of the structural proteins of the RBC membrane, such as spectrin, ankyrin, paladin, and the Rh-associated glycoprotein. The resulting decreased membrane elasticity causes loss of the normal biconcave shape of the RBC. These deformed, spherical RBCs are then detained and phagocytosed in the narrow fenestrations of the splenic cords. Less common related defects also exist, including hereditary elliptocytosis and hereditary stomatocytosis.

**Prevention**

For patients who have required splenectomy, immunization against *Pneumococcus* and *Meningococcus* is recommended for secondary prevention of sepsis.

**Clinical Findings**

**A. Symptoms and Signs**

HS can be classified as mild, moderate, or severe. Individuals with mild disease rarely manifest symptoms and signs.
Increased erythropoietin levels compensate for early destruction of RBCs. These patients often present as adolescents or adults on routine blood screenings. Individuals with moderate disease comprise 60%-75% of HS patients and can develop intermittent episodes of jaundice, dark urine, abdominal pain, and splenomegaly in infancy or early childhood. Individuals with severe disease have more marked jaundice and splenomegaly.

If bilirubin levels are chronically elevated, bilirubin gallstones can form, leading to right upper quadrant abdominal pain and tenderness, nausea, and a positive Murphy sign.

B. Laboratory Findings

Patients with mild disease may or may not be anemic. Patients with moderate and severe disease often have low Hb, reticulocyte counts between 5% and 20%, and elevated serum bilirubin level.

The mean corpuscular Hb concentration (MCHC) is a useful test in diagnosing HS. It is generally elevated to 36 g/dL in patients with HS, reflecting decreased membrane surface area and increased Hb concentration in the RBC.

The peripheral blood smear of a patient with HS shows characteristic spherocytes—small RBCs that have lost their central pallor. Although a patient with mild disease may have only a few spherocytes, patients with moderate or severe disease can have 30 or more spherocytes per high-power field.

Special tests can also be used to evaluate patients for HS. The osmotic fragility test involves suspending a patient’s RBCs in increasingly dilute salt solutions and observing for cell lysis. RBCs from patients with HS will be more sensitive to hypotonic solutions because of membrane instability. The newer acidified glycerol lysis test is also used.

Treatment

Individuals with mild disease rarely require treatment. For patients with moderate disease blood transfusions may be necessary, and for patients with severe disease regular transfusions are required. Folic acid supplementation is useful for patients with this and other hemolytic diseases.

The definitive treatment is splenectomy, which leads to significantly increased RBC life span. Although splenectomy virtually eliminates the need for transfusion, these patients are at risk for overwhelming sepsis with encapsulated organisms, and immunization against *Pneumococcus* and *Meningococcus* is recommended. Cholecystectomy may be necessary for patients with bilirubin gallstones.

2. Glucose-6-Phosphate Dehydrogenase Deficiency

ESSENTIALS OF DIAGNOSIS

- X-Linked inheritance pattern.
- African or Mediterranean heritage.
- Recent exposure to oxidizing substances such as primaquine, sulfa drugs, naphthalene (mothballs), or fava beans.

General Considerations

The World Health Organization classifies glucose-6-phosphate dehydrogenase (G6PD) deficiency into five variants, from class I (the most severe enzyme deficiency) to class V (no clinical significance). The deficiency is most common in people of African and Mediterranean heritage and, like thalassemia and sickle cell disease, is thought to protect against malaria. Although it is primarily seen in men, as are most X-linked disorders, women who carry the defective gene can also manifest symptoms due to inactivation of their normal X chromosomes.

Overall, G6PD deficiency is the most common enzymatic disorder of RBCs in humans and affects 200-400 million people. Less common enzymatic deficiencies also exist. Pyruvate kinase deficiency, for example, has a similar clinical presentation.

The most common variants are called G6PD A and G6PD Mediterranean. G6PD A is a class III variant in which patients have 10%-60% of the normal level of G6PD and therefore experience intermittent hemolysis, generally associated with infections or drugs. G6PD Mediterranean also generally manifests with intermittent hemolysis, but the enzyme deficiency is usually more severe (eg, ~10% of normal enzymatic activity).

Pathogenesis

G6PD is a cytoplasmic enzyme that prevents oxidative damage to RBCs by reducing nicotinamide adenine dinucleotide phosphate (NADP) to NADPH. Individuals who are deficient in this enzyme are more susceptible to damage from oxidative substances such as superoxide anion (O$_2^-$) and hydrogen peroxide. In addition to being normal by-products of cell metabolism, these substances are produced by certain drugs, household chemicals, and foods.

Clinical Findings

Persons affected with G6PD deficiency are often asymptomatic. However, a spectrum of clinical manifestations can occur, from infrequent mild episodic hemolysis to severe chronic hemolysis.
A. Symptoms and Signs
The most common clinical manifestations are jaundice, dark urine, pallor, abdominal pain, and back pain. These symptoms usually occur hours to days after an oxidative insult, which can be caused by a number of different agents (Table 31-3). Chemicals that can cause such an insult include primaquine, sulfa drugs, dapsone, nitrofurantoin, and naphthalene (found in mothballs). Aspirin and acetaminophen can precipitate hemolysis in certain individuals as well. Attacks can also be associated with infections (such as pneumonia, viral hepatitis, and Salmonella) and diabetic ketoacidosis. Finally, foods such as fava beans have been implicated. These beans are common in the Mediterranean and are harvested in late spring.

Infants with G6PD deficiency can also present with jaundice. Again a spectrum of disease exists, from mild transient jaundice to severe jaundice, kernicterus, and death. Those with class I G6PD deficiency can have lifelong, life-threatening chronic hemolysis.

B. Laboratory Findings
Hb levels mirror the severity of disease. During acute attacks in highly susceptible individuals, Hb levels can be as low as 3-4 g/dL. Many asymptomatic individuals, however, have only mildly depressed levels at 11-12 g/dL.

During periods of active hemolysis, other laboratory measures can be abnormal. To compensate for the loss of RBCs, reticulocytosis occurs and the absolute reticulocyte count is elevated above 2%-3%, and sometimes above 10%-15%. Haptoglobin levels are often depressed below 50 mg/dL, as this plasma protein binds Hb released from fragmented RBCs.

The peripheral blood smear in G6PD deficiency shows characteristic Heinz bodies, which represent masses of denatured, damaged Hb. “Bite cells,” which appear as RBCs with a small semicircular defect, can also be seen. The definitive test for G6PD deficiency is an enzymatic assay that measures in vitro production of NADPH.

Treatment
Individuals with mild disease require no treatment except for avoidance, whenever possible, of oxidative triggers. Individuals with class I disease may require inpatient treatment of acute exacerbations with transfusion, intravenous fluid support, and monitoring of renal function. Although vitamin E and splenectomy have been advocated as possible treatments in more severe cases, neither has provided consistent benefit.

Table 31-3. Selected sources of oxidative damage.

<table>
<thead>
<tr>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin, nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Antimalarial agents</td>
</tr>
<tr>
<td>Nitrofurantoin, sulfonamides</td>
</tr>
<tr>
<td>Quinidine</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Naphthalene</td>
</tr>
<tr>
<td>Fava beans</td>
</tr>
</tbody>
</table>

3. Sickle Cell Anemia

ESSENTIALS OF DIAGNOSIS

- African, Mediterranean, or Asian heritage.
- Family history.
- Autosomal-recessive inheritance.
- Characteristic pattern on Hb electrophoresis.

General Considerations
Sickle cell anemia (SCA) is a common genetic disorder. Traits that lead to SCA are common in those with African and South Asian heritage, as these traits confer resistance to malaria. The gene frequency for SCA in African Americans is about 4%.

A spectrum of other sickle cell syndromes exists. HbC results from a different mutation in the β Hb chain. Patients with HbSC disease have one of each mutation and generally experience a milder phenotype than those with homozygous sickle cell anemia (HbSS). Patients with the HbSA genotype have one sickle cell gene and one regular gene. They tend to have mild, if any, clinical manifestations of disease. Other permutations of abnormal Hb genes can cause similar syndromes. Patients with one sickle cell gene and one β-thalassemia gene, for example, can have significant clinical manifestations of hemoglobinopathy.

Pathogenesis
Patients with SCA are homozygous for a mutation in the β Hb chain; the sixth amino acid is valine instead of glutamate. The resulting HbS, which consists of two normal α Hb chains and two abnormal β Hb chains, is poorly soluble when deoxygenated. The polymerization of HbS into elongated fibers within the RBC leads to the characteristic “sickle” shape. These abnormal RBCs occlude capillary beds and lead to the many clinical manifestations of SCA.

Prevention
Newborn screening for HbSS, HbSA, and HbSC is highly recommended and required by law in all 50 states and the
District of Columbia. Several prophylactic measures can reduce the likelihood of pain crises and other manifestations of disease in patients with SCA (ie, secondary prevention). First, adequate hydration and oxygenation reduce the risk of Hb polymerization and subsequent vasoocclusive crises. Folic acid should be supplemented, 1 mg orally every day. Some physicians recommend hydroxyurea, which seems to reduce the likelihood of RBC sickling by stimulating production of fetal Hb. Infectious complications can be reduced by immunization against *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, hepatitis B, and influenza. Daily oral penicillin prophylaxis should be given until age 5 years. Use of penicillin prophylaxis, along with intensive medical care, has reduced the mortality of SCA from 25% to 3% during the first 5 years of life.

**Clinical Findings**

**A. Symptoms and Signs**

Patients with homozygous SCA manifest disease early. About 30% of patients are discovered by 1 year of age and over 90% by 6 years of age. Acute pain episodes are the most common presentations; they can occur in the extremities, abdomen, back, or chest. Many patients have several hospitalizations each year for acute episodes of pain. Although generally no inciting factor is found, stresses such as cold, infection, and dehydration can precipitate attacks. Fever, joint swelling, vomiting, and tachypnea can accompany pain episodes.

Most patients experience autoinfarction of the spleen by early childhood due to occlusion of splenic capillary beds. For this and other reasons, patients with SCA are significantly vulnerable to infection, especially from encapsulated pathogens such as *S pneumoniae* and *H influenzae*. Pneumonia, meningitis, osteomyelitis, and bacteremia are causes of significant morbidity and mortality in these patients.

Pulmonary complications are the most common causes of death in patients with SCA. RBCs in the pulmonary system are particularly vulnerable to sickling because of its low PO$_2$ and relatively low blood pressure. “Acute chest syndrome” refers to the clinical triad of chest pain, pulmonary infiltrate on x-ray, and fever, which can be due to pulmonary infarction, pneumonia, or both.

Sickled RBCs can occlude vasculature and cause infarction of nearly any tissue in the body. Therefore, other serious manifestations of SCA include stroke, myocardial infarction, bone infarction, retinopathy, leg ulcers, and priapism. Depression, low self-esteem, and social withdrawal are common, especially when adequate coping mechanisms are not in place.

**B. Laboratory Findings**

Laboratory findings often reflect the chronic hemolysis that accompanies SCA. Classically the patient has a reticulocyte count increased to 3%-15%, Hb mildly or moderately decreased to 7-11 g/dL, elevated direct bilirubin and lactate dehydrogenase, and a depressed haptoglobin level.

The peripheral blood smear shows sickling of half of the RBCs. Howell-Jolly bodies and target cells are also present on the smear, indicating hyposplenism. The white blood cell count can be elevated at 12,000-15,000/mm$^3$, even in the absence of infection.

**Treatment**

Despite the preventive measures discussed earlier, most patients with SCA require frequent hospitalization for acute vasoocclusive crises or infectious complications. During acute exacerbations, patients often require hydration and oxygenation, analgesia with nonnarcotic or narcotic medications, antibiotics if appropriate, and blood transfusions.

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4. Autoimmune Hemolytic Anemia

**ESSENTIALS OF DIAGNOSIS**

- Positive direct Coombs test.
- Elevated indirect bilirubin and decreased serum haptoglobin.
- Inciting factor such as medication or illness.

**General Considerations**

Autoimmune hemolytic anemia (AIHA) results when a patient produces antibodies directed against the body’s RBCs (Table 31-4). AIHA can be classified by the temperature at which the antibodies are most reactive. “Warm” autoanti-

**Table 31-4. Causes of immune hemolytic anemia.**

<table>
<thead>
<tr>
<th>Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion reaction</td>
</tr>
<tr>
<td>Drugs (methyldopa, penicillin, quinidine)</td>
</tr>
<tr>
<td>Connective tissue disorders</td>
</tr>
<tr>
<td>Hematologic malignancies (chronic lymphocytic leukemia, non-Hodgkin lymphoma)</td>
</tr>
<tr>
<td>Infections (<em>Mycoplasma</em>, syphilis)</td>
</tr>
</tbody>
</table>
ANEMIA

bodies bind most strongly near 37°C (98.6°F), whereas “cold” autoantibodies bind RBCs near 0-4°C (32-39.2°F). Occasionally, a mixture of both types of autoantibodies is present.

Pathogenesis

Although in nearly half of cases the production of autoantibodies is idiopathic, at other times an inciting factor can be found. Lymphoproliferative disorders such as chronic lymphoblastic leukemia and autoimmune disorders such as rheumatoid arthritis, for example, can induce production of either warm or cold autoantibodies. Infections such as Mycoplasma and syphilis have been implicated, primarily in cold AIHA.

Medications can induce a warm antibody autoimmune reaction. Some drugs, such as methyldopa, alter RBC antigens so that they become targets of the host immune system. Other drugs bind with RBC antigens to form immunogenic complexes. This “hapten” reaction can occur with penicillin as well as a variety of other drugs.

Prevention

Any patient who receives a splenectomy should also receive secondary prevention in the form of immunizations against Pneumococcus, Haemophilus, and Meningococcus.

Clinical Findings

A. Symptoms and Signs

Overall, a wide spectrum of possible manifestations exists. A typical patient with AIHA presents with pallor, fatigue, or headaches due to loss of circulating RBCs. Jaundice may also be present, due to elevation of indirect bilirubin resulting from the release and breakdown of RBC heme. A patient may also have splenomegaly due to increased sequestration of damaged RBCs within the splenic cords of Billroth. In some cases, hemoglobinuria can lead to renal failure. The rate of disease progression depends on the underlying cause of hemolysis. Although in some patients clinical manifestations progress slowly, in others severe symptoms can develop in a matter of hours.

B. Laboratory Findings

A positive direct Coombs test helps diagnose AIHA. Direct Coombs tests involve washing RBCs and then immersing them in a solution containing antibodies against immunoglobulin G (IgG), C3d (a fragment of complement), or both. RBCs with adherent autoantibodies or complement will tend to agglutinate or burst.

Other laboratory findings reflect the general hemolytic process. Levels of bilirubin and lactate dehydrogenase are increased, haptoglobin levels tend to decrease, and the corrected reticulocyte count is increased. Other appropriate laboratory investigations specific to underlying causes—such as collagen vascular diseases, cancer, and infections—may be warranted.

Treatment

Although further hemolysis can result, blood transfusion should be given when the Hb level is significantly low (5-7 g/dL). Corticosteroids are often considered the treatment of choice, especially when autoantibodies are warm. Those who need long-term treatment and cannot take steroids can use other immunomodulating agents such as azathioprine, cyclosporine, and rituximab. Intravenous immunoglobulin is advocated for the acute treatment of adults with AIHA, but it is not as effective in children. Exchange transfusion, which not only delivers new RBCs but also removes destructive autoantibodies and complement, can also be useful. Splenectomy should be considered in refractory cases; as previously noted, any patient who receives a splenectomy should also receive immunizations against Pneumococcus, Haemophilus, and Meningococcus. Finally, underlying disorders should be treated as appropriate.


5. Extrinsic Nonimmune Hemolytic Anemia

ESSENTIALS OF DIAGNOSIS

Negative Coombs test.

Negative family history.

Known mechanical trauma to RBCs, hemolytic infection, or drug or toxin exposure.

There are many causes of extrinsic hemolysis not related to immunity (Table 31-5). The first group of conditions results from mechanical damage to RBCs. Any process that enlarges the spleen, for instance, can lead to an acquired hemolytic process because the spleen is the major organ recycling RBCs. Mechanical damage can also occur as RBCs rush past a prosthetic valve or other internal machinery. Disseminated intravascular coagulation and thrombotic thrombocytopenic purpura can result in hemolysis of RBCs that flow through areas of intravascular coagulation. Mechanical destruction of RBCs can also be due to exposure to heat, burns, or even repeated trauma such as that encountered in the feet while marching long distances.

Infectious diseases such as malaria, babesiosis, and leishmaniasis can also cause an acquired hemolysis. This is due both to direct parasitic action and to increased activity of macrophages within the spleen.
Finally, drugs and toxins can lead to hemolysis. Medications such as primaquine, dapsone, nitrates, and even topical anesthesia can induce oxidative stress, damaging RBCs. This can occur even in patients without G6PD deficiency. Toxins such as lead, copper, and arsine gas, as well as venom from snakes, insects, and spiders, can also cause hemolysis.

Symptoms and signs, laboratory findings, and treatments will be based upon the specific diagnosis made. Rather than a specific disorder, extrinsic nonimmune hemolytic anemia is a general categorization of heterogeneous disease processes.

<table>
<thead>
<tr>
<th>Nonimmune causes of hemolysis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersplenism</td>
</tr>
<tr>
<td>Microangiopathy</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td>Physical destruction</td>
</tr>
<tr>
<td>Prosthetic valve</td>
</tr>
<tr>
<td>March hemoglobinuria</td>
</tr>
<tr>
<td>Burns</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Malaria, babesiosis</td>
</tr>
<tr>
<td>Leishmaniasis</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Primaquine</td>
</tr>
<tr>
<td>Dapsone</td>
</tr>
<tr>
<td>Nitrates</td>
</tr>
<tr>
<td>Toxins</td>
</tr>
<tr>
<td>Lead, copper</td>
</tr>
<tr>
<td>Arsine gas</td>
</tr>
<tr>
<td>Snake, spider venom</td>
</tr>
</tbody>
</table>

Table 31-5.

is idiopathic. However, drugs, toxins, radiation, infections (eg, hepatitis, parvovirus), and pregnancy can all induce aplastic anemia. Although it is uncommon—affecting only 2-4 persons per million per year—it is often an important consideration for differential diagnoses for undiagnosed anemias.

Pathogenesis

The etiology is unclear. Although some causative agents have been shown to be directly toxic to the bone marrow, others seem to induce an autoimmune process. The specific etiology plays a role in prognosis; drug-induced aplastic anemia carries a more favorable prognosis than idiopathic aplastic anemia. The more severe the pancytopenia, the worse is the prognosis. Age and gender do not seem to affect prognosis.

Clinical Findings

A. Symptoms and Signs

Anemia leads to pallor, fatigue, and weakness. Neutropenia increases susceptibility to bacterial infections. Thrombocytopenia can present as mucosal bleeding, easy bruising, or petechiae. Splenomegaly is common in advanced disease.

B. Laboratory Findings

Pancytopenia is the hallmark of aplastic anemia. The associated anemia can be severe and is generally normocytic. The reticulocyte count is often low. The white blood cell count can be lower than 1500/mm³ and the platelet count is generally less than 150,000/mL. The peripheral blood smear shows RBCs, neutrophils, and platelets that are normal in morphology but decreased in number. Bone marrow aspirate, which reveals marrow hypocellularity, is essential to the diagnosis of aplastic anemia and important in distinguishing it from other causes of pancytopenia.

Treatment

Patients with aplastic anemia should avoid sick contacts and razors. Other means of decreasing risk of infection include the use of stool softeners and antiseptic soaps. Fever or other signs of infection should be aggressively investigated. Often, empiric broad-spectrum antibiotics should be used. Menstrual blood loss can be suppressed with oral contraceptive pills. Although replacement of blood products is often necessary, it should be used as little as possible to avoid sensitizing potential candidates for bone marrow transplantation. Hematopoietic growth factors (erythropoietin and granulocyte colony-stimulating factor) are not routinely used due to transient or nil effect.

In a patient younger than 50 years with a human leukocyte antigen (HLA)—matched sibling, immediate bone marrow transplantation is the treatment of choice. The toxicity

associated with treatment increases with age, along with the risk of graft-versus-host disease. If successful, transplantation is curative. The 5-year survival rate is approximately 70%.

In those lacking matched siblings or those older than 50 years, treatment consists of immunosuppression with antithymocyte globulin, augmented with high-dose cyclosporine. Most patients relapse, but remission rates with additional antithymocyte globulin treatments are encouraging. Survival at 5 years is about 75%.


2. Anemia of Chronic Renal Insufficiency

**ESSENTIALS OF DIAGNOSIS**

- Elevated serum creatinine level.
- Clinical presentation consistent with renal insufficiency.

**General Considerations**

Although anemia of chronic renal insufficiency (CRI) commonly occurs in patients with a creatinine clearance of 30 mL/min/1.73 m² or less, it can appear in patients with serum creatinine as low as 2 mg/dL.

**Pathogenesis**

Anemia of CRI is caused in part by a decrease in renal production of erythropoietin. The milieu of CRI also adversely affects RBC function. Studies show that RBCs from healthy patients die prematurely when injected into patients with CRI, but RBCs from CRI patients have a normal life span when injected into healthy individuals. Platelets are also affected. Platelet count is decreased and function is impaired.

**Clinical Findings**

**A. Symptoms and Signs**

Patients may exhibit bleeding or bruising due to thrombocytopenia and platelet dysfunction. Pallor and fatigue are also common. Early symptoms of uremia include nausea, vomiting, weight loss, malaise, and headache. As the blood urea nitrogen (BUN) level rises, paresthesias, decreased urine output, and waning level of consciousness can be seen. Other signs and symptoms depend on the etiology of the patient’s renal insufficiency.

**B. Laboratory Findings**

BUN and serum creatinine are generally both elevated, above 30 and 3.0 mg/dL, respectively. The anemia tends to be normocytic and normochromic, but in some cases it can be microcytic. Hyperphosphatemia, hypocalcemia, and hyperkalemia can occur, as can metabolic acidosis. Reticulocyte count tends to be normal or decreased. The blood smear in the uremic patient can reveal acanthocytes, which are grossly deformed RBCs. Bone marrow is inappropriately normal for the degree of anemia.

**Treatment**

Given that the primary cause is insufficient production of erythropoietin by the affected kidneys, treatment involves erythropoietin replacement. Erythropoietin or darbepoetin is indicated when the Hb level is 11 g/dL or less. Both are recombinant products. Darbepoetin has a longer half-life and more predictable bioavailability. Prior to initiation of therapy, the patient should be screened for deficiency of iron, folate, and vitamin B₁₂, as well as for occult blood loss. Intravenous iron replacement may be necessary to ensure iron stores adequate to support erythropoiesis.

Erythropoietin is given at 80-120 U/kg/wk. The most common side effect of erythropoietin therapy is hypertension. There is growing evidence that treatment with erythropoietin has a favorable effect on the progression of renal disease, underscoring the importance of early diagnosis and treatment. The target Hb level is 11-12 g/dL.


3. Anemia Associated With Marrow Infiltration

**ESSENTIALS OF DIAGNOSIS**

- Anemia with abnormally shaped RBCs on peripheral smear, along with abnormalities of other cell lines.
- Bone marrow study showing infiltration or a “dry tap.”
- Underlying neoplastic, inflammatory, or metabolic disease with nonspecific systemic signs and symptoms.

**General Considerations**

The bone marrow can tolerate fairly extensive infiltration. When marrow infiltration causes anemia or pancytopenia, however, it is referred to as myelophthisic anemia. The most common cause of myelophthisis is metastatic carcinoma of the lung, breast, or prostate. Other causes include hematologic malignancies (leukemia, lymphoma), infections (tuberculosis, fungi), and metabolic diseases (Gaucher disease, Niemann-Pick disease).
Pathogenesis

As the marrow is infiltrated by one of these disease processes, hematopoietic precursor cells are unable to mature and differentiate. Eventually, the normal marrow becomes replaced by collagen, reticulin, and other fibrotic cells. The severity of the resulting pancytopenia reflects the degree of infiltration. Myelophthisis occurs in less than 10% of patients with metastatic disease. The prognosis in patients with marrow metastases is generally poor.

Clinical Findings

A. Symptoms and Signs

Anemia is most commonly manifested by pallor or fatigue. Thrombocytopenia can cause petechiae, bleeding, or bruising. Neutropenia can lead to frequent or atypical infections. Fractures, bony pain, bony tenderness, hepatomegaly, and splenomegaly may occur. Other presenting signs and symptoms are usually related to the underlying cause of marrow infiltration.

B. Laboratory Findings

The anemia tends to be normocytic and mild to moderate. White blood cells and platelets may also be decreased. The peripheral blood smear is characterized by abnormal cells, particularly tear-shaped RBCs. The smear may also show poikilocytes and anisocytes. “Leukoerythroblastosis” refers to the presence of immature nucleated RBCs, immature white blood cells, and megakaryocyte fragments on the peripheral blood smear—findings that are highly suggestive of infiltration. Because of the hypocellular marrow, aspirate often yields few cells (“dry tap”).

Treatment

Treatment targets the underlying disease. Successful treatment of the malignancy, through radiation, chemotherapy, or bone marrow transplantation, can resolve the anemia. Erythropoietin or blood transfusion may be used to augment the RBC count. Platelet transfusions may be needed.

GENERAL CONSIDERATIONS

Approximately 10%-20% of the population have gallstones, making biliary pathology an increasing consideration in a patient with abdominal pain. Females are twice as likely to have gallstones. Gallstones are more frequently seen with increasing age, in the obese, and are more common in Caucasians and native Americans than African Americans. Most with cholelithiasis remain asymptomatic and never require surgery, but the sequelae of biliary disease remain significant: symptomatic cholelithiasis, gallstone pancreatitis, acute cholecystitis, chronic cholecystitis, choledocholithiasis, and ascending cholangitis. Understanding the basic pathophysiology of each of these conditions is an essential to appropriately diagnose and treat these conditions.

A basic understanding of biliary disease requires a vocabulary of terms used in describing them. Many have similar sounding names and can be confusing. A summary of the definitions can be found in Table 32-1. Although, the treatment of most biliary diseases ultimately requires cholecystectomy, each condition must be evaluated and treated in a unique fashion.

CHOLELITHIASIS

Asymptomatic Cholelithiasis

A landmark study from the University of Michigan followed the course of 123 faculty members identified as having asymptomatic gallstones during a routine health examination. After over two decades of follow-up, 14 (11%) patients went on to develop complications requiring surgery. Subsequent studies have not demonstrated a survival advantage with prophylactic cholecystectomy. As a result of these studies, prophylactic cholecystectomy for asymptomatic cholelithiasis is generally not indicated.

Symptomatic Cholelithiasis

Episodic RUQ pain.

Ultrasound evidence of gallstones.

Unlike asymptomatic cholelithiasis, symptomatic cholelithiasis will generally necessitate operative intervention. The typical patient presentation will include right upper quadrant abdominal pain, usually following a fatty meal and frequently associated with nausea (biliary colic). The pain can be severe and debilitating, and a trip to the emergency room is not an infrequent occurrence. Symptoms are related to transient obstruction of the gallbladder neck or infundibulum by stones or biliary sludge. As the gallbladder attempts to contract in response to cholecystokinin, the obstructed cystic duct prevents the egress of bile from the gallbladder into the biliary system, resulting in acute right upper quadrant pain. In addition to right upper quadrant pain, the characteristic of biliary colic is often described as a colicky or crampy pain which may radiate to the back or shoulder. The pain is generally postprandial in nature and typically resolves within 1-2 hours. Persistence of pain beyond this time should prompt the clinician to suspect acute cholecystitis or other disorders discussed later.

In most circumstances, the patient with symptomatic cholelithiasis will have no abnormalities of their liver function tests or complete blood count. An abdominal ultrasound will reveal the presence of cholelithiasis without gallbladder wall thickening or pericholecystic fluid. The treatment of symptomatic cholelithiasis remains elective cholecystectomy in patients suitable to undergo a general anesthetic.

Laparoscopic cholecystectomy has replaced the open operation as the gold standard for removing the gallbladder. Many studies have documented the improved recovery time, decreased postoperative ileus, and decreased pain along with
improved aesthetics associated with laparoscopy. The most feared complication of laparoscopic cholecystectomy is injury to the common bile duct. The reported incidence of bile duct injuries varies from 0% to 3% depending on the underlying pathology necessitating cholecystectomy, but is generally less than 1% in the setting of symptomatic cholelithiasis. Minor biliary injuries include cystic duct leaks and biliary leaks from the hepatic parenchyma. These injuries may be managed with percutaneous drain placement or endoscopic retrograde cholangiopancreatography (ERCP) to facilitate drainage into the duodenum. Major biliary injuries include clipping or transection of the common hepatic or common bile duct. When identified intraoperatively, these injuries are best managed with immediate repair if a skilled surgeon is available. Those biliary injuries identified in the postoperative setting are best treated with externalization of the bile flow (percutaneous transhepatic biliary drainage) and definitive repair at a later date, generally 2-3 months following the initial injury. In most circumstances, a Roux-en-Y hepaticojejunostomy is required to reconstruct the biliary tree.

Although associated with less morbidity, laparoscopic cholecystectomy does require pneumoperitoneum (insufflation of carbon dioxide gas into the abdomen) and may not be feasible in patients with other comorbid conditions (eg, the morbidly obese, severe congestive heart failure, advanced pulmonary disease, uncontrolled coagulopathy). If operation is required, open cholecystectomy remains the only viable option for these patients.

Following cholecystectomy, almost all patients (95%) with symptomatic cholelithiasis will have no further sequela of biliary diseases.

### Chronic Cholecystitis

Chronic cholecystitis is a term used often synonymously with symptomatic cholelithiasis. It may also be a result of multiple episodes of untreated acute cholecystitis. The gallbladder will become scarred from multiple episodes of inflammation. Pathologic examination will demonstrate Rokitansky-Aschoff sinuses. The patient will usually describe multiple episodes of biliary colic. Ultrasound will demonstrate cholelithiasis and occasionally gallbladder wall thickening (from the scarring).

The treatment of chronic cholecystitis is cholecystectomy. Following cholecystectomy, most patients recover with no adverse effects.

**Table 32-1. Basic definitions.**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholelithiasis</td>
<td>Presence of gallstones in the gallbladder</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>Inflammation of the gallbladder</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>Presence of gallstones in the common bile duct</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>Inflammation (most commonly due to infection) of the bile ducts ascending into the liver</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>Surgical removal of the gallbladder</td>
</tr>
<tr>
<td>Cholecystic</td>
<td>Relating to the gallbladder</td>
</tr>
<tr>
<td>Calculus</td>
<td>Related to the presence of stones</td>
</tr>
<tr>
<td>Acalculous</td>
<td>In absence of stones</td>
</tr>
<tr>
<td>ERCP</td>
<td>Endoscopic retrograde cholangiopancreatography</td>
</tr>
</tbody>
</table>

### ACUTE CHOLECYSTITIS

**ESSENTIALS OF DIAGNOSIS**

- Persistent severe RUQ pain (>4-6 hours).
- RUQ tenderness.
- Fever, leukocytosis.
- Ultrasound evidence of gallstones.

Acute cholecystitis is caused most commonly by obstruction of the cystic duct, resulting in localized edema and inflammation. Biliary cultures of most patients reveal bacteria. Women are three times as likely to develop acute cholecystitis as men. Over 90% of cases of acute cholecystitis are related to gallstones causing obstruction (calculous cholecystitis). The remaining cases are classified as acalculous cholecystitis. Here other comorbid conditions result in gallbladder wall ischemia or biliary stasis.

Acute cholecystitis is defined by the triad of right upper quadrant pain, fever, and leukocytosis. Abdominal ultrasound will demonstrate gallbladder wall thickening (>3 mm) with pericholecystic fluid. Symptoms typically begin after a meal. The pain is similar to, but far more severe, that of symptomatic cholelithiasis. In cases where acalculous cholecystitis is suspected or when ultrasound is inconclusive, radionuclide scanning (ie, hepatobiliary iminodiacetic acid [HIDA]) may be used. Presence of radionuclide in the extrahepatic biliary tree without filling the gallbladder is diagnostic of acute cholecystitis.

The treatment of acute cholecystitis is cholecystectomy. The timing of the operation is a controversial subject matter for general surgeons. Localized edema and subsequent scar
formation after an episode of acute cholecystitis can make laparoscopic cholecystectomy difficult. Traditional teaching has been that cholecystectomy should be performed within 3 or 4 days of onset of symptoms—before myoepithelial changes can occur in the right upper quadrant. The localized edema associated with acute cholecystitis aids with dissection of tissue planes and facilitates cholecystectomy. Compared to delayed cholecystectomy (after 7 days of symptoms), this approach is associated with a decreased conversion rate to open operation (2% vs 30%) and decreased recovery time (12 vs 28 days). Many patients present, however, outside the initial 72-hour window. With each passing day of symptoms, the conversion rate to open operation increases. Many surgeons advocate a course of intravenous and (later) oral antibiotics with a plan to perform cholecystectomy in a delayed fashion approximately 6 weeks following the sentinel event. This delay will allow the scarring in the right upper quadrant to subside allowing for safer and easier dissection during laparoscopy. If the patient has continued pain or recurrence of cholecystitis during this waiting period, laparoscopic cholecystectomy should be attempted immediately. The patient should be counseled regarding the increased probability of conversion to an open operation. Alternatively, patients who are not operative candidates may undergo percutaneous tube cholecystostomy to drain the biliary tree. Percutaneous cholecystostomy serves as a bridge to elective cholecystectomy once the patient has stabilized.

Untreated cholecystitis can lead to gallbladder ischemia, necrosis, or perforation, resulting in biliary leak or fistula formation to surrounding structures. Those undergoing successful immediate cholecystectomy will generally have no further sequela of biliary disease. Consideration must be given for choledocholithiasis and common bile duct injury in a patient presenting with jaundice after cholecystectomy.


**Choledocholithiasis**

Choledocholithiasis or common bile duct stones are present in up to 10% of patients undergoing cholecystectomy. The treatment is cholecystectomy with evaluation of the biliary tree and clearance of all stones within the ductal system. Choledocholithiasis should be suspected in any patient with biliary ductal dilatation seen on imaging, the presence of elevated bilirubin levels (conjugated), elevated alkaline phosphatase levels, or elevated amylase and lipase levels. Patients presenting with choledocholithiasis may develop symptoms related to obstruction of the bile duct, pancreatic duct, or both.

**Gallstone Pancreatitis**

Gallstones, small enough to pass through the biliary tree, may obstruct at the level of the ampulla of Vater. These stones will then cause obstruction of the pancreatic ductal system and resultant pancreatitis. Gallstones are associated with approximately 45%-50% of all cases of pancreatitis in the United States.

Patients presenting with pancreatitis typically have varying degrees of abdominal pain—usually located in the epigastrium or right upper quadrant. The pain may radiate to the back or shoulders. Nausea and vomiting are common. Laboratory studies will reveal elevation of serum lipase and amylase levels. If gallstones are obstructing the bile duct as well, then liver transaminases, alkaline phosphatase, and bilirubin may also be elevated. Although ultrasound is useful to confirm presence of gallstones, CT scanning is useful in delineating the severity of pancreatitis.

The treatment of gallstone pancreatitis is eventual cholecystectomy. As the gallbladder is the source of the stones, cholecystectomy will prevent subsequent episodes of pancreatitis. Cholecystectomy should not be attempted until following the resolution of the pancreatitis. Treatment for pancreatitis involves bowel rest with intravenous hydration. Severe cases of pancreatitis may require ICU admission with cardiovascular and respiratory support. Regardless of the patient’s condition, cholecystectomy should be reserved until after the pancreatitis has resolved. It has been suggested that the morbidity and mortality associated with pancreatitis is improved when patients undergo ERCP within 2 days of onset of symptoms. ERCP may be able to remove an impacted stone and thus allow for pancreatic decompression. This approach is generally considered in patients with moderate or severe pancreatitis.

Consideration as to the presence of a persistent bile duct stone should be made prior to proceeding with cholecystectomy. In most circumstances, normalization of serum lipase, amylase, and liver function tests (if originally elevated) occurs rapidly. In these circumstances, no imaging of the biliary tree is required due to the low probability of a persistent bile duct stone. However, patients with persistent abnormalities of their liver functions, amylase, or lipase should be evaluated for the presence of common bile duct stones. Biliary imaging may be obtained by means of intraoperative cholangiography at the time of cholecystectomy, perioperative ERCP, or magnetic resonance cholangiopancreatography (MRCP). MRCP is least invasive of the modalities but is only
diagnostic. ERCP allows for both visualization and extraction of stones up to 1.5 cm in size. ERCP may be utilized to extract common bile duct stones either antecedent or subsequent to cholecystectomy. Common bile duct stones not amenable to endoscopic removal are generally removed operatively by performing a common bile duct exploration.

The overall long-term outcome of pancreatitis is related to the severity of the disease. Localized morbidity includes pancreatic necrosis, splenic vein thrombosis with gastric varices, hemorrhagic pancreatitis, and pancreatic abscess formation. Systemic morbidity can involve multisystem organ failure or even death.

**Cholangitis**

**ESSENTIALS OF DIAGNOSIS**

- Persistent RUQ pain.
- Jaundice.
- Fever.
- Hypotension, mental status changes (acute suppurative cholangitis).

**Cholangitis** is defined as inflammation of the biliary system. It is most commonly caused by an impacted gallstone at the ampulla of Vater preventing bile drainage into the duodenum, though other etiologies such as extrinsic compression from an adjacent mass or inflammatory process or a primary tumor of the ampulla, duodenum, or bile duct should also be considered. Cholangitis is considered a medical emergency.

Patients with cholangitis may present with Charcot’s triad (fever, right upper quadrant pain, and jaundice) or with Reynolds’ pentad (the addition of hypotension or mental status changes). Laboratory studies will show hyperbilirubinemia and leukocytosis. Ultrasound will likely show biliary ductal dilatation.

With clinical suspicion of cholangitis, patients should immediately be intravaneously resuscitated and given broad-spectrum antibiotics. Biliary decompression should be urgently performed by ERCP. If ERCP fails to resolve the obstruction or is not available, percutaneous transhepatic cholangiography (PTC) with drainage may be performed. In the presence of stones, once biliary decompression has been performed, cholecystectomy should be performed electively following resolution of the cholangitis. In rare circumstances in which percutaneous or endoscopic biliary drainage is not possible, urgent cholecystectomy with common bile duct exploration should be performed.

The mortality associated with cholangitis varies widely and is related to the underlying etiology of the cholangitis. Cholangitis secondary to stones is associated with a low overall mortality provided the patient can be successfully supported through the infectious period. Cholangitis related to an underlying perianpillary malignancy requires careful oncologic consideration prior to surgical intervention. This may require a more involved oncologic resection (such as a pancreaticoduodenectomy or extrahaepatic biliary resection) or palliative care, depending on the extent of the malignancy. In the event of an unresectable perianpillary tumor, a biliary bypass (hepaticojunostomy) may be considered. Most perianpillary malignancies are associated with poor 5-year survival even with complete extirpation of the tumor.

**Gallbladder Polyps**

Gallbladder polyps are present in about 5% of the population and are commonly found incidentally during abdominal ultrasonography. The different types of polyps include cholesterosis, adenomyomatosis, hyperplastic cholecystosis, and adenocarcinomatosis. The goal of surgical management is to identify which polyps are cancerous (adenocarcinoma) or at risk to develop cancer (adenomyomatosis) and select these patients for cholecystectomy.

Unfortunately, short of cholecystectomy, there is currently no way to distinguish among the different types of gallbladder polyps. With the relative safety of laparoscopic cholecystectomy, some advocate cholecystectomy for all gallbladder polyps. This strategy will result in the removal of many benign asymptomatic polyps. Retrospective studies have suggested that young patients (<50 years old) with small asymptomatic polyps (<1cm in size) and without associated gallstones may be observed with serial ultrasound examinations. Patients who have polyps with associated gallstones or are older than 50 years should be referred for cholecystectomy. Polyps larger than 1 cm should also warrant cholecystectomy. In the event of gallbladder cancer in the surgical specimen, the depth of invasion dictates the next course of therapy.

**Gallbladder Cancer**

Patients with gallbladder cancer may have similar presentations to those with symptomatic cholelithiasis or chronic cholecystitis. As most gallbladder cancer presents late in the
disease progression, systemic complaints including gradual weight loss and loss of appetite may also be apparent. Since presentation is often thought to be related to gallstone disease, ultrasound is usually the initial diagnostic modality used. Ultrasound findings of a mass larger than 1 cm, a calcified gallbladder wall, discontinuity of gallbladder wall layers, and loss of interface between the gallbladder wall and the liver should raise suspicion of gallbladder cancer. Computed tomography is useful in these circumstances to delineate anatomic structures for resectability, as well as evidence of metastatic disease.

Presence of para-aortic or peripancreatic lymphadenopathy is deemed unresectable disease. This can be confirmed with endoscopic ultrasound with biopsies. Cancers that are limited to the mucosa or muscular layer of the gallbladder can be treated with cholecystectomy with negative margins alone. Tumors that invade the pericholecystic connective tissue require resection of the gallbladder fossa with en bloc cholecystectomy. Tumors that invade the liver require formal resection of the involved segments. Tumors that invade the cystic duct into the common bile duct also require en bloc extra hepatic biliary resection. Unfortunately, 15%-50% of tumors that penetrate the muscular wall of the gallbladder have nodal disease that will make them unresectable. The 5-year survival of early tumors (those confined to the muscular or mucosal layer) is excellent (90%-100%). The survival for more advanced tumors is measured in terms of weeks or months.


**Choledochal Cyst**

Classically, choledochal cysts are described as a palpable right upper quadrant mass in a young female with jaundice. Most choledochal cysts are described in Asian populations but are increasingly seen in the United States, males, and in older patients. Choledochal cysts are classified by their anatomic location with most being solitary fusiform dilatation of the extrahepatic biliary tree. Their presentation in Western series is similar to symptomatic cholelithiasis. They can be easily seen on ultrasound provided the ultrasonographer evaluates the biliary tree in addition to the gallbladder.

Choledochal cysts are associated with a seventy-fold increased incidence of cholangiocarcinoma, so surgical resection is indicated when discovered. Operative treatment involves resection of the entire extra-hepatic biliary tree, cholecystectomy, and reconstruction with a Roux-en-Y hepaticojejunostomy. Surgical resection is considered curative; a recent study reported no subsequent malignancy over 30 years in patients without cancer at the time of cyst excision.


**Cholangiocarcinoma**

For a variety of reasons, cholangiocarcinomas along with other right upper quadrant malignancies are associated with very poor survival. (1) These lesions often present late and are not amenable to resection. (2) Their biological activity is not well understood and systemic therapy offers little benefit. (3) Operative resection is technically difficult and patients need to be seen in specialized centers.

The vast majority of cholangiocarcinomas present with jaundice, sometimes in the setting of cholangitis. Ultrasound will often show a dilated proximal biliary tree. ERCP and endoscopic ultrasound are useful to delineate the anatomy of the tumor. Preoperative endoscopic brushings are often nondiagnostic and should not be aggressively pursued in patients with resectable disease on cross-sectional imaging. While most proximal cholangiocarcinomas (70%) are not amenable to resection, approximately half of distal tumors may be resected. Resection involves pancreato-duodenectomy for distal tumors whereas cholangiocarcinoma of the proximal system requires an extrahepatic biliary resection with Roux-en-Y hepaticojejunostomy. Five-year survival remains poor even after complete resection (20%-25%). For patients with unresectable disease, survival is again measured in weeks or months.


**Liver Disease**

Samuel C. Matheny, MD, MPH

**Viral Hepatitis**

**Essentials of Diagnosis**

- Variable prodromal signs and symptoms.
- Positive specific viral hepatitis tests.
- Elevation of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Acute viral hepatitis is a worldwide problem, and in the United States alone there are probably between 200,000 and 700,000 cases per year according to the Centers for Disease Control and Prevention (CDC). Over 32% of cases are caused by hepatitis A virus (HAV), 43% by hepatitis B virus (HBV), 21% by hepatitis C virus (HCV), and the remainder are not
identified. Although few deaths (~250) are reported yearly from acute hepatitis, considerable morbidity can result from chronic hepatitis caused by HBV and HCV infections, and mortality from complications can be pronounced for years to come.

1. Hepatitis A

**General Considerations**

Hepatitis A, first identified in 1973, is the prototype for the former diagnosis of infectious hepatitis. Over the past several decades, the incidence of HAV infection has varied considerably, and a high number of cases are unreported. HAV is a very small viral particle that is its own unique genus (hepatovirus).

Most individuals infected worldwide are children. In general, there are four patterns of HAV distribution (high, moderate, low, and very low), which roughly correspond to differing socioeconomic and hygienic conditions. Countries with poor sanitation have the highest rates of infection. Most children younger than 9 years in these countries have evidence of HAV infection. Countries with moderate rates of infection have the highest incidence in later childhood; food and waterborne outbreaks are more common. In countries with low endemicity, the peak age of infection is likely to be at early adulthood, and, in very low endemic countries, outbreaks are uncommon.

HAV is usually transmitted by ingestion of contaminated fecal material of an infected person by a susceptible individual. Contaminated food or water can be the source of infection, but occasionally infection can occur by contamination of different types of raw shellfish from areas contaminated by sewage. The virus can survive 3-10 months in water. Other cases of infection by blood exposures have been reported but are less common. The incubation period for HAV averages 30 days, with a range of 15-50 days.

In countries of low endemicity, persons at greatest risk for infection include travelers to intermediate and high HAV-endemic countries, men who have sex with men (MSM), intravenous drug users, and persons with chronic liver disease, including those who have received transplants. In areas of high endemicity, all young children are at increased risk.

**Prevention**

Currently in the United States, the CDC recommends that certain populations at increased risk be considered for pre-exposure vaccination; these include the groups listed above. In addition, the CDC now recommends universal immunization for all children older than 1 year. The immunization schedule consists of three doses for children and adolescents, and two for adults. In groups with the potential for high risk of exposure, including any adult older than 40, prevaccination testing for prior exposure may be cost-effective. The appropriate test should evaluate the total anti-HAV. Travelers younger than 40 years who receive the vaccine may assume to be protected after receiving the first dose, although the second dose is desired for long-term protection. For certain travelers (older adults and those with underlying medical conditions), immunoglobulin (Ig) may be given in a different site for additional protection within 2 weeks of travel. A combination vaccine with HBV is available for persons older than 18 years who are immunocompetent and is used on the same three-dose schedule as HBV.

Ig or hepatitis A vaccine (if previously unvaccinated) may also be used for postexposure prophylaxis in healthy patients between 12 months and 40 years of age, if given within 14 days, and would most often be used for household or intimate contacts of an infected person, in some institutional settings, or if a common source is identified. For persons with chronic illness, or younger than 12 months or older than 40 years, Ig is preferred.

**Clinical Findings**

**A. Symptoms and Signs**

The symptoms and signs of acute viral hepatitis are quite similar regardless of type and are difficult to distinguish based on clinical findings. The prodrome for viral hepatitis is variable and may be manifested by anorexia, including changes in olfaction and taste, as well as nausea and vomiting, fatigue, malaise, myalgias, headache, photophobia, pharyngitis, cough, coryza, and fever. Dark urine and clay-colored stools may be noticed 1-5 days before jaundice.

Clinical jaundice varies considerably and may range from an anicteric state to rare hepatic coma. In acute HAV infection, jaundice is usually more pronounced in older age groups (ie, 70%-80% in those >14 years) and rare in children younger than 6 years (<10%). Weight loss may also be present, as well as an enlarged liver (70%) and splenomegaly (20%). Spider angiomata may be present without acute liver failure. Patients may also report a loss of desire for cigarette smoking or alcohol.

**B. Laboratory Findings**

Usually, the onset of symptoms coincides with the first evidence of abnormal laboratory values. Acute elevations of ALT and AST are seen, with levels as high as 4000 units or more in some patients. The ALT level is usually higher than the AST. When the bilirubin level is greater than 2.5, jaundice may be obvious. Bilirubin levels may go from 5 to 20, with usually an equal elevation of conjugated and unconjugated forms. The prothrombin time is usually normal. If significantly elevated, it may signal a poor prognosis. The complete blood count may demonstrate a relative neutropenia, lymphopenia, or atypical lymphocytosis. Urobilinogen may be present in urine in the late preicteric stage.

Serum IgM antibody (anti-HAV) is present in the acute phase and usually disappears within 3 months, although occasionally it persists longer. IgG anti-HAV is used to detect past exposure and persists for the lifetime of the patient. The more commonly available test for IgG anti-HAV is the total anti-HAV.
Treatment

Treatment for the most part is symptomatic, with many clinicians prohibiting only alcohol during the acute illness phase. Most patients can be treated at home.

Prognosis

In the vast majority of patients with HAV, the disease resolves uneventfully within 3-6 months. Rarely, fulminant hepatitis may develop, with acute liver failure and high rates of mortality. Rare cases of cholestatic hepatitis, with persistent bilirubin elevations, have also been reported. Some patients develop relapsing hepatitis, in which HAV is reactivated and shed in the stool. Affected patients demonstrate liver function test abnormalities, but virtually all recover completely. HAV does not progress to chronic hepatitis.

2. Hepatitis B

General Considerations

HBV is a double-shelled DNA virus. The outer shell contains the hepatitis B surface (HBsAg). The inner core contains several other particles, including hepatitis core antigen (HBcAg) and hepatitis B early antigen (HBeAg). These antigens and their subsequent antibodies are described in more detail later.

Worldwide, over 400 million people are infected with HBV, but the distribution is quite varied. More than 45% of the global population live in areas of high incidence (infections in >8% of population). There, the lifetime risk of infection is over 60%, and early childhood infections are very common. Intermediate risk areas (infections in 2%-7% of population) represent 43% of the global population. The lifetime risk of infection in these areas is between 20% and 60%, and infections occur in various age groups. In low-risk areas (infections in <2%), which represent about 12% of the global population, the lifetime risk of infection is less than 20% and is usually limited to specific adult risk groups.

In the United States, HBV is normally a disease of young adults. The largest numbers of cases are reported in adults between the ages of 20 and 39 years, but many cases in younger age groups may be asymptomatic and go unreported. Of the specific risk groups in the United States, over 50% in recent studies are those with sexual risk factors (more than one sex partner in the past 6 months, sexual relations with an infected person, or MSM transmission). Over 15% had a history of injection drug use, and 4% had other risk factors such as a household contact with HBV or a health care exposure. The mode of transmission can thus be sexual, parenteral, or perinatal, by contact of the infant’s mucous membranes with maternal infected blood at delivery.

Body fluids with the highest degree of concentration of HBV are blood, serum, and wound exudates. Moderate concentrations are found in semen, vaginal fluid, and saliva, and low or nondetectable amounts are found in urine, feces, sweat, tears, or breast milk. Saliva can be implicated in transmission through bites, but not by kissing.

The average incubation period for HBV is between 60 and 90 days, with a range of 45-180 days. Although the incidence of jaundice increases with age (<10% of children <5 years demonstrate icterus compared with 30%-50% of those >35 years), the likelihood of chronic infection with HBV is greater when infection is contracted at a younger age. Between 30% and 90% of all children who contract HBV before the age of 5 years develop chronic disease compared with 2%-10% of those older than 35 years.

Prevention

Current immunization recommendations in the United States call for routine immunization of all infants, children, adolescents, and adults in high-risk groups. Acknowledgment of a specific risk factor is not a requirement for immunizations. These recommendations include immunizing all children at birth, 1, and 6 months. Additionally, all high-risk groups should be screened, as well as all pregnant women. Prevaccination testing of patients in low-risk areas is probably not necessary, but in high-risk groups, this may be cost-effective. As illustrated in the first test scenario of Table 32-2, a negative HBsAg titer and a negative anti-HBs titer are evidence of susceptibility to HBV.

Table 32-2. Interpretation of the hepatitis B panel.

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>HBSAg</td>
<td>Positive</td>
<td>Immune due to natural factors</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Positive</td>
<td>Immune due to hepatitis B vaccination</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Positive</td>
<td>Acutely infected</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>IgM anti-HBc</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Positive</td>
<td>Chroniclly infected</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>IgM anti-HBc</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td>Four interpretations possible identified as carriers</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

*(1) May be recovering from acute HBV infection. (2) May be distinctly immune and the test is not sensitive enough to detect very low levels of anti-HBs in serum. (3) May be susceptible with a false-positive anti-HBc. (4) May be an undetectable level of HBsAg present in the serum and the person is actually a carrier.
The vaccine contains components of HBsAg. Pretesting with anti-HB core antibody (anti-HBc) is probably the single best test, because it would identify those who are infected and those who have been exposed. Posttesting for vaccine is not usually recommended, except for individuals who may have difficulty mounting an immune response (eg, immunocompromised patients). In these patients, the HB surface antibody (anti-HBs) would be the appropriate test. Some authorities recommend revaccinating high-risk individuals if titer levels have fallen below 10 IU/L after 5-10 years, or if they have failed to mount an appropriate immune response with the standard dosing and schedule.

Children born to women of unknown hepatitis B status should receive a first dose of hepatitis B vaccine at birth and hepatitis B immune globulin (HBIG) within 7 days of birth if maternal blood is positive. Repeat testing of all infants born to HBV-infected mothers should be performed at 9-15 months with HBsAg and anti-HBs. Infants born to HBV-infected mothers should receive both the first dose of hepatitis B vaccine at birth as well as 0.5 mL of HBIG in separate sites within 12 hours after birth. Recommendations for postexposure prophylaxis of HBV can be reviewed in the current CDC recommendations.

**Clinical Findings**

Acute infection may range from an asymptomatic infection to cholestatic hepatitis to fulminant hepatic failure. HBsAg and other markers usually become positive about 6 weeks after infection and remain positive into the clinical signs of illness. Other biochemical abnormalities begin to show abnormalities in the prodromal phase and may persist several months, even with a resolving disease process. Anti-HB core IgM becomes positive early, with onset of symptoms, and both anti-HB core IgM and anti-HB core IgG may persist for many months or years. Anti-HBs is the last antibody to appear and may indicate resolving infection. The presence of HBeAg indicates active viral replication and increased infectivity (Figure 32-1). Liver function tests should be obtained early in the course of infection, and evidence of prolonged prothrombin time (>1.5 INR) should raise concern for hepatic failure. Patients who remain chronically infected may demonstrate HBsAg and HBeAg for at least 6 months, with a usual trend in liver function tests toward normal levels, although results may remain persistently elevated (Figure 32-2). Extrahepatic manifestations of HBV infection may occur and include serum sickness, polyarteritis nodosa, and membranoproliferative glomerulonephritis.

**Complications**

Complications of chronic infection may include progression to cirrhosis and hepatocellular carcinoma (HCC). Patients with active viral replication are at highest risk of chronic disease, with 15%-20% developing progressive disease over a 5-year period. Continued positivity for HBeAg is associated with an increased risk of HCC. Most patients who are chronically infected remain HBsAg positive for their lifetime. There is no general agreement concerning the appropriate screening for patients with chronic infection for HCC. Some experts would not screen carriers if all laboratory tests are normal but would screen with ultrasonography and α-fetoprotein for evidence of chronic active hepatitis every 2-3 years, and more frequently in patients with cirrhosis. It appears that the incidence of progression of disease is greater in countries with high endemicity, and clinicians in these countries screen as frequently as every 6 months.

![Figure 32-1.](image-url) Acute hepatitis B virus infection with recovery.
Treatment for chronic disease depends on evidence of viral activity, HBeAg status, HIV and HCV comorbidity, histologic evidence of liver injury, and elevated liver function tests. Currently approved treatment modalities include interferon-alfa, lamivudine, telbivudine, adefovir, tenofovir, and entecavir. Other new antiviral agents are currently being tested. Sensitive tests for determination of response to therapy, such as covalently closed circuit (ccc) DNA and others may be more readily available in the future.

3. Hepatitis C

General Considerations

HCV has become the most common blood-borne infection as well as the leading cause of chronic liver disease and subsequently, liver transplantation in the United States. Worldwide, more than 180 million people are infected, but the infection rates vary considerably. In the United States, it is estimated that around 4 million people may be infected with HCV; it is the main cause of death from liver disease. The responsible virus is an RNA virus of the Flaviviridae family. Six major genotypes, numbered 1 through 6, are known, with additional subtypes. There are varying distributions of these genotypes, and they may affect the progression of disease and the response to treatment regimens.

HCV is spread primarily through percutaneous exposure to blood. Since 1992, all donated blood has been screened for HCV. Intravenous drug use is responsible for over 50% of new cases. Within 1-3 months after a first incident of needle sharing, 50%-60% of intravenous drug users are infected. Other risk factors include use of intranasal cocaine, hemodialysis, tattooing (debatable), and vertical transmission, which is rare. Breast-feeding carries a low risk of transmission. Sexual transmission is uncertain but is probably 1%-3% over the lifetime of a monogamous couple. Health care workers are at particular risk following a percutaneous exposure (1.8% average incidence).

Prevention

No immunizations are currently available for HCV infections. Prevention consists mainly of reduction of risk factors, including screening of blood and blood products, caution to prevent percutaneous injuries, and reduction in intravenous drug use.

Clinical Findings

A. Symptoms and Signs

1. Acute hepatitis—The incubation period for HCV varies between 2 and 26 weeks, but most commonly is 6-7 weeks. Most patients with HCV are asymptomatic at the time of infection. However, over 20% of all recognized cases of acute hepatitis in the United States are caused by HCV, and as many as 30% of adults who are infected may present with jaundice. Acute, fulminant hepatic failure is rare.

2. Chronic hepatitis—in contrast to HAV and HBV, most people infected with HCV (85%) develop a chronic infection. The
incidence of significant liver disease is 20%-30% for cirrhosis and 4% for liver failure; over 1%-4% of patients with chronic infection develop HCC annually, or 11%-19% over 4-11 years in one study. It appears that certain risk factors increase the likelihood of progression to serious disease. These include increased alcohol intake, age greater than 40 years, HIV coinfection, and possibly male gender and other liver coinfections.

Extrahepatic manifestations of chronic infection are fairly common and are similar to those of HBV, including autoimmune conditions and renal conditions such as membranous glomerulonephritis.

B. Laboratory Findings

Patients should be tested with both an approved anti-HCV screening test and a quantitative reverse transcriptase polymerase chain reaction (RT-PCR) for HCV RNA. (Diagnosis of acute infection may require the use of the RT-PCR, because anti-HCV may not be positive for several weeks.) All patients with HCV infection should have HCV genotyping performed prior to therapy in order to predict a therapeutic response as well as duration of therapy. The appropriate role of liver biopsy in decisions concerning therapy is in a state of flux, particularly regarding treatment for genotype 1 patients. Consultation with a liver specialist should be considered to ascertain the value of this additional information that a liver biopsy would provide.

Treatment

Treatment for both acute and chronic HCV has undergone significant strides in the past few years. A recent study documents the conversion of a significant number of patients to negative serology when treated in the acute phase of infection. Chronic HCV treated with a combination of pegylated interferon alfa 2b (PEG-IFN) or 2a and ribavirin is the current standard of care in the United States, although poorer responses are seen in patients with genotype 1, which is most common in this country. New treatments which involve targeting HCV-encoded proteins or host-encoded proteins are currently under investigation.

It is important to immunize patients with chronic HCV infection for HAV, because the incidence of fulminant hepatitis A has been shown to be significantly increased in this population. Patients infected with HCV should also abstain from alcohol. It has also been recommended that HCV-infected individuals be vaccinated for HBV owing to the poor prognosis of coinfected individuals. Chronic hepatitis C can also progress to cirrhosis and HCC and appropriate screening measures as discussed under Hepatitis B apply to hepatitis C-infected patients as well.

4. Other Types of Infectious Hepatitis

Over 97% of the viral hepatitis in the United States is either A, B, or C. Other types of viral hepatitis occur much less frequently, although worldwide, they may be more important.

Hepatitis D

Hepatitis D virus (HDV) is a virus that can replicate only in the presence of HBV infection. HDV infection can occur either as a coinfection with HBV or as a superinfection in a chronically infected individual with HBV. Although coinfection can produce more severe acute disease, a superinfection poses the risk of more significant chronic disease, with 70%-80% of patients developing cirrhosis. The mode of transmission is most commonly percutaneous. The only tests commercially available in the United States are IgG–anti-HDV. Prevention of HDV depends on prevention for HBV. There are no products currently available to prevent HDV infection in patients infected with HBV.

Hepatitis E

Hepatitis E virus (HEV) is the most common cause of enterically transmitted non-A, non-B hepatitis. Acute HEV infection is similar to other forms of viral hepatitis; no chronic form is known. Severity of illness increases with age, and for reasons that are unclear, case fatality rates are particularly high in pregnant women. Most cases of HEV reported in the United States have occurred in travelers returning from areas of high endemicity. In certain areas of the world (Mexico, North Africa, the Middle East, and Asia) epidemics of HEV may be common. Prevention includes avoidance of drinking water and other beverages of unknown purity, uncooked shellfish, and uncooked vegetables and fruits. No vaccines are currently available although one is in trial, and pooled gamma globulin does not appear to be effective.

Hepatitis F & G

The existence of a hepatitis F has been debated, and very rare cases of another newly identified virus have been reported, labeled hepatitis G. Very little is currently known of transmission or patterns of illness, although the infectivity level in the United States may be significant.

5. Acute Hepatitis: A Cost-Effective Approach

Because the vast majority of cases of viral hepatitis are caused by HAV, HBV, or HCV, tests to determine the precise etiology are necessary for appropriate primary and secondary prevention for the patient, as well as potential for therapy. Figure 32-3 outlines one cost-effective approach. If these tests fail to indicate a diagnosis, the etiology may be due to less frequent causes of viral hepatitis such as Epstein-Barr virus, in which jaundice can rarely accompany infectious mononucleosis; cytomegalovirus or herpesvirus in immunocompromised patients; or other nonviral etiologies, such as alcoholic hepatitis, drug toxicity, Wilson disease, or an autoimmune hepatitis.


Weinbaum CM et al; Centers for Disease Control and Prevention (CDC): recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep 2008 September 19;57(RR-8):1-20 [PMID: 18802412]

**Web Sites**

American Liver Foundation, Liver Update: Function and Disease (excellent survey of issues pertaining to hepatitis):http://www.liverfoundation.org

Centers for Disease Control National Center for Infectious Diseases, hepatitis information (references for immunization and testing, as well as patient information in several languages): http://www.cdc.gov/ncidod/diseases/hepatitis


**ALCOHOLIC LIVER DISEASE**

**ESSENTIALS OF DIAGNOSIS**

- History of alcohol use.
- Mildly elevated serum ALT and AST.
- Variable clinical signs (may include jaundice, hepatomegaly).

**General Considerations**

Alcoholic liver disease includes several different disease entities, spanning a large clinical spectrum. These diseases range from the syndrome of acute fatty liver to severe liver damage as manifested by cirrhosis. **Fatty liver** is usually asymptomatic except for occasional hepatomegaly and is the histologic result of excessive use of alcohol over a several-day period. In **perivenular fibrosis**, fibrous tissue is...
deposited in the central areas of the liver, particularly the central veins; this is an indication that the individual may then rapidly progress to more severe forms of liver disease. Patients can progress from this stage directly to cirrhosis. **Alcoholic hepatitis** is a condition in which necrosis of hepatic cells occurs as part of an inflammatory response, which includes polymorphonuclear cells, along with evidence of fibrosis. **Cirrhosis** may result from continued progression of disease from alcoholic hepatitis or may occur without evidence of prior alcoholic hepatitis. Cirrhosis is characterized by distortion of the liver structure, with bands of connective tissue forming between portal and central zones. Changes in hepatic blood circulation may also occur, resulting in portal hypertension. Additionally, evidence of abnormal fat metabolism, inflammation, and cholestasis may be seen. Progression to **hepatocellular carcinoma (HCC)** may also occur, although the exact risk of cirrhosis itself in the progression to HCC is not clear.

It is known that women are more likely than men to develop alcoholic liver disease, although the reasons for this phenomenon are only now being clarified. There may be additional genetic factors, most notably in specific enzyme systems, such as the metabolism of tumor necrosis factor (TNF) and alcohol-metabolizing systems, which affect the development of disease. Concomitant disease, such as HCV infection, is also a risk factor. Other factors (eg, obesity) may also play a role in the progression of disease.

**Clinical Findings**

**A. Symptoms and Signs**

A history of drinking alcohol in excess of 80 g/day (six to eight drinks) is seen with the development of more advanced forms of the disease, although there is considerable individual variation. Numerous questionnaires have been designed for detection of excessive drinking, but the CAGE questionnaire (Cut down, Annoyed by criticism, Guilty about drinking, Eye-opener drinks) is probably the most useful.

Clinical findings may be limited at this stage to occasional hepatomegaly. Patients with alcoholic hepatitis may present with classic signs and symptoms of acute hepatitis, including weight loss, anorexia, fatigue, nausea, and vomiting. Hepatomegaly may be evident, as well as other signs of more advanced disease, such as cirrhosis, because the development of cirrhosis may occur concomitant with a new episode of alcoholic hepatitis. These signs include jaundice, splenomegaly, ascites, spider angiomas, and signs of other organ damage secondary to alcoholism (eg, dementia, cardiomyopathy, or peripheral neuropathy).

**B. Laboratory Findings**

Various commercially available laboratory tests have been used to detect excessive alcohol intake in the early stages. The sensitivity and specificity of these tests vary. Liver function tests for elevations of AST, ALT, and GGT are frequently used. Elevation of mean corpuscular volume (MCV) has also been noted in patients with early-stage disease.

Transaminase levels are usually only mildly elevated in pure alcoholic hepatitis unless other disease processes, such as concomitant viral hepatitis, or acetaminophen ingestion are present (Figure 32-4). AST elevation is usually greater than ALT. Elevated prothrombin time and bilirubin levels have a significant negative prognostic indication. *The presence of jaundice may have special significance in any actively drinking person and should be carefully evaluated.* Several instruments have been used for evaluation of
severity, but the most common is the Maddrey discriminant function (MDF):

\[
\text{MDF} = 4.6 \times (\text{prothrombin time in seconds} - \text{control}) + \text{serum bilirubin (mg/dL})
\]

A score higher than 32 is indicative of high risk of death.

### Treatment

Abstinence from alcohol is essential, and is probably the most important of all therapies. Recovery from the acute episode is associated with an 80% 7-year survival rate in patients who can abstain from alcohol versus 50% survival in those who continue drinking. The use of naltrexone or acamprosate in conjunction with counseling and support groups to prevent recidivism should be considered.

Initial treatment of the acutely ill patient centers on ensuring adequate volume replacement, with concern for the ability to handle normal saline. Diuretics should be avoided. Adequate nutrition should be given, parenterally if necessary. There is no indication that avoidance of protein is helpful in patients with encephalopathy. Broad-spectrum antibiotics should be considered early in the treatment course. Many patients develop spontaneous peritonitis, pneumonia, or cellulitis, which should be treated aggressively. Corticosteroids have been suggested as beneficial, but considerable debate still ensues as to whether there is any benefit to survival, although current recommendations are that patients with severe disease (MDF ≥32) with or without encephalopathy and without contraindications for steroid use should be considered for a 4-week course of prednisone followed by a 2-week taper. Pentoxifylline, which modifies tumor necrosis factor alpha (TNF-α) may also be considered, especially if steroids are contraindicated.

Liver transplantation may be an option. Alcoholic liver disease is currently the second most common reason for liver transplantation in the United States. To be considered for transplantation, patients should not have active alcoholic hepatitis, should have remained sober for more than 6 months, and should have had addictive treatment. The prognosis is excellent if relapse from drinking can be avoided. Relapse occurs in 15%-30% of patients.

Other treatment methodologies in various stages of testing include other TNF-α modifiers; antioxidant therapy with agents such as S-adenosyl-L-methionine (SAM-e), silymarin, or vitamin E; antifibrotics such as polyethylene glycol-als (PPC); or other medications such as colchicine. Further studies are needed before these therapies can be recommended.

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1. **Nonalcoholic Fatty Liver Disease**

A new condition described around 1980, nonalcoholic fatty liver disease (NAFLD) encompasses a wide clinical spectrum of patients whose liver histology is similar to patients with alcohol-induced hepatitis, but without the requisite history. Women are affected more frequently than men. Many of these patients progress to cirrhosis. NAFLD is now the most common liver disease in the United States, occurring in up to 20% of the population in some studies. This condition is common in obese patients, as well as in patients with type 2 diabetes mellitus. It may be a part of the syndrome X, which includes obesity, diabetes mellitus, dyslipidemia, and hypertension. Clinical features include hepatomegaly (75%) and splenomegaly (25%), but no pathognomonic laboratory markers. Elevations of ALT and AST may be up to five times normal, with the AST:ALT ratio less than 1. Evidence of steatosis can be seen on hepatic ultrasonography. Treatment includes weight reduction, treatment of diabetes, and lipid disorders. There is no current evidence of the efficacy of specific pharmacologic therapy.

2. **Wilson Disease**

Wilson disease, which is characterized by hepatolenticular degeneration, is caused by abnormal metabolism of copper. It is inherited in an autosomal-recessive pattern and has a prevalence in the general population of about 1 in 30,000. Although patients in asymptomatic stages may manifest only transaminasemia or Kayser-Fleisher rings (golden-greenish granular deposits in the limbus), hepatomegaly or splenomegaly may already be present. In most symptomatic patients (96%), the serum ceruloplasmin level is less than 20 mg/dL. In patients with more advanced disease, symptoms of acute hepatitis or cirrhosis may be present. Neurologic signs include dysarthria, tremors, abnormal movements, and psychological disturbances. HCC may occur in patients with advanced disease. Treatment includes penicillamine, trientine, or zinc salts.

3. **Hemochromatosis**

An inborn error of iron metabolism leading to increased iron absorption from the diet, hemochromatosis is associated with diabetes, bronze skin pigmentation, hepatomegaly, loss of libido, and arthropathy. Patients may also show signs of cardiac or endocrine disorders. Symptoms usually first manifest between 40 and 60 years of age, and men are 10 times more likely than women to be affected. Hemochromatosis is the most common inherited liver disease in people of European descent. Physical signs include hepatomegaly (95% of symptomatic patients), which precedes abnormal liver function tests. Cardiac involvement includes congestive heart failure and arrhythmias. Many patients have cirrhosis by the time they are symptomatic.

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(50%-70%), 20% have fibrosis, and 10%-20% have neither. HCC is very common in patients with cirrhosis (30%) and is now the most common cause of death. Laboratory findings include elevated serum iron concentration, increased serum ferritin, and increased transferrin saturation. Treatment involves treatment of the complications of hemochromatosis, removal of excess iron by phlebotomy, and, in patients with cirrhosis, surveillance for HCC and treatment of hepatic and cardiac failure.

4. Autoimmune Hepatitis
Autoimmune hepatitis is a hepatocellular inflammatory disease of unknown etiology. Diagnosis is based on histologic examination, hypergammaglobulinemia, and presence of serum autoantibodies. The condition may be difficult to discern from other causes of chronic liver disease, which need to be excluded in making the diagnosis. Immunoassay tests that are essential for diagnosis are assays for antinuclear antibodies (ANA), smooth muscle antibodies (SMA), and antibodies to liver and kidney microsome type 1 (anti-LKM1), as well as perinuclear antineutrophil cytoplasmic antibodies (pANCA).

5. Drug-Induced Liver Disease
More than 600 drugs or other medicinals have been implicated in liver disease. Worldwide, drug-induced liver disease represents about 3% of all adverse drug reactions; in the United States, more than 20% of cases of jaundice in the elderly are caused by drugs. Acetaminophen and other drugs account for 25%-40% of fulminant hepatic failure. Diagnosis is based on the discovery of abnormalities in hepatic enzymes or the development of a hepatitis-like syndrome or jaundice. Most cases occur within 1 week to 3 months of exposure, and symptoms rapidly subside after cessation of the drug, returning to normal within 4 weeks of acute hepatocellular injury. Hepatic damage may manifest as acute hepatocellular injury (isoniazid, acetaminophen), cholestatic injury (contraceptive steroids, chlorpromazine), granulomatous hepatitis (allopurinol, phenylbutazone), chronic hepatitis (methotrexate), vascular injury (herbal tea preparations with toxic plant alkaloids), or neoplastic lesions (oral contraceptive steroids).

Statins, on the other hand, are widely used and can commonly cause mild liver enzyme elevations, but mild elevations of ALT or AST (<3 times the upper limit of normal) do not appear to contribute to liver toxicity.

6. Primary Biliary Cirrhosis
This autoimmune disease of uncertain etiology is manifested by inflammation and destruction of interlobular and septal bile ducts, which can cause chronic cholestasis and biliary cirrhosis. It is predominantly a disease of middle-aged women (female-to-male ratio of 9:1) and is particularly prevalent in northern Europe. The condition may be diagnosed on routine testing or be suspected in women with symptoms of fatigue or pruritus, or in susceptible individuals with elevated serum alkaline phosphatase, cholesterol, and IgM levels. Antimitochondrial antibodies are frequently found. Ursodeoxycholic acid is the only therapy currently available, although some patients may benefit from liver transplantation.

7. Hepatic Tumors & Cysts
HCC is the most common malignant tumor of the liver; it is the fifth most common cancer in men and the eighth most common in women. Incidence increases with age, but the mean age in ethnic Chinese and black African populations is lower. Signs of worsening cirrhosis may alert the clinician to consider HCC, but, in many cases, the onset is subtle. There are no specific hepatic function tests to detect HCC, but elevated serum tumor markers, most notably α-fetoprotein, are useful. Ultrasonography can detect the majority of HCC but may not distinguish it from other solid lesions. CT and MRI are also helpful in making the diagnosis. Risk factors for HCC include HBV, HCV, all etiologic forms of cirrhosis, ingestion of foods with aflatoxin B1, and smoking. In these patients, ultrasonography and α-fetoprotein measurements every 4-6 months are recommended. In moderate-risk patients (ie, with later-onset HBV), measurement of α-fetoprotein every 6 months and annual ultrasound study are suggested.

8. Benign Tumors
Benign tumors include hepatocellular adenomas, which have become more common with the use of oral contraceptive steroids, and cavernous hemangiomas, which may occur with pregnancy or oral contraceptive steroid use and are the most common benign tumor of the liver.

9. Liver Abscesses
Liver abscesses can be the result of infections of the biliary tract or can have an extrahepatic source such as diverticulitis or inflammatory bowel disease. In about 40% of cases, no source of infection is found. The most common organisms are Escherichia coli, Klebsiella, Proteus, Pseudomonas, and Streptococcus species. Amoebic liver abscesses are the most common extraintestinal manifestation of amebiasis, which occurs in over 10% of the world’s population and is most prevalent in the United States in young Hispanic adults. Amoebic abscesses may have an acute presentation, with symptoms present for several weeks; few patients report typical intestinal symptoms such as diarrhea. Ultrasonography or CT scans with serologic tests such as enzyme-linked immunosorbent assay (ELISA) or indirect fluorescent antibody tests help confirm the diagnosis.
**Acute Pancreatitis**

**ESSENTIALS OF DIAGNOSIS**

- Sudden, severe, abdominal pain in epigastric area, with frequent radiation to the back.
- Elevated serum amylase and lipase.
- Elevated ALT (biliary pancreatitis).
- Evidence of etiology on ultrasound (biliary causes) or CT and MRI (other causes).

**General Considerations**

Hospital admissions for acute pancreatitis are fairly frequent, and the most common causes vary with the age and sex of the patient. In the United States, gallstones and alcohol abuse are the most frequent etiologies (20%-30%), but infectious causes such as mumps virus or parasitic disease should be considered, as well as medications, tumors, trauma, and metabolic conditions. About 20% of cases are idiopathic. It is important to determine the etiology of pancreatitis, as early recognition of acute biliary pancreatitis in particular may be important in selecting the appropriate therapeutic approach.

A more detailed discussion of gallstone pancreatitis appears earlier in this chapter.

**Clinical Findings**

**A. Symptoms and Signs**

Abdominal pain—usually epigastric, which may radiate to the back—is the common presenting sign. However, the pain may not be significant, and some cases of acute pancreatitis are missed or diagnosed after more significant complications have occurred. Abdominal tenderness ranging from rigidity to mild tenderness may be present. Lack of a specific diagnostic test may affect the accuracy of an early diagnosis.

**B. Laboratory Findings**

Useful laboratory tests include serum amylase (elevated 3-5 times above normal), serum lipase (more than twice normal), and, for determining the etiology, liver function tests, especially ALT. Serum amylases that are significantly elevated in the presence of epigastric pain are strong indicators of pancreatitis. However, amylase clears rapidly from the blood and levels may be normal even in patients with severe pancreatitis. A urine dip-stick test for trypsinogen-2 may also be useful. The triglyceride levels should be checked, as well as calcium in an attempt to identify pancreatitis associated with hyperlipemia and hyperparathyroidism.

**C. Prognostic Tests**

Over 20% of patients have a severe case of pancreatitis, and of these a significant number die. It is therefore important to accurately stage the severity of the illness and treat accordingly. Attempts to quantify severity of disease have led to certain scoring criteria, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score (>7 on admission is indicative of severe illness), or the Ranson or Glasgow scores. All are complicated and have varying degrees of sensitivity and specificity. Peritoneal lavage has also been used, but it is difficult to justify in patients with mild symptoms. C-reactive protein scores that exceed 150 mg/L in the first 48 hours, interleukin-6 values greater than 400 pg/mL, and interleukin-8 values greater than 100 pg/mL on admission have also been suggested as indicators of severe pancreatitis. Other prognostic tests that may indicate severe illness include the following: urine trypsinogen activation peptide (TAP) greater than 35 nmol/L, urine trypsinogen-2 greater than 2000 μg/L, and polymorphonuclear elastase (PMN-e) greater than 300 μg/L, all measured within the first 24 hours of hospitalization.

**D. Imaging Studies**

Although ultrasonography is helpful in identifying the etiology of pancreatitis, it has limited value in staging the severity of disease. Contrast-enhanced CT is the most common currently available imaging technique for staging the severity of pancreatitis and can determine the presence of glandular enlargement, intra- and extrapancreatic fluid collections, inflammation, necrosis, and abscesses. This study may not be necessary for patients with mild disease. MRCP may be as accurate as and has some advantages over contrast-enhanced CT in certain patients.

**Complications**

Complications include organ failure, cardiovascular collapse, and fluid collections around the pancreas. The latter may be asymptomatic or they may enlarge, causing pain, fever, and infection. Pancreatic pseudocysts may occur in patients with very high amylase levels and obstruction of the pancreatic duct. Pancreatic necrosis may also occur and can be fatal. Infection of
necrotic tissue should be suspected in patients with unexpected deterioration, fever, and leukocytosis, and confirmed by CT scan and fine-needle aspiration. Sterile necrosis should probably be managed nonoperatively unless progressive deterioration occurs. Septic necrosis usually requires surgical debridement.

**Treatment**

Patients who have the potential to develop severe pancreatitis, or who already have severe pain, dehydration, or vomiting, should be hospitalized and their hydration needs monitored closely. These patients should receive nothing by mouth and should be given intravenous pain medication. Patients should be monitored carefully to assess adequate renal function, because renal failure is a major cause of morbidity and mortality. Signs of worsening condition include rising hematocrit, tachycardia, and lack of symptom improvement in 48 hours.

Nutritional treatment has evolved in recent years, but areas of controversy remain. Increasing evidence indicates that in cases of mild pancreatitis, there is no benefit to nasogastric suction, and patients who are not vomiting may continue oral fluids or resume oral fluids after the first week. There is also growing evidence that in severe pancreatitis, early enteral feeding within the first week may lower endotoxin absorption and reduce other complications. If patients cannot absorb adequate quantities via the enteric route, then parenteral feeding may be necessary.

The use of antibiotics is also controversial. Prophylactic antibiotics have been used in severe pancreatitis, but some concern exists that they may predispose patients to fungal infections. General consensus is to use antibiotics, preferably broad-spectrum agents, for severe pancreatitis and for as brief a period as possible (ie, <7 days).


**ESSENTIALS OF DIAGNOSIS**

- Anorexia, jaundice, weight loss, epigastric pain radiating to back, dark urine, and light stools.
- Spiral CT of the abdomen or endoscopic ultrasonography showing evidence of tumor.
- CA 19-9 serum tumor marker.

**General Considerations**

Although pancreatic cancer is diagnosed in only 30,000 patients each year in the United States, it is the fourth most common cause of death from cancer and the second most common gastrointestinal malignancy. Pancreatic cancer has a very poor prognosis: over 80% of patients die within the first year, and the 5-year survival rate is less than 4%. In the vast majority of patients, the cancer is discovered at too late a stage to benefit from resection, and the response to chemotherapy is very poor. Over 90% of pancreatic cancers are ductal adenocarcinoma.

Cigarette smoking is the major risk factor established to date. Diet may also be a factor, with high intake of fat or meat and obesity associated with an increased risk, and fruits, vegetables, and exercise being protective. Likewise, a history of chronic pancreatitis is considered a risk factor, along with surgery for peptic ulcer disease, hereditary pancreatitis, and some genetic mutations (eg, BRCA2, associated with hereditary breast cancer). No guidelines currently exist regarding screening of the general population for pancreatic cancer, although some experts feel that patients with a family history of hereditary pancreatitis should be screened.

**Clinical Findings**

**A. Symptoms and Signs**

The clinical presentation of pancreatic cancer can vary widely; tumors that occur in the head of the pancreas (two-thirds of all pancreatic cancer) may produce early signs of obstructive jaundice. Tumors in the body and tail of the pancreas may grow quite large and cause fewer signs of obstruction. Symptoms more likely to be associated with pancreatic cancer include abdominal pain, jaundice, dark urine, light-colored stools, and weight loss. Pain may be worse when the patient is lying flat or eating. Other physical signs associated with pancreatic cancer include Courvoisier sign (palpable, nontender gallbladder in a patient with jaundice).

**B. Laboratory Findings**

Laboratory evaluation should include liver function tests. The serum tumor antigen CA 19-9 may be useful in confirming a diagnosis but is not an appropriate screening tool. Other markers such as human chorionic gonadotropin (β-hCG) and CA 72-4 are under consideration.

**C. Imaging Studies**

There is some debate as to the best imaging study. Dual-phase spiral CT with a pancreatic protocol has a high rate of sensitivity and can also assist in staging of the tumor, which is important for clinical management. Endoscopic ultrasonography may become the most accurate test for diagnosis.
Treatment

Because the only hope for a cure is surgical resection, staging of pancreatic tumors is important for management. The difficulty lies in identifying the small fraction of patients who will benefit from surgery from those who will not—patients with metastatic disease who would otherwise be subjected to unnecessary invasive procedures and the resultant increased morbidity and mortality.

For patients with metastatic disease, chemotherapy and palliative care should be offered; surgery is avoided. Patients with advanced local disease but no metastases may benefit from radiotherapy and chemotherapy, and those without invasion or metastases may be candidates for resection. Even with resection, the outlook is poor (5-year survival rates of <25%). Radiation therapy may be useful in some patients with localized but nonresectable tumors, and chemotherapy (5-fluorouracil and gemcitabine) has some limited success.

Pain management can be a significant problem, and various modalities may need to be utilized. Biliary decompression may be required for jaundice.

Vaginal Bleeding

Patricia Evans, MD, MA

General Considerations
Abnormal bleeding affects up to 30% of women at some time during their lives. Evaluating vaginal bleeding involves an examination of the patient’s menstrual cycle. The normal menstrual cycle is generally 21-35 days in length with a menstrual flow lasting 2-7 days and a total menstrual blood loss of 20-60 mL. During the normal menstrual cycle the endometrium is exposed initially to estrogen, followed by ovulation and production of progesterone as well as estrogen, and finally the withdrawal of estrogen and progesterone causing menstruation. Different diseases are associated with certain patterns of vaginal bleeding, although there is a wide variation in presentation within each. Common terminology used to discuss vaginal bleeding includes menorrhagia, metrorrhagia, menometrorrhagia, hypermenorrhea, polymenorrhea, and oligomenorrhea. The bleeding patterns associated with each term are listed in Table 33-1.

Throughout their lifetimes there are normal changes in most women’s menstrual patterns. Just as anovulation is common during the years following menarche, the perimenopausal patient usually experiences changes in her menstrual cycle related to decreasing, irregular anovulation. Although age plays an important role in constructing a differential diagnosis in a patient presenting with vaginal bleeding, many of the causes can occur in any adult woman.


Clinical Findings
A. Symptoms and Signs
1. History—Taking a history of a patient presenting with vaginal bleeding should begin with an exploration of the patient’s usual bleeding pattern. The physician should try to establish whether the patient’s pattern is cyclic or anovulatory. If the patient menstruates every 21-35 days her cycle is consistent with an ovulatory pattern of bleeding. To confirm ovulation patients can check their basal body temperature, cervical mucus, and luteinizing hormone (LH) levels. Basal body temperature can be checked using a basal body temperature thermometer, which allows for a precise measurement of the patient’s temperature within a narrower range than a standard thermometer. The patient takes her temperature orally as soon as she awakens in the morning and records it on a chart. After ovulation the ovary secretes an increased amount of progesterone, causing an increase in temperature of approximately 0.5°F over the baseline temperature in the follicular phase. The luteal phase is often accompanied by an elevation of temperature that lasts 10 days. In addition, patients can be taught to check the consistency of their cervical mucus, watching for a change from the sticky, whitish cervical mucus of the follicular phase to the clear, stretching mucus of ovulation. Finally, the patient can use an enzyme-linked immunosorbent assay (ELISA) available as a home testing kit to check for the elevation of LH over baseline that occurs with ovulation.

The patient should then be asked by the physician to describe the current vaginal bleeding in terms of onset, frequency, duration, and severity. This history will help the physician to focus the differential diagnosis. For example, if the patient reports a long-standing history of anovulatory bleeding the workup can focus on causes for chronic hyperandrogenicity such as polycystic ovarian syndrome and congenital adrenal hyperplasia. Age, parity, sexual history, previous gynecological disease, and obstetrical history will further assist the physician in focusing the evaluation of the women with vaginal bleeding. These questions will help in evaluating the likelihood of pregnancy-related causes of vaginal bleeding, infectious disease, and cancer.

The physician should ask about medications, including contraceptives, prescription medications, and over-the-counter medications and supplements. Contraception is a common cause of vaginal bleeding in women. The patient should be directly asked about any over-the-counter preparations she
may be taking. Patients may not be aware that herbal preparations may contribute to vaginal bleeding. Ginseng, which has estrogenic properties, can cause vaginal bleeding and St John’s Wort can interact with oral contraceptives to cause breakthrough bleeding. A review of symptoms should include questions regarding fever, fatigue, abdominal pain, hirsutism, galactorrhea, changes in bowel movements, and heat/cold intolerance. A careful family history will aid in identifying patients with a predisposition to polycystic ovarian syndrome, congenital adrenal hyperplasia, thyroid disease, premature ovarian failure, fibroids, and cancer. Physicians should also keep in mind that women usually present complaining of vaginal bleeding when symptoms deviate from the patient’s normal bleeding pattern. Patients with chronic anovulatory bleeding patterns or lifelong heavy menses secondary to von Willebrand disease may not perceive their underlying menses pattern as abnormal. Therefore, the physician should avoid asking the patient if her periods have been “normal” and instead should ask for specific details regarding the patient’s bleeding pattern.

2. Physical examination—The physical examination for women complaining of vaginal bleeding should begin with an evaluation of the patient’s vital signs. Does the patient present with a fever (indicating possible infection), increased pulse, low blood pressure, or significant orthostatic changes in her blood pressure (indicating significant acute blood loss)? Has she had a significant weight change and an enlarged or tender thyroid gland indicating thyroid disease? The physician should also evaluate the patient’s weight for obesity and hair distribution for hirsutism. These can indicate possible chronic anovulation syndromes. The pelvic examination will aid in identifying other causes of bleeding including anatomic abnormalities such as cervical polyps; signs of infections such as cervical discharge, cervical motion tenderness, and uterine or adnexal tenderness; signs of pregnancy such as changes in the cervix and a symmetrically enlarged uterus; and signs of fibroids such as an enlarged but irregular uterus.

### Table 33-1. Patterns of vaginal bleeding.

<table>
<thead>
<tr>
<th>Descriptive Term</th>
<th>Bleeding Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menorrhagia</td>
<td>Regular cycles, prolonged duration, excessive flow</td>
</tr>
<tr>
<td>Metrorrhagia</td>
<td>Irregular cycles</td>
</tr>
<tr>
<td>Menometrorrhagia</td>
<td>Irregular cycles, prolonged duration, and excessive flow</td>
</tr>
<tr>
<td>Hypermenorrhea</td>
<td>Regular cycles, normal duration, and excessive flow</td>
</tr>
<tr>
<td>Polymenorrhea</td>
<td>Frequent cycles</td>
</tr>
<tr>
<td>Oligomenorrhea</td>
<td>Infrequent cycles</td>
</tr>
</tbody>
</table>

### B. Evaluation

The evaluation of patients presenting with vaginal bleeding includes a combination of laboratory testing, imaging studies, and sampling techniques. The evaluation is directed both by patient presentation and a risk evaluation for endometrial cancer. For example, a patient who presents with a history and physical examination consistent with pelvic inflammatory disease will obviously be tested for gonorrhea and chlamydia. If the physician feels an enlarged uterus on physical examination the initial evaluation will include a pregnancy test followed by a pelvic ultrasound. If the results are inconclusive a sonohysterogram can aid in detecting a focal versus a diffuse lesion. This in turn can lead to a hysteroscopy for further evaluation of a focal lesion or an endometrial biopsy for a diffuse lesion.

The choice of evaluation is also based on the risk of endometrial cancer. For a patient who is at risk, an endometrial biopsy should be included in the evaluation. Patients having prolonged exposure to unopposed estrogen (either iatrogenically or because of chronic anovulation) for more than a year, regardless of age, should also have an endometrial biopsy. In addition, because the incidence of endometrial cancer begins to increase after the age of 35, any patient older than this should also have an endometrial biopsy during an evaluation for unexplained vaginal bleeding.

### C. Laboratory Studies

Most patients presenting with vaginal bleeding should be evaluated with a complete blood count. In addition, every woman of reproductive age should have a urine or serum pregnancy test. A thyroid-stimulating hormone (TSH) should be drawn on women presenting with symptoms consistent with hypo- or hyperthyroidism or in women presenting with a change from a normal menstrual pattern.

Adolescents presenting with menorrhagia at menarche should have an evaluation for coagulopathies including a prothrombin time (PT), partial thromboplastin time (PTT), and bleeding time.

There is no general agreement on the diagnostic criteria for polycystic ovarian syndrome (PCOS). In patients with symptoms suggestive of PCOS it is reasonable to check for elevated LH, testosterone, and androstenedione. These may be elevated in patients with PCOS, but due to the large variation among individual women these tests are not definitive. Therefore, the physician needs to interpret test results in conjunction with the clinical picture to make a diagnosis of PCOS.

Overall, the incidence of adult-onset congenital adrenal hyperplasia (CAH) is about 2% in women with hyperandrogenic symptoms. The incidence is higher in individuals of Italian, Ashkenazi, and Yugoslav heritage. Deciding on screening for adult-onset CAH should be based on both the patient’s clinical presentation and the patient’s ethnic background. A basal 17-hydroxyprogesterone (17-HP) should be drawn in the early morning to screen for adult-onset CAH. Patients with an
abnormal result can have another 17-HP level drawn after receiving a dose of adrenocorticotropic hormone (ACTH).

D. Imaging Studies

1. Pelvic ultrasound—A pelvic ultrasound can be used to evaluate the ovaries, uterus, and endometrial lining for abnormalities. An evaluation of the ovaries can assist in the diagnosis of PCOS as many women with PCOS will have enlarged ovaries with multiple, small follicles. As with the laboratory testing, this study will not provide a definitive diagnosis.

A pelvic ultrasound is also useful for evaluating an enlarged uterus for the presence of fibroids. Fibroids will appear as hypoechoic, solid masses seen within the borders of the uterus. Subserosal fibroids can be pedunculated and therefore can be seen outside the borders of the uterus.

An endovaginal ultrasound can be used to evaluate the thickness of the endometrial stripe. The results need to be interpreted based on the whether a patient is pre- or postmenopausal. For all women the thicker the endometrial stripe, the more likely the patient has an endometrial abnormality.

An endovaginal ultrasound is a sensitive test for patients with postmenopausal bleeding whether or not they are using hormone replacement therapy. Therefore, postmenopausal patients with an endometrial stripe thicker than 4-5 mm should have a histological biopsy. Hormone replacement therapy can cause proliferation of a patient’s endometrium, making an endovaginal evaluation less specific.

An endovaginal ultrasound is also useful in evaluating the endometrial stripe in premenopausal or perimenopausal patients. Whereas the normal endometrial stripe is thicker in the premenopausal patient than in the postmenopausal patient, the median thickness of an abnormal endometrium is similar for both. The endovaginal ultrasound examination is less likely to detect myomas and polyps.

2. Sonohysterography—In a patient who has an endometrial strip thicker than 5 mm, a saline infusion sonohysterography (SIS) may be helpful in delineating the cause. SIS involves performing a transvaginal ultrasound following installation of saline into the uterus. Done after an abnormal vaginal ultrasound, the study is most useful in differentiating focal from diffuse endometrial abnormalities. Detection of a focal abnormality indicates evaluation by hysteroscopy and detection of an endometrial abnormality indicates the need to perform an endometrial biopsy or dilatation and curettage. This can be considered as a study of first choice in premenopausal women with abnormal uterine bleeding.

3. Magnetic resonance imaging (MRI) can be used to evaluate the uterine structure. The endometrium can be evaluated with an MRI, but the endometrial area seen on MRI does not correspond exactly to the endometrial stripe measured with ultrasound. In most situations, a transvaginal ultrasound is the preferred imaging modality, but if the patient cannot tolerate the procedure MRI does provide an option for evaluation. MRI is better than ultrasound in distinguishing adenomyosis from fibroids, so if the history and examination suggests adenomyosis, an MRI may be the best first choice. MRI is also sometimes used to evaluate fibroids prior to uterine artery embolization or to map multiple myomas.

E. Endometrial Sampling

The workup for endometrial cancer should be pursued most aggressively with patients at greatest risk for the disease, such as postmenopausal patients who present with vaginal bleeding. In patients younger than 40 years, endometrial cancer is usually seen in obese patients and/or patients who are chronically anovulatory. Therefore, a patient who presents with an anovulatory pattern of bleeding for greater than a year should be evaluated for hyperplasia and neoplasm with an endometrial sample. In addition, the evaluation of women older than 35-40 years presenting with a new onset of menorrhagia should include endometrial sampling since the incidence of endometrial cancer increases after the age of 35.

Findings from the initial workup and response to treatment will determine the need for additional studies including sonohysterography, diagnostic hysteroscopy, and MRI.

1. Dilatation and curetage—Dilatation and curetage (D&C) provides a blind sampling of the endometrium. The D&C generally will provide sampling of less than half of the uterine cavity. Because an endometrial biopsy can be completed in the office setting, it has generally replaced the D&C as the initial method of obtaining an endometrial sample. The D&C is useful in patients with cervical stenosis or other anatomic factors that prevent an adequate endometrial biopsy. The D&C is not effective as the sole treatment for menorrhagia.

2. Endometrial biopsy—An endometrial biopsy is an adequate method of sampling the endometrial lining to identify histological abnormalities. A number of devices can be used. Early devices were hooked to an external suction source. More commonly clinicians will use one of the clear, flexible endometrial curettes with an inner plunger or piston that generates suction during the procedure. The different devices available (eg, Pipelle, Explora, Z-Sampler, and Endosampler) provide similar biopsy results. The rates of obtaining an adequate endometrial sample depend on the age of the patient. Because many postmenopausal women will have an atrophic endometrium, sampling in this group will more often result in an inadequate endometrial specimen for examination. In this situation, the clinician must use additional diagnostic studies to fully evaluate the cause of the vaginal bleeding.

3. Diagnostic hysteroscopy—Hysteroscopes come in a variety of forms including rigid, semirigid, and flexible. Diameters range from less than 3 mm to 6 mm. All hysteroscopes use a light source, camera, and dilating medium to visualize the uterine cavity. The direct exploration of the uterus is useful in identifying structural abnormalities such as fibroids and endometrial polyps. Small-caliber hysteroscopes allow the
endometrium to be evaluated without the need for cervical dilatation. Currently these instruments are limited by the fact that instruments cannot be passed through the endoscope and by their limited field of view. Larger-diameter hysteroscopes allow specific biopsy of lesions. In general, the diagnostic hysteroscopy is combined with a D&C or endometrial biopsy to maximize identification of abnormalities.


Differential Diagnosis

The differential diagnosis of vaginal bleeding encompasses a wide range of possible etiologies. The patient’s history and physical examination will determine the direction of the workup. Age and ovulatory status play important roles in determining the direction of the workup once relatively straightforward causes of vaginal bleeding such as pregnancy and infection have been eliminated.

The history and physical examination will often lead to a narrowing of the differential diagnosis (Table 33-2). The physician should not narrow the differential diagnosis too quickly, as a patient can have more than one possible cause of vaginal bleeding. For example, a patient on oral contraceptives could also present with pelvic inflammatory disease or hypothyroidism. Generating the differential diagnosis will

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical Presentation</th>
<th>Most Commonly Associated Bleeding Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraception</td>
<td>Known OCP/Depo use</td>
<td>OCP: spotting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depo: irregular or continuous bleeding</td>
</tr>
<tr>
<td>HRT</td>
<td>Known HRT use</td>
<td>Sequential: menorrhagia or spotting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuous: irregular spotting</td>
</tr>
<tr>
<td>Fibroids</td>
<td>Asymptomatic, pelvic pain, and/or dysmenorrhea</td>
<td>Menorrhagia</td>
</tr>
<tr>
<td>Adenomyosis</td>
<td>Dysemorrhagia</td>
<td>Menorrhagia</td>
</tr>
<tr>
<td>Endometrial polyps</td>
<td>Asymptomatic</td>
<td>Intermenstrual spotting, metrorrhagia and/or menorrhagia</td>
</tr>
<tr>
<td>Cervical polyps</td>
<td>Asymptomatic</td>
<td>Intermenstrual and/or postcoital bleeding</td>
</tr>
<tr>
<td>PID</td>
<td>High-risk sexual behavior, fever, pelvic pain, tenderness</td>
<td>Menorrhagia and/or metrorrhagia</td>
</tr>
<tr>
<td>PCOS, Adult-onset CAH</td>
<td>Hirsutism, acne, central obesity, or asymptomatic</td>
<td>Oligomenorrhagia, menometrorrhagia</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Nervousness, heat intolerance, diarrhea, palpitations, weight loss</td>
<td>Oligomenorrhagia, amenorrhagia, polymenorrhagia, or amenorrhagia</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Fatigue, cold intolerance, dry skin, hair loss, constipation, weight gain</td>
<td>Menorrhagia, polymenorrhagia, oligomenorrhagia, amenorrhagia</td>
</tr>
<tr>
<td>Bleeding disorder</td>
<td>Asymptomatic mucocutaneous bleeding, easy bruising</td>
<td>Menorrhagia</td>
</tr>
<tr>
<td>Endometrial hyperplasia</td>
<td>Asymptomatic</td>
<td>Menorrhagia and/or metrorrhagia</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>Asymptomatic</td>
<td>Postmenopausal: irregular spotting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perimenopausal: menometrorrhagia</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Asymptomatic</td>
<td>Irregular spotting, postcoital bleeding</td>
</tr>
</tbody>
</table>

OCP, oral contraceptive pills; HRT, hormone replacement therapy; PID, pelvic inflammatory disease; PCOS, polycystic ovarian syndrome; CAH, congenital adrenal hyperplasia.
aid the physician in deciding how to further evaluate and treat the patient.

**A. Pregnancy-Related Bleeding**

The initial evaluation of any patient presenting with vaginal bleeding should include testing for pregnancy. In recent years urinary assays for β-human chorionic gonadotropin (hCG) have become so sensitive that they are a viable alternative to serum testing. The differential diagnosis for vaginal bleeding for pregnancy varies depending on the estimated gestational age. Early in pregnancy it includes spontaneous miscarriage, ectopic pregnancy, and trophloblastic disease. Later in pregnancy the appearance of bleeding should lead the physician to investigate the possibilities of placenta previa and placental abruption.

**B. Bleeding Secondary to Hormone Medications**

1. **Contraception**—Vaginal bleeding is a common side effect of many forms of contraception. Many women starting oral contraceptive pills (OCPs) experience breakthrough bleeding in the initial months. Lower dose oral contraceptive pills have higher rates of spotting and breakthrough bleeding. Possible causes of vaginal bleeding in patients taking OCPs include inadequate estrogenic or progestogenic stimulation of the endometrium, skipped pills, or altered absorption and metabolism of the pills. Breakthrough bleeding is common among users of extended contraceptive regimens. Having the patient institute a three-day hormone-free interval at the onset of breakthrough bleeding is an effective treatment for this side effect.

   Vaginal bleeding is also frequent with Depo Provera, and is the most commonly cited reason women discontinue taking it as well as OCPs. For this reason, when initiating either form of contraception the expected course of possible bleeding should be discussed with the patient. After the initial dose of Depo Provera, 50% of women will experience irregular bleeding or spotting. After a year this decreases to 25%.

2. **Hormone replacement therapy**—The indications for hormone replacement therapy have been greatly decreased since the findings of the Women’s Health Initiative study were released. Nonetheless, some women will continue to receive hormone replacement therapy. Bleeding is common with hormone replacement therapy, and can occur with both the sequential and continuous regimens. With sequential administration of estrogen and progesterone, most women will experience bleeding near the end or right after taking the progesterone therapy. Although most women taking sequential therapy will continue to bleed every month, women can experience abnormal bleeding patterns including heavy or prolonged bleeding during the regular cycle or bleeding between cycles.

   Theoretically patients taking continuous estrogen and progesterone therapy should not experience any bleeding, as the therapy is meant to result in an atrophic endometrium. In reality about 40% of women starting continuous regimens will experience bleeding in the first 4-6 months after starting treatment. To avoid higher rates of irregular bleeding many physicians will use sequential hormonal therapy for 12 months after the start of menopause to avoid the effects of endogenous ovarian function.

**C. Anatomic Causes**

1. **Fibroids**—Fibroids or leiomyomas are benign uterine tumors that are often asymptomatic. The most common symptoms associated with fibroid tumors are pelvic discomfort and abnormal uterine bleeding. Fibroids can be subserosal, intramural, or submucosal. Fibroids located subserosally may be felt on the physical examination as an irregular enlargement of the surface. Depending on the size of the fibroid, intramural and subserosal fibroids can be more difficult to palpate on examination. Most commonly, women with symptomatic fibroids experience either heavy or prolonged periods. In the past theories about possible mechanisms of uterine bleeding included increased vascularity, interference with uterine contractility, endometrial ulceration, and increased endometrial surface area. More recently, there is evidence to suggest that fibroids involve abnormalities of growth factors that in turn have direct effects on vascular function and angiogenesis.

2. **Adenomyosis**—Adenomyosis is defined as the presence of endometrial glands within the myometrium. This is typically asymptomatic, but women can present with heavy or prolonged menstrual bleeding as well as dysmenorrhea. The dysmenorrhea can be severe and begin up to 1 week prior to menstruation. The appearance of symptoms usually occurs after the age of 40.

3. **Endometrial and cervical polyps**—Endometrial polyps can cause intermenstrual spotting, irregular bleeding, and/or menorrhagia. In contrast, cervical polyps usually cause intermenstrual spotting or postcoital bleeding. Other cervical lesions such as condyloma and herpes simplex virus (HSV) ulcerations can present with similar abnormal bleeding patterns.

**D. Infectious Causes**

Microorganisms including sexually transmitted microorganisms, respiratory pathogens, and endogenous vaginal bacteria can ascend into the endometrium and fallopian tubes, causing pelvic inflammatory disease (PID). Factors that increase endocervical accessibility increase a patient’s risk for PID. This occurs during menstruation, and with alterations in the cervical mucus secondary to alterations in the vaginal flora due to bacterial vaginosis. PID in its classic form presents with fever, pelvic discomfort, cervical motion tenderness, and adnexal tenderness. Patients can present atypically with nothing but a change in their bleeding pattern. PID can cause amenorrhea or metrorrhagia, so the patient presenting with abnormal vaginal bleeding should be fully evaluated for PID.
The squamous epithelium of the ectocervix is a continuation of the vaginal epithelium. Therefore, cervical inflammation occurs in the ectocervix when invaded by microorganisms causing vaginitis. The physician will see a bright red cervix (the “strawberry” cervix) in patients with severe cases of trichomonias. The pathogens causing mucopurulent endocervicitis (Neisseria gonorrhoeae and Chlamydia trachomatis) invade the glandular epithelium of the endocervix. Both kinds of cervical inflammation can cause intermenstrual spotting and postcoital bleeding.

E. Anovulatory Bleeding

When a woman does not ovulate she does not produce a corpus luteum, and then does not produce any progesterone. As a result, the endometrium of the uterus continues to proliferate. Eventually the growth of the endometrium cannot be sustained, resulting in irregular sloughing of the uterine lining. This irregular sloughing causes the bleeding pattern associated with anovulatory bleeding: irregular, heavy periods.

There are multiple causes of anovulation including physiological and pathological etiologies. During the first year following menarche, anovulation is a normal result of an immature hypothalamic-pituitary-gonadal axis. Irregular ovulation also is a normal physiological result of declining ovarian function during the perimenopausal years, and the hormonal changes associated with lactation.

Hyperandrogenic causes of anovulation include PCOS, adult-onset CAH, and androgen-producing tumors. The etiology of PCOS is uncertain, and its clinical features vary. Most recently research has focused on the underlying disorder of insulin resistance in these patients, and the possibility that hyperinsulinemia stimulates excess ovarian androgen production. Making the diagnosis of PCOS involves the evaluation of clinical features and endocrine abnormalities, and the exclusion of other etiologies. Women with PCOS can present with oligomenorrhea or dysfunctional uterine bleeding from prolonged anovulation. In addition, these women can have hirsutism, acne, and central obesity. Endocrinologically they can have increased testosterone activity, elevated luteinizing hormone concentration with a normal follicle-stimulating hormone level, and hyperinsulinemia due to insulin resistance. PCOS usually has its onset during puberty, and so these women often report a long history of irregular periods.

Adult-onset CAH results from an enzyme defect in the adrenal gland, most commonly a deficiency of 21-hydroxylase. There are three hypothesized allelic variants of the 21-hydroxylase deficiency gene: a normal variant, a mild variant, and a severe variant. Patients with adult-onset CAH are either homozygous for the mild allele or have one mild and one severe allele. The genetic defect causes an abnormality in steroid synthesis of glucocorticoids. The hypothalamic-pituitary axis compensates by increasing secretion of ACTH. This in turn causes a hyperplastic adrenal cortex, which produces increased androgens as well as corticoid precursors. Phenotypically women can present in a variety of ways: with PCOS symptoms, with hirsutism alone, or with hyperandrogenic laboratory work but no hyperandrogenic symptoms. Typically patients will present at or after puberty. As a result, these women will also report a long history of irregular periods.

Other causes of anovulation, including androgen-producing tumors, hypothalamic dysfunction, hyperprolactinemia, pituitary disease, and premature ovarian failure, are more likely to present as amenorrhea than vaginal bleeding.

F. Endocrine Abnormalities

Both hyper- and hypothyroidism can cause changes in a woman’s menstrual cycle. Hyperthyroidism can cause amenorrhea, oligomenorrhea, hypermenorrhea, or polymenorrhea. Of all the menstrual abnormalities, oligomenorrhea is the most common in patients with hyperthyroidism. Patients who smoke and have higher total thyroxine (T4) levels tend to have more menstrual disturbances.

A patient with hypothyroidism may experience changes in her menstrual cycle including amenorrhea, oligomenorrhea, polymenorrhea, or menorrhagia. Menstrual abnormalities occur more frequently with severe than with mild hypothyroidism. Hypothyroidism most likely causes menorrhagia through a combination of anovulation and subsequent breakthrough bleeding as well as decreased levels of coagulation factors.

G. Bleeding Disorders

Formation of a platelet plug is the first step of homeostasis during menstruation. Patients with disorders that interfere with the formation of a normal platelet plug can experience menorrhagia. The two most common disorders are von Willebrand disease and thrombocytopenia. Bleeding can be particularly severe at menarche, due to the dominant estrogen stimulation causing increased vascularity. Patients with von Willebrand disease will usually present with a long history of heavy periods. Patients with thrombocytopenia can present with menorrhagia with the onset of their disease.

Bleeding disorders resulting from coagulation deficiencies cause impaired formation of fibrin from fibrinogen. These deficiencies are more common in men. They more often cause bleeding in soft tissues and mucocutaneous tissues. Cases of menorrhagia in women with coagulation deficiencies have been reported.

H. Endometrial Hyperplasia

Endometrial hyperplasia is an overgrowth of the glandular epithelium of the endometrial lining. This usually occurs when a patient is exposed to unopposed estrogen, either estrogenically or because of anovulation. Retrospectively, we know that the rate of neoplasms found with simple hyperplasia is 1% and that the rate with complex hyperplasia is much higher, reaching almost 30% when atypia is present.
Patients having hyperplasia with atypia should have a hysterectomy due to the high incidence of subsequent endometrial cancer. There is not a consensus regarding the management of nonatypical hyperplasia. Most patients without atypia will respond to treatment to high dose progestin treatment for 21 days. Endometrial ablation may also play a role in the treatment of hyperplasia.

I. Neoplasms

Uterine cancer is the fourth most common cancer in women. Risk factors for endometrial cancer include nulliparity, late menopause (after age 52), obesity, diabetes, unopposed estrogen therapy, tamoxifen, and a history of atypical endometrial hyperplasia. Endometrial cancer most often presents as postmenopausal bleeding in the sixth and seventh decade, although when investigated only 10% of patients with postmenopausal bleeding will have endometrial cancer. In the perimenopausal period endometrial cancer can present as menometrorrhagia.

Vaginal bleeding is the most common symptom in patients with cervical cancer. The increased cervical friability associated with cervical cancer usually results in postcoital bleeding, but also can appear as irregular or postmenopausal bleeding.

A. Bleeding from Contraception

Physicians often change formulations of OCPs to try to decrease the incidence of intermenstrual bleeding, although conflicting study results make it difficult to determine whether different formulations actually make a difference. All formulations share the characteristic of a higher incidence of intermenstrual bleeding during the first cycle of use. Therefore, one of the most important things physicians can do is to reassure the patient and encourage continued use. The physician can try adding exogenous estrogen daily for 7-10 days to control prolonged intermenstrual bleeding, but no clinical trials support this strategy. Physiologically, this approach makes sense, as OCPs cause endometrial atrophy.

Similarly, bleeding is common with Depo Provera, especially early during the treatment. Reassurance and patience should be the initial treatment of any bleeding. With continued bleeding physicians can consider the unstudied practice of adding low-dose estrogen supplementation for 1-3 months.

B. Fibroids

Medical management of fibroids is fairly limited. Oral contraceptives have not been found to effectively treat fibroid symptoms. They also have not been found to increase fibroid size and therefore can be used in women with fibroids for other reasons. Recently there is some evidence that depot medroxyprogesterone acetate may significantly improve menorrhagia attributed to fibroids. Mifepristone and selective estrogen receptor modulator (SERM) have been studied and may be available as treatment options after further study. Administration of a gonadotropin-releasing hormone (GnRH) agonist can greatly reduce the volume of a patient’s fibroids. Unfortunately this effect is temporary. As a result, this treatment is largely reserved for preoperative therapy to facilitate the removal of the uterus or fibroid. Pretreatment can also improve the patient’s hematological parameters by decreasing vaginal bleeding prior to surgery. The exception to these restrictions is the perimenopausal patient. If a woman is close to menopause, treatment with a GnRH agonist is reasonable. To achieve success, this approach depends on the woman beginning menopause during treatment. This reduces the chance that myomas will increase in size after the cessation of treatment. Because it is impossible to predict the start of menopause, the number of patients benefiting from this approach is limited.

Treatment with nonsteroidal anti-inflammatory drugs may be effective in decreasing abnormal uterine bleeding, but there is a lack of randomized trials examining this treatment. Ibuprofen at doses of 1200 mg daily effectively reduces bleeding in patients with primary menorrhagia, but this may not be as effective in women with fibroids.

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References:

Matytsina L, Zoloto EV, Sinenko LV, Greydanus DE: Dysfunctional uterine bleeding in adolescents: concepts of pathophysiology and management Prim Care 2006;33:503–515. [PMID 16713772]
If patients fail these ambulatory approaches surgical options include a myomectomy, hysterectomy, or uterine embolization. Although the primary care physician will refer the patient out for these procedures, patients will often want to discuss possible treatment options with their physicians. Myomectomy is a good option for the patient who does not want her uterus removed or desires future childbearing. The risk exists for the growth of new fibroids and the growth of fibroids too small for removal at the time of surgery. Women having hysterectomies may have the option of an abdominal or vaginal hysterectomy. Vaginal hysterectomies involve fewer complications and shorter hospital stays. The size of the uterus at the time of surgery determines the feasibility of this approach, as the surgeon must be able to remove the uterus completely through a vaginal incision.

Women wanting to avoid hysterectomy now have the option of uterine fibroid embolization. In this procedure an interventional radiologist injects tiny polyvinyl alcohol particles into the uterine arteries. Because the hypervascular fibroids have no collateral vascular supply, they undergo ischemic necrosis. Women with pedunculated or subserosal fibroids are not considered ideal candidates for this procedure. In addition, because the effects of uterine artery embolization on childbearing are not well known, the procedure is generally not done on women desiring future fertility. Menorrhagia is improved in over 90% of women undergoing uterine artery embolization.

C. Anovulatory Bleeding

In general, medical management is the preferred treatment for anovulatory bleeding. Treatment goals should include alleviation of any acute bleeding, prevention of future noncyclic bleeding, a decrease in the patient’s future risk of long-term health problems secondary to anovulation, and improvement in the patient’s quality of life. Treatment options include prostaglandin synthetase inhibitors, estrogen (for acute bleeding episodes), contraceptive methods, and cyclic progesterones. Those failing medical management have surgical options including hysterecomy and endometrial ablation.

Blood loss can be reduced by 50% in women treated with prostaglandin synthetase inhibitors including mefenamic acid, ibuprofen, and naproxen. Because many of the studies evaluating the role of prostaglandin synthetase inhibitors were completed in women with ovulatory cycles, the results cannot be directly applied to women with anovulatory bleeding; women with anovulatory bleeding may not find this approach as effective. In addition, this treatment does not address the issues of future noncyclic bleeding and decreasing future health risks due to anovulation.

Estrogen alone is usually used to treat an acute episode of heavy uterine bleeding. Premarin used intravenously will temporarily stop most uterine bleeding, regardless of the cause. The dose commonly used is 25 mg of conjugated estrogen every 4 hours. Nausea limits using high doses of estrogen orally, but lower doses can be used in a patient with acute heavy bleeding who is hemodynamically stable. One suggested regimen is 2.5 mg conjugated estrogen every 4-6 hours. After acute bleeding is controlled, the physician should add a progestin to the treatment regimen to induce withdrawal bleeding. A combination of estrogen and progesterone is given for 7-10 days and then stopped, inducing a withdrawal bleed. To decrease the risk of future hyperplasia and/or endometrial cancer, a progestin is continued for 10-14 days each cycle. Traditionally, treatment has been with medroxypregesterone acetate (Provera) 10 mg. Other progestational agents include norethindrone acetate (Agestin), norethindrone (Micronor), norgestrel (Ovrette), and micronized progesterone (Prometrium, Crinone). The micronized progestones are natural progesterones modified to have a prolonged half-life and less destruction in the gastrointestinal tract. Women having problems with mood changes from synthetic progestins may better tolerate treatment with micronized progesterone.

OCPs provide an option for treatment of both the acute episode of bleeding and future episodes of bleeding as well as prevention of long-term health problems from anovulation. Acutely, one option to control bleeding is to use a 50-μg estrogen OCP four times a day until bleeding ceases, then continue the OCP for a week. This may not be as effective as estrogen alone for quick stoppage of bleeding, but is very convenient and easy. Long-term OCPs are effective in treating all patterns of dysfunctional uterine bleeding. Although the triphasic norgestimate/ethinyl estradiol combination has been studied in a double-blind, placebo-controlled study, various oral contraceptives have been used for decades to control uterine bleeding. Patients with a history of thromboembolism, cerebrovascular disease, coronary artery disease, estrogen-dependent neoplasias, or liver disease should not be started on an oral contraceptive. Relative contraindications include migraine headaches, hypertension, diabetes, age greater than 35 in a smoking patient, and active gallbladder disease.

Other methods of combined hormone treatment can be considered, including the transdermal contraceptive patch, the vaginal contraceptive ring, and the levonorgestrel intrauterine device (IUD). Menstrual blood loss is significantly reduced with the use of the levonorgestrel IUD and may represent a better option than cyclic progesterone for the treatment of menorrhagia.

When evaluating various treatment regimens for dysfunctional uterine bleeding the clinician should realize that there are few studies evaluating the most effective type, dose, regimen, and administrative route. This contributes to a wide range of suggested treatment options, none of which has been proven to be more superior to another.

Patients who are unable to tolerate hormonal management can consider endometrial ablation. Using electrocautery, laser, cryoablation, or thermoablation, these techniques all result in destruction of the endometrial lining. Initially used exclusively in patients with menorrhagia, these
treatments are now also used in women with anovulatory bleeding, although outcomes are not well studied for this indication. Because endometrial glands often persist after ablative treatment, most women will not experience long-term amenorrhea after treatment. Also, because endometrial glands do persist, the risk of endometrial cancer is not eliminated after treatment. Women at risk for endometrial cancer from long-term unopposed estrogen exposure still need preventive treatment. This procedure should be used only in women who choose not to preserve future fertility. As pregnancies have occurred after endometrial ablation, some form of contraception may be needed after the procedure.

D. Alternative Therapies

Although no controlled studies have been completed, small studies suggest that acupuncture may be an option for young women with dysfunctional bleeding and for women with PCOS.

The nomenclature used in traditional Chinese medicine differs from western medicine, so making a direct comparison of treatments is difficult. Again, no controlled studies have been completed, but smaller studies suggest a possible role in certain situations for patients interested in pursuing alternative therapies. Keishi-bukuryo-gan (KBG) is a traditional herbal remedy that may act as a luteinizing hormone-releasing hormone antagonist and a weak antiestrogen. It has been used successfully in the treatment of uterine fibroids. A smaller number of patients have been treated for acute bleeding and then induction of ovulation.

General Considerations

As of 2005 data, at least 73.6 million people older than 20 years in the United States have hypertension, defined as systolic blood pressure greater than or equal to 140 mm Hg or diastolic blood pressure greater than or equal to 90 mm Hg, or both. This translates to one in four adults and more than half of those older than 60 years of age. The incidence of hypertension increases with age. If an individual is normotensive at age 55, the lifetime risk for hypertension is 90%. High blood pressure resulted in the death of 57,356 Americans in 2005. From 1995 to 2005, the death rate from hypertension rose 25.2% and the actual number of deaths rose 56.4%. Of persons with high blood pressure, 78.7% are aware of their diagnosis. Of this group, 69% are under treatment, 45% are well controlled, and 55% are not. Hypertension is most prevalent among the black population, affecting one of every three African Americans. Non-Hispanic blacks and Mexican Americans are also more likely to suffer from high blood pressure than non-Hispanic whites.

Chobanian AV et al: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) was released. It provided updated recommendations based on recent studies, including more concise clinical guidelines and a simplified blood pressure classification (Table 34-2). The eighth edition is anticipated to be released in Fall of 2011.

Pathogenesis

A. Primary or Essential Hypertension

In 90%-95% of cases of hypertension, no cause can be identified. A role for genetics has been implicated in the development of high blood pressure (e.g., hypertension is more prevalent in some families and in African Americans). Additional risk factors include increased salt intake, excess alcohol intake, obesity, sedentary lifestyle, and certain personality traits, including aggressiveness and poor stress coping skills.

### Table 34-1. Trends in awareness, treatment, and control of high blood pressure in adults aged 18-71 years.

<table>
<thead>
<tr>
<th>NHANES (%)</th>
<th>NHANES (%</th>
<th>NHANES (%)</th>
<th>NHANES (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awareness</td>
<td>51</td>
<td>73</td>
<td>68</td>
</tr>
<tr>
<td>Treatment</td>
<td>31</td>
<td>55</td>
<td>54</td>
</tr>
<tr>
<td>Control</td>
<td>10</td>
<td>29</td>
<td>27</td>
</tr>
</tbody>
</table>

NHANES, National Health and Nutrition Examination Survey.

Table 34-2. Classification and management of blood pressure in adults.

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP&lt;sup&gt;a&lt;/sup&gt; (mm Hg)</th>
<th>DBP&lt;sup&gt;a&lt;/sup&gt; (mm Hg)</th>
<th>Lifestyle Modification</th>
<th>Without Compelling Indication</th>
<th>With Compelling Indication (see Table 34-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120</td>
<td>&lt; 80</td>
<td>Encourage</td>
<td>No antihypertensive drug indicated</td>
<td>Drug(s) for compelling indications&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-90</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140-159</td>
<td>90-99</td>
<td>Yes</td>
<td>Thiazide-type diuretics for most; may consider ACE inhibitor, ARB, β-blocker, calcium channel blocker, or combination</td>
<td>Drug(s) for compelling indications&lt;sup&gt;c&lt;/sup&gt;; other antihypertensive drugs (diuretics, ACE inhibitors, β-blockers, calcium channel blockers) as needed</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥160</td>
<td>≥100</td>
<td>Yes</td>
<td>Two-drug combination for most&lt;sup&gt;d&lt;/sup&gt; (usually thiazide-type diuretic and ACE inhibitor or ARB or β-blocker or calcium channel blocker)</td>
<td></td>
</tr>
</tbody>
</table>

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

<sup>a</sup>Treatment determined by highest BP category.

<sup>b</sup>Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mm Hg.

<sup>c</sup>Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

B. Secondary Hypertension

In only 5% of cases can a cause for hypertension be found; however, it is reasonable to look for an underlying cause in patients diagnosed with hypertension. History or physical examination may suggest an underlying etiology, or the first clue may come later when patients fail to respond appropriately to standard drug therapy. In addition, secondary hypertension should be considered in those with sudden onset of hypertension; in those with suddenly uncontrolled blood pressure that had previously been well controlled; and in patients younger than 30 years of age without a family history of hypertension.

Etiologies of secondary hypertension that must be considered in the appropriate patient include use of certain medications such as oral contraceptives, sympathomimetics, decongestants, nonsteroidal anti-inflammatory drugs, appetite suppressants, antidepressants, adrenal steroids, cyclosporine, and erythropoietin. All of these medications can contribute to an elevation in blood pressure. Hypertension can also be related to excessive use of caffeine, ingestion of licorice, or use of illicit drugs such as cocaine or amphetamines.

Hypertension can also occur secondary to acute and chronic kidney disease, which might be suggested by a flank mass, elevated creatinine level, or abnormal findings such as proteinuria, hematuria, or casts on routine urinalysis. Rarely, hypertension may be related to renal artery stenosis, particularly if onset is before the age of 20 or after the age of 50 years. Abdominal bruits with radiation to the renal area may be heard. Other causes to consider in the differential diagnosis include hypo- or hyperthyroidism, primary hyperaldosteronism, Cushing syndrome, coarctation of the aorta, pheochromocytoma, and sleep apnea syndrome in the appropriate clinical presentation. When such causes are entertained, appropriate evaluation should be undertaken.

Prevention

A healthy lifestyle is hailed both as prevention and as initial therapy for hypertension (Table 34-3). Clinical trials assessing both prevention (Trials of Hypertension Prevention—Phase II, TONE) and nonpharmacologic treatment of mild hypertension (TOMHS, DASH, low-sodium DASH, PREMIER) support the positive impact of maintaining optimal weight, a regular aerobic exercise program, and a diet low in sodium, saturated fat, and total fats and rich in fruits and vegetables. Excessive alcohol intake should be reduced and smoking cessation encouraged.

Clinical Findings

Before patients with hypertension can be offered adequate treatment, they must be properly diagnosed. Because patients are often asymptomatic, the risk factors for hypertension must be understood and appropriate patients screened. In addition to the modifiable risk factors noted earlier, there are nonmodifiable factors, including African-American race, family history of hypertension, and increasing age.

Table 34-3. Lifestyle modifications to manage hypertension.

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate SBP Reduction (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight (BMI 18.5-24.9 kg/m²)</td>
<td>5-20 mm Hg/10 kg weight loss</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat</td>
<td>8-14 mm Hg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>Reduce dietary sodium intake to no more than 100 mmol/d (2.4 g sodium or 6 g sodium chloride)</td>
<td>2-8 mm Hg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Engage in regular aerobic physical activity such as brisk walking (at least 30 min/d, most days of the week)</td>
<td>4-9 mm Hg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>Limit consumption to no more than 2 drinks (1 oz or 30 ml ethanol; eg, 24 oz beer, 10-oz wine, or 3 oz 80-proof whiskey) per day in most men and to no more than 1 drink per day in women and lighter weight persons</td>
<td>2-4 mm Hg</td>
</tr>
</tbody>
</table>

SBP: systolic blood pressure; BMI: body mass index; DASH: Dietary Approaches to Stop Hypertension.

A. Symptoms and Signs

There are usually no physical findings early in the course of hypertension. In some patients, the presence of hypertension may be signaled by early morning headaches or, in those with severe hypertension, by signs or symptoms associated with target organ damage. Such symptoms might include nausea, vomiting, visual disturbance, chest pain, or confusion. More typically, the first indication is an elevated blood pressure measurement taken with a sphygmomanometer during a routine visit to a medical provider or after the patient has had a stroke or MI.

For proper measurement of blood pressure, the patient should be seated in a chair with his or her back supported and the arm bared and supported at heart level. Caffeine and tobacco should be avoided in the 30 minutes preceding measurement, and measurement should begin after 5 minutes of rest. The cuff size should be appropriate for the patient’s arm, defined by a cuff bladder that encircles 80% of the arm. It is important that the diagnosis be made after the elevation of blood pressure is documented with three separate readings, on three different occasions, unless the elevation is severe or is associated with symptoms requiring immediate attention (hypertensive urgency or emergency). Transient elevation of blood pressure secondary to pain or anxiety, as experienced by some patients when they enter a physician’s office (“white coat syndrome”), does not require treatment. In cases in which the diagnosis is in question, properly taken home blood pressure measurements can be useful.

1. Classification of blood pressure—A goal of JNC VII was to simplify blood pressure classification when making the diagnosis of hypertension (see Table 34-2). A new category, designated prehypertension, was added, and stages 2 and 3 from JNC VI were combined to form a single category (stage 2). These classifications are based on the average of two or more provider-obtained blood pressure measurements from a seated patient.

2. Self-monitoring—Patients should be encouraged to do self-monitoring of their blood pressure at home. Many easy-to-use blood pressure monitors are commercially available at reasonable cost for use at home. Validated electronic devices are recommended, and independent reviews of available devices, such as that published by Consumer Reports, are available to assist the consumer. These devices should be periodically checked for accuracy. Self-measurement can be helpful, not only in establishing the diagnosis of hypertension, but also in assessing response to medical therapy, and in encouraging patient compliance with therapy by providing regular feedback on therapy response.

B. Evaluation

Patients with documented hypertension must undergo a thorough evaluation that includes objectives advanced by JNC VII: assessment of lifestyle and identification of cardiovascular risk factors, identification of comorbidities that would guide therapy, and surveillance for identifiable causes of high blood pressure and to establish whether the patient already manifests evidence of target end-organ damage.

1. History—A thorough history should be obtained. Any prior history of hypertension should be elicited as well as response and side effects to any previous hypertension therapy. It is important to inquire about any history or symptoms suggestive of coronary artery disease or other significant comorbidities, including diabetes mellitus, heart failure, dyslipidemia, renal disease, and peripheral vascular disease. The family history should also be reviewed, with special attention to the presence of hypertension, premature coronary artery disease, diabetes, renal disease, dyslipidemia, or stroke. Use of tobacco, alcohol, or illicit drugs should be documented, as well as dietary intake of sodium, saturated fat, and caffeine. Recent changes in weight and exercise level should be queried. Current medications used by the patient should be reviewed, including over-the-counter medications and herbal formulations.

2. Physical examination—The initial physical examination should be comprehensive and should pay careful attention to the areas outlined in Table 34-4.

![Table 34-4: Physical examination: hypertension.](image-url)

<table>
<thead>
<tr>
<th>Component of Examination</th>
<th>Assessment Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Baseline height, weight, and waist circumference</td>
</tr>
<tr>
<td></td>
<td>Upper and lower extremity blood pressure measurement to assess for coarctation of the aorta</td>
</tr>
<tr>
<td></td>
<td>Features of Cushing syndrome</td>
</tr>
<tr>
<td>Eyes</td>
<td>Funduscopic examination for signs of hypertensive retinopathy (eg, arteriolar narrowing, focal arteriolar constriction, atrophicentricular nicking, hemorrhages, exudates)</td>
</tr>
<tr>
<td>Neck</td>
<td>Carotid bruits</td>
</tr>
<tr>
<td></td>
<td>Neck vein distention or thyroid gland enlargement</td>
</tr>
<tr>
<td>Heart</td>
<td>Abnormalities in rate, rhythm, murmurs, or extra heart sounds</td>
</tr>
<tr>
<td>Lungs</td>
<td>Rales, rhonchi, or wheezes</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Abdominal bruits suggestive of renal artery stenosis</td>
</tr>
<tr>
<td></td>
<td>Enlargement of kidneys (mass) or aortic pulsation suggesting aneurysm</td>
</tr>
<tr>
<td>Extremities</td>
<td>Diminished or absent peripheral arterial pulsations</td>
</tr>
<tr>
<td></td>
<td>Edema</td>
</tr>
<tr>
<td></td>
<td>Signs of vascular compromise</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Neurologic deficits</td>
</tr>
</tbody>
</table>
C. Laboratory and Diagnostic Studies

JNC VII specifically recommends that the following tests be performed: electrocardiogram (ECG), urinalysis, fasting blood glucose level, potassium level, creatinine level, calcium level, and fasting lipid panel. Urinalysis should be assessed for evidence of hematuria, proteinuria, or casts suggestive of intrinsic renal disease. The complete blood count is helpful to rule out anemia or polycythemia. Potassium levels help assess for hyper-aldosteronism, and creatinine levels reflect renal function. The fasting blood glucose level is used to assess for diabetes mellitus, and the lipid profile is an indicator of cardiovascular risk. Further testing is warranted if blood pressure control is not achieved. Additional tests to consider include hemoglobin A1c, thyroid-stimulating hormone, urine microalbumin, creatinine clearance, and 24-hour urine for protein. Echocardiograms and chest x-rays are not routinely recommended for evaluation of hypertensive patients. In certain cases, however, an echocardiogram may prove useful in guiding therapy when baseline abnormalities are found on the ECG (eg, left ventricular hypertrophy or signs of previous silent MI). A chest radiograph may be useful if there are abnormal findings on physical examination. Tests that evaluate for rare causes of hypertension, such as renal artery stenosis (renal ultrasound) or pheochromocytoma (24-hour urine for catecholamines), should only be ordered in patients whose history and physical examination findings raise suspicion.

Treatment

A. Cardiovascular Risk Stratification

In treating hypertension, the public health goal is reduction of cardiovascular and renal morbidity and mortality. Hypertension is clearly important, but it is not the only risk factor. JNC VII defines specific components of cardiovascular risk and recommends evaluation of patients for evidence of target organ damage in performing risk stratification and in considering recommendations for therapy (Table 34-5).

The JNC VII guidelines include an algorithm for use when considering initial therapy for patients with hypertension (Figure 34-1). It is recognized that most patients, especially those aged 50 years and older, will reach their diastolic blood pressure goal once the systolic blood pressure goal is reached. Lifestyle modification may be used initially if blood pressure is in the prehypertensive range (<140/90 mm Hg). When no risk factors, no target organ damage, and no evidence of cardiovascular disease are identified in a patient, the target blood pressure for treatment is less than 140/90 mm Hg. If diabetes mellitus or renal disease is present, the blood pressure goal is reached, or more frequently in patients with significant comorbidities. Once patients reach their goal, 3-6-month intervals for visits are appropriate. Follow-up visits should occur at approximately monthly intervals until the blood pressure goal is reached, or more frequently in patients with significant comorbidities. Once patients reach their goal, 3-6-month intervals for visits are appropriate.

When lifestyle modification is used as initial therapy but successful control is not achieved, drug therapy should be initiated (see section Pharmacotherapy, later). Further reassessments should consider optimization or titration of the drug regimen in terms of dosage or use of combinations, as well as reinforcing adherence to lifestyle modification. If the blood pressure goal is not achieved with triple-drug therapy (ie, agents from different classes, including a diuretic), further investigation must ensue. A lack of motivation on the patient’s part can undo the most effective regimen; however, this outcome can be minimized through positive experiences with the clinician to address misunderstandings about the condition and treatment. Poor response to therapy by patients receiving a triple regimen of antihypertensive drugs should also prompt consideration of referral to a hypertension specialist for evaluation and recommendations concerning treatment.
B. Lifestyle Modification

JNC VII cites the adoption of lifestyle modifications as critical, not only for the prevention of hypertension but also in the treatment thereof. Major recommendations include encouraging the overweight patient to lose weight. Even small amounts of weight loss (10 lb [4.5 kg]) can improve blood pressure control and reduce cardiovascular risk. Weight loss can be facilitated through dietary changes and increased exercise. Patients should be encouraged to set their exercise goal for 30-45 minutes of aerobic activity most days of the week. Adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan is also recommended. This plan promotes potassium and calcium intake, reduced sodium and fat intake, exercise, and moderation of alcohol consumption. The blood pressure reduction gained is roughly equivalent to that of single-drug therapy. However, patients taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers should be cautioned regarding potassium intake, because these medications can result in potassium retention. Any use of tobacco should be discouraged, and patients currently using tobacco should be counseled to quit, as this may help lower blood pressure.
C. Pharmacotherapy

Many medications are available to treat hypertension. Medication should be initiated at a low dose and titrated slowly to achieve desired blood pressure control. When available, formulations available in once-daily dosing are preferred due to increased patient compliance. Also useful are the many combination formulations now available that incorporate two different classes of drugs. Good clinical outcomes and trial data exist demonstrating reduction in complications of hypertension with blood pressure lowering by β-blockers, calcium channel blockers, thiazide diuretics, ACE inhibitors, and angiotensin II receptor blockers. When selecting a medication, side effect profile and patient comorbidities should help guide choice as well as the possible out-of-pocket cost that the patient may have to incur due to varying economic status and insurance coverage depending on the patient population being treated (please refer to Table 34-6 for price comparisons).

Favorable effects of selective antihypertensive agents may increase interest in their use. Thiazide diuretics slow demineralization in osteoporosis. β-Blockers are useful for atrial arrhythmias and fibrillation, migraine headache prophylaxis, thyrotoxicosis, and essential tremor. Calcium channel blockers are useful in Raynaud syndrome and some arrhythmias, and α-blockers are helpful in prostatism.

Unfavorable effects include cautions for the use of thiazide diuretics in patients with gout or a history of hypokalemia. β-Blockers should be avoided in patients with asthma or with second- or third-degree heart block. ACE inhibitors and angiotensin II receptor blockers have the potential to cause birth defects and thus should be avoided in women likely to become pregnant and discontinued in those who do become pregnant. Hyperkalemia may be caused by aldosterone antagonists and potassium-sparing diuretics.

Ethnic differences have been noted in the blood pressure response to monotherapy. African Americans, who have increased prevalence and severity of hypertension, have demonstrated blunted response to β-blockers and ACE inhibitors versus diuretics or calcium channel blockers. This effect is eliminated by combination therapy.

The recommendations that follow are based on JNC VII (Table 34-7). If a single drug does not achieve control, a second drug from a different class should be added. If the blood pressure remains more than 20/10 mm Hg above goals, two-drug therapy should be considered. Effective and timely control for most patients will be accomplished with at least two antihypertensive medications. The clinician should advise patients—especially those who are diabetic, have autonomic dysfunction, or are elderly—of the risk for orthostatic hypotension.

1. Diuretics—JNC VII recommends initially treating uncomplicated hypertension with diuretics, in the absence of a compelling reason to use another agent. This strong recommendation is based on the many randomized controlled trials that have demonstrated a superior response for diuretics in reduction of morbidity—including stroke, coronary artery disease, and congestive heart failure—and total mortality. ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) was one
of the largest such trials. It compared diuretics, calcium channel blockers, and ACE inhibitors as initial therapies in a population with a large number of African-American participants. The authors concluded that regardless of age, sex, or race, the use of diuretics in hypertensive, high-cardiovascular-risk patients was associated with similar risk of cardiovascular events equivalent to that of calcium channel blockers and ACE inhibitors, but was superior in performance in patients with underlying heart conditions including heart failure.

Diuretics should be used cautiously in patients with gout, as worsening hyperuricemia can result. They may also cause muscle cramps or impotence in some individuals. Diuretics may be effective at lower doses in patients with dyslipidemia and diabetes mellitus, but patients placed on higher doses must be observed closely for worsening hyperglycemia or hyperlipidemia. The thiazide diuretics are most commonly used in the treatment of hypertension, because loop diuretics are more likely to lead to electrolyte abnormalities such as hypokalemia and to have a shorter duration of action. However, loop diuretics can sometimes be useful in the treatment of hypertension in patients with chronic renal disease and a serum creatinine level greater than 2.5 mg/dL. The loop diuretics have found most utility in the treatment of congestive heart failure.

D, diuretic; BB, β-blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; Aldo ANT, aldosterone antagonist.

Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the blood pressure.

Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs.


### Table 34-7. Clinical trial guideline basis for compelling indications for individual drug classes.

<table>
<thead>
<tr>
<th>Compelling Indication&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Recommended Drugs</th>
<th>Clinical Trial Basis&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>D</td>
<td>BB</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High coronary disease risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the blood pressure.

<sup>b</sup>Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs.

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2. **β-Blockers**—Whether used as first-line agents in the case of compelling indications or in a drug therapy combination, β-blockers have favorable effects on migraine headache, hyperthyroidism, and anxiety. Patients should be informed that β-blockers may cause sexual dysfunction. These agents should be used with caution, if at all, in patients with a history of depression, asthma or reactive airway disease, second- or third-degree heart block, or peripheral vascular disease. In patients with mild to moderate reactive airway disease, β-blockers do not produce adverse effects in the short term. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that β-blockers can be used safely and effectively for type 2 diabetes mellitus, although there is concern that hypoglycemic episodes might be masked. Any patient with diabetes mellitus placed on a β-blocker should, therefore, be carefully monitored. Although previously not recommended, patients with congestive heart failure are now being successfully treated with β-blockers lacking intrinsic activity.
sympathomimetic activity, including two of the most studied agents, carvedilol and metoprolol. Careful use of these agents has shown promise in reducing mortality and improving ejection fraction in patients with New York Heart Association class II or III congestive heart failure.


3. Calcium channel blockers—There are two classes of calcium channel blockers: the dihydropyridine calcium channel blockers, which vasodilate (nifedipine, amlodipine, felodipine), and the rate-lowering calcium channel blockers (verapamil, diltiazem). They have relatively few side effects but may cause headache, nausea, rash, or flushing in some patients. Calcium channel blockers are not recommended as first-line therapy by JNC VII, although the guidelines suggest use of long-acting dihydropyridine calcium channel blockers as an alternative to β-blockers in patients with stable angina in ischemic heart disease, and in diabetics. nondihydropyridines, with their negative inotropic and chronotropic actions, have a beneficial role in atrial fibrillation and supraventricular tachyarrhythmias. Data for the use of calcium channel blockers in the elderly are mixed. The Systolic Hypertension in Europe (SYSEUR) trial, released in 1997, randomized 5000 elderly patients with isolated systolic hypertension to treatment with either placebo or the long-acting dihydropyridine calcium channel blocker nitrrendipine. In 2 years of follow-up there was significant reduction in stroke and cardiovascular events. Similar benefits were reported in elderly patients with hypertension and diabetes using nitrrendipine, although the findings were not superior to other antihypertensive agents. In African Americans, response to monotherapy using β-blockers, ACE inhibitors, and angiotensin II receptor blockers is blunted. This is not the case when using calcium channel blockers or diuretics. Use of combination regimens with a diuretic eliminates these differential responses.


4. ACE inhibitors—The ACE inhibitors stimulate vasodilation by blocking the renin-angiotensin-aldosterone system and inhibiting degradation of bradykinin. In several randomized, controlled clinical trials, these agents have been shown to reduce cardiovascular events in hypertensive patients (CAPP trial), including particular subgroups (high-risk patients >55 years [HOPE study], older men [ANBP study], and diabetic patients [FACET and ACAPP trials]). Compelling indications exist for ACE inhibitor use in patients with diabetes mellitus, congestive heart failure, and chronic kidney disease, and in patients who have had a MI with systolic dysfunction. ACE inhibitors have been shown to reduce progression of renal disease in African Americans (AASK trial) and diabetics but may increase the risk of stroke when used as monotherapy in African Americans (ALLHAT trial). These agents have also been shown to be more effective in promoting regression of left ventricular hypertrophy than diuretics, β-blockers, or calcium channel blockers. Left ventricular hypertrophy is considered one of the best predictors of cardiovascular events in patients with hypertension.

ACE inhibitors have relatively few side effects and are well tolerated by most patients. A dry cough may be reported in as many as 25% of patients. Because hyperkalemia may occur, particularly in patients who are also receiving potassium-sparing diuretics, periodic monitoring of electrolytes and serum creatinine should be performed.

ACE inhibitors must be used cautiously in patients with known renovascular disease and, when used, may need dose adjustment due to reduced drug clearance. When creatinine elevations exceed 30% above baseline, temporary cessation or reduction of dose is warranted. These agents should be used with extreme caution, if at all, in patients whose serum creatinine level exceeds 3.0 mg/mL. ACE inhibitors should not be used in patients with bilateral renal artery stenosis. Angioedema may occur with these agents, and this complication is two to four times more frequent in African Americans.

Wright JT et al: African American Study of Kidney Disease and Hypertension Study Group: effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. JAMA 2002;288:2421. [PMID: 12435255]

5. Angiotensin II receptor blockers (ARBs)—ARBs selectively block angiotensin II activation of AT_1 receptors, which are responsible for mediating vasoconstriction, salt and water retention, and central and sympathetic activation among others. Angiotensin II is still able to activate AT_2 blockers, facilitating vasodilation and production of bradykinin, which aids
in reduction of blood pressure. This class of medication is well tolerated and has a favorable side effect profile. ARBs are a good alternative for patients who cannot tolerate ACE inhibitor— it is associated cough, but should be avoided in patients with ACE inhibitor–associated angioedema. JNC VII does not recommend that ARBs be used for initial therapy in treatment of hypertension; however, compelling indications for use include heart failure, diabetes mellitus, and chronic kidney disease. ARBs have been shown to be more effective than β-blockers in preventing cardiovascular events in hypertensive patients with left ventricular hypertrophy, both with and without diabetes (LIFE trial). Renal protective effects of ARBs have been shown clinically to reduce the progression of nephropathy in diabetic hypertensive patients (RENAAL trial) and to reduce the incidence of new-onset diabetes (VALUE trial). Recently, it has been demonstrated that ARBs reduce subsequent events in patients with acute ischemic stroke (ACCESS study).

6. Other drugs—Other drugs, including α-blockers and direct vasodilators, are used to treat hypertension, although less commonly than the other classes of drugs. They are typically used as second- or third-line agents because of increased side effects. The ALLHAT trial suggested that α-blockers and direct vasodilators such as doxazosin may increase the risk of stroke and congestive heart failure when used in the treatment of hypertension, resulting in discontinuation of that arm of the trial. Eplerone (Inspra), a selective aldosterone receptor antagonist, was recently approved for the treatment of hypertension. Interest is focused on its use in patients with congestive heart failure or in combination with other antihypertensives; however, data on morbidity and mortality are not yet available.

7. Combination therapy—It is important to also consider the recent developments in combination therapy that allows patients who are on a multiple drug regimen to take less pills overall. This has been done with various antihypertensive classes such as combining an ACE-I and a diuretic. Many patients will eventually require a multi-drug regimen and by having to take less pills, compliance can be improved. Studies have examined the value in combining medications especially in the elderly who, often times, take many pills per day. One study showed favorable outcomes with an ACE-I/diuretic combination in the elderly over the course of 1 year. The drug was well tolerated and compliance was improved.

These medications tend to be more expensive for patients so it is important to weigh cost and compliance issues to maximize the likelihood of successful treatment. This is where the family physician’s role is crucial to the overall care of the patient. More research still needs to be conducted to see the long-term efficacy of various combination therapies, for example, combining a calcium channel blocker with a diuretic to combat the side effects of the latter. There may even be a place for combination medication for first-line therapy in patients with comorbidities such as diabetes mellitus (ie, ACE-I and diuretic). Current research is being done to examine these issues and how they will affect the care of hypertensive patients with different comorbidities.

D. Special Considerations

The drug selections noted in Table 34-7 are based on favorable outcome data from clinical trials and should be considered in light of current medications, tolerability, and blood pressure target goal.

1. Ischemic heart disease—β-Blockers are the first-line drug for patients with stable angina; alternatively, long-acting calcium channel blockers may be considered. ACE inhibitors should be added in patients with acute coronary syndromes, and consideration should be given to aldosterone antagonists post-MI.

2. Heart failure—ACE inhibitors and β-blockers are recommended for asymptomatic patients with ventricular dysfunction. Symptomatic or end-stage heart disease should be treated with ACE inhibitors, β-blockers, ARBs, aldosterone blockers, and loop diuretics.

3. Diabetes mellitus—All classes of antihypertensive medications have proven beneficial in reducing the incidence of cardiovascular disease and stroke in diabetic patients. The progression of diabetic nephropathy is reduced with ACE inhibitors or ARBs.

4. Chronic kidney disease—Goals for these patients include slowing deterioration of renal function and preventing
cardiovascular disease. Typically a combination of three drugs is needed to accomplish aggressive blood pressure management. ACE inhibitors and ARBs should be used and may be continued in patients with an increase in serum creatinine clearance of 35% above baseline, unless hyperkalemia develops. Increasing doses of loop diuretics are usually needed once the creatinine level reaches 2.5-3.0 mg/dL.

5. Cerebrovascular disease—The combination of an ACE inhibitor and thiazide diuretic has been shown to lower recurrent stroke rates.

6. Pregnancy—chronic hypertension occurs in up to 5% of pregnant women. It may result in perinatal morbidity and mortality for both mom and baby. It is important to differentiate chronic hypertension from other pregnancy related conditions including pregnancy induced hypertension (PIH) and preeclampsia because the management and treatments differ. According to the American College of Obstetrics and Gynecology (ACOG), chronic hypertension in pregnancy is defined as the use of antihypertensive medication before pregnancy, onset of elevated blood pressures prior to the 20th week of gestation, or the persistence of high blood pressure beyond the “usual” postpartum period. Mild hypertension is considered SBP greater than, or equal to, 140 mm Hg and/or DBP above 90 mm Hg. Severe is considered SBP greater than, or equal to, 180 mm Hg, and DBP above 110 mm Hg. Women with mild hypertension who are doing well generally do not need medication. Current evidence has yet to show whether antihypertensive therapy at this level improves perinatal outcomes. Studies have shown that outcomes are improved and thus medications are indicated when necessary to keep blood pressure under 160/110 mm Hg.

Classically, methyldopa and labetalol have been used to control severe hypertension in pregnancy with demonstrated improvement in outcomes. There is little difference in outcomes when comparing these medications. The use of β-blockers has been associated with a higher rate of babies that are small for gestational age. Calcium channel blockers, such as nifedipine, have proven neither beneficial nor detrimental to the health of either mom or baby in the long term. According to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, diuretics can potentiate the positive effects of other antihypertensives and are not contraindicated unless uteroplacental perfusion is already present due to another issue such as preeclampsia or intrauterine growth restriction (IUGR). Angiotensin-converting enzyme (ACE) inhibitors are contraindicated in the second and third trimesters due to an association with teratogenic effects including severely underdeveloped clavicular bone, renal failure, oligohydramnios, anuria, renal dysgenesis, and others including death.

E. Hypertensive Urgency and Emergency

Hypertensive urgencies are situations in which the blood pressure must be lowered within several hours, either due to an asymptomatic, severely elevated blood pressure (> 240/130 mm Hg) or a moderately elevated blood pressure (> 200/120 mm Hg) with associated symptoms, including angina, headache, and congestive heart failure. When such symptoms are present, even lower blood pressures may warrant more urgent treatment. Oral therapy can often be utilized with good response.

Hypertensive emergencies require treatment of elevated blood pressures within 1 hour to avoid significant morbidity and mortality. The symptomatology with which the patient presents warrants the immediate attention, not the actual blood pressure value itself. Such patients show evidence of end-organ damage from the elevated blood pressure, including encephalopathy (headache, irritability, confusion, coma), renal failure, pulmonary edema, unstable angina, MI, aortic dissection, and intracranial hemorrhage. Hypertensive emergency is an indication for hospital admission, and such patients typically require intravenous therapy with antihypertensives.

The goal of therapy is reduction of systolic pressure by 20-40 mm Hg and diastolic pressure by 10-20 mm Hg. The initial blood pressure target is a systolic blood pressure in the range of 180-200 mm Hg and a diastolic blood pressure in the range of 110-120 mm Hg. Blood pressure should not be lowered too quickly, because doing so can result in hypoperfusion of the brain and myocardium. Once initial treatment goals are achieved, blood pressure can subsequently be reduced gradually to more appropriate levels.

Nitroprusside is the preferred agent in emergencies such as hypertensive encephalopathy, because the infusion can be titrated easily to effect. When myocardial ischemia is present, intravenous nitroglycerin or intravenous β-blockers such as labetalol or esmolol are preferred. Once blood pressure has been brought under control using intravenous therapy, oral agents should be initiated slowly as intravenous therapy is gradually withdrawn. Whether a patient is being treated for hypertensive urgency, emergency, or benign hypertension, long-term therapy and lifestyle modification are essential. Patients must receive regular follow-up and meet the treatment goals established by JNC VII to prevent unnecessary morbidity and mortality.
ESSENTIALS OF DIAGNOSIS

- Two separate measurements of any combination of the following:
  - Random plasma glucose ≥200 mg/dL with polydipsia, polyuria, polyphagia, and/or weight loss
  - Fasting plasma glucose ≥126 mg/dL
  - Two-hour oral glucose tolerance test ≥200 mg/dL after a 75-g glucose load
  - A1C ≥6.5%. (by lab using a method that is NGSP certified and standardized to the DCCT assay.

General Considerations

The increasing acquisition of processed food combined with decreasing physical activity has led to an explosion in worldwide obesity and type 2 diabetes mellitus, with the greatest rate of increase in the young. Diabetes is now the sixth (www.cdc.gov/diabetes) leading cause of death in the United States, and its treatment consumes one in every seven health care dollars, with 63% spent on inpatient care. It is a major cause of blindness, renal failure, lower extremity amputations, cardiovascular disease, and congenital malformations. With 90% of patients receiving their care from primary care physicians, diabetes is the epitome of a chronic disease requiring a multidisciplinary management approach.


Pathogenesis

Diabetes develops from a complex interaction of genetic and environmental factors. In type 1 diabetes this leads to destruction of the pancreatic β cells and loss of the body’s ability to produce insulin. Type 2 diabetes is the result of increasing cellular resistance to insulin, a process accelerated by obesity and inactivity. A very small percentage of diabetic patients may have latent autoimmune diabetes with an onset similar to type 2, but with destruction of the β cells, and a more rapid progression to insulin dependence.


Prevention

Diet and exercise have been shown to reduce the risk of developing type 2 diabetes by 58%. Several medications including metformin may also delay its onset by a more modest percentage. Tight control of hyperglycemia and blood pressure significantly reduce the complications of diabetes, and a sustained reduction in hemoglobin A1c (HbA1c) is associated with significant cost savings within 1–2 years.

Motivating individuals to make lifestyle changes is difficult but cost-effective and safe, and can result in reduced obesity and hypertension and improvement of lipid profiles. A low-fat, high-fiber diet, modest exercise, and smoking cessation are modalities vastly superior to the complexities of the care of patients with diabetes and its complications.

Screening

Fasting glucose is the screening method of choice, although a random glucose is acceptable. The US Preventive Services Task Force (USPSTF) recommends screening for diabetes in adults with hypertension. The American Diabetes Association (ADA) recommends screening every 3 years beginning at age 45 especially if BMI $\geq 25 \text{ kg/m}^2$. Testing should occur earlier and more frequently in patients with risk factors listed in Table 35-1.

A consensus panel has recommended screening of overweight children (weight $>120\%$ of ideal or a body mass index (BMI) $>85\%$ percentile) every 2 years beginning at age 10 or onset of puberty with two of the following risk factors:

1. Family history of diabetes in first- or second-degree relative
2. High-risk racial or ethnic group (Native Americans, African Americans, Hispanics, or Pacific Islanders)
3. Signs of, or conditions associated with insulin resistance (eg. acanthosis nigricans, hypertension, dyslipidemia, and polycystic ovarian syndrome)

Universal screening in pregnancy is controversial. Table 35-2 lists the risk factors for which screening is recommended by the ADA and the diagnostic criteria in pregnancy.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Criteria for diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age $&gt;25$ years</td>
<td>Initial screen: 1-h glucose tolerance test (GTT) $50\text{-g glucose load between 10 and 28 weeks’ gestation}$</td>
</tr>
<tr>
<td>High-risk racial or ethnic group</td>
<td>Positive screen $\geq 135-140 \text{ mg/dL}$</td>
</tr>
<tr>
<td>Body mass index $\geq 25$</td>
<td>Diagnosis: 3-h GTT with a $100\text{-g glucose load}$ After an overnight fast with two abnormal values $\geq 95 \text{ mg/dL}$</td>
</tr>
<tr>
<td>History of abnormal glucose tolerance test</td>
<td>1 h $\geq 180 \text{ mg/dL}$</td>
</tr>
<tr>
<td>Previous history of adverse pregnancy outcomes usually associated with gestational diabetes</td>
<td>2 h $\geq 165 \text{ mg/dL}$</td>
</tr>
<tr>
<td>Diabetes in a first-degree relative</td>
<td>3 h $\geq 140 \text{ mg/dL}$</td>
</tr>
</tbody>
</table>

Complications
- Type 1: congenital abnormalities
- Type 2: macrosomia

Clinical Findings

A. Signs and Symptoms

The classic signs of diabetes are polyuria, polydypsia, and polyphagia, but first signs may be subtle and nonspecific.

Patients with type 1 diabetes exhibit fatigue, malaise, nausea and vomiting, irritability and weight loss. Abdominal pain is a common complaint in children. They present early in the disease process, but usually are quite ill at presentation, often already ketoacidotic. Signs and symptoms of ketoacidosis include those associated with dehydration (dry skin and mucous membranes, decreased skin turgor, tachycardia, and hypotension), tachypnea, and labored respirations with the classic “fruity” breath, abdominal pain, and confusion.

In type 2 diabetes symptoms are seen well after onset of the disease and may be due to complications. The classic signs are still prominent, but patients may also complain of fatigue, irritability, drowsiness, blurred vision, numbness or tingling in the extremities, slow wound healing, and frequent infections of the skin, gums, or urinary tract including candidal infections.

B. History and Physical Examination

The initial assessment for newly diagnosed diabetics is extensive (Table 35-3). The use of written checklists or questionnaires, electronic health records, or the assistance of a trained nurse or assistant can decrease physician time. Standing orders are an excellent way to make the visits more efficient.
and utilize nursing expertise (Table 35-4). It is important to update routine screening examinations (Papanicolaou [Pap], mammogram, colonoscopy) and ensure all immunizations are current (tetanus, pneumococcal, and yearly influenza vaccines). Interim visits focus attention on compliance and patients’ special issues with management (Table 35-5). Visit frequency is based on control of diabetes and the patient’s understanding and comfort. Patients initiating insulin therapy may require daily contact, by phone or e-mail. Those with poor control or making frequent changes may require weekly to monthly visits. When diabetes is well-controlled, visits are usually scheduled quarterly. Novel approaches to patient visits, such as group visits where several patients are seen simultaneously, maximize physician teaching time and allow sharing of ideas and information among the patients.

### Table 35-3. Necessary elements of the initial history and physical examination in patients with diabetes mellitus.

<table>
<thead>
<tr>
<th>History</th>
<th>Physical Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current and previous symptoms consistent with diabetes</td>
<td>Height, weight, and body mass index (BMI)</td>
</tr>
<tr>
<td>Weight changes/history of obesity</td>
<td>Blood pressure (including orthostatic)</td>
</tr>
<tr>
<td>Eating patterns/nutritional status (growth and development in children)</td>
<td>Ophthalmoscopic examination</td>
</tr>
<tr>
<td>Exercise history and ability to exercise</td>
<td>Oral examination</td>
</tr>
<tr>
<td>Details of previous treatment; HbA₁c, and monitoring records</td>
<td>Thyroid palpation</td>
</tr>
<tr>
<td>Current treatment (medications, diet)</td>
<td>Cardiac examination</td>
</tr>
<tr>
<td>Previous acute complications (Ketoacidosis, hypoglycemia)</td>
<td>Evaluation of pulses, including carotid</td>
</tr>
<tr>
<td>History of infections particularly of skin, feet, and genitourinary system</td>
<td>Abdominal examination</td>
</tr>
<tr>
<td>History of hypertension, hyperlipidemia, coronary artery disease, and insulin resistance</td>
<td>Skin examination (including injection sites if applicable)</td>
</tr>
<tr>
<td>Chronic complications (eg, retinopathy, nephropathy, neuropathy, sexual dysfunction, and gastrointestinal, vascular, or foot problems)</td>
<td>Neurologic examination with particular attention to reflexes, vibratory, senses, light touch (monofilament examination of both feet), and proprioception</td>
</tr>
<tr>
<td>History of gestational diabetes, large-for-gestational-age infants, or miscarriages</td>
<td></td>
</tr>
<tr>
<td>Medications and allergies</td>
<td></td>
</tr>
<tr>
<td>Family history of diabetes, endocrine disorders, or heart disease</td>
<td></td>
</tr>
<tr>
<td>Tobacco, alcohol, and drug use</td>
<td></td>
</tr>
<tr>
<td>Lifestyle, cultural, psychosocial, educational, and economic factors influencing control</td>
<td></td>
</tr>
</tbody>
</table>

### Table 35-4. Standing orders for diabetic patients.

1. Update the electronic record or place an updated flowsheet in the patient’s chart.
2. Monitor and record blood pressure in the same arm at each visit.
3. Measure and record the patient’s weight.
4. If HbA₁c has not been evaluated in the past 6 mo, complete a requisition and attach to the patient’s chart.
5. If urinalysis and microalbumin testing have not been done in the past year:
   a. Perform a urine dipstick and record the results on the flowsheet.
   b. Complete a requisition for a urine microalbumin test and attach it to the patient’s chart.
6. If a lipid profile has not been obtained in the past year, complete a requisition and attach it to the patient’s chart.
7. If a dilated eye examination has not been performed in the past year, complete a referral for an ophthalmology examination and attach it to the patient’s chart.
8. Ask the patient to remove his/her shoes and socks.
   a. Palpate dorsalis pedis and posterior tibial pulses.
   b. Inspect the skin for any skin breakdown.
   c. Record the findings on the patient’s flowsheet.
9. Check to see if patient has received a pneumococcal vaccine, a dt or Tdap vaccine in the last 10 years, and a flu shot for the current season. If patient has not received the flu shot, administer following standard clinic protocol.

Physician Signature: ______________ Date: ____________

### Table 35-5. Features of the interim history and physical examination.

<table>
<thead>
<tr>
<th>History</th>
<th>Physical Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemic episodes</td>
<td>Weight and BMI</td>
</tr>
<tr>
<td>Glucose monitoring results</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>Adjustments in therapeutic regimen</td>
<td>Funduscopic examination</td>
</tr>
<tr>
<td>Complications</td>
<td>Cardiac examination</td>
</tr>
<tr>
<td>Medications</td>
<td>Brief skin examination</td>
</tr>
<tr>
<td>Psychosocial issues</td>
<td>Foot evaluation (visualization, pedal pulses, and monofilament examination [see Figure 35-1])</td>
</tr>
<tr>
<td>Lifestyle changes</td>
<td></td>
</tr>
<tr>
<td>Patient goals and motivation</td>
<td></td>
</tr>
</tbody>
</table>

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hypothesis is common especially in women. Depending on age and duration of disease an electrocardiogram (ECG) may be performed, but as microalbuminuria is a marker for cardiovascular disease, an ECG should be performed once microalbuminuria is detected. HgbA\(_1c\) is measured every 3 months. Random microalbumin levels or microalbumin/creatinine ratios may be used for screening and/or monitoring, but patients may require a 24-hour urine for protein and creatinine clearance when there are significant changes. Common findings are elevations in glucose, HgbA\(_1c\), triglycerides, BUN and creatinine, and microalbumin with decreased HDL (high-density lipoprotein) cholesterol.

Complications

Preventing and delaying progression of all complications in patients with diabetes is dependent on lifestyle modification, tight control of blood glucose and blood pressure, and smoking cessation. The ACCORD trial, however, found that intensive glycemic control (HgbA\(_1c\) ≤6%) did not lower the incidence of adverse microvascular outcomes.

A. Ketoacidosis

Ketoacidosis occurs when there is insufficient insulin to meet the body’s needs, resulting in increased gluconeogenesis, fatty acid oxidation, and ketogenesis. This leads to metabolic acidosis, osmotic diuresis, and dehydration. Ketoacidosis is one of the leading causes of death in children with diabetes with an incidence in children of about 8 per 100 person-years.

It increases with age in girls, and is highest for children with poor control, inadequate insurance, or psychiatric disorders. Treatment involves rehydration with normal saline and an insulin drip and the patient should be monitored in a telemetry bed. Potassium is added to fluids when serum glucose approaches 250 mg/dL. Labs are initially monitored hourly, and the insulin drip is continued until acidosis is resolved and ketones are cleared.

B. Infections

Patients with diabetes are at greater risk for infections including community-acquired pneumonia (particularly pneumococcal), influenza, cholecystitis, urinary tract infections, and pyelonephritis. Persistent fever and flank pain for more than 3-4 days despite appropriate antibiotic treatment should elicit an evaluation (preferably by CT) for a perinephric abscess. Fungal infections are frequently seen, especially vaginal candidiasis, but also mucormycosis, eye and skin infections. Foot infections include cellulitis, osteomyelitis, plantar abscesses, and necrotizing fasciitis.

C. Nephropathy

Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) in the United States. The incidence is much higher in type 1 diabetes, but the prevalence is higher in type 2. Risk factors include poor glycemic control, smoking, hypertension, family history, and glomerular hyperfiltration. All patients should be screened yearly with a microalbumin or microalbumin/creatinine ratio. Microalbuminuria is defined as 30–300 mg protein in a 24-hour urine collection, a more accurate but significantly more cumbersome test. More than 300 mg/24 hour constitutes macroalbuminuria or nephropathy.

Intensive therapy reduces the incidence of microalbuminuria with greatest benefit seen with tight control early in the disease. The risk of microalbuminuria increases by 25% for each 10% rise in HgbA\(_1c\). Angiotensin-converting enzyme (ACE) inhibitors are the drugs of choice. Ramipril has been shown to reduce ESRD and death by 41% and proteinuria by 20% compared with amlodipine. Angiotensin II receptor blockers (ARBs) have comparable efficacy and should be used when use of ACE inhibitors is limited. Referral to a nephrologist is indicated in the presence of rising creatinine or microalbuminuria.


D. Retinopathy

About 20% of type 2 diabetic patients show signs of retinopathy at the time of diagnosis, and progression is orderly from mild abnormalities (small retinal hemorrhages) to proliferative retinopathy with growth of new vessels on the retina and into the vitreous culminating in vision loss.
The risk of retinopathy increases with increasing HgbA1c and duration of the disease, so improving glycemic control may delay onset. Patients with type 1 diabetes may begin yearly ophthalmology visits 5 years after diagnosis, but type 2 diabetics should begin yearly office visits as soon as the diagnosis is made. Laser photocoagulation therapy is currently the only treatment option once the disease progresses. In the ACCORD trial, intensive glycemic therapy lowered retinopathy but not vision loss.


E. Neuropathy

Peripheral neuropathy leads to a loss of sensation and pain in the extremities and is the major cause of foot problems in diabetic individuals. Treatment of peripheral neuropathy remains symptomatic. Pregabalin (Lyrica) is indicated for its treatment, but other treatment options that may be effective include nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants (amitriptyline, desipramine), anticonvulsants (gabapentin, carbamazepine, lamotrigine), duloxetine, opioids, topical capsaicin cream and lidocaine patches, transcutaneous electrical nerve stimulation, and alternative therapies (relaxation therapy, biofeedback).

Autonomic neuropathy may be difficult to detect, and patients should be asked about symptoms of orthostatic hypotension, diarrhea or constipation, incontinence, impotence, and heat intolerance. It is also important to check for any of the following: resting tachycardia, orthostatic hypotension, dependent edema (to assess impaired venoarteriolar reflex), and decreased diameter of dark-adapted pupil. Gastrointestinal motility may be improved with metoclopramide or erythromycin.


F. Cardiovascular Disease

Heart disease is the leading cause of death in patients with diabetes. Men have double and women four to five times the risk for myocardial infarction (MI) with a higher incidence of diffuse, multivessel disease, plaque rupture, superimposed thrombosis, and in-hospital mortality. Five-year survival following angioplasty or coronary artery bypass graft (CABG) is lower in patients with diabetes; however, survival rates are significantly higher with CABG. Aspirin therapy at 81 mg/d is indicated for men older than 50 and women older than 60 years of age with one additional cardiovascular risk factor. Smoking cessation must be emphasized.

ACE inhibitors are the first-line choice for treatment of hypertension in diabetic patients producing a significant decrease in stroke, MI, cardiac death, post-MI mortality, and ischemic events following revascularization procedures. In the Heart Outcomes Prevention Evaluation (HOPE) trial the use of ACE inhibitors correlated with a 34% reduction in the onset of new cases of diabetes and a mild improvement in lipid profiles. They may be used in all diabetic patients with systolic blood pressure more than 100 mm Hg and for hypertension in patients with signs of insulin resistance. They can be used at all creatinine levels, but potassium levels must be carefully monitored as creatinine rises. The most troublesome side effect is a bradykinin-induced dry cough, and they are contraindicated in pregnancy. Increasing data support the use of angiotensin receptor blockers for cardiovascular risk reduction as well, and they are better tolerated than ACE inhibitors.

Thiazide diuretics and β-blockers are effective in lowering blood pressure and have been shown to reduce cardiovascular morbidity and mortality. Although they can have some effect on glucose control, they are acceptable for use in diabetes if used judiciously. For further information about treatment of hypertension in patients with diabetes, see Chapter 34.


G. Hyperlipidemias

Patients with type 2 diabetes often have a distinct triad of elevated triglyceride and LDL (low-density lipoprotein) levels with decreased HDL levels. Each of these abnormalities has been shown to be an independent factor in atherogenesis. Current recommendations are to maintain total cholesterol below 200 mg/dL, triglycerides below 150 mg/dL, and LDL cholesterol less than 100 mg/dL or below 70 mg/dL in the presence of cardiovascular disease.

Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the drugs of choice in treating hyperlipidemia in diabetic patients. Most outcome studies on lipid management have excluded patients with diabetes, but subgroup analysis shows a reduction in cardiovascular events of 25%-37% with the use of statins to improve the lipid profile. They are contraindicated in pregnancy and must be used with extreme caution in adolescents. Fish oil is helpful for reducing triglycerides, but fibrates are sometimes needed as well. (See Chapter 21 for further information).

H. Diabetic Feet

Diabetes is the leading nontraumatic cause of foot amputation and Charcot foot in the United States due to the combination of neuropathy, altered foot structure, and vasculopathy.
Fifteen percent of diabetics will have a foot ulcer, and 20% of these will lead to amputation. Feet should be examined at every office visit and patients instructed in good foot care. Medicare will pay for special shoes and the fitting of these shoes by a podiatrist or orthotist; however, careful attention to foot care by primary providers was found to be more effective at preventing ulcers than special shoes or inserts.

Treatment of diabetic foot ulcers requires removing pressure on the ulcer and good wound care with deep debridement and appropriate dressings. The best indication of ability to heal is an intact pulse, and revascularization may be necessary if pulses are absent. Betadine is not appropriate for cleaning as it kills normal tissue; antibiotics should be used only if infection is clearly present as they have been shown to retard healing in the noninfected foot. Wound cultures almost always yield multiple organisms, and are usually not helpful unless taken from the bone in osteomyelitis. Becaplermin (Regranex) can aid in healing, but is very expensive. The test of choice for diagnosis of osteomyelitis is the magnetic resonance imaging (MRI), although bone scans are a good alternative. Treatment efficacy can be followed by monitoring the sedimentation rate.

### Treatment

Glycemic control is cost effective in minimizing microvascular complications, and blood pressure control independently affects the progression of microvascular and macrovascular complications. There is good clinical evidence to support aggressive management of hyperglycemia, hypertension, and hyperlipidemia to reduce nephropathy, retinopathy, neuropathy, and cardiovascular events.

The management goals are to maintain fasting glucose levels of 80-100 mg/dL and HgbA1c levels <7%; the American College of Endocrinology recommends a 2-hour postprandial glucose < 140 mg/dL and has set a goal for HgbA1c at <6.5%. Blood pressure should be maintained below 130/80 mm, but lower pressures incur more benefit with no recognized threshold. Less stringent treatment goals may be appropriate for patients with limited life expectancies, in the very young, in older adults at risk for hypoglycemia, or in patients with comorbid conditions. See evidence-based recommendations in Table 35-6.

### A. Education

Education is the cornerstone of diabetes management, and it is imperative that the patient take ownership of the disease and develop skills for managing it. Clinicians, nurse practitioners, nurses, diabetes educators, dietitians, and others can all contribute to the educational process using didactic discussions, reading materials, Internet sites, and self-tests. Patients need to have a basic understanding of diabetes and the complications of both the disease and its treatments. This includes the interrelationship of lifestyle changes, smoking cessation, home monitoring, management of blood pressure and lipids, and foot and skin care. Additionally they need to know and understand their medication and insulin regimens and how to recognize problems with medications. Some patients will need instruction in special situations that may

<table>
<thead>
<tr>
<th>Table 35-6</th>
<th>Evidence-based recommendations for diabetes.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
<td><strong>Source</strong></td>
</tr>
<tr>
<td>1. In patients with type 2 diabetes, the risk of diabetic complications was strongly associated with previous hyperglycemia. Any reduction in HgbA1c is likely to reduce the risk of complications, with the lowest risk being in those with HgbA1c values in the normal range (&lt;6.0%).</td>
<td>SOR-B: <a href="http://www.icsi.org/knowledge/detail.asp?cat-ID=29&amp;itemID=182">http://www.icsi.org/knowledge/detail.asp?cat-ID=29&amp;itemID=182</a></td>
</tr>
<tr>
<td>2. Both vigorous exercise and moderate exercise reduce the risk of type 2 diabetes in women. The more exercise taken, the greater the risk reduction.</td>
<td>RCT: <a href="http://www.jr2.booth/hliving/excer2diab.html">http://www.jr2.booth/hliving/excer2diab.html</a></td>
</tr>
<tr>
<td>4. Patients with microalbuminuria or proteinuria should be considered for angiotensin II antagonist therapy.</td>
<td>SOR-A: <a href="http://www.guideline.gov/summary/summary.aspx?doc_id=3078">http://www.guideline.gov/summary/summary.aspx?doc_id=3078</a></td>
</tr>
</tbody>
</table>
Table 35-7. Daily dietary recommendations.

<table>
<thead>
<tr>
<th>Carbohydrates</th>
<th>% of daily intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fats</td>
<td>%</td>
</tr>
<tr>
<td>Protein</td>
<td>%</td>
</tr>
<tr>
<td>Sodium</td>
<td>% of daily intake</td>
</tr>
</tbody>
</table>

- Carbohydrates: 55%-60% of daily intake. Whole grains, low-fat dairy, 5 daily servings of fruits, vegetables, high fiber.
- Fats: <30% saturated. <7%-10% cholesterol > 200-300 mg.
- Protein: 10%-20% of daily intake. 10%-15% in the presence of Microalbuminuria.
- Sodium: <2400 mg or if hypertensive.

C. Exercise

Exercise increases strength and endurance, HDL cholesterol, and insulin sensitivity, reduces stress, improves circulation, digestion, sleep, energy levels, and self-esteem, controls appetite and reduces weight, and lowers heart rate, blood pressure, lipid levels, and blood glucose, thereby delaying the onset of diabetes and reducing the risk of cardiovascular disease. Prescribe a regular exercise program adapted to complications for all patients including moderate aerobic or physical activity for 20-60 minutes at least every 48 hours. Older patients and those at increased risk of coronary artery disease should have a careful physical examination and an exercise stress test prior to beginning or significantly advancing an exercise program and should avoid sudden strenuous exercise. Athletes with type 1 diabetes may not participate in strenuous exercise when their blood glucose is more than 300 mg/dL or more than 250 mg/dL with urine ketones.

D. Home Glucose Monitoring

The consensus panel of the American Diabetes Association (ADA) has recommended that all patients with diabetes should perform home glucose monitoring. Eighty-four percent of patients who monitor their blood glucose are within 20% of their target range. Newer glucose monitors are smaller, more rapid, require less blood, and have memory and download capabilities. A wristwatch style device and a monitoring system are available but are very expensive.

Type 1 diabetics should monitor blood glucose at least four times a day. Patients with type 2 diabetes can monitor once or twice a day with fasting and postprandial values most helpful. However, when values are stable and no changes are being made, the cost of monitoring outweighs the utility.

E. Pharmacological Therapy

In most cases, therapy is begun with one medication and dosage is increased before adding a second, but two may be synergistic. Efficacy is variable between drugs and individuals, but expected lowering of HgbA1c is 0.5%-2.0%. Choices of medication should be made to maximize efficacy and minimize side effects (Table 35-8). When patients with type 2 diabetes present with high serum glucose levels, insulin can be used initially in combination with an oral medication to lower glucose levels to a manageable level. Maintaining tight control of blood glucose early in the course of the disease has been shown to delay the complication rate later in the disease.

1. Biguanides—Metformin is the initial choice in most obese diabetics as it is weight neutral and reduces cardiovascular deaths and all-cause mortality. It is used in metabolic syndrome to delay the onset of diabetes and is commonly used in children with type 2 diabetes. Because it is associated with lactic acidosis (mortality 50%), metformin cannot be used in patients with renal insufficiency or when using IV contrast material. It is a category B in pregnancy and can be used in children but not while breastfeeding. **Metformin may induce Vitamin B12 malabsorption, and regular B12 monitoring is advised.**

2. Sulfonylureas—The oldest oral medications for diabetes, they can be used in patients with hepatic or renal insufficiency and cautiously in the elderly. They should be taken 1 hour before meals to induce insulin secretion or at bedtime.

B. Nutrition

Individualization of nutrition therapy is necessary to achieve glucose and lipid goals, health, and well-being. Dietary recommendations for diabetic patients are summarized in Table 35-7. A weight loss of 10%-15% significantly improves glucose control and insulin sensitivity and decreases mortality and can be achieved with a reduction of 300-400 kcal/d. Structured programs designed to promote lifestyle changes that include education, decreased fat and overall caloric intake, regular exercise, and follow-up have been shown to produce a long-term weight loss of about 5%-7%. The Mediterranean diet with exercise and not smoking can prevent the onset of diabetes and lower risk of death by more than 50%. Moderate use of nonnutritive sweeteners is acceptable, but alcohol intake should be limited. Individuals receiving fixed daily doses of insulin should try to maintain a consistent daily caloric intake. Those on intensive insulin therapy should adjust their insulin based on the carbohydrate content of their meals. Weight-loss surgery can lead to normalization of blood glucose, significant weight loss, and resolution of diabetes.
where they limit hepatic glucose production. About 20% of patients will not respond, and sulfonylureas lose efficacy over time. Glyburide has the greatest potential for hypoglycemia, but is a category B in pregnancy. Glimepiride has a more rapid onset and longer duration of action but induces less hypoglycemia, and may be the best choice in patients with known coronary disease.

3. Thiazolidinediones—Useful as an adjunct medication or with marked insulin resistance. Rosiglitazone has been

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dosage Range (mg)</th>
<th>Mechanism of Action</th>
<th>Advantages</th>
<th>Side Effects and Precautions</th>
<th>Approx. Cost (1 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td></td>
<td>↓ gluconeogenesis in the liver ↑ insulin sensitivity</td>
<td>No hypoglycemia, lowers insulin levels, possible weight loss, improves lipids and endothelial function, decreases mortality</td>
<td>Nausea and diarrhea, not for use when creatinine is ≥1.5 mg/dL, caution with congestive heart failure and hepatic dysfunction</td>
<td>On generic $4 lists</td>
</tr>
<tr>
<td>Metformin (Glucophage)</td>
<td>500-2500</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin XR (Glucophage XR)</td>
<td>500-2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td></td>
<td>Induce insulin secretion from pancreatic β cells</td>
<td>Can be used in renal or hepatic failure</td>
<td>Hypoglycemia, weight gain</td>
<td>On generic $4 lists</td>
</tr>
<tr>
<td>Glipizide (Glucotrol)</td>
<td>5-40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glipizide XL (Glucotrol XL)</td>
<td>2.5-20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide (DiaBeta, Micronase)</td>
<td>2.5-20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide, micronized (Glynase)</td>
<td>1-8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride (Amaryl)</td>
<td>1-6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride (Amaryl)</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td></td>
<td>Insulin sensitizers in muscle and adipose tissue</td>
<td>Cannot use in class III or IV heart failure, must monitor liver function tests</td>
<td></td>
<td>$150-250</td>
</tr>
<tr>
<td>Pioglitazone (Actos)</td>
<td>15-45</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone (Avandia)</td>
<td>2-8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td></td>
<td>Induce secretion of insulin from pancreatic β cells</td>
<td>Can be used in renal failure, rapid onset and short half-life</td>
<td>Caution in hepatic insufficiency</td>
<td>$70-90</td>
</tr>
<tr>
<td>Repaglinide (Prandin)</td>
<td>0.5-2 tid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nateglinide (Starlix)</td>
<td>60-120 tid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td></td>
<td>Inhibit breakdown of disaccharides and delay carbohydrate absorption in brush border of the small intestine</td>
<td>No hypoglycemia</td>
<td>Flatulence, cannot use with GI disorders, cirrhosis, Cr &gt;2 mg/dL, caution in hepatic insufficiency</td>
<td>$70-80</td>
</tr>
<tr>
<td>Acarbose (Precose)</td>
<td>25-100 tid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miglitol (Glyset)</td>
<td>25-100 tid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td></td>
<td>Block the breakdown of natural incretins</td>
<td>Once a day oral, do not cause hypoglycemia, lowers postprandial glucose</td>
<td>Nausea and vomiting, must decrease dose in renal impairment</td>
<td>$150-170</td>
</tr>
<tr>
<td>Sitagliptin (Januvia)</td>
<td>100 (25-50 renal impairment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saxagliptin (Onglyza)</td>
<td>2.5 and 5 mg daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incretin mimetics</td>
<td></td>
<td>Enhance glucose-dependent insulin secretion, suppress inappropriate glucagon secretion and slow gastric emptying</td>
<td>Early satiety and weight loss</td>
<td>Nausea and vomiting, hypoglycemia, exenatide associated with hemorrhagic or necrotizing pancreatitis</td>
<td>$180-225</td>
</tr>
<tr>
<td>Exenatide (Byetta)</td>
<td>5C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pramlintide (Symlin)</td>
<td>5-10 μg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15-120 μg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
shown to increase triglycerides and nonfatal myocardial infarctions. Pioglitazone decreases triglyceride levels by 33% and increases HDL cholesterol, but improvement in outcomes has not been shown. It may take 12 weeks for the medication to reach its maximum potential, so increases in dosage should be made only after several weeks on the same dose. Teratogenic in rats, they are not recommended for use in pregnancy or in children.

4. Meglitinides—These rapid acting medications are taken only with meals and are useful in patients whose fasting glucose levels are well controlled but who have high postprandial values or for patients who eat few or irregular meals. Nateglinide has a more rapid onset and shorter duration of action than repaglinide and is indicated for combination therapy with metformin.

5. α-Glucosidase inhibitors—Taken only with meals, they blunt postprandial hyperglycemia. Therapy should be initiated at a low dose and increased slowly to minimize side effects. If they are used with a sulfonylurea or insulin, and hypoglycemia occurs, the patient must be treated with simple sugars (glucose or lactose), not sucrose. Efficacy is altered with digestive enzymes, antacids, or cholestyramine. Serum transaminase levels must be followed every 3 months for the first year.

6. DPP-4 inhibitors—Glucagon-like peptide 1 (GLP-1) stimulates insulin secretion and biosynthesis and inhibits glucagon secretion and gastric emptying. It is degraded by dipeptidyl peptidase-4 (DPP-4). Sitagliptin inhibits DPP-4 effectively increasing GLP-1. Taken once daily, it significantly decreases postprandial glucose levels.

7. Incretin mimetics—Exenatide is a GLP-1 analog derived from Gila monster saliva and given by subcutaneous injection prior to morning and evening meals. It is used as an adjunct to metformin, sulfonylureas, or thiazolidinediones. It may be even more efficacious if given in a once weekly dose. Pramlintide is an analog of human amylin, given as a subcutaneous injection with insulin prior to meals. Both increase insulin in response to glucose at meals, promote satiety, and may lead to significant weight loss.

6. Combination therapy—Combining drugs with different mechanisms of action is most efficacious, but caution must be exercised in combining drugs with similar side effects (TZDs and α-Glucosidase inhibitors are both hepatotoxic). Metformin can be combined with any of the other medications, and there are now multiple commercial combinations of metformin, thiazolidinediones, sulfonylureas, and sitagliptin.

7. Insulin—The UKPDS trial did not show any increase in cardiovascular disease due to the use of insulin but did demonstrate a significant improvement in all complications of diabetes with tight control. A long-acting insulin provides a basal rate that minimizes hepatic glucose production. A rapid-acting insulin is used with meals to minimize the postprandial insulin peak.

The new synthetic insulins, lispro, aspart, and glulisine, have a short onset, rapid peak, and 2-4 hour duration of action more closely mimicking the pharmacokinetics of human insulin in vivo (Table 9). They are preferred over regular insulin with its slower onset and longer duration of action necessitating regular snacking. They may be combined with a protamine form in a 75/25 mix producing an insulin with both a short- and long-acting component.

The long-acting insulin analogs glargine and detemir are peakless insulins with a consistent 24-hour duration. They are less soluble in subcutaneous tissue, prolonging absorption, and can be used with any of the short-acting insulins and oral medications. They cannot, however, be mixed with other insulins. They are usually taken once a day but may be divided into two doses (especially helpful when giving over 100 units). Neutral protamine hagedorn (NPH) insulin has a duration of

<table>
<thead>
<tr>
<th>Rapid acting</th>
<th>Onset of Action</th>
<th>Peak (h)</th>
<th>Duration (h)</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro (Humalog)</td>
<td>15 min</td>
<td>0.5-1.5</td>
<td>2-4</td>
<td>$50-100</td>
</tr>
<tr>
<td>Aspart (NovoLog)</td>
<td>15 min</td>
<td>1-3</td>
<td>3-5</td>
<td></td>
</tr>
<tr>
<td>Glulisine (Apidra)</td>
<td>15 min</td>
<td>1-1.5</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Short acting</th>
<th>Onset of Action</th>
<th>Peak (h)</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular (Humulin)</td>
<td>30 min</td>
<td>2-4</td>
<td>5.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate</th>
<th>Onset of Action</th>
<th>Peak (h)</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH (Novolin)</td>
<td>1-3 h</td>
<td>5-7</td>
<td>16-18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Long acting</th>
<th>Onset of Action</th>
<th>Peak (h)</th>
<th>Duration (h)</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine (Lantus)</td>
<td>1 h</td>
<td>None</td>
<td>24</td>
<td>$80-120</td>
</tr>
<tr>
<td>Detemir (Levemir)</td>
<td>1 h</td>
<td>None</td>
<td>20</td>
<td>$100-140</td>
</tr>
</tbody>
</table>

Table 35-9. Available insulins.
less than 24 hours necessitating twice daily dosing with peaks occurring in the afternoon and early morning. Dosage changes are made based on finger sticks taken about 8 hours following the dose. Its primary utility lies in its low cost.

When initiating insulin therapy in type 1 diabetics, the total insulin requirement for 24 hours should be estimated. Half of this amount may be given as a long-acting insulin and the other half as a rapid-acting insulin. Adjustments in the long-acting insulin dosage are based primarily on fasting glucose levels. The rapid-acting portion can be divided with 40% given before breakfast, 40% before dinner, and the remaining 20% prior to lunch. It should then be adjusted based on caloric intake and resulting postprandial finger stick glucose levels.

Bioavailability with insulin changes with the site of injection with the abdomen the fastest. It is recommended that injections be rotated within the same area.

8. Insulin pump—Current insulin pumps weigh about 4 oz and are about the size of a beeper, allowing for continuous use of short-acting insulin with a more consistent absorption rate. Half of the insulin is given continuously as a basal dose and the other half is divided into mealtime boluses. Patients must monitor their blood glucose three or more times a day and count carbohydrates at meals. When compliant, patients can achieve tighter control with the pump while gaining more flexibility in eating habits and a more normal lifestyle with fewer episodes of severe hypoglycemia, a reduction of total insulin usage, and less weight gain. Particularly good candidates for insulin pump therapy are patients who are difficult to control or have wide glucose swings, have erratic schedules, or have a significant dawn phenomenon, pregnant women, and teenagers with poor control and/or frequent episodes of ketoacidosis.

9. Transplant—Ilet cells can now be infused abdominally in patients with type 1 diabetes. The process may require more than one injection, but patients usually have a substantial decrease in their insulin requirement or can give up insulin entirely. Each transplant requires only two cadaver donors. The limited supply of donated organs will continue to make this an option only for those diabetics who are most difficult to control.


G. Cultural Considerations

Diabetes is a disease that currently affects all races and nationalities. In the United States, most minorities are at greater risk for diabetes and its complications. Asian Americans develop diabetes at a younger age and lower body mass and are more likely to develop ESRD. African Americans have greater rates of obesity and higher insulin resistance and four times the rate of nephropathy. Peripheral vascular disease is 80% more common in Latino Americans. Native Americans have high rates of foot infections and some tribes have diabetes rates higher than 50% coupled with unique beliefs about their disease and American medicine. Helping them to maintain a healthy lifestyle consistent with their heritage is the best way to avoid cultural gaffes and to affect long-term results.


H. Systems Approach

Development of guidelines helps practitioners to cover all areas of diabetes care in an efficient manner. Diabetes
improvement models that target education and quality review of providers have been shown to improve provider compliance. Use of electronic medical records or computerized registry systems can provide recurrent review for all aspects of diabetes care, and can be used for call-back and reminder systems, so fewer patients are lost to care. Most importantly, the patients must become empowered and take ownership of their disease. The health care team is a resource for assisting them in the care of their disease. Diabetes is a complicated, chronic disease with a complex management, requiring a multidisciplinary team approach. The evidence is clear that lifestyle change is the most efficacious and cost-effective therapy for this deadly disease.

Web Sites

- American Association of Diabetes Educators: http://www.diabeteseducator.org/
- American Diabetes Association (ADA): http://www.diabetes.org/
- Centers for Disease Control and Prevention (CDC), Division of Diabetes: http://www.cdc.gov/diabetes/
- Joslin Diabetes Center: http://www.joslin.org/
- National Institute of Diabetes and Digestive and Kidney Diseases: http://www2.niddk.nih.gov/
THYROID DISORDERS

Thyroid disorders affect 1 in 200 adults but are more common in women and with advancing age. The incidence of hypothyroidism, for instance, is 0.3–5 cases per 1000 individuals per year, including 7% of women and 3% of men aged 60–89 years. Hypothyroidism is much more common than hyperthyroidism, nodular disease, or thyroid cancer. Thyroid nodules occur in 4%–8% of all individuals and, like other thyroid problems, increase in incidence with age.

Thyroid disease is more common in people who have conditions such as diabetes or other autoimmune diseases (eg, lupus); in those with a family history of thyroid disease or a history of head and neck irradiation; and in patients who use certain medications, including amiodarone and lithium. Recent guidelines from the American Thyroid Association suggest that all adults have their serum thyroid-stimulating hormone (TSH) concentrations measured, beginning at age 35 and every 5 years thereafter.

HYPOTHYROIDISM

General Considerations

Causes of hypothyroidism are outlined in Table 36-1. The most common noniatrogenic condition causing hypothyroidism in the United States is Hashimoto thyroiditis. Other common causes are post–Graves disease, thyroid irradiation, and surgical removal of the thyroid. Hypothyroidism may also occur secondary to hypothalamic or pituitary dysfunction, most commonly in patients who have received intracranial irradiation or surgical removal of a pituitary adenoma. In addition, some patients may have mild elevations of TSH despite normal thyroxine levels, a condition termed subclinical hypothyroidism.

Clinical Findings

A. Symptoms and Signs

Patients with hypothyroidism present with a constellation of symptoms that can involve every organ system. Symptoms include lethargy, weight gain, hair loss, dry skin, slowed mentation or forgetfulness, depressed affect, cold intolerance, constipation, hair loss, muscle weakness, abnormal menstrual periods (or infertility), and fluid retention. Because of the range of symptoms seen in hypothyroidism, clinicians must have a high index of suspicion, especially in high-risk populations. In older patients, hypothyroidism can be confused with Alzheimer disease or other conditions that cause dementia. In women, hypothyroidism is often confused with depression.

Physical findings that can occur with hypothyroidism include low blood pressure, bradycardia, nonpitting edema, generalized hair thinning along with hair loss in the outer third of the eyebrows, skin drying, and a diminished relaxation phase of reflexes. The thyroid gland in a patient with chronic thyroiditis may be enlarged, atrophic, or of normal size. Thyroid nodules are common in patients with Hashimoto thyroiditis.

B. Laboratory Findings

The most valuable test for hypothyroidism is the sensitive TSH assay. Measurement of the free thyroxine ($T_4$) level may also be helpful. TSH is elevated and free $T_4$ decreased in overt hypothyroidism (Table 36-2). Other laboratory findings may include hyperlipidemia and hyponatremia. Hashimoto thyroiditis, an autoimmune condition, is one of the most common causes of hypothyroidism. Testing for thyroid autoantibodies (antiperoxidase, antithyroglobulin) is positive in 95% of patients with Hashimoto thyroiditis.

Patients with associated subclinical hypothyroidism have a high TSH level (usually in the 5–10 μIU/mL range)
in conjunction with normal free $T_4$ level. Between 3% and 20% of these patients will eventually develop overt hypothyroidism. Patients who test positive for thyroid antibodies are at increased risk.

**Treatment**

In patients with primary hypothyroidism, therapy should begin with thyroid hormone replacement. In patients with secondary hypothyroidism, further investigation with provocative testing of the pituitary can be performed to determine if the cause is a hypothalamic or pituitary problem.

Most healthy adult patients with hypothyroidism require about 1.6 $\mu$g/kg of thyroid replacement, with requirements falling to 1 $\mu$g/kg for the elderly. The initial dosage may range from 12.5 $\mu$g to a full replacement dose of 100-150 $\mu$g of levothyroxine (0.10-0.15 mg/d). Doses will vary depending on age, weight, cardiac status, duration, and severity of the hypothyroidism. Therapy should be titrated after at least 6 weeks following any change in levothyroxine dose. The serum TSH level is the most important measure to gauge the dose, and a free $T_4$ estimate may be included as well.

Treatment of subclinical hypothyroidism remains controversial. The American Association of Clinical Endocrinologists (AACE) guidelines suggest treating patients with TSH levels higher than 10 $\mu$IU/mL as well as those with TSH levels between 5 and 10 $\mu$IU/mL in conjunction with goiter or positive antithyroid peroxidase antibodies, or both. (Level of evidence for American Thyroid Association recommendations: level 3 or 4, clinical consensus based on the literature).

Once the TSH level reaches the normal range, the frequency of testing can be decreased. Each patient’s regimen must be individualized, but the usual follow-up after TSH is stable is at 6 months; the history and physical examination should be repeated on a routine basis thereafter.

Thyroid hormone absorption can be affected by malabsorption, age, and concomitant medications such as cholestyramine, ferrous sulfate, sucralfate, calcium, and some antacids containing aluminum hydroxide. Drugs such as anticonvulsants affect thyroid hormone binding, whereas others such as rifampin and sertraline hydrochloride may accelerate levothyroxine metabolism, necessitating a higher replacement dose. The thyroid dose may also need to be adjusted during pregnancy. There has been some interest in using a combination of $T_4$ and triiodothyronine ($T_3$) or natural thyroid preparations in pregnant women with hypothyroidism, but studies to date have been small and findings inconsistent.

**Table 36–1. Causes of hypothyroidism.**

<table>
<thead>
<tr>
<th>Primary Hypothyroidism (95% of cases)</th>
<th>Secondary Hypothyroidism (5% of cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic hypothyroidism (probably old Hashimoto thyroiditis)</td>
<td>Pituitary or hypothalamic neoplasms</td>
</tr>
<tr>
<td>Hashimoto thyroiditis</td>
<td>Congenital hypopituitarism</td>
</tr>
<tr>
<td>Post-thyroid irradiation</td>
<td>Pituitary necrosis (Sheehan syndrome)</td>
</tr>
<tr>
<td>Postsurgical</td>
<td></td>
</tr>
<tr>
<td>Late-stage invasive fibrous thyroiditis</td>
<td></td>
</tr>
<tr>
<td>Iodine deficiency</td>
<td></td>
</tr>
<tr>
<td>Drugs (lithium, interferon)</td>
<td></td>
</tr>
<tr>
<td>Infiltrative diseases (sarcoidosis, amyloid, scleroderma, hemochromatosis)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 36–2. Laboratory changes in hypothyroidism.**

<table>
<thead>
<tr>
<th>TSH</th>
<th>Free $T_4$</th>
<th>Free $T_3$</th>
<th>Likely Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Primary hypothyroidism</td>
</tr>
<tr>
<td>High (&gt; 10 $\mu$IU/mL)</td>
<td>Normal</td>
<td>Normal</td>
<td>This is not consistent with the AACE guideline mentioned previously. Subclinical hypothyroidism with high risk for future development of overt hypothyroidism</td>
</tr>
<tr>
<td>High (6-10 $\mu$IU/mL)</td>
<td>Normal</td>
<td>Normal</td>
<td>Subclinical hypothyroidism with low risk for future development of overt hypothyroidism</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Congenital absence of $T_4$-$T_3$-converting enzyme or amiodarone effect</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Peripheral thyroid hormone resistance</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Pituitary thyroid deficiency or recent withdrawal of thyroid replacement after excessive replacement</td>
</tr>
</tbody>
</table>

TSH, thyroid-stimulating hormone; $T_4$, thyroxine; $T_3$, triiodothyronine.
HYPERTHYROIDISM

A. Symptoms And Signs

Patients with hyperthyroidism usually present with progressive nervousness, tremor, palpitations, weight loss, dyspnea on exertion, fatigue, difficulty concentrating, heat intolerance, and frequent bowel movements or diarrhea. Physical findings include a rapid pulse and elevated blood pressure, with the systolic pressure increasing to a greater extent than the diastolic pressure, creating a wide pulse-pressure hypertension. Exophthalmos (in patients with Graves disease), muscle weakness, sudden paralysis, dependent low-extremity edema, or pretibial myxedema may also be present. Cardiac arrhythmias such as atrial fibrillation may be evident on physical examination or electrocardiogram, and a resting tremor may be noted on physical examination.

In patients with subacute thyroiditis, symptoms of hyperthyroidism are generally transient and resolve in a matter of weeks. There may be a recent history of a head and neck infection, fever, and severe neck tenderness. Postpartum thyroiditis may occur in the first few months after delivery. Both types of thyroiditis may have a transient hyperthyroid phase, a euthyroid phase, and occasionally a later hypothyroid phase.

B. Laboratory And Imaging Evaluation

Hyperthyroidism is detected by a decreased sensitive TSH assay and confirmed, if necessary, by the finding of an elevated free $T_4$ level. Testing for thyroid autoantibodies, including TSH receptor antibodies (TRAb) or thyroid-stimulating immunoglobulins (TSI), may be done as necessary. Once hyperthyroidism is identified, radionucleotide uptake and scanning of the thyroid, preferably with iodine-123, is useful to determine whether hyperthyroidism is secondary to Graves disease, an autonomous nodule, or thyroiditis (ie, by showing activity and anatomy of the thyroid). In scans of patients with Graves disease, there is increased uptake on radionucleotide imaging with diffuse hyperactivity. In contrast, nodules demonstrate limited areas of uptake with surrounding hypoactivity, and in subacute thyroiditis, uptake is patchy and decreased overall.

Complications

Thyroid storm represents an acute hypermetabolic state associated with the sudden release of large amounts of thyroid hormone. This occurs most often in Graves disease but can occur in acute thyroiditis. Individuals with thyroid storm present with confusion, fever, restlessness, and sometimes with psychotic-like symptoms. Physical examination shows tachycardia, elevated blood pressure, and sometimes fever. Cardiac dysrhythmias may be present or develop. Patients will have other signs of high-output heart failure (dyspnea on exertion, peripheral vasoconstriction) and may exhibit signs of cardiac or cerebral ischemia. Thyroid storm is a medical crisis requiring prompt attention and reversal of the metabolic demands from the acute hyperthyroidism.

Treatment

A. Radioactive Iodine

Radioactive iodine is the treatment of choice for Graves disease in adult patients who are not pregnant. It has also been used on an individual basis in patients younger than 20 years of age. To date, studies have shown no evidence of adverse effects on fertility, congenital malformations, or increased risk of cancer in women who were treated with radioactive iodine during their childbearing years or in their offspring.
Patients should be advised to postpone pregnancy for at least 6 months postablation therapy.

Radioactive iodine should not be used in breast-feeding mothers. There is also concern that the administration of radioactive iodine in patients with active ophthalmopathy may accelerate progression of eye disease. For this reason, some experts initially treat Graves disease with oral suppressive therapy until the ophthalmologic disease has stabilized.

B. Pharmacotherapy

Antithyroid drugs are well tolerated and successful at blocking the production and release of thyroid hormone in patients with Graves disease. These drugs work by blocking the organification of iodine. Propylthiouracil (PTU) also prevents peripheral conversion of T₄ to the more active T₃. PTU must be given in divided doses (two or three times a day), whereas methimazole and carbimazole can be administered once a day. PTU can be used during pregnancy. The most serious side effect of these drugs is agranulocytosis, which occurs in 3 per 10,000 patients per year. Antithyroid drugs are especially useful in adolescents, in whom Graves disease may go into spontaneous remission after 6-18 months of therapy.

If it has been determined that symptoms of hyperthyroidism are due to thyroiditis, symptomatic treatment with a β-blocker can be used temporarily with little need for long-term therapy.

C. Surgical Intervention

Surgery is reserved for patients in whom medication and radioactive iodine ablation are not acceptable treatment strategies or in whom a large goiter is present that compresses nearby structures or is disfiguring.

D. Treatment of Thyroid Storm

For patients with thyroid storm, aggressive initial therapy is essential to prevent complications. Treatment should include the administration of high doses of PTU (100 mg every 6 hours) to quickly block thyroid release and reduce peripheral conversion of T₄ to T₃. In addition, high doses of β-blockers (propranolol, 1-5 mg intravenously or 20-80 mg orally every 4 hours) can be used to control tachycardia and other peripheral symptoms of thyrotoxicosis. Hydrocortisone (200-300 mg/d) is used to prevent possible adrenal crisis.

E. Postablation Follow-up

Follow-up is necessary to evaluate possible hypothyroidism postablation. Follow-up can begin 6 weeks after therapy and continue on a regular basis until there is evidence of early hypothyroidism, as confirmed by an elevated TSH level. Therapy should then be started as described earlier in the discussion of hypothyroidism.
B. Laboratory And Diagnostic Findings

Laboratory and diagnostic evaluation relies on ultrasound, measurement of TSH level, and fine-needle aspiration (FNA). Ultrasound is not useful as a universal screening tool but can be helpful in screening patients whose history places them at high risk for developing thyroid cancer (see section Symptoms and Signs, earlier).

1. Workup of a palpable thyroid nodule—If the nodule is palpable, TSH assay and ultrasonography of the thyroid should be performed. These two modalities will help guide clinical decision making. If the nodule appears suspicious on ultrasound (based on position, shape, size, margins, or echogenic pattern), FNA should be done irrespective of whether the patient’s TSH level is elevated, normal, or suppressed. For instance, it has been reported that nodules in patients with Graves disease may be malignant in 9% of the cases. If the nodule on ultrasound does not appear suspicious, the clinician can proceed with workup of the abnormal TSH level. For example, if the TSH level is suppressed, the patient may have hyperthyroidism caused by either a single autonomous nodule or a multinodular goiter. The patient would then be evaluated for hyperthyroidism and therapy initiated, as appropriate.

In patients with an elevated TSH level suggestive of hypothyroidism, the next steps would be based on the ultrasound findings. If the nodule does not appear suspicious, thyroid peroxidase antibodies (useful for diagnosing Hashimoto thyroiditis) can be measured and treatment of hypothyroidism initiated (ie, using levothyroxine therapy). If the nodule appears suspicious, FNA should be performed.

2. Workup of an “incidental” thyroid nodule—If the thyroid nodule is found incidentally by ultrasonography, the next step is to obtain a TSH level. If the TSH level is normal, the nodule is less than 10 mm, the patient does not have risk factors for thyroid malignancy, and the ultrasound findings do not appear suspicious, clinical follow-up is done. If the nodule is greater than 10 mm or the patient has risk factors for thyroid malignancy, FNA should be performed.

About 70% of FNA specimens are classified as benign, 5% are malignant, 10% are suspicious, and 10%-20% are nondiagnostic. If FNA reveals malignant cells, surgical intervention is indicated and further treatment will be based on the characteristics noted at surgery (pathologic findings, positive lymph nodes, etc).

Treatment

Patients with malignant thyroid nodules should be referred to surgical and medical oncologists familiar with the management of these tumors. The remainder of this discussion focuses on follow-up and management of patients with FNA-negative thyroid nodules.

Use of exogenous levothyroxine therapy in a euthyroid patient in an effort to “suppress the TSH” (decrease TSH level below 0.1 IU/mL) and “shrink” the nodule is of benefit in only a few patients with palpable nodules. The side effects of exogenous thyroid therapy (cardiac arrhythmias, osteoporosis, etc) must be considered, especially in older patients and in postmenopausal women; its use in these populations is thus relatively contraindicated.

Patients with very large nodules may require surgery, especially if symptoms secondary to the size (eg, dysphagia) are present. If there is a change in size of the nodule, a repeat FNA should be performed.

Ultrasound-guided percutaneous ethanol injection (PEI) is a therapeutic option for patients with benign nodules that have a large fluid component (thyroid cysts). Aspiration (eg, during FNA) itself may drain a cyst and shrink the size, but recurrences are common. Surgery is sometimes needed if the cyst is very large. Some data show that PEI is more effective in decreasing the size of a nodule than aspiration alone.

ADRENAL DISORDERS

ADRENAL INSUFFICIENCY

General Considerations

The most common cause of primary adrenal insufficiency is autoimmune adrenalitis (Addison disease). Other possible causes include AIDS and the antiphospholipid syndrome. Secondary adrenal insufficiency may result from pituitary or hypothalamic disease. Iatrogenic tertiary adrenal insufficiency caused by suppression of hypothalamic-pituitary-adrenal function secondary to glucocorticoid administration is a more common secondary cause of adrenal insufficiency (Table 36-3).

Clinical Findings

A. Symptoms And Signs

Adrenal insufficiency presents with a wide range of symptoms and signs, including weakness, malaise, anorexia, hyperpigmentation (especially of the gingival mucosa, scars, and skin creases), vitiligo, postural hypotension, abdominal pain, nausea and vomiting, diarrhea, constipation, myalgia, and arthralgia. The most specific sign of primary adrenal insufficiency is hyperpigmentation of the skin and mucosal surfaces. Another specific symptom of adrenal insufficiency is a craving for salt. Autoimmune adrenal disease can be
accompanied by other autoimmune endocrine deficiencies, such as thyroid disease, diabetes mellitus, pernicious anemia, hypoparathyroidism, and ovarian failure.

In acute adrenal failure, adrenal crisis occurs. Adrenal crisis is characterized by hypotension, bradycardia, fever, hypoglycemia, and a progressive deterioration in mental status. Abdominal pain, vomiting, and diarrhea also may be present. In the patient with spontaneous adrenal insufficiency, acute adrenal hemorrhage and adrenal-vein thrombosis should be considered.

B. Laboratory Findings

Laboratory abnormalities occur in nearly all patients and include hyponatremia, hyperkalemia, acidosis, slightly elevated plasma creatinine concentrations, hypoglycemia, hypercalcemia, mild normocytic anemia, lymphocytosis, and mild eosinophilia. The diagnosis of adrenal insufficiency relies on a finding of inadequate cortisol production. Plasma cortisol concentration fluctuates throughout the day in a diurnal pattern that is normally high in the early morning and low in the late afternoon. Cortisol levels also increase with stress. A low plasma cortisol level of less than 3 μg/dL (83 nmol/L) either in the morning or at a time of stress provides presumptive evidence of adrenal insufficiency. Conversely, a level of 20 μg/dL (550 nmol/L) or greater rules out adrenal insufficiency. An intermediate plasma cortisol level of 3-19 μg/dL (83-525 nmol/L) is not diagnostic.

Cushing syndrome refers to overproduction of cortisol due to any cause (eg, adrenal hyperplasia, exogenous steroid use). Cushing disease is a more specific term that refers to excessive
cortisol resulting from excessive ACTH produced by pituitary corticotrophic tumors. ACTH-producing tumors account for 80% of cases of Cushing syndrome. The remaining 20% are caused by adrenal tumors, such as adenomas, carcinomas, and micronodular and macronodular hyperplasia, associated with autonomous production of glucocorticoids.

Cushing syndrome is rare, with a prevalence estimated at about 10 per one million persons. Cushing disease is four to six times more prevalent in women than in men, whereas ectopic ACTH secretion is more common in men, largely due to the higher incidence in men of bronchogenic lung cancers that produce ACTH.

### Clinical Findings

#### A. Symptoms and Signs

The most common signs of Cushing syndrome are sudden onset of central weight gain, often accompanied by thickening of the facial fat, which rounds the facial contour (“moon facies”), and a florid complexion due to telangiectasia. Other concomitant signs include an enlarged fat pad (“buffalo hump”), hypertension, glucose intolerance, oligomenorrhea or amenorrhea in premenopausal women, decreased libido in men, and spontaneous ecchymoses (Table 36-5).

#### B. Laboratory Findings

The evaluation of suspected excessive glucocorticoid production includes screening and confirmatory tests for the

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**Table 36-4. Approach to treating acute adrenal insufficiency.**

<table>
<thead>
<tr>
<th>Step</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Stabilize blood pressure and replace fluids</td>
</tr>
<tr>
<td></td>
<td>Administer bolus with normal saline (500 mL/m²) over 1 h then adequate fluids to maintain sufficient urine output</td>
</tr>
<tr>
<td>2.</td>
<td>Correct other metabolic problems</td>
</tr>
<tr>
<td></td>
<td>Give 25% glucose if hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Treat with polystyrene sulfonate (Kayexalate) oral suspension every 3–4 h; give 10% calcium gluconate for dangerously high potassium levels, monitoring heart rate for bradycardia</td>
</tr>
<tr>
<td>3.</td>
<td>Emergency corticosteroid replacement therapy</td>
</tr>
<tr>
<td></td>
<td>Give 25 mg (divided into doses of 15 and 10 mg)</td>
</tr>
<tr>
<td></td>
<td>Adults: 100 mg bolus dose followed by infusion of 100-200 mg/24 h</td>
</tr>
<tr>
<td></td>
<td>Children: 25-50 mg/m²/24 h</td>
</tr>
<tr>
<td>4.</td>
<td>Chronic corticosteroid replacement</td>
</tr>
<tr>
<td></td>
<td>Adults: 25 mg (divided into doses of 15 and 10 mg)</td>
</tr>
<tr>
<td></td>
<td>Children: 25 mg/m²/day in 3 divided doses</td>
</tr>
<tr>
<td></td>
<td>Adults: 37.5 mg (divided into doses of 25 and 12.5 mg)</td>
</tr>
<tr>
<td></td>
<td>Children: 32 mg/m²/day divided 3 times daily</td>
</tr>
<tr>
<td>5.</td>
<td>Evaluate for mineralocorticoid deficiency and replace if needed</td>
</tr>
<tr>
<td></td>
<td>Give 50-200 mcg (single daily dose)</td>
</tr>
<tr>
<td></td>
<td>Adults: 50-150 mcg (single daily dose)</td>
</tr>
</tbody>
</table>


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**Table 36-5. Clinical symptoms and signs of Cushing syndrome.**

<table>
<thead>
<tr>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central obesity</td>
</tr>
<tr>
<td>Proximal muscle weakness</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Headaches</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide (&gt;1 cm), purple striae</td>
</tr>
<tr>
<td>Spontaneous ecchymoses</td>
</tr>
<tr>
<td>Facial plethora</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
</tr>
<tr>
<td>Acne</td>
</tr>
<tr>
<td>Hirsutism</td>
</tr>
<tr>
<td>Fungal skin infections</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endocrine and metabolic derangements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalemic alkalosis</td>
</tr>
<tr>
<td>Osteopenia</td>
</tr>
<tr>
<td>Delayed bone age in children</td>
</tr>
<tr>
<td>Menstrual disorders, decreased libido, impotence</td>
</tr>
<tr>
<td>Glucose intolerance, diabetes mellitus</td>
</tr>
<tr>
<td>Kidney stones</td>
</tr>
<tr>
<td>Polyuria</td>
</tr>
</tbody>
</table>

Elevated white blood cell count

diagnosis and localization of the source of hormone excess. Tests that can be used to confirm excessive glucocorticoid production include a 24-hour urinary free cortisol test, an overnight dexamethasone suppression test, and a midnight cortisol level determination. The 1-mg overnight dexamethasone suppression test has been considered the screening test of choice, but problems associated with its low specificity have led to the use of the urinary free cortisol excretion rate as the preferred test for many patients.

Affective psychiatric disorders (ie, major depression) and alcoholism can be associated with the biochemical features of Cushing syndrome and, therefore, may decrease the reliability of test results.

C. Imaging Studies

Following confirmation of Cushing syndrome, imaging studies should be performed to look for adenomas (MRI scan) or adrenal tumors (CT scan). If both of these studies are negative, chest radiography or CT scanning should be performed to look for ectopic sources of ACTH production.

▶ Treatment

For patients with a pituitary adenoma (Cushing disease) in whom a circumscribed microadenoma can be identified and resected, the treatment of choice is transphenoidal microadenomectomy. If an adenoma cannot be clearly identified, patients should undergo a subtotal (85%-90%) resection of the anterior pituitary gland. Patients who wish to preserve pituitary function (ie, in order to have children) should be treated with pituitary irradiation. If radiation does not decrease exogenous ACTH production, bilateral total adrenalectomy is a final treatment option. For adult patients not cured by transsphenoidal surgery, pituitary irradiation is the most appropriate choice for the next treatment.

Patients who have a nonpituitary tumor that secretes ACTH are cured by resection of the tumor. Unfortunately, most nonpituitary tumors that secrete ACTH are not amenable to resection. In these cases, cortisol excess can be controlled with adrenal enzyme inhibitors, alone or in combination, with the proper dose determined by measurements of plasma and urinary cortisol.

For patients with adrenal hyperplasia, bilateral total adrenalectomy is required. Patients with an adrenal adenoma or carcinoma can be managed with unilateral adrenalectomy. Patients with hyperplasia or adenomas almost invariably have recurrences that are not amenable to either radiation or chemotherapy.

Patients who are taking corticosteroids for prolonged periods of time may exhibit signs or symptoms of Cushing syndrome. Once the primary problem for which steroids are being prescribed is controlled, patients should be withdrawn from their corticosteroid treatment slowly to avoid symptoms from adrenal suppression. There are few studies evaluating methods of withdrawal from chronic steroid use, however. Clinicians should be guided by the severity of the underlying condition, the duration that steroids have been used, and the dosage of steroids in determining how quickly dosages of steroids should be reduced.


HYPERALDOSTERONISM

▶ General Considerations

Primary hyperaldosteronism accounts for 70%-80% of all cases of hyperaldosteronism and is usually caused by a solitary unilateral adrenal adenoma. Other causes of hyperaldosteronism include bilateral adrenal hyperplasia, so-called idiopathic hyperaldosteronism, and glucocorticoid-remediable hyperaldosteronism. Adrenal carcinoma and unilateral adrenal hyperplasia are rare causes.

▶ Clinical Findings

A. Symptoms and Signs

Patients with hyperaldosteronism present with hypertension and hypokalemia. Other complaints include headaches, muscular weakness or flaccid paralysis caused by hypokalemia, or polyuria. Inappropriate hypersecretion of aldosterone is an uncommon cause of hypertension, accounting for fewer than 1% of cases. Any patient presenting with hypertension and unprovoked hypokalemia should be considered for the evaluation of hyperaldosteronism. Hypertension may be severe, although malignant hypertension is rare. The peak incidence occurs between 30 and 50 years of age, and most patients are women.

B. Laboratory Findings

Initially, laboratory evaluation is used to document hyperaldosteronemia and suppressed renin activity. Further diagnostic tests, including imaging procedures, are used to determine whether the etiology is amenable to surgical intervention or requires medical management.

Screening aldosterone measurements can be made on plasma or 24-hour urine collection. Plasma aldosterone is usually measured after 4 hours of upright posture. Plasma renin activity should be measured in the same sample. A ratio of plasma aldosterone concentration to plasma renin activity greater than 20:25 is very suspicious for hyperaldosteronism.

In the hypertensive patient with hypokalemia or kaliuresis or with an elevated plasma aldosterone-renin ratio, the diagnosis of hyperaldosteronism is confirmed by demonstrating failure of normal suppression of plasma
aldosterone. Urine aldosterone excretion of more than 30 nmol (14 μg)/d after oral sodium loading over 3 days establishes the diagnosis.

The intravenous saline suppression test is also widely used to confirm hyperaldosteronism. In this test, isotonic saline is infused intravenously at a rate of 300–500 mL/h for 4 hours, after which plasma aldosterone and renin activity are measured. Aldosterone levels normally fall to less than 0.28 nmol/L (10 ng/dL) and renin activity is suppressed. Failure to suppress normally identifies patients with aldosterone-producing adenomas, because most patients with secondary forms of hyperaldosteronism suppress normally. False-negative results are most often seen in patients with bilateral hyperplasia.

Once the diagnosis is established, it is necessary to distinguish between aldosterone-producing adenoma and bilateral adrenal hyperplasia. A widely used test is based on the less complete suppression of renin activity in hyperaldosteronism caused by bilateral hyperplasia. Plasma renin activity rises slightly and aldosterone concentration increases significantly after the stimulation of 2-4 hours of upright posturing in these patients. In contrast, renin remains suppressed and aldosterone does not rise in patients with adenomas, in whom plasma aldosterone level may fall.

C. Imaging Studies

Imaging procedures can assist in differentiating causes of hyperaldosteronism and lateralizing adenomas. The diagnostic accuracy of high-resolution CT scans is only about 70% for aldosterone-producing adenomas, largely because of the occurrence of nonfunctioning adenomas. MRI is no better than CT in differentiating aldosterone-secreting tumors from other adrenal tumors. Scintigraphic imaging with iodo-131–labeled cholesterol derivatives during dexamethasone suppression provides an image based on functional properties of the adrenal gland. Asymmetric uptake after 48 hours indicates an adenoma, whereas symmetric uptake after 72 hours indicates bilateral hyperplasia. Diagnostic accuracy is 72%. However, if the adrenal CT scan is normal, iodocholesterol scanning is unlikely to be helpful.

Treatment

For adrenal adenoma, total unilateral adrenalectomy is the treatment of choice and provides a cure in most cases. Although some patients with primary bilateral hyperplasia may benefit from subtotal adrenalectomy, these patients cannot be accurately identified preoperatively. Following surgery, the electrolyte imbalances usually correct rapidly, whereas blood pressure control may take several weeks to months.

Medical therapy is indicated for most patients with bilateral adrenal hyperplasia or for patients with adrenal adenomas who are unable to undergo adrenalectomy. Spironolactone controls the hyperkalemia, although it is not a very potent antihypertensive agent. Amiloride and calcium channel blockers are often used to control blood pressure.

Hypercaldemia (serum calcium level >10.5 mg/dL when corrected for serum albumin level) is the most important clue to the diagnosis. In patients who have an elevated calcium level with no apparent cause, serum PTH should be determined using a two-site immunometric assay. An elevated PTH level in the presence of hypercalcdemia confirms the diagnosis of primary hyperparathyroidism.

Other findings may include a low serum phosphate level (<2.5 mg/dL) with excessive phosphaturia. Urine calcium excretion may be high or normal. Alkaline phosphatase
levels are elevated only in the presence of bone disease, and elevated plasma chloride and uric acid levels may be seen.

**C. Imaging Studies**

With chronic hyperparathyroidism, diffuse bone demineralization, loss of the dental lamina dura, and subperiosteal resorption of bone (particularly in the radial aspects of the fingers) may be apparent on x-rays. Cysts may be noted throughout the skeleton, and “salt-and-pepper” appearance of the skull may be seen. Pathologic fractures can occur, and renal calculi and soft tissue calcification may be visualized.

Imaging studies are usually reserved for patients with resistant or recurrent disease. In these cases, ultrasonography, CT scanning, MRI, and thallium-201–technetium-99m scanning may help locate ectopic parathyroid tissue.

**Treatment**

Treatment of severe hypercalcemia and parathyroidectomy are the mainstays for therapy. When hypercalcemia is severe, treatment includes aggressive hydration. Correction of any underlying hyponatremia and hypokalemia should be initiated, along with administration of a loop diuretic to accelerate calcium clearance. Other medications that can be effective in reducing hypercalcemia include etidronate, plicamycin, and calcitonin. Any medications or other products that increase calcium levels, such as estrogens, thiazides, vitamins A and D, and milk, should be avoided.

In addition to management of acute hypercalcemia, surgical removal of parathyroid tissue should be undertaken. Surgical resection provides the most rapid and effective method of reducing serum calcium in these patients. Hyperplasia of all glands requires removal of three glands along with subtotal resection of the fourth. Surgical success is directly related to the experience and expertise of the operating surgeon.

For mild cases and poor surgical candidates, conservative therapy with adequate hydration and long-term pharmacologic therapy is recommended. Patients should avoid drugs and products that elevate calcium and should have their serum calcium monitored closely.

**HYPOPARATHYROIDISM**

**General Considerations**

Hypoparathyroidism results from underproduction of PTH. The most common cause is the removal of the parathyroid glands during a thyroidectomy or following surgery for primary hyperparathyroidism. Less commonly, hypoparathyroidism is idiopathic, familial, or the result of a congenital absence of the parathyroid glands (DiGeorge syndrome). Patients with idiopathic hypoparathyroidism often have antibodies against parathyroid and other tissues, and an autoimmune component may play a role. Other unusual causes of hypoparathyroidism include previous neck irradiation, magnesium deficiency, metastatic cancer, and infiltrative diseases.

**Clinical Findings**

**A. Symptoms and Signs**

The lack of PTH results in hypocalcemia, which produces most of the symptoms associated with hypoparathyroidism. Symptoms associated with hypocalcemia include tetany, carpopedal spasms, paresthesias of the lips and hands, and a positive Chvostek sign or Trousseau sign. Patients may also exhibit less specific symptoms such as anxiety, depression, or fatigue. Additionally, hyperventilation, respiratory alkalosis with or without respiratory compromise, laryngospasm, hypotension, and seizures may occur with severe hypocalcemia.

**B. Laboratory Findings**

On laboratory evaluation, patients with hypoparathyroidism have low serum calcium and elevated serum phosphate levels, with a normal alkaline phosphatase level. Urinary levels of calcium and phosphate are decreased. The key finding is a low to absent PTH value.

**Treatment**

Acute hypocalcemia with tetany requires aggressive therapy with multiple drugs. Therapy should be started with calcium gluconate administered intravenously in a 10% solution. The infusion is given slowly until tetany resolves. Oral calcium along with vitamin D supplementation should be given after the acute crisis has resolved. Hypomagnesemia should be corrected with intravenous magnesium sulfate administered at a dose of 1-2 g every 6 hours. Chronic replacement of magnesium can be accomplished using 600-mg magnesium oxide tablets once or twice daily.

For the maintenance of normal calcium, vitamin D supplementation along with oral calcium should be given. Calcium in the form of calcium carbonate (40% elemental calcium) is the drug of choice, administered in a dose of 1-2 g of calcium a day. Serial calcium levels should be obtained regularly (every 3-6 months), and “spot” urine calcium levels should be maintained below 30 mg/dL.
Approximately 20% of all office visits to primary care providers involve musculoskeletal complaints. The purpose of this chapter is to survey the most common presenting complaints of the upper and lower extremities, highlighting the etiology, clinical findings, differential diagnosis, and evidence-based treatment options for each.

### UPPER EXTREMITY

#### ROTATOR CUFF IMPINGEMENT

**General Considerations**

The term *subacromial impingement* defines any entity that compromises the subacromial space and irritates the enclosed rotator cuff tendons. Impingement can involve any of the structures within the subacromial space, and the term encompasses various entities from subacromial bursitis to rotator cuff calcific tendonitis and tendinosis. Often these entities arise in a similar fashion and may be difficult to differentiate.

Impingement syndrome is classified into external, internal, and secondary impingement. The most common form is *external impingement*, which is caused by compression of the rotator cuff tendons as they pass under the coracoacromial arch. Subacromial bursitis can develop subsequently and intensify the compression. *Internal impingement* is caused by fraying of the infraspinatus tendon where it contacts the posterior glenoid. This occurs while the arm is maximally abducted and externally rotated and is seen in athletes who participate in overhead and throwing activities. Lastly, *secondary impingement* is caused by glenohumeral instability. Diagnosis is made with a meticulous history and physical examination, and appropriate imaging.

**Clinical Findings**

**A. Symptoms and Signs**

Diagnosis of subacromial impingement is primarily clinical. The patient complains of dull shoulder pain of insidious onset over weeks to months. Less often, these symptoms arise following trauma. Pain is typically localized to the anterolateral acromion and radiates to the lateral deltoid. Pain is aggravated at night, by sleeping with the arm overhead or lying on the involved shoulder. Overhead activities, throwing motions, and activities in which the humerus is flexed with an inward rotation also exacerbate symptoms.

Physical examination usually reveals normal range of motion (ROM), although the patient may experience a painful arc of motion or pain upon approaching maximum internal rotation and forward flexion. Muscular weakness is sometimes seen in the supraspinatus muscle or the internal and external rotators of the shoulder. Supraspinatus strength (empty can test) is tested with the arm in 90 degrees of abduction and 30 degrees of forward flexion, with the thumb pointing downward. Decreased strength indicates a positive test. To differentiate weakness caused by pain from actual loss of strength, it may be necessary to perform a subacromial injection with an anesthetic to alleviate the pain variable.

**B. Imaging Studies**

Radiographs that may aid in diagnosis include anteroposterior (AP), outlet, and axillary views of the affected shoulder. Curvature of the acromion or acromial spurs can be seen on an outlet view and may contribute to compression of the rotator cuff musculature or subacromial impingement.

**C. Special Tests**

Provocative testing includes the Neer test and the Hawkins-Kennedy test. The Neer test involves passive elevation of an internally rotated, forward-flexed arm. In the Hawkins-Kennedy test, the arm is positioned in 90 degrees of forward flexion and is internally rotated with a bent elbow. This causes impingement of the supraspinatus tendon against the anterior inferior acromion. Pain with either maneuver is considered a positive test; however, these tests may also be positive in patients with other pathology.
Differential Diagnosis

Differential diagnosis includes acromioclavicular joint arthritis, osteolysis of the distal clavicle, rotator cuff tear, cervical disc herniation, adhesive capsulitis, supraspinatus nerve entrapment, glenohumeral instability, and arthritis.

Treatment

Treatment is initially conservative, using modified activity and nonsteroidal anti-inflammatory drugs (NSAIDs). The goal is to relieve inflammation, reestablish pain-free ROM, prevent atrophy, and enable return to previous activity. Current evidence supports the use of physical therapy to initiate rotator cuff and scapular musculature strengthening and joint mobilization techniques. A subacromial corticosteroid injection can also relieve symptoms when used with muscular strengthening. Surgical intervention is considered only after failure of conservative treatment.

Calcific Tendonitis

General Considerations

Calcific tendonitis of the shoulder is an acute or chronic condition caused by inflammation around calcium deposits adjacent to the rotator cuff tendons. It affects about 10% of the population and is more common in women and in individuals older than 30 years.

Clinical Findings

Onset is usually abrupt and severely limits activities. It is theorized that the disease becomes painful only when the calcium is undergoing resorption; therefore, the patient may be pain free initially. The diagnosis is clinical; it is based on a history of shoulder pain similar to impingement along with abrupt onset and tenderness over the greater tuberosity.

Radiographic evidence of a calcified tendon is best seen on plain films. To localize the calcification, it is recommended that the radiographic views include AP, internal and external rotation, scapular Y (or outlet), and axillary views. Magnetic resonance imaging (MRI) is not routinely indicated.

Rotator Cuff Tears

General Considerations

Rotator cuff tears have been noted in 5%-39% of people examined in cadaver and MRI studies. Their prevalence increases with age. The exact cause and best treatment are still being explored.

The rotator cuff complex is made up of four muscles: the subscapularis, supraspinatus, infraspinatus, and teres minor. Biomechanically, the rotator cuff abducts the arm with the assistance of the deltoid and also acts to rotate the humerus with respect to the scapula. The supraspinatus, infraspinatus, and teres minor externally rotate the humerus, while the subscapularis acts as a strong internal rotator. Together, the rotator cuff muscles contract to maintain the humeral head in the glenoid during movement and thus maintain shoulder stability.

Clinical Findings

A. Symptoms and Signs

Many rotator cuff tears are asymptomatic. If symptoms are present, patients describe pain, stiffness, and occasional weakness around the shoulder. The pain is located at the front of the shoulder and radiates down the arm. It may be aggravated by overhead activity or sleeping on the affected side. Generally, pain is worse with resisted muscle activity in patients with a partial-thickness rotator cuff tear. Those patients with a full-thickness tear may exhibit only muscular weakness without pain.

Careful examination may demonstrate subtle atrophy of the supraspinatus and infraspinatus muscles, which is a sign of advanced disease. Tenderness at the insertion site of the supraspinatus tendon (just below anterolateral acromion) is common. Occasionally, with a complete tear, a defect can be palpated.

Limitations in ROM are caused by muscle weakness and pain. Full-thickness tears are characterized by a decrease in active abduction, but normal passive ROM. Although quite variable, there is usually pain and slight weakness in patients with partial-thickness rotator cuff tears, and weakness without pain in patients with full-thickness tears. The supraspinatus muscle is often weak in patients with a tear (positive empty can test).
Patients often describe a “painful arc” (pain or weakness between 60 and 120 degrees of abduction). With a complete tear, patients may also demonstrate a “drop arm sign” (the arm dropping from abduction) because there is no muscle to control the arm as the patient brings the raised arm back to the side.

**B. Imaging Studies**

Plain films can be useful to rule out other causes of shoulder pain (eg, calcific tendonitis or osteoarthritis). Changes seen on plain films that may be consistent with rotator cuff disease include loss of space between the humeral head and acromion, acromial spurs, and sclerosis with cystic changes in the greater tuberosity. Ultrasound can diagnose a rotator cuff tear (91% sensitive) if read by a skilled radiologist, but MRI is considered the gold standard in the diagnostic imaging of rotator cuff disease.

**Treatment**

Treatment focuses on pain management using NSAIDs. Patients should be referred for physical therapy early in order to take advantage of pain-reducing modalities such as heat, cold, and ultrasound. Flexibility and strengthening of the shoulder (rotator cuff muscles), scapula, and surrounding musculature are also helpful in treatment. Patients should be advised to avoid movements and activities that provoke symptoms.

Once a rotator cuff tear has been confirmed, referral should be made to an orthopedic surgeon. There is some evidence of improved results with surgical repair for both partial- and full-thickness tears. Patients with acute tears tend to have better outcomes than patients who have had pain for more than 6 months.


**BICEPS TENDONITIS & INSTABILITY**

**General Considerations**

Disorders of the biceps tendon have been labeled as either tendinitis or overuse syndromes (tendinosis). *Biceps tendonitis* is an inflammatory process involving the portion of the tendon located in the intertubercular groove. *Tendinosis* is an overuse injury that begins with an influx of inflammatory cells and progresses to exudation of fluid into the tendon sheath. In either case, this tissue thickens and becomes more painful. Many investigators believe that biceps tendonitis is secondary to shoulder impingement and rarely occurs alone. Alternatively, some consider biceps tendonitis to be secondary to biceps tendon instability in the bicipital groove which, if present, is usually associated with subscapularis tendon pathology.

**Clinical Findings**

Patients typically complain of pain in the bicipital groove at the anterior aspect of the shoulder. The pain can radiate toward the deltoid insertion and it may be difficult to distinguish biceps tendon pathology from shoulder impingement or rotator cuff disease. Usually there is a history of repetitive overhead activity, which either initiates or aggravates symptoms. There may also be an audible or palpable “snap” at the bicipital groove during the arc of motion if instability is present.

The most common finding on physical examination is tenderness over the tendon within the bicipital groove. It is best localized when the arm is internally rotated to 10 degrees; at this angle, the biceps tendon is about 3 in. below the acromion.

**A. Imaging Studies**

Standard plain radiographs of the shoulder (AP, outlet, axillary views) are most often normal. For this reason, MRI should be considered (98% sensitive). An MRI-arthrogram may be ordered if there is high suspicion of an associated cartilaginous tear of the labrum.

**B. Special Tests**

Data supporting the sensitivity and specificity of provocative special tests of the biceps tendon are limited. The Speed and Yergason tests may, however, be used to assist in making the diagnosis of biceps tendonopathy. In the Speed test, the patient is asked to flex the arm against resistance with the elbow extended and forearm supinated. In the Yergason test, the patient supinates against resistance with the elbow flexed at 90 degrees. With either test, the presence of pain at the bicipital groove indicates a positive test.

Biceps instability is elicited by fully abducting and then externally rotating the patient’s arm. An audible or palpable snap detected at the bicipital groove as the tendon subluxes or dislocates is a positive result indicating biceps instability.

An injection of anesthetic into the subacromial space (not the biceps tendon sheath) can be used to aid in diagnosis and to help rule out rotator cuff tendonitis. Pain caused by biceps tendonitis will remain following injection.

**Treatment**

Initial treatment of biceps tendonitis is conservative, consisting of NSAIDs, rest, and activity modification. Physical therapy is useful to strengthen the rotator cuff but should not be aggressive during the acute pain stage. Subacromial corticosteroid injections are also useful in the treatment of biceps tendonitis, but direct injection into the biceps tendon should be avoided.

Treatment of biceps instability is similar. Older, sedentary patients may benefit from conservative therapy, including injections; however, younger, more active patients should be referred promptly for surgical repair.
RUPTURE OF THE LONG HEAD OF THE BICEPS

General Considerations

Ruptures of the proximal biceps tendon are most often found in association with rotator cuff tears, but isolated ruptures can occur.

Clinical Findings

A. Symptoms and Signs

History includes pain in the anterior shoulder just prior to a complete tendon rupture. At the time of rupture, the patient usually hears an audible “pop” followed by immediate relief of symptoms. There is commonly an associated tear of the cartilaginous labrum, so the patient may also complain of catching, popping, or locking of the shoulder.

Physical examination may reveal pain over the bicipital groove, bruising on the anterior aspect of the arm, and a “Popeye muscle” (particularly with biceps flexion) due to the distal retraction of the muscle mass.

B. Imaging Studies

Radiographs are usually normal. MRI can confirm biceps tendon rupture. Gadolinium-enhanced MRI is preferred if a labral tear is also suspected.

Treatment

Treatment of an isolated rupture of the long head of the biceps is conservative and nonsurgical if the patient is inactive or would not be hindered significantly by loss of strength in the injured arm. Pain is managed with NSAIDs and modified activity, and activity is slowly advanced as tolerated. Physical therapy is useful to improve rotator cuff strength, if an associated rotator cuff tear is not present. If a labral or rotator cuff tear is suspected along with the rupture of the biceps long head, referral to an orthopedic surgeon is warranted.

SHOULDER INSTABILITY

General Considerations

Shoulder instability can be viewed as any condition in which the balance of various stabilizing structures in the shoulder is disrupted, resulting in increased humeral head translation. Most dislocations are anterior, but they can also be posterior and, on rare occasion, inferior. In younger patients, dislocations are most often caused by trauma and sports injuries, whereas in the elderly, falls are the predominant cause (usually accompanied by a fracture). This discussion focuses on anterior subluxation and dislocation.

Anterior instability is categorized using two acronyms: TUBS (traumatic, unidirectional, Bankart surgery) and AMBRI (atraumatic, multidirectional, bilateral, rehabilitation, inferior capsular surgery). TUBS describes the cause and the direction of instability. An avulsion of the anteroinferior glenohumeral ligament and labrum (Bankart lesion) is also seen with a probable avulsion fracture. Treatment for this type of instability is surgical repair. AMBRI describes an atraumatic mechanism and instability that is usually multidirectional and bilateral. This type of injury usually responds well to rehabilitation. If symptoms do not improve with rehabilitation, surgical repair (inferior capsular shift) is indicated.

Clinical Findings

A. Symptoms and Signs

The patient with a shoulder dislocation generally presents with shoulder pain, an unwillingness to move the affected arm, and a tendency to cradle the arm. The history usually includes a traumatic event, and a detailed description of the trauma—including arm position, energy level, and subsequent treatment adherence—is essential for diagnosis. Most subluxations and dislocations occur during abduction and maximal external rotation. Inspection reveals a bulge (due to the displaced location of the humeral head), as well as dimpling inferior to the acromion where the humeral head should be.

If the patient is not dislocated at the time of the examination, but the history details episodes of subluxation, the apprehension test should be performed. In this test, the patient is supine with the arm in 90 degrees of abduction; the examiner then applies an external rotation stress. Patient apprehension due to subluxation of the humeral head is considered a positive test. Posterior pressure on the proximal humeral head can provide relief of symptoms if shoulder instability is the cause of pain (relocation test).

B. Imaging Studies

Radiographs are required to confirm shoulder dislocations. AP and outlet views are standard; however, an axillary view shows the relationship of the humeral head to the glenoid fossa and is more accurate when assessing for dislocation. Occasionally a bony defect in the posterolateral portion of the humeral head (Hill-Sachs lesion) is seen radiographically.

Treatment

Treatment for a shoulder dislocation consists of pain management and relocation. After relocation, the shoulder must be immobilized for 7-10 days to allow capsular healing. ROM exercises are then started, along with rotator cuff strengthening. Because younger patients with shoulder dislocations tend to have a high recurrence rate, surgical repair is warranted and early referral should be made in this population.
If the patient has signs of AMBRI, the standard treatment is a rehabilitation program to strengthen the rotator cuff and scapular musculature. If no improvements occur after rehabilitation, the patient should be referred for possible surgical repair.


De Quervain Tenosynovitis

▶ General Considerations
De Quervain stenosing tenosynovitis involves the abductor pollicis longus and the extensor pollicis brevis of the thumb. Although once thought to be an inflammatory condition, recent evidence has shown that degeneration of the tendon is present. The condition can arise with repetitive activity that requires grasping with ulnar deviation or repetitive thumb use.

▶ Clinical Findings
Diagnosis is largely clinical. Patients may complain of difficulty gripping items and often rub the area over the radial styloid. Pain is located on the radial side of the wrist and thumb, and occasionally radiates proximally.
There is tenderness to palpitation just distal to the radial styloid. Pain can also be reproduced with resisted thumb abduction and extension, or with thumb adduction into a closed fist and passive ulnar deviation (Finkelstein test). Pain over the tendons represents a positive test; however, the test may also be positive in patients with an arthritic flare of the first carpometacarpal joint.
Radiographs are unnecessary for diagnosis, but they may be useful to rule out osteoarthritis of the first carpometacarpal joint or a scaphoid fracture.

▶ Treatment
The goals of treatment are to decrease inflammation, prevent adhesion formation, and prevent recurrent tendinitis. Brief periods of icing and use of NSAIDs are helpful initially, and the patient should be placed in a thumb restricting splint (thumb spica splint). If pain continues, a corticosteroid injection should be considered. In most patients, symptoms resolve after a single steroid injection. Steroid injection may be repeated after 4-6 weeks if symptoms are not 50% improved. If no improvement occurs after two injections within the year, a referral for surgical consultation should be obtained.

Hong E: Hand injuries in sports medicine. Prim Care 2005;32:91. [PMID: 15831314]

Lateral & Medial Epicondylitis

▶ General Considerations
For many years epicondylitis was thought to be caused by inflammation at the tendon origin; however, recent evidence shows that it is actually due to a breakdown of collagen from aging, microtrauma, or vascular compromise. Although properly termed tendinosis, the condition is referred to by its longstanding name “epicondylitis” throughout this discussion to avoid confusion. Lateral and medial epicondylitis occur at the elbow and are primarily overuse or repetitive stress disorders.

▶ Clinical Findings
A. Symptoms and Signs
Lateral epicondylitis is a tendinosis at the origin of the extensor tendons on the lateral epicondyle of the humerus. It is commonly known as “tennis elbow” because it is seen in activities that involve repetitive wrist extension. Patients complain of pain over the lateral elbow that may radiate down the forearm. There is tenderness to palpation over the origin of the extensor carpi radialis brevis tendon, which is anterior and distal to the lateral epicondyle. Pain is aggravated with resisted wrist extension or forearm supination.
Medial epicondylitis (“golfer’s elbow”) is seen after repetitive use of the flexor and pronator muscles of the wrist and hand (as occurs when playing golf, using a screwdriver, or hitting an overhead tennis stroke). Pain is insidious at the medial elbow and is worse with resisted forearm pronation and wrist flexion. Patients may also complain of a weak grasp. Tenderness to palpation occurs just distal and anterior to the medial epicondyle.

B. Imaging Studies
Imaging is not warranted for diagnosis of either lateral or medial epicondylitis; however, plain films of the elbow should be performed prior to any injections.

▶ Differential Diagnosis
Differential diagnosis of lateral epicondylitis includes radial tunnel syndrome and posterior intersosseous nerve syndrome.
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The differential for medial epicondylitis should include ulnar neuritis (cubital tunnel syndrome) and ulnar ligament injury.

Treatment

Initial treatment for either entity consists of activity modification and pain management with NSAIDs. A counterforce brace may be used during activities. In addition, biomechanics should be evaluated (ie, racquet grip, golf swing technique, etc). Physical therapy can be prescribed once acute symptoms have been controlled to establish pain-free ROM and strengthen muscles around the wrist and elbow. If pain is refractory, a steroid injection can be administered for either medial or lateral epicondylitis. Surgical treatment is recommended if no improvement occurs after 3-6 months of conservative management.

Lower Extremity

PATELLAR TENDINOPATHY

General Considerations

The patellar tendon is an extension of the quadriceps femoris tendon and traverses from the inferior pole of the patella to its anchor point at the tibial tuberosity. Patellar tendinopathy, formerly known as “jumper’s knee,” is a painful condition at the inferior pole of the patella.

Pathogenesis

Traditionally, pain at the patellar tendon was thought to originate from inflammation. However, evidence now indicates that, as with other chronic tendinopathies, patellar tendinopathy is caused primarily by tendon overload. Repeated strain causes microtearing, tenocyte death, fibrosis, and neovascularization, creating a zone of tendinosis within the tendon. Therefore, use of the term patellar tendinopathy should be encouraged over former terms such as patellar tendinitis, and treatment should also be directed toward more evidence-based and pathology-focused management.

Clinical Findings

A. Symptoms and Signs

Clinically, patellar tendinopathy presents with the insidious onset of well-localized anterior knee pain, primarily at the inferior pole of the patella. Pain is exacerbated by activity, prolonged knee flexion, and ascending or descending stairs. Discomfort often manifests when there has been an increase in intensity or frequency of activity. Pain may be present initially only after activity but will generally progress to the point where it occurs during or even between periods of activity.

The diagnosis of patellar tendinopathy is primarily clinical. On physical examination, the most consistent finding is tenderness over the tendon at the inferior pole of the patella with the leg in extension. Although radiographs may show associated bony anomalies such as Osgood-Schlatter disease or tendinous calcification, the clinical relevance of these changes is debatable.

Treatment

With the understanding that patellar tendinopathy is more accurately a degenerative tendinosis caused by overload than an inflammatory tendonitis, treatment strategies have shifted away from the traditional anti-inflammatory approach to focus on diminishing tendon stress and on muscle strengthening. Recommendations include the use of eccentric strengthening exercises, improving quadriceps and hamstring flexibility, proprioception, evaluation of biomechanics, and modification of aggravating activities. Patients with acute tendon pain may benefit from NSAIDs, but their widespread use in tendinopathy is not evidence based. The utility of other modalities, including ultrasound and extracorporeal shock wave therapy, are promising but require further confirmation. Depending on the chronicity of symptoms, recovery may require up to 6 months.

PATELLOFEMORAL PAIN SYNDROME

General Considerations

Patellofemoral pain syndrome (PFPS) is a broad term used to define anterior knee pain not related to intra-articular pathology, bursitis, tendinitis, fracture, patellar subluxation, or Osgood-Schlatter disease.

The patella normally sits comfortably in a groove with its posterior cartilaginous surface “molded” to complement the trochlea of the femur. The patella is held in place by its natural shape, by the trochlea, and by the tension of the medial and lateral patellar retinacula (Figures 37-1 and 37-2). When flexing or extending the knee, the muscles of the hamstring and quadriceps function like reins to direct the patella within the trochlea and to rotate the tibia. In extension, the patella sits at the proximal aspect of the trochlea. As the knee flexes, the posterior patella becomes engaged in the trochlea. Compressive forces at the posterior cartilaginous surface of
**Figure 37-1.** Anatomy of the anterior knee. (Illustration by Anne S. Boyd, MD)

**Figure 37-2.** Intra-articular structures of the knee. (Illustration by Anne S. Boyd, MD)
the patella intensify with increasing flexion and can reach impressive levels at 90 degrees of flexion.

\section*{Pathogenesis}

Although the cartilage itself does not possess pain fibers, the pain of PFPS is associated with friction between the subpatellar chondral surface and the trochlea of the femur. Three major contributing factors have been evaluated in relation to PFPS: malalignment of the lower extremity, muscular imbalances, and overactivity. Lower extremity alignment factors associated with PFPS include torsion of the femur or tibia, genu valgum, genu recurvatum, increased Q angle, femoral anteverision, and foot pronation. Additionally, various patterns of muscle weakness have been reported in the quadriceps. It seems logical that each of these factors has the potential to draw the patella laterally and contribute to abnormal patellar tracking. Research has not been convincing in showing significant biomechanical differences between asymptomatic individuals and those with symptoms of PFPS, or that the muscular imbalances observed are a cause or an effect of PFPS. Nonetheless, the most recent theory embraces the idea that each individual has an independent “comfort zone” based on his or her own specific biomechanics, joint history, and activity level. Exceeding this comfort zone via overuse surpasses the reserve of the joint and creates patellofemoral symptoms. Therefore, the same person may be asymptomatic when not training but can develop symptoms with increased activity despite the consistency of the individual’s joint biomechanics.

\section*{Clinical Findings}

\subsection*{A. Symptoms and Signs}

Historically, patients with PFPS are young patients who present with an insidious onset of diffuse, aching, anterior knee pain. Pain is often bilateral and is aggravated by climbing stairs, ascending hills, squatting, or sitting with the knee flexed for a prolonged period of time (theater sign).

Although the extent of their contributions is unclear, alignment, gait, and stance should be assessed and gross abnormalities addressed. Maltracking of the patella and chronic irritation of the patellar cartilage often produce tenderness at the postero medial or posterolateral patellar facets, as well as a positive “patellar grind” or Clarke sign (pain with slight compression of the patella that is exacerbated by quadriceps contraction). It is paramount to note that children may have significant hip pathology that presents solely as knee pain; pediatric patients must therefore be considered as a distinct population with a broader differential diagnosis.

\subsection*{B. Imaging Studies}

Radiographs are usually not indicated unless pain is prolonged or associated with trauma, or if bony pathology is suspected.

\section*{Treatment}

Treatment is directed at altering patellar tracking, correcting biomechanical factors that lead to overuse, and decreasing the intensity of the aggravating activity. Exercises designed to strengthen the medial quadriceps and hip muscles have proven helpful as well as stretching exercises for the hamstrings, iliobtibial band, and lateral patellar retinaculum. The use of foot orthotics should be considered for those with structural foot problems. Bracing and taping may also be effective in some patients. Limited evidence exists for the effectiveness of NSAIDs, and their utility is questioned in patients with this disorder. Surgery is reserved for patients with damage to the chondral surface and those who have failed prolonged therapy.

instability or giving way with walking, particularly with pivoting motions.

An acute ACL injury can often be diagnosed acutely; however, the majority of patients present a day or more after the injury. By that time, muscle spasm and pain may limit the examination. The most sensitive test in the setting of an acutely swollen knee is the Lachman test. With the patient supine and the relaxed knee in 30 degrees of flexion, the examiner stabilizes the distal femur with one hand, grasps the proximal tibia with the other, and attempts to sublux the tibia anteriorly. The anterior drawer test also assesses the integrity of the ACL. With the knee flexed to 90 degrees, the examiner stabilizes the relaxed leg by sitting on the patient’s foot, grasps the calf with both thumbs on the tibial tubercle, and applies an anteriorly directed force. With either test, significant anterior translation of the tibia or lack of a discrete end point indicates a positive test.

B. Imaging Studies

Although radiographs are of limited value in diagnosing ACL tears, a standard knee series—including a bilateral standing AP view, a lateral view, a bilateral posteroanterior (PA) flexion weight-bearing or tunnel view (45 degrees of flexion), and a patellar profile (Merchant or skyline) view—is recommended to rule out other bony pathology. MRI is the imaging modality of choice to confirm a clinically suspected ACL tear.

Treatment

Initial treatment includes a brief period of immobilization, protected weight bearing with crutches for 7-10 days, cryotherapy, and early ROM exercises. Physical therapy is then initiated to restore motion and strength. Bracing may provide some subjective benefit. There is insufficient evidence to recommend conservative over operative treatment of ACL tears. General consensus holds that in relatively inactive individuals nonoperative treatment is a viable option. These patients, however, may have to accept some degree of chronic instability and acknowledge the potential for further episodes involving running, jumping, or pivoting.

2. Posterior Cruciate Ligament Injury

- **Pathogenesis**

The PCL limits posterior displacement of the tibia on the femur. PCL tears occur less often than ACL tears, may be asymptomatic, and often go undetected. The usual mechanism of injury is a posteriorly directed force on the proximal tibia with a flexed knee, such as a fall on a bent knee with the foot plantar flexed, or a bent knee striking the dashboard in a motor vehicle crash.

- **Clinical Findings**

Unlike with ACL tears, patients often do not report a “pop.” The initial trauma may be subtle and subsequent symptoms are frequently vague. Limping, a moderate knee effusion, difficulty with the last 10-20 degrees of flexion, and posterior knee pain often accompany this injury. Unsteadiness may be a complaint, but significant instability is more likely to be reported with combined injuries.

The posterior drawer test is the most accurate test for assessing PCL integrity. Imaging preferences are the same as with suspected ACL injuries.

- **Treatment**

Nonoperative management is acceptable for chronic and for isolated, low-grade, acute PCL tears. Initially, treatment is similar to that of an ACL tear, except crutches are utilized for 14 days and physical therapy emphasizes quadriceps strengthening. Indications for expeditious surgical referral include combined ligamentous injury, significant laxity, and avulsion fractures.


3. Injuries of the Medial Collateral & Lateral Collateral Ligaments

- **Pathogenesis**

Of the main stabilizing ligaments of the knee, the MCL is the most commonly injured. A medially directed or valgus force, as occurs with a noncontact twisting injury or a blow to the lateral side of the knee, is the most common cause of MCL disruption. Isolated LCL disruption is relatively rare and occurs with a blow to the anteromedial knee.

- **Clinical Findings**

Patients with an isolated collateral ligament tear generally present with a classic mechanism of injury and may report the sensation of a “pop” with the trauma. Patients complain...
of localized pain and tenderness over the damaged ligament but rarely report significant instability or locking. Localized swelling may be seen with isolated tears, but a significant effusion is rare.

Valgus and varus stress testing, to evaluate the MCL and LCL respectively, is performed at full extension (0 degrees) and 30 degrees. Laxity that is apparent only at 30 degrees of flexion suggests an isolated MCL or LCL injury. Additional laxity in full extension suggests concomitant soft tissue injury.

Radiographs are helpful in ruling out other bony pathology but are usually not necessary to diagnose isolated tears of the MCL or LCL. MRI is useful when examination findings are equivocal.

### Treatment

Treatment of isolated collateral ligament tears is primarily conservative. Ice and use of a compression wrap control local swelling. Crutches and toe-touch weight bearing may be all that a patient with a high-grade sprain may tolerate initially. However, regardless of severity, the patient must be encouraged to gradually increase weight bearing as soon as possible. Although hinged bracing does not speed healing, it provides some protection and a subjective sense of stability. Prior to full return to sports, athletes should have achieved full ROM and completed a functional rehabilitation program, and they should have minimal pain and nearly complete quadriceps and hamstring strength. Recovery may vary from days to weeks, but nonoperative management is routinely favored.

**MENISCAL TEARS**

#### General Considerations

The lateral and medial menisci are C-shaped wedges of fibrocartilaginous tissue with attachments at the anterior and posterior aspects of the tibial plateau (see Figure 37-2). The menisci have many functions which include load bearing and distribution, shock absorption, passive stabilization, and proprioception.

Meniscal tears tend to involve the medial meniscus; it is more fixed than the lateral meniscus and therefore more susceptible to injury. Younger patients often have associated injuries, while adults older than 40 years frequently develop atraumatic tears related to degeneration.

#### Clinical Findings

**A. Symptoms and Signs**

Acute, isolated meniscal tears primarily occur due to shearing forces during a twisting or hyperflexion injury. Pain is moderate and may subside, allowing some to return to activity following the tear. Effusion is slower to develop (24-36 hours) and is generally moderate. Occasionally, large bucket-handle tears displace and lodge in the joint, preventing full extension and creating a "locked knee." This presentation requires early surgical referral. More often, patients present days to weeks after the original injury and have full ROM. They complain of pain with squatting and of painful locking or catching, reflecting the meniscal fragment within the joint. Patients with degenerative tears tend to present without a history, insidious onset, mechanical symptoms, and mild intermittent swelling.

Physical examination may demonstrate an effusion. ROM should be assessed to ensure that there is no loss of extension or flexion. Joint line tenderness over the affected meniscus is the best clinical indicator of a meniscal tear (74% sensitivity; 50% positive predictive value). Several provocative maneuvers have been developed to recreate impingement of the torn fragment. These tests include the McMurray test and the Apley test, which are helpful but marginally sensitive or specific.

**B. Imaging Studies**

Although radiographs cannot confirm the diagnosis of a meniscal tear, a standard knee series (see section Anterior Cruciate Ligament Injury, earlier) is obtained to rule out additional bony pathology and to examine for joint space narrowing. MRI is the confirmatory imaging modality of choice.

#### Treatment

Initial treatment for isolated meniscal pathology includes cryotherapy, rest, NSAIDs, crutches and weight-bearing as tolerated for 7-10 days, and early ROM exercises. If full ROM is attained, and neither pain nor effusion recurs, the patient may gradually return to activity. Partial response to conservative measures warrants physical therapy. Indications for surgical referral include failure to respond to nonoperative treatment or recurrent episodes of catching or giving way.

**ANKLE SPRAINS**

#### General Considerations

Ankle ligament sprains are the most common ankle injuries and account for 19%-23% of all sports injuries. The overwhelming majority of these sprains are inversion injuries affecting the lateral ligamentous complex, including the anterior talofibular ligament (ATFL), the calcaneofibular ligament (CFL), and the posterior talofibular ligament (Figure 37-3). Medially, the deltoid ligament provides restraint to eversion.
Clinical Findings

A. Symptoms and Signs

Patient history is the key to assessing ankle trauma. Generally, patients with a lateral ankle sprain report an inversion, internal rotation injury with the foot in plantar flexion. Pain over the involved ligaments is common. Discomfort with weight-bearing and ecchymosis are variable. Usually after an acute injury, the ankle is too swollen or the patient too guarded to permit a diagnostic examination, and a repeat physical examination may be necessary several days after the initial injury.

Observation of the patient’s gait, inspection, palpation, and the anterior drawer and talar tilt tests are the cornerstones of the physical examination. Inspection demonstrates variable swelling, and palpation yields focal tenderness over the involved ligaments, generally the ATFL and CFL. The anterior drawer test is performed with the patient’s foot relaxed off the edge of the table. The examiner stabilizes the distal tibia with one hand, then grasps the calcaneus in the palm of the other hand, and applies an anterior force. Excessive anterior motion or a “clunk” suggests disruption of the ATFL. The talar tilt test is performed by stabilizing the tibia with one hand, then grasping the calcaneus in the palm of the opposite hand and inverting or everting the hindfoot. Significant laxity with inversion suggests disruption of the ATFL and CFL, whereas laxity with eversion suggests disruption of the deltoid ligament.

B. Imaging Studies

The Ottawa ankle rules provide high-yield criteria for ordering radiographs (level of evidence C). Indications for radiographs include bony tenderness at the distal, posterior portions of the lateral or medial malleolus, or inability to bear weight immediately and during the examination. Routine radiographs include anterior, lateral, and mortise views.

Treatment

Initial treatment of isolated, acute ankle sprains consists of rest, ice, compression or support, and elevation (RICE). Occasionally, crutches, a posterior splint, cast, or walking boot are required initially. Regardless, rest is relative and temporary. Early protected mobilization and weight bearing have been shown to facilitate return to activity and should be encouraged. Application of ice works as well as or better than heat to speed recovery at any stage of the injury (level of recommendation B). Options for supportive devices for ankle sprains are numerous. Although the use of an elastic bandage has fewer complications, the use of a semi-rigid ankle support (such as an Aircast Stirrup) appears to be associated with less subjective instability and more rapid return to work and to sports. A lace-up ankle support seems to significantly reduce swelling and is also a reasonable option. NSAIDs may increase bleeding and swelling acutely, so acetaminophen or mild narcotics should be used for pain within the first 48 hours. Rehabilitation follows the initial therapy with the goals of...
restoring motion, strengthening the ankle everters and dorsiflexors, stretching the Achilles tendon, and gradually progressing to proprioceptive and functional conditioning.

Worsening symptoms or lack of improvement in the first several weeks after a lateral ankle sprain should prompt the physician to consider other causes of ankle pain. Differential diagnosis should include fracture or osteochondral lesion of the talus; peroneal tendon subluxation; fractures of the calcaneus, distal fibula, fifth metatarsal, or navicular; and subtalar or Lisfranc sprain.

Medial ankle sprains are caused by eversion and dorsiflexion and involve sequential tearing of the deltoid ligament, the anterior tibiofibular ligaments, and the interosseous membrane. These significant injuries are beyond the scope of this chapter; however, readers are cautioned that symptoms are prolonged and treatment is significantly more aggressive with these types of injury.

Clinical Findings

A. Symptoms and Signs

Patients present with complaints of dull pain along the middle or distal posteromedial tibia. Pain often coincides with a significant increase in the intensity, frequency, or duration of the patient’s activity, or with a change in the patient’s footwear or running surface. Initially, pain may be present only at the beginning or the end of activity, and symptoms are promptly relieved with rest. If training continues, however, pain may become more severe and persistent.

Physical examination reveals diffuse tenderness along the posteromedial border of the middle and distal tibia. Provocative maneuvers include passive dorsiflexion, active plantar flexion, standing toe raises, and one- or two-legged hop. Excessive foot pronation, hindfoot or forefoot varus, and heel cord tightness are thought to be risk factors for MTSS.

B. Imaging Studies

Radiographs are frequently normal. A bone scan, however, is particularly useful for distinguishing MTSS from a stress fracture. In contrast to the focal uptake seen with a stress fracture, MTSS demonstrates diffuse, longitudinal uptake at the posteromedial tibia only on the delayed phase of the scan.

Differential Diagnosis

The differential diagnosis of exertional leg pain includes MTSS, deep venous thrombosis, fascial herniations, muscle strains, nerve or artery entrapment, chronic exertional compartment syndrome, and stress fracture.

Treatment

Initial treatment of MTSS consists of activity modification and avoidance of aggravating factors. If normal ambulation causes pain, crutches may be used to eliminate weight bearing temporarily. Activities that do not cause discomfort may be continued. Activities that induce pain must be discontinued and resumed only when the activity can be performed pain free. Thereafter, training level may be increased gradually over a 3- to 6-week period as long as the patient remains asymptomatic with each advancing stage. Although unproven, several adjuvant treatments may be beneficial, including ice massage, NSAIDs, shock-absorbent inserts, heel cord stretching, and correction of malalignment. Surgical referral for fasciotomy is reserved for patients with extraordinarily resistant and painful symptoms.

MEDIAL TIBIAL STRESS SYNDROME

General Considerations

Medial tibial stress syndrome (MTSS) is a common overuse injury that causes activity-related pain over the posteromedial aspect of the distal two-thirds of the tibia. The term MTSS has replaced the previously favored term shin splints, as it is far less generic and more accurately reflects the etiology and location of the pain. Runners are most commonly affected, but MTSS is also quite prevalent in athletes who participate in jumping sports such as basketball and gymnastics, and in military recruits.

Pathogenesis

Although multiple muscle groups have been implicated and the roles of inflammation versus bone remodeling have been investigated, the precise pathophysiologic mechanism of MTSS remains unclear. The most recent theory implicates the fascial insertion of the medial soleus as the probable source of pathology. Theory holds that during activity the medial soleus contracts to plantar flex and invert the foot, disrupting the fascial fibers at the muscle insertion onto the tibial periosteum.
PLANTAR FASCIITIS

General Considerations
Plantar fasciitis is extremely common in young runners, and it is reportedly the most common cause of heel pain in adults as well. The peak incidence in the general population is between the ages of 40 and 60 years.

Pathogenesis
The plantar fascia is a fibrous aponeurosis that extends from the medial calcaneus to the metatarsal heads. It provides static support of the longitudinal arch of the foot and dynamic shock absorption. The etiology of plantar fasciitis is likely multifactorial. Although data are limited, several risk factors have been identified, including obesity, pes planus, pes cavus, and a tight Achilles tendon. In athletes, the primary risk factor is thought to be overactivity. Athletes commonly report a change in the intensity, distance, or duration of their activity or an alteration in their running surface or footwear that accompanied the onset of symptoms.

Although the term fasciitis implies inflammation, histologic specimens from patients undergoing plantar fascia release have shown predominantly degenerative and chronic inflammatory changes in the tissue. Therefore, this entity may more appropriately be considered a fasciosis.

Clinical Findings

A. Symptoms and Signs
Classically, patients present with insidious onset of pain on the plantar surface of the heel that is worse with the first steps in the morning or when standing after a prolonged period of rest. Pain usually diminishes with rest but may recur at the end of the day. Athletes report that running, hill climbing, and sprinting exacerbate the pain. Pain is bilateral in up to one-third of cases.

Physical examination generally demonstrates tenderness along the anteromedial aspect of the calcaneus which intensifies with stretching of the plantar fascia by passive dorsiflexion of the toes. Limited ankle dorsiflexion associated with a tight heel cord may also be noted.

B. Imaging Studies
Radiographs are rarely indicated for the initial diagnosis and treatment of plantar fasciitis. Heel spurs on the anterior calcaneus can be misleading; these are present in 15%-25% of the general population without symptoms, and many symptomatic patients do not have spurs. Therefore, the detection of heel spurs is of no value in either confirming or excluding the diagnosis of plantar fasciitis.

Differential Diagnosis
The differential diagnosis of heel pain includes calcaneal stress fracture, plantar fascia rupture, fat pad atrophy, retrocalcaneal bursitis, nerve entrapment syndromes, spondyloarthropathies, infection, tumor, and Paget disease.

Treatment
Fortunately, 80% of patients with plantar fasciitis will improve, regardless of therapy. However, resolution of symptoms can take 6-18 months, and there is limited evidence supporting the value of many of the treatments. Nonetheless, initially it seems reasonable to recommend conservative, low-risk interventions. These include activity modification, NSAIDs, heel cushions or arch supports, and an aggressive Achilles and plantar fascia stretching program. Support for the use of ice, heat, massage, or strengthening of the intrinsic muscles of the foot is predominantly anecdotal. Corticosteroid injections may provide short-term benefit. More intensive treatments, including custom orthotics, night splints, and cast immobilization, may be beneficial in patients with recalcitrant symptoms. Extracorporeal shock wave therapy is a promising option on the horizon, but its efficacy is still controversial in the literature. Surgical release is generally reserved for patients who have not responded to appropriate conservative treatment of at least 6-9 months’ duration.


PEDiatric MUSCULOSKELETAL DISORDERS

Legg-Calve-Perthes Disease & Slipped Capital Femoral Epiphysis

General Considerations
LCPD is defined by idiopathic osteonecrosis and collapse of the femoral head. Most cases occur between 4 and 8 years of age. Boys are more commonly affected. Slipped capital femoral epiphysis (SCFE) is a disorder of the growth and development of the proximal femur resulting from excessive stress to the proximal femoral epiphysis. The peak incidence occurs in early adolescence at
about 12-13 years of age, and there is again a male predominance. Both conditions may be found bilaterally in the same individual.

Clinical Findings

A. Symptoms and Signs

The presentations of both LCPD and SCFE are characterized by aching pain in the groin, medial thigh, or knee. Pain is often accompanied by an altered gait or limp, and it is usually worsened by activity. SCFE may present as knee pain in up to 23% of cases, and it cannot be overstated that the investigation of knee pain in children should include a history and physical examination that addresses the hips as well.

Physical examination may produce pain at the extremes of motion, particularly in hip abduction and internal rotation. Loss of normal motion may be evident as well, and restricted internal rotation is noted particularly with SCFE.

B. Imaging Studies

Anteroposterior (AP) and frog-leg lateral radiographs of the pelvis should be obtained. Plain radiographs nearly always confirm the diagnosis of SCFE by demonstrating displacement of the femoral head. In the early stages of LCPD, plain radiographs may be normal. However, there are also a variety of abnormal radiographic findings which may include increased density of the femoral head or epiphysis.

Differential Diagnosis

The differential diagnosis includes developmental dysplasia of the hip, septic arthritis, transient synovitis, labral pathology, and benign or malignant neoplasms. Inflammatory causes (juvenile rheumatoid arthritis, spondyloarthopathies, lyme arthritis) are possible as well.

Clinical Findings

A. Symptoms and Signs

Transient synovitis most commonly presents with unilateral hip or groin pain that is associated with a limp or refusal to bear weight. Typically, the child is well-appearing, but some are mildly ill with a fever. The leg may be held in a flexed position with slight abduction and external rotation. There is mild restriction of hip motion.

Several investigators have attempted to define clinical prediction tools for differentiating septic arthritis from transient synovitis of the hip, as the treatment is drastically different. One prospective study found fever (temperature >38.5°C) to be the best predictor of septic arthritis, followed by an elevated C-reactive protein level (CRP), an elevated erythrocyte sedimentation rate (ESR), refusal to bear weight, and an elevated serum white blood cell count. Such criteria, however, are meant only to assist in clinical decision making, rather than to establish a diagnosis.

B. Imaging Studies

AP and frog-lateral radiographs may be obtained based on the degree and duration of symptoms, but they are usually normal. Advanced imaging is favored when infectious or neoplastic diagnoses are entertained.

C. Laboratory Studies

Complete blood count (CBC), ESR, and CRP may be obtained to aid in diagnosis if there is suspicion for septic arthritis or other infectious or neoplastic conditions. It should be noted, however, that laboratory test values may also be abnormal in children with transient synovitis. Therefore, if septic arthritis remains a consideration, then hip aspiration is mandatory.

Treatment

Transient synovitis is self-limited and requires no specific treatment. Most children will have complete resolution of symptoms within 2 weeks of onset.

SPONDYLOLYSIS

General Considerations

Spondylolysis is one of the most common causes of back pain in active children and adolescents. It is defined as a defect, or “stress fracture,” in the pars interarticularis of the posterior neural arch of the vertebrae. It occurs at the L5 level
in up to 95% of cases. The etiology is often repetitive hyper-extension of the lumbar spine.

### Clinical Findings

#### A. Symptoms and Signs

Spondylolisthesis is usually characterized by the insidious onset of low back pain which is worse with activity and lumbar extension. Pain may be severe at times, but neurologic symptoms and radiculopathy are rare. Physical examination may be relatively normal, or the child may have localized lumbosacral tenderness or reproducible pain with gentle extension. The single-leg hyperextension (stork) test is a provocative test which may also elicit pain at the site of the defect.

#### B. Imaging Studies

The initial imaging for suspected spondylolisthesis includes anteroposterior (AP), lateral, and right and left oblique radiographs of the lumbar spine. However, if clinical suspicion remains high despite normal radiographs, then more advanced imaging is warranted. Several other modalities have proven useful in detecting pars defects, including bone scan, single-photon emission CT (SPECT), conventional CT, and MRI.

### Differential Diagnosis

The differential diagnosis of acute back pain in the pediatric population includes spondylolisthesis, scoliosis, lumbosacral strain, and discogenic pain. Inflammatory arthropathies should be considered in the context of chronic pain. Night pain, fever, or other systemic symptoms should prompt an evaluation for infection or neoplasm.

### Treatment

Treatment of symptomatic spondylolisthesis generally involves a combination of rest, bracing, and rehabilitation. Successful healing of the bony defect is often achieved with nonoperative management over the course of several months. Surgical fixation is reserved for those cases in which pain persists beyond 9-12 months of conservative treatment, or if there is advanced spondylolisthesis (as with bilateral pars defects).

### OSTECHONDRODYSPLASIA

#### General Considerations

Osteochondritis dissecans (OCD) is described as an idiopathic lesion of the cartilage and subchondral bone in the skeletally immature patient. It most commonly affects the weight-bearing surfaces of the distal femur (>70% on the medial femoral condyle) and is an increasingly recognized cause of knee pain in the adolescent population. There is a greater incidence in males. Undiagnosed or asymptomatic juvenile cases may later be identified in adulthood.

### Clinical Findings

#### A. Symptoms and Signs

The clinical presentation is poorly localized knee pain which is worsened by activity. The patient may report swelling and/or mechanical symptoms, such as locking, if the lesion is unstable or a loose body is present. Palpation of the femoral condyle may yield tenderness. A positive Wilson test indicates pain with internal rotation of the tibia followed by gentle extension of the knee. A joint effusion may be present.

#### B. Imaging Studies

Anteroposterior and lateral radiographs of the knee are indicated to roughly localize the lesion and determine its size. An additional tunnel or notch view (PA view with knee flexed to 50 degrees) should also be performed to visualize the posterior femoral condyles. MRI is recommended to further characterize and classify OCD lesions.

### Treatment

Much controversy surrounds the treatment of OCD. Because stable lesions in skeletally immature patients often heal, nonoperative management is the initial treatment of choice. This involves a variable period of immobilization, protected weight-bearing, and activity restriction, followed by rehabilitation. Surgery may be necessary in those who fail conservative management, particularly if nearing physeal closure, or in patients with unstable lesions or loose fragments.

### APOPHYSAL INJURIES

#### General Considerations

An apophysis is a growing bony prominence at which secondary ossification occurs in the skeletally immature individual. Apophysitis is a painful, inflammatory condition at the tendinous insertion onto these bony prominences. This condition is unique to active youth in their late childhood and adolescent years. Repetitive stress and traction on the apophysis (“overuse”) are the offending causes. The most common sites of apophysitis are the tibial tuberosity (Osgood-Schlatter disease), inferior patella (Sinding-Larsen-Johansson syndrome), medial epicondyle of the elbow (little league elbow), and posterior calcaneus (Sever disease). It is important to note that tendinopathies are unusual in children since the apophysis is intrinsically weaker and more susceptible to injury than the tendon.

### Clinical Findings

#### A. Symptoms and Signs

These conditions are diagnosed clinically by history and physical examination. Patients generally describe an insidious onset of well-localized pain at the site of injury or...
inflammation. Pain is uniformly present during or shortly after activity. Tenderness is easily elicited by palpation. The presence of mechanical symptoms (locking, catching, or loss of motion), particularly in the elbow, should prompt consideration of an alternative diagnosis.

B. Imaging Studies

While plain radiographs may serve to exclude other causes of pain, they are not routinely necessary in establishing the diagnosis.

Treatment

Apophysitis is generally self-limited and resolves once skeletal maturity is reached and the apophysis fuses. In the meantime, treatment is accomplished by activity modification, ice, NSAIDs, and physical therapy in certain cases. Sever disease may sometimes benefit from a period of immobilization, and little league elbow can often be prevented by proper pitch training and adherence to pitch count recommendations.


CLAVICLE FRACTURES

Clinical Findings

A. Symptoms and Signs

A direct blow to the clavicle or a fall on the lateral shoulder may cause a clavicular fracture. Fractures of the clavicle occur in the middle (80%), distal (15%), and medial (5%) thirds. Patients hold the affected arm adducted and resist motion. Typically, there is swelling and tenderness over the fracture site and a visible and palpable deformity.

B. Imaging Studies

Imaging studies should include an anteroposterior (AP) view. Sometimes an apical lordotic view (AP view 45 degrees cephalad) helps visualize the clavicle without rib interference. A distal third fracture with articular involvement may require cone views or a lateral view. Likewise, at times a medial third fracture is seen with cone and lateral views. A computed tomography (CT) scan helps visualize articular fractures.

Complications

Complications may include subclavian vascular injuries and nerve root avulsion or contusion. Middle third fractures may develop malunion, excessive callus formation, and nonunion. Displaced distal third fractures with torn coracoclavicular ligaments may lead to delayed union. It may require years for a large callus to remodel. Articular surface involvement in either the medial or distal third can lead to degenerative arthritis.

Treatment

Treatment includes ice, analgesics, sling immobilization, and physical therapy. Initial radiographs may show early callus formation. At 2-week follow-up, radiographs should be obtained to evaluate for displacement and angulation. Significant callus typically forms between 4 and 6 weeks, along with disappearance of the fracture line. If the fracture is not clinically healed, repeat radiographs at 6-8 weeks are indicated. Once the fracture is clinically and radiographically healed, radiographs can be discontinued. The patient may return to normal activity when the clavicle is painless, the fracture is healed on radiograph, and the shoulder has a full range of motion and near-normal strength.

Displaced fractures, open fractures, nonunion, and persistent pain 6-8 weeks post-fracture are indications for referral.

COLLE FRACTURES (DISTAL RADIUS FRACTURE)

Clinical Findings

A. Symptoms and Signs

A fall-on-outstretched-hand (FOOSH) injury can lead to a Colle fracture. Patients typically present with pain, swelling, and tenderness at the distal forearm. On examination a “dinner fork” deformity (dorsal displacement of the distal fragment and volar angulation of the distal intact radius with radial shortening) may be identified.

Complications

There are early and late complications of Colle fractures. Early complications include median nerve compression, tendon damage, ulnar nerve contusion or compression, compartment
syndrome, and fragment displacement with loss of reduction. Patients may develop a decreased range of motion of the wrist and prolonged swelling. Possible late complications include stiffness of the fingers, shoulder, or radiocarpal joint, shoulder-hand syndrome, cosmetic defects, rupture of the extensor pollicis longus, malunion, nonunion, flexor tendon adhesions, and chronic pain of the radioulnar joint with supination. If there is distal radial ulnar joint disruption and radial shortening, decreased grip strength, decreased range of motion with supination, and difficulty writing may develop.

**Treatment**

A nondisplaced distal radial fracture or minimally displaced fracture with little comminution can be managed by the primary care provider. Treatment steps include anesthesia, reduction of the fracture with traction and manipulation, and immobilization with casting. Afterward, postreduction radiographs are taken to ensure proper alignment.

Reduction is necessary to maintain radial length and volar tilt. A short arm cast may be used in an elderly patient and for others with a nondisplaced fracture. All others should be placed in a long arm cast for 3-6 weeks followed by a short arm cast. Physical therapy is helpful for maintaining elbow range of motion. The cast should extend to the proximal palmar crease volarly and to the metacarpophalangeal (MCP) prominences dorsally to allow finger and MCP motion and allow opposition. Care should be taken to ensure there is adequate padding around the edges of the cast.

At 2 weeks, AP and lateral radiographs may show little or no callus formation. These should be compared with the original radiographs. Rereduction may be necessary. At the 4- to 6-week follow-up, radiographs may show a bridging callus. If there is adequate callus and no tenderness or motion at the fracture site, then cast immobilization may be discontinued. Physical therapy for wrist and elbow range of motion should be started. At 6-8 weeks bridging callus should be visualized. Radiographs should be checked to assess for malunion, radial shortening, and delayed union as well as for functionality of the wrist. The cast should be discontinued if criteria at the 4- to 6-week follow-up are met. At the 8- to 12-week follow-up, additional callus should be seen. Nonunion occurs with no healing at 4-6 months postinjury.

Indications for referral include fractures with radiocarpal or radioulnar joint involvement, significantly comminuted fractures, and displaced articular fractures.

**SCAPHOID FRACTURES**

**Clinical Findings**

**A. Symptoms and Signs**

Scaphoid fractures are caused by a forceful hyperextension of the wrist. This is typically due to a FOOSH with the wrist dorsiflexed and radially deviated. Fracture locations are the distal pole, waist, proximal pole, and tubercle. Another important factor is stability of the fracture. A scaphoid fracture is stable unless there is (1) displacement greater than 1 mm, (2) scapholunate angulation greater than 60 degrees, or (3) radiolunate angulation greater than 15 degrees. Associated injuries to look for include perilunate dislocation, lunate dislocation, trapezium fractures, triquetrum fractures, radial styloid fractures, distal radius fractures (Colle fractures), fractures of metacarpals 1 and 2, and capitate fractures. Patients present with a painful wrist and may report swelling or paresthesias of the affected hand. On examination, there is maximal tenderness in the anatomic snuff box, pain with radial deviation of the wrist, and pain with axial compression of the thumb.

Bone healing occurs at different rates depending on the location of the fracture. A tuberosity fracture usually heals in 4-6 weeks, and a scaphoid waist fracture in 10-12 weeks. A proximal pole fracture can require 16-20 weeks for healing.

**B. Imaging Studies**

Imaging studies include AP (hand in neutral position), AP (tube tilted 40 degrees distally), lateral (distal arm elevated 15 degrees), and oblique (hand in 10 degrees of supination and maximal ulnar deviation) radiographic views. Occasionally, right and left oblique views or a scaphoid view may be necessary. Further imaging with a magnetic resonance imaging (MRI) scan is appropriate when a fracture is clinically suspected but radiographs are negative and the patient needs to return to activity as early as possible.

**Complications**

Several complications are associated with a scaphoid fracture: delayed union (no healing, no trabeculae crossing the fracture line, at 3 months), avascular necrosis (radiographs show...
COMMON UPPER & LOWER EXTREMITY FRATURES

sclerosis and cyst development), compartment syndrome (rarely), and compression neuropathy (rarely). Of utmost concern is malunion or nonunion (absence of evidence of healing at 4-6 months). Malunion resulting in a humpback deformity can lead to carpal instability, loss of wrist extension, weakness of grip, carpal collapse, and degenerative changes in the wrist.

**Treatment**

Nondisplaced or minimally displaced (<1 mm) scaphoid fractures are placed in a thumb spica cast. A short arm cast is used for tuberosity fractures and long arm casts for all other nondisplaced or minimally displaced scaphoid fractures. When casting, the wrist should be in a neutral flexion-extension, neutral to radial deviation with the thumb included. A long arm cast is used for 6 weeks and is then replaced with a short arm cast for another 6 weeks.

Follow-up should occur at 2 weeks with AP, lateral, and oblique radiographic views, checking for step-offs, angulation, and displacement. At this point no callus and possible fracture site resorption are seen. Later, at 4-6 weeks, there is no callus because there is no periostial membrane. However, trabecular bone may be visible across the fracture line. At 8-12 weeks the fracture line begins to disappear. The normal trabecular bone pattern returns in 12-16 weeks. Rehabilitation takes 3-6 months. Union rates vary; for a nondisplaced fracture the rate is 100%. Angulated fracture union rates are 65% and displaced rates are 45%. The proximal one-third fracture union rate range is 60%-70% with immobilization.

Consultation is required for open reduction and internal fixation for displaced, delayed union, and nonunion scaphoid fractures. Referral is also appropriate for a patient initially presenting more than 3 weeks after the injury.

**Web Sites**

http://www.physsportsmed.com/issues/1996/06_96/gutierrez.htm

**METACARPAL FRACTURES**

**Clinical Findings**

**A. Symptoms and Signs**

Metacarpal fractures are caused by direct trauma to the hand. These fractures can be stable or unstable. Stable fractures can be impacted or isolated fractures with little or no displacement. Unstable fractures are comminuted, displaced, oblique, or spiral, often multiple fractures. Patients present with tenderness and swelling.

Special fractures include the following:

- Bennett fracture (two-part intra-articular fracture of the base of the first metacarpal)
- Rolando fracture (three-part intra-articular fracture of the base of the first metacarpal)
- Reverse Rolando fracture (three-part intra-articular fracture of the base of the fifth metacarpal)
- Boxer’s fracture (fifth metacarpal neck fracture)

**B. Imaging Studies**

AP and lateral radiographs are needed and comparison views are sometimes helpful. However, it is recommended that initial radiographs of fractures of the fourth and fifth metacarpals be AP and oblique pronated views. Additional lateral radiographs are helpful only after confirmation of a proximal comminuted fracture or signs of a pronounced AP dislocation. A CT scan may be helpful for fractures of the metacarpal head and base.

**Complications**

Complications are many and include decreased grip strength, arthritis if the articular surface is involved, prolonged swelling, reflex sympathetic dystrophy, compartment syndrome, decreased MCP prominence with metacarpal shaft dorsal prominence, and decreased range of motion.

**Treatment**

Treatment depends on a variety of factors. Casting is appropriate in the following situations: no degree of rotational deformity; an intra-articular fracture, with no more than a 1- to 2-mm step-off; stable neck and shaft fractures; extra-articular metacarpal base fractures; comminuted metacarpal head fractures; and second, third, and fourth intra-articular metacarpal base fractures. Certain angular restrictions must be adhered to.

For shaft fractures:

- First digit: no more than 30 degrees of apex dorsal angulation
- Second and third digits: no more than 10 degrees of apex dorsal angulation
- Fourth and fifth digits: no more than 20 degrees of apex dorsal angulation

For neck fractures:

- Second digit: no more than 10 degrees of apex dorsal angulation
- Third digit: no more than 20 degrees of apex dorsal angulation
- Fourth digit: no more than 30 degrees of apex dorsal angulation
- Fifth digit: no more than 40 degrees of apex dorsal angulation

If the metacarpal fracture meets the preceding conditions it may be casted or splinted. The affected digit is buddy taped. The wrist is casted in 30 degrees of extension. The MCP joints are flexed 60-90 degrees. The distal and proximal interphalangeal joints are placed in 5-10 degrees of flexion. The cast should be trimmed to allow visualization of the tip of the injured digit and the adjacent buddy-taped digit. This step facilitates checking capillary refill. Recheck for loss of correction after casting.
At 2 weeks postcasting, a radiograph should be checked for loss of correction. Bridging callus should be seen at 4-6 weeks. If there is tenderness, motion, or inadequate callus formation, the digit should be recasted and rechecked every 2 weeks. If there is no tenderness, no motion at the fracture site, and adequate callus formation is noted, a protective splint can be considered for an additional 1-2 weeks. If symptoms continue beyond 6 weeks, cast immobilization and reassessment at 2-week intervals should be continued until radiographic and clinical healing is achieved.

Unstable fractures of the metacarpal neck or shaft should be referred to an orthopedic surgeon. Most intra-articular fractures of the base of the first and fifth metacarpals also need referral. These fractures will likely be treated by closed reduction and percutaneous pinning. Open reduction and internal fixation are indicated for intra-articular fractures of the metacarpal base that cannot be maintained by closed reduction and for fractures of the metacarpal head with mild comminution.

RADIAL HEAD FRACTURES

Clinical Findings

A. Symptoms and Signs

Radial head fractures can be caused by a FOOSH while the arm is pronated or partially flexed. Another mechanism of injury is a valgus force on the elbow, forcing the humeral capitellum into the radial head. Patients present with elbow pain and swelling. Physical findings are tenderness over the radial head, pain that is increased with supination, reduced range of motion, and swelling secondary to a hemarthrosis. Swelling in the center of a triangle formed by the lateral epicondyle, olecranon, and radial head may occur. The patient should be evaluated for neurovascular compromise, checking capillary refill, sensation, and posterior interosseous nerve function. The medial collateral ligament should be evaluated for tenderness and opening with valgus stress.

B. Imaging Studies

AP and lateral views of the wrist should be obtained to rule out disruption of the distal radial ulnar joint. Imaging studies of the elbow include AP, lateral, and radiocapitellar (45 degrees from the lateral toward the radial head) views. Look for the radiocapitellar line and a fat pad sign. Follow-up radiographs at 2 weeks will not show a callous; however, at 4-6 weeks a bridging callous should be noted. Bone healing is visible between 6 and 8 weeks. Rehabilitation should begin as soon as the fracture is stable, to maintain functional range of motion. At 8-12 weeks there should be abundant bridging callous and a resolving fracture line. In the rare case of nonunion, the patient will report pain and examination will reveal tenderness.

Complications

Possible complications include reflex sympathetic dystrophy, compartment syndrome of the elbow and forearm, heterotropic...
ossification, increased carrying angle of the elbow, arthritis with restricted range of motion, deformity, valgus instability, decreased grip strength, posterior interosseous or median nerve injury, and brachial artery injury.

**Classification (Mason)**

- Type I: Nondisplaced
- Type II: Marginal fractures with displacement, depression, or angulation
- Type III: Comminuted fractures of the entire head or completely displaced fractures of the radial head
- Type IV: Type I, II, or III with elbow dislocation

**Treatment**

The primary care physician can treat type I (nondisplaced radial head) fractures. Treatment includes aspiration (to decrease the hematoma and capsular distention; injection of anesthetic may aid in evaluation), early range of motion, and a sling for 5-7 days. Bone healing typically occurs in 6-8 weeks. Range of motion rehabilitation should be started as soon as possible, when the fracture is stable.

Based on the Mason classification, type II fractures (displacement of 2-3 mm, greater than 25-degree involvement of the articular surface) require open reduction with internal fixation. Additionally, type III fractures (nonreparable comminuted) may require radial head excision. Patients with type IV fractures (posterior dislocation) should be referred.

**Web Sites**

http://www.orthoseek.com/articles/fractman.html
http://www.physsportsmed.com/issues/1996/06_96/cordas.htm

**LOWER EXTREMITY FRACTURES**

**STRESS FRACTURES**

**General Considerations**

Management of traumatic fractures of the lower extremity long bones is relatively straightforward if a few simple rules are recognized. Orthopedic referral is required for any traumatic fracture that is displaced or involves a joint line. The physician who seeks to obtain competence in acute traumatic fracture management, requiring casting, should seek other references. The goal of this section is to guide the primary care physician through a basic understanding of concepts surrounding bone stress pathogenesis, including epidemiology, clinical signs and symptoms, physical examination, radiographic diagnostic aids, and treatment of four difficult-to-treat areas of stress reaction in the lower extremities. The population most at risk for stress reaction is athletes. This population presents therapeutic challenges secondary to their increased activity, predilection to overuse injury, and desire to return to competition as quickly as possible, which may lead them to compete before the stress injury fully resolves.

Stress fractures are estimated to make up 10% of all athletic injuries. Ninety-five percent of stress injuries occur in the lower extremities secondary to the extreme repetitive weight-bearing loads placed on these bones. The peak incidence occurs in people 18-25 years of age. However, with recent emphasis on exercise for the elderly, the diagnosis of stress fracture should not be neglected in this population. There is a decreased incidence of stress fracture in men secondary to greater lean body mass and overall bone structure. It has been estimated that women military recruits have a relative risk of stress fracture that is 1.2-10 times greater than men while engaging in the same level of training. In athletic populations a gender difference is not as evident, possibly because athletic women are more fit and better conditioned. Incidence is estimated to be comparable for all races.

Stress fracture is most common after changes in an athlete’s training regimen. Injury is especially prevalent in unconditioned runners who increase their training regimen. Training error, which can include increased quantity or intensity of training, introduction of a new activity, poor equipment, and change in environment (ie, surface), is the most important risk factor for stress injury. Low bone density, dietary deficiency, abnormal body composition, menstrual irregularities, hormonal imbalance, sleep deprivation, and biomechanical abnormalities also place athletes at risk. Keeping this in mind and recognizing the increasing incidence of female athletic triad (amenorrhea, eating disorder, and osteoporosis), it is easy to understand why women can have an increased risk for stress injury.

**Clinical Findings**

**A. Symptoms and Signs**

Stress fractures are related to a maladaptive process between bone injury and bone remodeling. Bone reacts to stress by early osteoclastic activity (old bone resorption) followed by strengthening osteoblastic activity (new bone formation). With continued stress, bone resorption outpaces new bone formation and a self-perpetuating cycle occurs, with continued activity allowing weakened bone to be more susceptible to continued microfracture and ultimately progressing to frank fracture. The initiation of stress reaction is unclear. It has been postulated that excessive forces are transmitted to bone when surrounding muscles fatigue. The highly concentrated muscle forces act across localized area of bone, causing mechanical insults above the stress-bearing capacity of bone. These insults occur at the insertion of tendons and lead to insults in the bone that may propagate into a stress fracture. Athletic stress fracture follows a crescendo process. Symptoms start insidiously with dull, gnawing pain at the
end of physical activity. Pain increases over days to the point where the activity cannot be continued. At first pain decreases with rest, then shorter and shorter duration of activity causes pain. More time is then needed for pain to dissipate until it is present with minimal activity and at night. After a few days of rest, pain resolves, only to return once again with resumption of activity. More specific historical and physical examination findings are discussed below in conjunction with specific anatomic regions.

B. Imaging Studies

The diagnosis of stress fracture is primarily clinical and is based on history and physical examination. It is prudent to start with plain radiographs, which have poor sensitivity but high specificity, as the initial study. The presence of stress reaction is confirmed by the presence of periostial reaction, intramedullary sclerosis, callus, or obvious fracture line. Plain films typically fail to reveal a bony abnormality unless symptoms have been present for at least 2-3 weeks.

The technetium triple-phase bone scan is often employed to improve diagnostic power. Stress reactions can often be visualized within 48-72 hours from symptom onset. Triple-phase bone scan can differentiate soft tissue and bone injury. The first phase flow image, taken immediately after intravenous injection of tracer, shows perfusion in bone and soft tissue. The second phase (static blood pool phase), taken 1 minute after injection, reflects the degree of hyperemia and capillary permeability of bone and soft tissue showing acute inflammation. In the third phase (delayed image), taken 3-4 hours after injection of tracer, approximately 50% of the tracer has concentrated in the bone matrix. All three phases can be positive in an acute fracture. In soft tissue injuries, with no bony involvement, the first two phases are often positive, whereas the delayed image shows minimal or no increased uptake. In conditions such as medial tibial stress syndrome (MTSS), in which there is early bony stress reaction, the first two phases are negative and the delayed image is positive. Bone scan does not visualize the fracture and is not used to monitor healing secondary to delayed images showing uptake 12 months after initial studies.

CT scans can identify conditions that mimic stress fracture on bone scan, confirm fracture suspected on bone scan, or help to make treatment decisions as with navicular stress fractures.

MRI offers the advantage of visualizing soft tissue changes in anatomic regions in which the soft tissue structures often cloud the differential diagnosis. Bone stress is identified as marrow edema, whereas frank stress fracture can be visualized as a line at the cortex surrounded by an intense zone of edema in the medullary cavity. Clinically the high sensitivity of bone scan and MRI is necessary only when the diagnosis of stress fracture is in question or the exact location or extent of injury must be known in order to determine treatment.

1. Femoral Stress Fractures

General Considerations

Stress fractures involving the femur can occur in a variety of locations, most commonly the femoral shaft and neck. One study that looked at 320 athletes with bone scan–positive stress fractures revealed the femur to be the fourth most frequent site of injury.

Differential Diagnosis

The symptom most commonly encountered with stress fractures of the femur is pain at the anterior aspect of the hip. Differentiating the diagnosis can be difficult secondary to the multiple number of structures in the hip that have the potential to produce similar pain syndromes and the deep nonpalpable structures of the anatomic region. The differential diagnosis is broad but must include consideration of disease processes such as apophysyal and epiphyseal injury in adolescents, arthritis in adults, along with inflammatory arthritides, muscle strains, tendinitis, stress fractures, sports hernia with nerve entrapment, osteitis pubis, and acetabular labral tears across all age groups. Diagnosis can be made complex by the multitude of structures in this region from which pain may emanate; thus, the physician must be attuned to the history to narrow the differential down to a list in which stress fracture is prominent. This is important in order to avoid severe complications associated with fractures of the femoral neck.

Femoral Shaft Fractures

Femoral shaft stress fractures are more common than expected, with an incidence in athletes of 3.7%. Onset of pain can be gradual over a period of days to weeks. Average time from symptom onset to diagnosis is approximately 2 weeks. The fulcrum test is well suited to act as a guide for ordering radiologic tests and thereby decreasing time to diagnosis. It is also a useful clinical test to assess healing. For this test, the athlete is seated on the examination table with legs dangling as the examiner’s arm is used as a fulcrum under the thigh. The examiner’s arm is moved from the distal to proximal thigh as gentle pressure is applied to the dorsum of the knee with the opposite hand. A positive test is elicited by sharp pain or apprehension at the site of the fracture. Plain films usually are not sensitive in detecting stress fractures within the first 2-3 weeks of symptoms. Bone scan or MRI may be useful in this time period to aid in diagnosis. The most common site of injury in athletes is the midmedial or posteromedial cortex of the proximal femur.

Once diagnosis is confirmed, treatment depends on the underlying causes responsible for the injury. If the fracture is consistent with a compression-sided fracture, treatment consists of rest with gradual resumption of activity (Figures 38-3 and 38-4). This usually is adequate for healing of nondisplaced fractures. Treatment protocols are based on empiric data gathered from clinical observation. An example of a treatment protocol may consist of rest for a period of 1-4 weeks of toe-touch weight bearing progressing to full weight bearing. This would be followed by a phase of low-impact activity (ie, biking, swimming). Once patients are able to perform low-impact activity for a prolonged time without pain, they may gradually advance to high impact. Resumption of full activity averages between 8 and 16 weeks. Surgical treatment should be considered if there is displacement of the fracture, delayed union, or nonunion following conservative therapy.

► Femoral Neck Fractures

Stress fractures of the femoral neck are uncommon but carry a high complication rate if the diagnosis is missed or the fracture is improperly treated. The primary presenting symptom is pain at the site of the groin, anterior thigh, or knee. Pain is exacerbated by weight bearing or physical activity. The athlete may have an antalgic gait or painful, limited hip range of motion in internal rotation or external rotation. MRI is the diagnostic modality of choice for evaluating femoral neck stress fractures.
Stress fractures of the femoral neck are divided into two categories: compression and tension type. Compression fractures are more common in younger patients. The fracture line, if seen on the radiograph, can propagate across the femoral neck. A nondisplaced, incomplete compression fracture is treated with rest until the patient is pain free with full motion. Non-weight-bearing ambulation with the patient on crutches follows until radiographic healing as shown on plain films is complete. Frequent radiographs may need to be obtained to monitor propagation of the fracture. If the compression fracture becomes complete, or fails to heal with rest, then internal fixation may be necessary (Figure 38-5). Patients treated nonsurgically may not achieve full activity for several months.

Tension (distraction)-sided femoral neck fractures are an emergency because of the potential for complications (ie, nonunion or avascular necrosis). The patient is immediately made non-weight-bearing and will acutely need internal fixation. If the fracture is displaced the patient will need open reduction and internal fixation urgently.

Figure 38-5. Intramedullary screw fixation of a femoral neck stress fracture.


2. Tibial Stress Fracture

General Considerations

Tibial stress fractures account for half of all stress fractures diagnosed. Most tibial stress fractures in athletes are secondary to running. An average of 3-6 weeks of overtraining has been shown to be associated with increased incidence of tibial stress fractures.

Two sites located within the tibia are most commonly associated with stress fractures. The first of these is located between the middle and distal third of the tibia along the posteromedial border. This type of injury is most often associated with running. The second site is along the middle third of the anterior cortex. This injury is most commonly associated with activities involving a great deal of jumping (ie, dancing, basketball, gymnastics).

Clinical Findings

A. Symptoms and Signs

On history the patient commonly describes pain occurring in the region of the fracture with activity (ie, running or jumping) and resolving with rest. The pain eventually progresses and lasts longer after the activity until the patient is symptomatic at rest. Physical examination often reveals localized pain to palpation. Sometimes persistent thickening, secondary to periosteal reaction, can be appreciated by palpation along the tibia.

B. Imaging Studies

Diagnosis by radiographic plain film may be possible if symptoms have been present for at least 4-6 weeks. Triple-phase bone scan is very sensitive and may allow diagnosis within 48-72 hours of symptom onset. Tibial stress fractures can be seen clearly on MRI with sensitivity comparable to triple-phase bone scan. Both bone scan and MRI allow differentiation of medial tibial stress syndrome and stress fracture.

Differential Diagnosis

Medial tibial stress syndrome (MTSS) is the most commonly confused diagnosis in the classification of tibial stress injuries with stress fracture. MTSS usually occurs diffusely along the middle and distal third of the posteromedial tibia and is commonly seen in runners. This condition, however, can also be seen with activities involving persistent jumping. The symptom spectrum commonly progresses, as does that of stress fractures, with continued activity. MTSS represents a stress reaction within bone whereby the usual remodeling process becomes maladaptive. This injury responds well to rest in a shorter time period as compared with stress fracture and is easily differentiated from stress fracture on triple-phase bone scan. If symptoms do not resolve or are consistent with distal numbness or in a region of nerve traversing one of the four involved compartments of the lower leg, the diagnosis of chronic compartment syndrome must be considered.

Treatment

Once the diagnosis of tibial stress fracture has been made, a distinction between a compression versus tension-sided injury must be made. Fractures along the posteromedial border are considered compression stress injuries and respond well to conservative therapy (Figure 38-6). The average recovery time for this injury is approximately 12 weeks when the patient is treated with rest alone. Most guidelines for treatment of this injury involve relative or absolute rest.
These stress fractures can be effectively treated in a pneumatic leg brace. Athletes treated in the pneumatic brace (long leg air cast) showed decreased time to pain-free symptoms (14 ± 6 days) and time to competitive participation (21 ± 2 days) versus traditional mode non-weight-bearing treatment (77 ± 7 days). Athletes in the brace may continue exercising, but modifications of the training routine must be made to maintain pain-free activities. Patients are progressed based on a functional activity progression as outlined by Swenson and colleagues.

Tibial stress fractures of the midanterior cortex, also known as “the dreaded black line,” radiographically (Figure 38-7), are very difficult to manage conservatively. This fracture occurs at the tension side of the tibial cortex, most commonly in athletes who jump. Two significant complications—delayed union and complete fracture—plague this fracture site, and average time to symptom-free return to activity from symptom onset is more than 12 months with conservative care. Conservative treatment revolves around rest, or immobilization, or both. Patients who do not respond to conservative treatment or are involved in activities (career or competitive athletics) are individuals in whom surgical treatment with tibial intramedullary nailing would be beneficial (Figure 38-8). Patients with these fractures, secondary to the prolonged treatment and risk of complication, should be referred to a sports medicine specialist.


3. Tarsal Navicular Stress Fracture

**General Considerations**
Tarsal navicular stress fractures are an underdiagnosed source of prolonged, disabling foot pain predominantly seen in active athletes involved in sprinting and jumping. One study, involving 111 competitive track and field athletes, found that navicular stress fractures are the second most common lower extremity stress fracture.

**Clinical Findings**

**A. Symptoms and Signs**
These fractures are prone to misdiagnosis secondary to the vague nature of pain. The pain may radiate along the medial arch and not directly over the talonavicular joint. Sometimes pain radiates distally, causing the physician to suspect a Morton neuroma or metatarsalgia. The pain often disappears with a few days of rest, often tricking the athlete into not believing the potential seriousness of the diffuse foot pain.

The diagnosis is also clouded because the fractures are rarely seen on plain film.

**B. Imaging Studies**
A retrospective multicenter study by Khan and colleagues looking at 86 fractures of the tarsal navicular bone, all with CT confirmation of clinical diagnosis, reported a range in time of diagnosis from symptom onset to be 3-60 months (average 4 months). Symptoms suggesting a clinical diagnosis consisted of (1) insidious onset of vague pain over the dorsum of the medial midfoot or over the medial aspect of the longitudinal arch, (2) ill-defined pain, soreness, or cramping aggravated by activity and relieved by rest, (3) well-localized tenderness to palpation over the navicular bone or medial arch, and (4) little swelling or discoloration. Certain foot abnormalities, including short first metatarsal and metatarsus adductor and limited dorsiflexion of the ankle, may concentrate stress on the tarsal navicular region, predisposing to stress reaction.

**Treatment**
The retrospective study by Khan and colleagues confirmed that the best treatment modality is 6-8 weeks of non-weight-bearing cast immobilization. This study also offered guidelines for treatment, the CT appearance of the fracture after conservative treatment, and parameters used to follow fracture healing. When seriously considering diagnosis of tarsal navicular stress fractures, plain film radiographs should be obtained in an AP, lateral, and oblique standing...
position ([Figure 38-9]). If the radiograph is normal, a bone scan should be obtained. If the bone scan is positive and the radiograph is negative, a CT scan to confirm stress fracture as opposed to stress reaction should be obtained. The CT slices must be no wider than 1.5 mm apart and must include the dorsal proximal cortical surface. Most fractures are located in the sagittal plane and in the central third of bone along the proximal articular surface corresponding to angiographic studies indicating this to be a relatively avascular region ([Figure 38-10]).

Data indicate that 6-8 weeks of non-weight-bearing cast immobilization compares favorably with surgical treatment for failed weight-bearing treatment. Surgery is recommended for a displaced, complete fracture with a small transverse fragment (ossicle), or failure of conservative management. Conservative management, however, may be warranted initially for patients with these fractures. Surgical treatment often consists of either bone graft or screw fixation ([Figure 38-11]) followed by non-weight-bearing cast immobilization for 6 weeks.

After 6 weeks of non-weight-bearing cast immobilization, fracture healing is followed clinically by palpation of the fracture site along the dorsal proximal region of the navicular bone. Persistent tenderness over this “N” spot requires an additional 2 weeks of non-weight-bearing immobilization before reassessment. If the fracture site is not tender after casting, the patient may begin weight bearing. Plain films do not provide a reliable indication of fracture healing secondary to low sensitivity. Bone scan often remains positive long after clinical union. A CT scan up to 3-6 months following therapy, although asymptomatic, can show blurring of the fracture line and cortical bridging. The CT scan may not show complete obliteration on 3-month repeat films. For this reason the recommendation is not to repeat the CT scan but instead to rely on clinical examination (palpation of the “N” spot).

Of note is the topic of “bone strain.” During this phenomenon the bone scan may be positive but the patient is asymptomatic. This can be seen when the bone scan is ordered to assess MTSS and activity is picked up in the navicular bone. The CT scan remains normal. Persistent training results in progression to stress fracture. Treatment of bone strain does not require cast immobilization. This condition can be managed successfully with 6 weeks of strict limitation of activity with weight bearing.


4. Metatarsal Stress Fractures

**General Considerations**

Metatarsal stress fractures in athletes are very common. Depending on the study referenced they are either third or fourth in incidence. These fractures are also known as “March fractures” because of the large numbers of military recruits who obtained these fractures after sudden increases in their level of activity. The second meta-tarsal is the most common location followed by the third and fourth metatarsals. The second metatarsal is subjected to three to four times body weight during loading and push-off phases of gait.
CHAPTER 38

Clinical Findings

A. Symptoms and Signs
Clinical suspicion for this injury is raised when the athlete complains of forefoot or midfoot pain of insidious onset. On examination these injuries present as areas of point tenderness overlying the metatarsal shaft.

B. Imaging Studies
Radiographs are usually sufficient to document stress fracture, which is visualized as a frank fracture or periosteal reaction at the affected site. As with most stress fractures the patient may be symptomatic 2-4 weeks prior to visualizing the fracture on radiograph. If the diagnosis is in question, bone scan and MRI have significantly higher sensitivity and specificity for detecting these injuries at an earlier time frame.

Treatment
Treatment is easily managed by the primary care physician. The injury is treated symptomatically, allowing the athlete to participate in activities that are not painful. Immobilization in the form of a steel shank insole or stiff, wooden-soled type shoe may be necessary for a limited time, until no longer painful. At times the patient may benefit from a short leg walking cast or removable walking boot for severe pain. Four weeks of rest is usually sufficient for healing. During these 4 weeks, the athlete may continue modified conditioning with non-weight-bearing exercises (ie, swimming and pool running), followed by cycling and stair climbing.

Although most of these fractures heal well with conservative management, fractures of the proximal fifth metatarsal have a high incidence of delayed union and nonunion. A thorough understanding of the classification and anatomy of fractures in this location is required for proper identification to determine conservative versus surgical treatment.

Fractures of the Proximal Fifth Metatarsal
Fractures of the proximal fifth metatarsal include tuberosity avulsion fractures, acute Jones fractures, and diaphyseal stress fractures. Diaphyseal stress fractures in this area can further be classified as early, delayed union, and nonunion fractures.

The fifth metatarsal consists of a base tuberosity, shaft (diaphysis), neck, and head. The tuberosity protrudes plantarward from the base. The metaphysis tapers to the diaphysis. There are three articulations, including the cuboid fourth metatarsal, cuboid fifth metatarsal, and the fourth and fifth intermetatarsal articulation in this region. The proximal fifth metatarsal serves as the insertion of the lateral band of the plantar fascia, peroneus brevis tendon, and peroneus tertius tendon (Figure 38-12).

Tuberosity Fractures
Tuberosity fractures are typically known as dancer fractures because they are usually associated with an ankle inversion plantar flexion injury. It was commonly thought that these injuries were associated with tearing of the peroneus brevis...
tendon insertion. However, this injury is more likely secondary to the plantar aponeurosis pulling from the base of the fifth metatarsal. Nondisplaced fracture carries an excellent prognosis, almost always healing in 4-6 weeks with conservative therapy. The athlete’s treatment consists of limited weight bearing to pain with modified activity such as that used with second, third, and fourth metatarsal injuries. If needed the athlete can be immobilized in a walking cast, wooden (or steel shank)–soled shoe, or walking boot. The immobilization can usually be removed by 3 weeks (average 3-6 weeks) in favor of modified footwear if pain has diminished. The patient then gradually may return to vigorous activity, with most athletes returning to full sports activity in 6-8 weeks. Bony union usually takes place by 8 weeks. Orthopedic referral is needed for displaced fractures or comminuted fractures involving more than 30% of the cubometatarsal articulart surface or step-off greater than 2 mm. Sometimes small displaced fractures at this site may require surgical removal if bony union does not occur secondary to chronic irritation. As a side note, the physician should be aware that certain conditions, such as apophysis of the tuberosity and accessory ossicles (os peroneum and os vesatranium), may radiographically mimic an avulsion fracture. Usually, these entities have smooth radiolucent lines on radiograph as compared with that of a fracture.

**Jones Fractures**

Jones fractures consist of a transverse fracture at the junction of the diaphysis and metaphysis corresponding to the area between the insertion of the peroneus brevis and tertius tendons without extending past the fourth and fifth intermetatarsal articulation (Figure 38-13).

The Jones fracture is believed to occur when the ankle is in plantar flexion and a large adduction force is applied to the forefoot. It is important to realize this is a midfoot injury with no prodromal symptoms. Therefore, the injury is classified as acute.

Torg and colleagues showed that this fracture, in nonathletes, could heal in 6-8 weeks with strict non–weight-bearing immobilization. However, secondary to low vascularity and high stresses at the site of the Jones fracture, the injury is associated with a poor outcome; it is plagued by delayed union and nonunion if treated conservatively in athletic patients. Many athletes are unwilling to tolerate non–weight-bearing ambulation for this extended period of time. Failure
to heal by 12 weeks in this population is not uncommon. Those who undergo conservative treatment are placed on a non–weight-bearing immobilization protocol, in a plaster cast, for 6-8 weeks. If there is lack of clinical healing by 6-8 weeks, therapy is individualized. If clinical healing is present by 6-8 weeks, immobilization is continued in a fracture brace with range of motion and gradual weight bearing. If there are no signs of clinical healing, treatment must be individualized either with continued cast immobilization or surgical intervention. Surgical intervention for Jones fracture consists of either intramedullary screw fixation (first choice; Figure 38-14) or bone grafting.

Diaphyseal Fractures

Stress fractures distal to the site of Jones fractures and acute-on-chronic fractures occurring in the same position as Jones fractures are commonly seen in athletes who run. Pain is usually over the lateral aspect of the foot, over the fifth metatarsal base. Usually no significant trauma has been associated with these fractures. Prodromal symptoms occurring weeks to months in advance of an acute injury can often be elicited in the history.

Torg and colleagues classified these stress fractures into three types based on radiographic appearance. By adhering to this classification, much of the guesswork for determining treatment can be avoided. Type I can show minimal periosteal reaction, indicating early stress reaction with no intramedullary sclerosis. Type II shows features of delayed union represented by a fracture line involving both cortices with associated periosteal bone union, a widened fracture line with adjacent radiolucency related to bone reabsorption, and, most importantly, evidence of intramedullary sclerosis. Type III represents nonunion fractures revealing a widened fracture line, new periosteal bone and radiolucency, and complete obliteration of the medullary canal by sclerotic bone. Acute or chronic injuries show a fracture line at the same site as a Jones fracture but also evidence of stress injury, as previously described. Careful history reveals the patient had a prodrome of symptoms consisting of intermittent pain.

Treatment of choice for acute nondisplaced diaphyseal stress fracture is non–weight-bearing immobilization. Ninety-three percent of the patients in Torg’s series healed within 7 weeks. Treatment for type II stress fractures is individualized. Conservative treatment may take up to 20 weeks and result in nonunion. Complications of prolonged immobilization include recurrence of fracture and significant dysfunction from muscle atrophy and loss of range of motion. For athletes, surgical options are recommended. Symptomatic nonunion fracture or type III fractures require surgical treatment. Casting and prolonged immobilization of acute or chronic fractures frequently fail, giving rise to delayed or nonunion fractures. Surgery is often needed and is the recommended procedure of choice.

The difference between screw fixation and bone grafting is recovery time. It takes up to 12 weeks to return to prefracture activity with grafting versus 6-8 weeks with screw fixation. Grafting carries a higher failure rate. Screw fixation is now recommended first and bone grafting if fixation fails.

Yu WD, Shapiro MS: Fractures of the fifth metatarsal. Phys Sportsmed 1998;26:47. [9811705]
Healthy Aging & Assessing Older Adults

Cynthia M. Williams, DO, MA, FAAFP

The population of the United States, like that of other industrialized nations, is aging. This rapid growth is evident with the aging of the “baby boomers” born between 1946 and 1964 who will begin turning 65 in 2011. The aging population is also heterogeneous with individuals expressing the poorest health often identified as “frail” or “at risk” elders.

In the rapidly changing fields of health care financing and delivery, services that promote or improve functional abilities, prevent or delay disease progression, and improve the overall health status of this aging population are needed. Little information and evidence are available about what constitutes the best practices in health promotion, prevention, and counseling for older adults. This chapter defines successful and healthy aging, provides recommendations for prevention and health promotion, and describes how to assess for at-risk elders.


CHARACTERISTICS OF HEALTHY AGING

In a highly heterogeneous population, some individuals are ravaged early by a multitude of chronic conditions and disabilities, whereas others appear to have excellent health and a high level of functioning. Aging is a process, and the term healthy aging does not imply an absence of limitations, but rather an adaptation to the changes associated with the aging process that is acceptable to the individual. Successful or healthy aging appears to include three factors: (1) low probability of disease and disability, (2) higher cognitive and physical functioning, and (3) an active engagement with life. (Table 39-1). Health care providers can promote healthy aging by assisting the older adult in developing competence in directing and managing future roles, thereby maintaining autonomy and a sense of self-worth.


EPIDEMIOLOGY OF AGING

Most older adults are healthy and independent, and contribute to the society in which they live. The epidemiology of aging evaluates not only the demographic changes associated with aging but also those diseases and conditions causing excess morbidity, mortality, disability, and decline in independent function. Many epidemiologic studies on aging focus on prevention in an attempt to establish a scientific basis for minimizing the illnesses associated with aging and their related burden. Health status in the elderly is a function of the chronic diseases associated with aging as well as the “geriatric syndromes” most commonly associated with this population (Table 39-2).

The overall health status and well-being of older adults is highly complex and results from many interacting processes, including risk factor exposure (tobacco, alcohol, drugs, diet, sedentary lifestyle), biological age-related changes, and the development and consequences of functional impairments. Many of the conditions previously thought of as “normal aging” are now known to be modifiable or even preventable if disease prevention and health promotion strategies are taken seriously not only by health care providers but also by the patients for whom they care.

Prevention in geriatrics attempts to delay morbidity and disability and is a primary goal of any medical practice caring for older individuals. The primary strategy for prevention lies in the alteration of lifestyle and environmental factors that contribute to the development of chronic disease.

Health promotion is a broad term that encompasses the objective of improving or enhancing the individual’s current health status. The purpose of health promotion, especially as applied to the elderly, is the prevention of avoidable decline, frailty, and dependence, thereby promoting healthy aging.

Frailty is emerging as a new geriatric syndrome. It is multifaceted and can be considered the midway point between independence and near-death as the older adult becomes more vulnerable and is at greatest risk for adverse health outcomes. Frailty has been associated with numerous conditions, many of which may be preventable if recognized early (Table 39-3). Important evidence of frailty includes slow walking speed, low physical activity, weight loss, and cognitive impairment. Preventive services for older adults need to be addressed within the framework of disability (frailty) prevention or, put another way, of function preservation.

For health promotion to be effective with older adults, it must be individualized in terms of patient age, functional status, patient preference, and culture. Culture is important in understanding the older adult’s health belief system. Without this understanding, a health care provider may be unable to negotiate a treatment strategy (including prevention practices) that is acceptable to the patient and the provider. The benefits of secondary prevention, including cancer screening, are uncertain for older adults. There is a paucity of evidence due to the lack of randomized clinical trials in patients older than 75 years, and most prevention and health promotion recommendations are extrapolated from younger subjects. The US Preventive Services Task Force (USPSTF) has set the standard for providing recommendations for clinical practice on preventive interventions, including screening tests, counseling interventions, immunizations, and chemoprophylactic regimens. These standards are established by a review of the scientific evidence for the clinical effectiveness of each preventive service. In considering screening strategies, major causes of death (Table 39-4), remaining life expectancy of the older adult should be considered along with the benefits and burdens not only on the preventive screening but the potential further evaluation and management. This is, especially important for individuals who have had repeated negative screenings in the past, who are frail, demented, or who have a limited quantity and quality of life remaining.

Many of the leading causes of death in this population are amenable to both primary and secondary preventive strategies, especially if targeted early in life. The major targets of...
Table 39-4. Preventable major causes of death associated with aging.

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Percentage of All Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>47</td>
</tr>
<tr>
<td>Cancer</td>
<td>20</td>
</tr>
<tr>
<td>Stroke</td>
<td>11</td>
</tr>
<tr>
<td>Lung disease</td>
<td>6</td>
</tr>
<tr>
<td>Accidents/falls</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
</tr>
</tbody>
</table>


Prevention should therefore be focused at the major causes of death—including coronary heart disease, cancer, and stroke—with the goals of reducing premature mortality caused by acute and chronic illness, maintaining function, enhancing quality of life, and extending active life expectancy. A priority in screening should be given to preventive services that are both easy to deliver and associated with beneficial outcomes. Table 38-5 summarizes the primary health promotion preventive practices for older adults that received A or B ratings by the US Preventive services Task Force. Up-to-date details on preventive services can be found online at http://www.ahrq.gov.

Promoting an Active Lifestyle

To make an expected change in physical activity the older adult needs to understand the importance and benefit of increasing physical activity. Obtaining and documenting a detailed history and physical examination should be one of the first steps to embarking on an increased physical activity plan (Table 39-6). The American College of Sports Medicine recommends stress testing for any older adult who intends to begin a vigorous exercise program such as strenuous cycling or running (Table 39-7). Conditions that are absolute and relative contraindications to exercise stress testing or embarking on an exercise program should be evaluated (Table 39-8). Finally, an exercise prescription should be written on a prescription pad to strengthen the endorsement for increased physical activity. The prescription should include frequency, intensity, type, and time of exercise.

It is important to “start low and go slow,” especially if the older adult has been relatively sedentary. It is more important to get the older adult to do any physical activity than to prescribe something that is unattainable. The health of older adults may be better served if they perform a little more exercise or activity than the previous week, attempting to incorporate the activity into their normal daily lives such as walking to a store or gardening. The goal should be for the person to feel “pleasantly” tired a few hours after the activity with the aim of increasing the activity slowly until a desired level of fitness is obtained.

Promotion of an active lifestyle is important at all ages and the benefits to older adults are numerous. Health care providers need to realize that for exercise to be beneficial it need not be strenuous or prolonged. Just encouraging patients to get up out of their chairs and start moving will improve not only the quality, but the quantity, of disability-free years.

Physical Activity in Older Adults

Exercise and physical activity as a form of primary prevention have many benefits even for sedentary older adults. A recent meta-analysis of physical activity and well-being in advanced age concluded that physical activity had its strongest effect on self-efficacy (self-confidence), and improvements in cardiovascular status, strength, and functional capacity also improved well-being. Lifestyle physical activities that are more unstructured as compared with a formal exercise plan are being shown to increase levels of physical activity in sedentary populations.

Nutrition in Older Adults

Nutrition is a priority for Healthy People 2010. As individuals age, chronic diseases, functional impairments, polypharmacy, and age-related physiologic and socioeconomic changes may all act in concert to place an older adult nutritionally at risk. Undernutrition is a major factor associated with mortality in older persons. Health care providers, however, rarely take the time to consider the diet and nutritional status of their patients.

Many disorders affecting older adults relate to nutritional status. Poor nutritional status may be the result of too little dietary intake leading to malnutrition, too much dietary content for actual expenditure leading to obesity, and inappropriate dietary intake exacerbating such conditions as diabetes, hypertension, and renal insufficiency. Weight tends to increase with aging until the seventh decade, when it stabilizes or begins to decrease.
to decline. Obesity tends to be a problem for patients younger than 75 years, whereas undernutrition is commonly encountered in those older than 85. Energy requirements decrease in the elderly. The recommended daily allowance (RDA) of 2300 kcal for a 77-kg man and 1900 kcal for a 65-kg woman should be reduced by 10% based on basal energy expenditure between ages 51 and 75 years, with an additional 10%-15% reduction after age 75. Although animal studies have indicated increased longevity with lower body weight and caloric restriction without malnutrition, studies on the relative risk of obesity to mortality in older adults are inconsistent, ranging from a protective effect for hip fractures to increased functional disability.

A multitude of interrelated factors can place an older adult at nutritional risk (Table 39-9 and Table 39-10). An older adult with an unintentional weight loss of 10% or more or a basal metabolic index (BMI) of less than 17 kg/m² needs to be evaluated. Because anorexia, weight loss, and undernutrition in older persons have such deleterious effects, factors that can be treated or reversed are of major importance. Treatment with orexigenic agents to promote weight gain is controversial but should be considered. Megestrol acetate in doses up to 800 mg per day increases weight (fat mass) in older persons and must be used with caution if the individual has a history of clotting disorders. Dronabinol, a cannabis derivative, can enhance weight gain but has a tendency to cause dysphoria in the elderly, which limits its usefulness.

The significance of mild to moderate obesity in the elderly is unclear. Individual consideration is required. Height/weight charts for ideal body weight based on life expectancy are needed.
insurance tables are probably relevant only to the age of 54 years. Recommending weight loss, especially to an older individual should be done with caution because weight loss in general carries a poor prognosis. For patients younger than 70 years of age who are 20% above ideal body weight, prudent weight loss should be recommended. For patients older than 70, if a medical condition is likely to be significantly improved by prudent dieting then it should be recommended. Such conditions would include severe hypertension, back pain from obesity, degenerative joint disease, gait and balance problems, and diabetes mellitus. Dietary management of hypercholesterolemia is controversial, especially if the individual is already close to or at ideal body weight. Severe restriction of fat may lead to weight loss, causing more harm than good. A dietician can assist the primary care physician in formulating a weight loss program for older patients, with a goal of 0.5-1 lb of weight loss per week.

The old adage “we are what we eat” is applicable to older adults. Promotion of a balanced, healthy diet for all older adults, including recognition and remediation of micronutrient deficiencies, should be incorporated into the health promotion strategies of all primary care physicians caring for older adults.


Table 39-6. Contents of a physical activity preparticipation evaluation for older adults.

<table>
<thead>
<tr>
<th>History, to include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s lifelong pattern of activities and interests</td>
</tr>
<tr>
<td>Activity level in the past 2-3 mo to determine a current baseline</td>
</tr>
<tr>
<td>Concerns and perceived barriers regarding exercise and physical activity:</td>
</tr>
<tr>
<td>Lack of time</td>
</tr>
<tr>
<td>Unsafe environment</td>
</tr>
<tr>
<td>Cardiovascular risks</td>
</tr>
<tr>
<td>Limitations of existing chronic diseases</td>
</tr>
<tr>
<td>Level of interest and motivation for exercise</td>
</tr>
<tr>
<td>Social preferences regarding exercise</td>
</tr>
<tr>
<td>Physical examination, with emphasis on cardiopulmonary systems, musculoskeletal, and sensory impairments</td>
</tr>
</tbody>
</table>


Table 39-7. Graded exercise test (GXT) recommendations according to coronary heart disease (CHD) risk factors and exercise stratification.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Moderate Intensity Exercise</th>
<th>Vigorous Intensity Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Walking at 3-4 mph</td>
<td>Walking briskly uphill or with a load</td>
</tr>
<tr>
<td>Low</td>
<td>Cycling for pleasure&lt;10 mph</td>
<td>Cycling fast or racing&gt;10 mph</td>
</tr>
<tr>
<td>Low</td>
<td>Moderate effort swimming</td>
<td>Swimming, fast tread or crawl</td>
</tr>
<tr>
<td>Low</td>
<td>Racket sports Pulling or carrying golf clubs</td>
<td>Singles tennis or racquetball</td>
</tr>
<tr>
<td>Low</td>
<td>GXT not necessary</td>
<td>GXT not necessary</td>
</tr>
<tr>
<td>Low</td>
<td>GXT not necessary</td>
<td>GXT recommended</td>
</tr>
<tr>
<td>Low</td>
<td>GXT not necessary</td>
<td>GXT recommended</td>
</tr>
<tr>
<td>Moderate</td>
<td>Men ≥54 and women ≥55 y old or those with ≥2 CHD risk factors</td>
<td>GXT not necessary</td>
</tr>
<tr>
<td>Moderate</td>
<td>GXT recommended</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Individuals with symptoms of disease or known metabolic, cardiovascular, or pulmonary disease</td>
<td>GXT recommended</td>
</tr>
</tbody>
</table>

Geriatric assessment is a way to obtain information about functional performance in older adults in order to identify elders at risk for increasing frailty. Health care providers by clinical judgment alone can diagnose severe functional impairment but have difficulty identifying moderate impairments, which are more likely to affect a community-dwelling older population. The multitude and complexity of problems that may be experienced by a frail older adult requires more than just management of their diseases. It is important to identify elders who may be frail or vulnerable in the outpatient clinical practice because they will benefit from a coordinated and comprehensive care plan. The vulnerable elderly are adults older than 65 years of age who are at risk for functional decline and death. Family physicians assessing this population should strive to identify the conditions and clinical situations most affecting this group (Table 39-11).

In general, geriatric assessment attempts to obtain a “big picture” in order to provide quality care for the elderly (Table 39-12). Geriatric assessment is often necessary to accurately define an older person’s problems, develop interventions, and serve as a baseline from which to measure outcomes of treatment.


Who Needs Assessment?
Which older person needs assessment, and what is the best approach to implement this screening? Because geriatric assessment is an attempt to gain a complete picture of the health status of an older individual, the primary care provider must become involved not only in diagnosing and treating medical problems but also in all the factors that affect the health of older patients. A geriatric assessment is a diagnostic tool, not a therapeutic intervention for the cure of chronic disease and the reversal of disability. Table 39-13 details the components of a geriatric assessment.

The majority of older adults do not need an extensive evaluation; instead, assessment should be oriented toward screening to uncover problems. If screening uncovers a problem or problems, a more extensive evaluation can then be performed and a treatment plan can be implemented. Table 39-14 presents a common screening tool that can be used by nonphysician office staff to screen ambulatory older patients. Another validated self-administered screening tool, developed by the Assessing Care of Vulnerable EldersProject, the VES-13 (Vulnerable Elders Survey-13) which can be found online at http://www.rand.org/health/projects/acove/ identified over 30% of individuals as vulnerable with four times the risk of death or functional decline when compared to older adults who have maintained functional capacity. The VES-13 assesses functional and health status and can be used as a case finding tool before implementing more extensive screening.


Functional Assessment
A. Predictors of Functional Decline
The ability to function independently in the community is an important public health and quality-of-life issue for all older adults. A recent trend toward declining disability has

<table>
<thead>
<tr>
<th>Table 39-8. Absolute and relative contraindications to exercise stress testing or starting an exercise program.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absolute Contraindications</strong></td>
</tr>
<tr>
<td>Acute myocardial infarction within 2 days</td>
</tr>
<tr>
<td>Critical or severe aortic stenosis</td>
</tr>
<tr>
<td>Active endocarditis</td>
</tr>
<tr>
<td>Decompensated heart failure</td>
</tr>
<tr>
<td>High-risk unstable angina</td>
</tr>
<tr>
<td>Active myocarditis or pericarditis</td>
</tr>
<tr>
<td>Acute pulmonary embolism or infarction</td>
</tr>
<tr>
<td>Serious cardiac arrhythmias causing hemodynamic compromise</td>
</tr>
<tr>
<td>Acute noncardiac condition that may affect exercise performance or may exacerbate the condition (infection, renal failure, thyrotoxicosis)</td>
</tr>
<tr>
<td>Physical disability that precludes safe and adequate test performance Inability to obtain consent</td>
</tr>
</tbody>
</table>

Table 39-9. Nutrient requirements in older adults, with signs of excess and deficiency.

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Requirement</th>
<th>Signs of Deficiency</th>
<th>Signs of Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>Requirements decrease with advancing age 3333 IU for men 2667 IU for women</td>
<td>Loss of bright, moist appearance yes; dry conjunctiva; gingivitis</td>
<td>Toxic effects include headache, lassitude, anorexia, reduced white blood cell count, impaired hepatic function, and bone pain with hypercalcemia; hip fracture</td>
</tr>
<tr>
<td>Vitamin $B_1$ (thiamine)</td>
<td>1.1-1.2 mg/d</td>
<td>Common in alcoholic elderly and institutionalized elderly; disordered cognition (delirium), neuropathies, and cardiomegaly</td>
<td>Liver damage and exacerbation of peptic ulcer disease especially with those using megadoses</td>
</tr>
<tr>
<td>Vitamin $B_2$ (riboflavin)</td>
<td>1.1-1.3 mg/d</td>
<td>Cheilosis, angular stomatitis, gingivitis; changes to tongue papillae</td>
<td></td>
</tr>
<tr>
<td>Vitamin $B_6$ (pyridoxine)</td>
<td>1.5-1.7 mg/d</td>
<td>Glossitis, peripheral neuropathy, and dementia especially related to alcohol abuse</td>
<td>Liver damage and nervous system dysfunction especially with those using megadoses</td>
</tr>
<tr>
<td>Vitamin $B_12$</td>
<td>2.4 μg/d</td>
<td>Pallor, optic neuritis, hype refl exia, ataxia, anorexia; loss of proprioception, vibratory sense, and memory loss; megaloblastic anemia</td>
<td>Megadose use can cause diarrhea, oxalate kidney and bladder stones; impaired absorption of vitamin $B_{12}$; interfere with serum and urine glucose testing; falsenegative hemoccult testing</td>
</tr>
<tr>
<td>Vitamin C</td>
<td></td>
<td>Gingival hypertrophy; bleeding gums, petechiae, and ecchymoses</td>
<td>Megadose use can cause diarrhea, oxalate kidney and bladder stones; impaired absorption of vitamin $B_{12}$; interfere with serum and urine glucose testing; falsenegative hemoccult testing</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>10-15 μg/d (400-600 IU/d)</td>
<td>Osteomalacia; severe bone pain and osteoporosis; muscular hypotonia; pulmonary macrophage dysfunction</td>
<td>Nausea, headache, anorexia, weakness, and fatigue; interferes with vitamin K absorption</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Widely distributed in food and provided by synthesis of intestinal bacteria; supplements advised for fat malabsorption syndromes and long-term antibiotic therapy</td>
<td>Hemorrhages in skin or gastrointestinal tract; unexplained prolongation of prothrombin time</td>
<td>Unknown</td>
</tr>
<tr>
<td>Folic acid</td>
<td>400 μg/d</td>
<td>Pallor, stomatitis, glossitis, memory impairment, depression</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>400 IU/d</td>
<td>Deficiency is rare; abundant in diet</td>
<td>Interferes with vitamin K metabolism; thrombophlebitis; gastrointestinal (GI) distress; possible reduction in wound healing</td>
</tr>
<tr>
<td>Niacin</td>
<td>14-16 mg/d</td>
<td>Fissured tongue; dry, thickened, scaling, hyperpigmented skin; diarrhea; dementia</td>
<td>Histamine flush; liver toxicity</td>
</tr>
<tr>
<td>Calcium</td>
<td>1200-1500 mg/d</td>
<td>Osteoporosis</td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td></td>
<td>Rare secondary to increased iron stores; usually secondary to pathologic blood loss</td>
<td>Constipation; excess iron usually given when anemia of chronic disease is misdiagnosed as iron deficiency anemia; some association between neoplasia and coronary artery disease</td>
</tr>
<tr>
<td>Zinc</td>
<td></td>
<td>Impaired wound healing; diarrhea; decreased vision, olfaction, insulin, and immune function; anorexia; impotence</td>
<td>GI disturbance; sideroblastic anemia from impaired copper absorption; adverse effect on cellular immunity; interfere with other vitamin absorption</td>
</tr>
</tbody>
</table>

been noted among older persons, especially those with higher levels of education. For example, older adults who walk a mile at least once a week show decreasing decline in functional limitations and disability than their sedentary counterparts. However, these trends are not indicative of the total population. Non–Hispanic black and Mexican American men and women generally report more functional limitations and disability and represent a vulnerable subpopulation within the United States.

Several predictors of functional decline and mortality have been reported. Health status belief and decreased abilities in Table 39-10. Factors associated with undernutrition in the elderly.

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Dementia</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>Poor dental health</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Sensory alterations</td>
</tr>
<tr>
<td>Impaired function</td>
</tr>
<tr>
<td>Dietary restrictions</td>
</tr>
<tr>
<td>Social isolation</td>
</tr>
<tr>
<td>Impotencyisness Alcoholism</td>
</tr>
<tr>
<td>Swallowing dysfunction</td>
</tr>
</tbody>
</table>


Table 39-11. Common chronic syndromes among the vulnerable elderly.

<table>
<thead>
<tr>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Falls and mobility disorders</td>
</tr>
<tr>
<td>Hearing impairment</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Pneumonia and influenz</td>
</tr>
<tr>
<td>Pressure ulcers</td>
</tr>
<tr>
<td>Stroke and atrial fibrillation</td>
</tr>
<tr>
<td>Urinary incontinence</td>
</tr>
<tr>
<td>Vision impairment</td>
</tr>
</tbody>
</table>


Table 39-12. Goals of geriatric assessment.

<table>
<thead>
<tr>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>To define the functional capabilities and disabilities of older patients</td>
</tr>
<tr>
<td>To appropriately manage acute and chronic diseases of frail elders</td>
</tr>
<tr>
<td>To promote prevention and health</td>
</tr>
<tr>
<td>To establish preferences for care in various situations (advance care planning)</td>
</tr>
<tr>
<td>To understand financial resources available for care</td>
</tr>
<tr>
<td>To understand social networks and family support systems for care</td>
</tr>
<tr>
<td>To evaluate an older patient’s mental and emotional strengths and weakness</td>
</tr>
</tbody>
</table>

Table 39-13. Components of geriatric assessment.

<table>
<thead>
<tr>
<th>Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Functional assessment</td>
</tr>
<tr>
<td>1. Basic activities of daily living (BADLs): fundamental to self-care:</td>
</tr>
<tr>
<td>Bathing</td>
</tr>
<tr>
<td>Dressing</td>
</tr>
<tr>
<td>Toileting</td>
</tr>
<tr>
<td>Transfers</td>
</tr>
<tr>
<td>Continence</td>
</tr>
<tr>
<td>Feeding</td>
</tr>
<tr>
<td>2. Instrumental activities of daily living (IADLs): complex daily activities fundamental to independent community living and interactions):</td>
</tr>
<tr>
<td>Housework: Can you do your own housework?</td>
</tr>
<tr>
<td>Traveling: Can you get places outside of walking distance?</td>
</tr>
<tr>
<td>Shopping—Can you go shopping for food and clothing?</td>
</tr>
<tr>
<td>Money: Can you handle your own money?</td>
</tr>
<tr>
<td>Meal preparation: Can you prepare your own meals?</td>
</tr>
<tr>
<td>3. Advanced activities of daily living (AADLs): &quot;functional signature&quot;</td>
</tr>
<tr>
<td>Gait-mobility and balance</td>
</tr>
<tr>
<td>Upper extremity evaluation</td>
</tr>
<tr>
<td>B. Cognitive and affective assessment</td>
</tr>
<tr>
<td>Dementia</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Suicide</td>
</tr>
<tr>
<td>Alcohol misuse</td>
</tr>
<tr>
<td>Sensory impairments</td>
</tr>
<tr>
<td>Nutrition</td>
</tr>
<tr>
<td>Incontinence</td>
</tr>
<tr>
<td>C. Social assessment (caregivers, environment, finances)</td>
</tr>
<tr>
<td>Driving</td>
</tr>
<tr>
<td>Sexuality</td>
</tr>
<tr>
<td>Advance care planning</td>
</tr>
</tbody>
</table>

*In order of most difficult to least difficult—knowing a person can perform one item indicates they can perform item below it.

Table 39-14. A geriatric screening for impaired ambulatory elderly.

<table>
<thead>
<tr>
<th>1. Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did the patient bring in all bottles or a list of medications?</td>
</tr>
<tr>
<td>List all medications</td>
</tr>
<tr>
<td>Remember to ask about over-the-counter medications</td>
</tr>
<tr>
<td>Remember to ask about supplements and herbs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weigh patient and record</td>
</tr>
<tr>
<td>Have you lost more than 10 lb in the last 6 months?</td>
</tr>
<tr>
<td><strong>Positive screen:</strong> 10 lb weight loss or &lt; 100 lb</td>
</tr>
<tr>
<td><strong>Intervention:</strong> Further evaluation with the Mini-Nutritional Assessment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Hearing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use handheld audioscope at 40 dB and screen both ears at 1000 and 2000 Hz</td>
</tr>
<tr>
<td><strong>Positive screen:</strong> Patient unable to hear 1000 or 2000 Hz frequency in both ears or unable to hear the 1000 and 2000 Hz frequency in one ear</td>
</tr>
<tr>
<td><strong>Intervention:</strong> Evaluate for cerumen impaction; refer to audiology</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask: “Do you have any problems driving, watching TV, reading, or doing any of your activities because of your eyesight?” If yes</td>
</tr>
<tr>
<td>Do Snellen eye chart</td>
</tr>
<tr>
<td><strong>Positive screen:</strong> 20/40 or greater</td>
</tr>
<tr>
<td><strong>Intervention:</strong> Refer to optometry or ophthalmology</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Mental status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask to remember three objects: “ball, cat, and flag” (have them repeat objects after you)</td>
</tr>
<tr>
<td><strong>Positive screen:</strong> Unable to remember all three items after 1 min</td>
</tr>
<tr>
<td><strong>Intervention:</strong> Administer more formal mental status testing such as the 7-Minute Neurocognitive Screening Battery or MMSE; assess for causes of cognitive impairment including delirium, depression, and medications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask: “Are you depressed?” or “Do you often feel sad or depressed?”</td>
</tr>
<tr>
<td><strong>Positive screen:</strong> Yes</td>
</tr>
<tr>
<td><strong>Intervention:</strong> Perform a more thorough depression screen (Geriatric Depression Scale); evaluate medications; consider pharmacological treatment and/or refer to psychiatry</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. Urinary incontinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask: “In the last year have you ever lost urine or gotten wet?” if yes</td>
</tr>
<tr>
<td>Ask: “Have you lost urine in at least 6 separate days?”</td>
</tr>
<tr>
<td><strong>Positive screen:</strong> Yes to both</td>
</tr>
<tr>
<td><strong>Intervention:</strong> Initiate workup for incontinence; consider urology referral</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8. Physical disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask: Are you able to do strenuous activities like fast walking or biking? Heavy work around the house like washing windows, floors, and walls? Go shopping for groceries or clothes? Get to places out of walking distance? Bathe, either sponge bath, tub bath, or shower? Dress, like putting on a shirt, buttoning and zipping, and putting on your shoes?</td>
</tr>
<tr>
<td><strong>Positive screen:</strong> Unable to do any of the above independently or able to do only with assistance from another</td>
</tr>
<tr>
<td><strong>Intervention:</strong> Corroborate responses if accuracy uncertain with caregivers; determine reason for inability to perform task; institute appropriate medical, social, and environmental interventions; patient may benefit from physical and/or occupational therapy and a home visit</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. Mobility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask: “Do you fall or feel unbalanced when walking or standing?”</td>
</tr>
<tr>
<td><strong>Positive screen:</strong> Yes</td>
</tr>
<tr>
<td><strong>Intervention:</strong> “Get-Up and Go” test: Get up from the chair, walk 20 feet, turn, walk back to the chair, and sit down (walk at normal, comfortable pace)</td>
</tr>
<tr>
<td><strong>Positive screen:</strong> Unable to complete the task in 15 s</td>
</tr>
<tr>
<td><strong>Intervention:</strong> Refer to physical therapy for gait evaluation and assistance with use of appropriate adaptive devices; home safety evaluation; patient may need to be instructed in strengthening of both upper and lower extremities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10. Home environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask: Do you have trouble with stairs either inside or outside of your house? Do you feel safe at home?</td>
</tr>
<tr>
<td><strong>Positive Screen:</strong> Yes</td>
</tr>
<tr>
<td><strong>Intervention:</strong> Supply the older patient or caregiver with a home safety self-assessment check list; consider making a home visit or use a visiting nurse or other community resource to evaluate the home; make appropriate referrals to help remediate safety issues</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>11. Social support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask: Who would be able to help you in case of an illness or emergency?</td>
</tr>
<tr>
<td>Record identified person(s) in medical record with contact information</td>
</tr>
<tr>
<td><strong>Intervention:</strong> Become familiar with available resources for the elderly within your community or know who can provide you with that assistance</td>
</tr>
</tbody>
</table>

activities of daily living (ADLs) appear to be important predictors of mortality. Older individuals (both men and women) with high depressive symptomatology have increased risk of ADL disability, as it appears depressive symptoms undermine efforts to maintain physical functioning. Social networks, and overdependence on these networks, may have a negative impact on ADLs by provoking dependency and a sense of “learned” helplessness, especially in older men.


B. Evaluation of Functional Status

Assessment of function is at the core of caring for older adults. The capacity to perform functional tasks necessary for daily living can be used as a surrogate measure of independence or a predictor of decline and institutionalization. A specific evaluation of functional status is necessary in older individuals, because functional impairment cannot be predicted by an individual’s medical diagnoses. Functional status needs to be assessed directly and independently of medical, laboratory, and cognitive evaluation, because specific functional loss is not disease specific and cognitive impairment does not necessarily imply inability to function independently in a familiar environment. Functional assessment can identify an older individual’s capabilities and, by noting changes in these, can prompt the search for possible illness such as cognitive impairment, depression, substance abuse, adverse drug events, or sensory impairment, and then guide interventions using the appropriate support and resources.

Functional assessment can be seen as a hierarchy. The basic activities of daily living (BADLs) are self-care activities that are at the most basic level of functioning, such as bathing, dressing, toileting, transfers, continence, and feeding (see Table 39-13). An older adult may be fully independent, need assistance, or be fully dependent in any or all of these activities. Individuals may move in and out of needing assistance or dependence, especially at the time of and after the onset of an acute illness or disease process.

Assessment of BADL items allows the primary care provider to focus on functional abilities, thus matching services to needs. The hierarchy for loss of BADL abilities is associated with increasing age and appears to be dependent on lower extremity strength, such that bathing, mobility, and toileting are lost before dressing and feeding, which rely on upper extremity strength. Of all the BADL measures, dependence with regard to going to the toilet has been shown to be an indicator of overall performance and the need for overall higher levels of assistance.

The next higher level of functioning is known as the instrumental activities of daily living (IADLs). These activities are required for independent living within the community and include a set of more complex and demanding tasks (see Table 39-13). Older individuals living in the community who cannot perform IADLs may have difficulty functioning at home. The more IADLs that are impaired in a community-dwelling elder, the greater the likelihood of developing dementia within 1 year.

The advanced activities of daily living (AADLs) are those tasks that may be considered the “functional signature” of a well community-dwelling older individual. These tasks include voluntary social, occupational, or recreational activities. An older person who does not successfully participate in such activities may not be dysfunctional, but an assessment that uncovers significant involuntary loss of such function may be an important risk factor for further functional losses. Globally knowing how an elderly person spends his or her days can give the physician a reference point for potential functional decline at subsequent visits. Online reference tools for completing a detailed functional assessment can be found at http://www.medicine.uow.edu/igeck/tools/default.asp and http://www.geriatricsatyourfingertips.org/.


Other Considerations in Geriatric Assessment

The remainder of this chapter focuses on issues that need to be addressed in the evaluation of older adults. Issues relating to mobility and balance (Chapter 40), incontinence (Chapter 41), depression (Chapter 41), and sensory impairments (Chapter 44) are covered elsewhere in this book, and the reader is referred to those chapters for more detailed information.

A. Alcohol Misuse

Alcohol consumption and alcoholism are commonplace among the elderly, with 10.5% of men and 3.9% of women in one primary care practice reporting problem alcohol use. Detection of alcoholism in the elderly is difficult for numerous reasons, including the idea that elderly patients do not see alcoholism as a disease, but rather as a sign of weakness. Physicians create their own barriers to the diagnosis, including uncertainty of the diagnosis, pessimism concerning treatment, and possible subconscious hostility toward the alcoholic older patient. Preventive care should include screening all elders at least once to detect problems or hazardous drinking by taking a history of alcohol use and using
a standard screening questionnaire, such as the 4-item CAGE or the 10-item AUDIT.


B. Driving Competence

Evaluating the driving competence of an older patient is a challenge for physicians. The automobile is the ultimate symbol of freedom and the most important source of transportation for older adults. The ability to drive is closely linked to independence and self-esteem, allowing the older adult to maintain important links within the community. Those who are unable to drive or who stop driving risk social isolation, depression, and functional decline. Driving is an instrumental activity of daily living composed of complex tasks that require not only physical but mental integrity. It is estimated that by 2020, 15% of all drivers will be older than 65 years. Adults older than 65 years of age are expected to account for 27% of all automobile fatalities in 2015, an increase of 373% since 1975.

In an attempt to reduce risk, many older drivers alter their driving habits by driving shorter distances, driving only during daylight, and avoiding rush hour, major highways, and inclement weather. However, not all older drivers avert risk. One study found that older adults diagnosed with Alzheimer dementia and those needing help with dressing and bathing still persisted in driving. Adults who voluntarily stop driving are usually older (>85 years), female, nonwhite, and has driven less than 50 miles per week. Heart disease and hearing impairment are more often associated with reports of adverse driving events. Driving accidents with older adults rarely involve high speeds or alcohol. Their accidents are usually related to issues involving visual-spatial difficulties and cognitive and motor skills.

Assessment of the older driver is made all the more difficult because chronic illness, functional status, or even cognitive impairment cannot consistently predict adverse driving events. An assessment of the older driver should include a review of the driving record, medications, alcohol use, and functional measures including vision, hearing, attention (spell “world” backward), visual-spatial skills (clock drawing), muscle strength, and joint flexibility. Older drivers should be advised on the importance of safety restraints, obeying speed limits, use of a helmet if riding a motorcycle or bicycle, taking a driving refresher course, and avoidance of drinking and use of cellular telephones while driving. It is important for primary care physicians to know the laws of their state with regard to driving and reportable medical conditions. A physician’s guide to assessing and talking to older drivers can be obtained from the National Traffic and Safety Board at http://www.nhtsa.dot.gov/people/outreach/media/catalog/topic.cfm.


C. Social Assessment

An important aspect of caring for older persons, especially vulnerable older persons, is understanding their social environment. Social assessment includes the sources and kinds of help available to the older adult and assessment of the primary caregiver, often called the “hidden patient.” The social assessment is important in the development of an effective care plan and all parts of the social assessment should be covered, usually over several patient visits.

1. Social support—It is important to understand the social networks of an older person. The social networks consist of informal supports such as family and close longtime friends, formal supports such as social welfare and other social service and health care delivery agencies, and semiformal supports such as church groups, neighborhood organizations, and clubs. Relationships with family and friends are intricate and can have consequences for the vulnerable elder. The availability of assistance from family or friends frequently determines whether a functionally dependent elder remains at home or is institutionalized, and identifying who would be available to help the elder if he or she becomes ill should be documented even for healthy elders. Other important information to obtain from older persons is outlined in Table 39-15. For a more formal assessment of social support, the Norbeck Social Support Questionnaire or the Lubben Social Network Scale should be considered.

Table 39-15. Social support screening.

<table>
<thead>
<tr>
<th>Question</th>
<th>Response Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many relatives do you see or hear from in the course of a month?</td>
<td>Tell me about the relative with whom you have the most contact.</td>
</tr>
<tr>
<td>How many relatives do you feel close to—such as to discuss private matters?</td>
<td>How many friends do you see or hear from in the course of a month? Tell me about the friend with whom you have the most contact. When you have an important decision to make, do you have someone you can talk to about it? Do you rely on anybody to assist you with shopping, cooking, doing repairs, cleaning house, etc? Do you help others with shopping, cooking, transportation, childcare, etc? Do you live alone? With whom do you live?</td>
</tr>
</tbody>
</table>

2. Caregiver burden—For individuals caring for a frail, often cognitively impaired elder, the demands can be overwhelming. Caregiver burden has been defined as the strain or load borne by the person who cares for an elderly, chronically ill, or disabled family member or other person. Caregivers are at higher risk for mortality if there is increased mental or emotional strain. Caregiver burden is linked to the caregiver’s ability to cope and handle stress. The physician should be alert for signs of possible caregiver burnout, including multiple somatic complaints, increased stress and anxiety, circular thinking, social isolation, depression, and weight loss. More formal assessment tools include the Caregiver Strain Index and the Zarit Burden Interview, for which a short version and screening version are available.

3. Economic factors—Economic factors have important consequences with respect to an older person’s health, nutrition, and living environment. Understanding the impact of financial status of the elderly may provide insight into how the individual copes, such as buying food versus medications. The primary care provider should have a working knowledge of Medicare and state and local assistance programs and know where the older person could go to obtain needed assistance in applying for appropriate financial benefits. The physician can inquire by asking if older individuals have enough financial resources to meet their needs. The physician also needs to know if a proposed treatment will be an economic burden on the individual.

4. Physical environment—The physical environment of the older person, including home environment, neighborhood, and transportation system, is critical to maintaining independence. Environmental hazards within the home are high and can be a potential constraint not only on the day-to-day functioning of frail elders but also on older persons without any specific physical deficits. Common environmental hazards within the home include loose throw rugs, curled carpet edges, obstructed pathways, lack of grab bars in tub and shower, and low and loose toilet seats. These hazards could lead to an increased risk of falls and fractures. The physician should inquire about the safety of the neighborhood and ask if older persons have transportation or transportation services available in close geographic proximity to where they live. This is especially important for elders who are dependent in IADLs and still living within the community.

5. Sexual health—Sexuality late in life is a normal and important part of aging. Primary care providers need to be aware of their own comfort level in taking a sexual health history from older adults. Older adults prefer that the provider initiate the discussion surrounding sexual functioning. Using open-ended questions allows the individual to give as much or as little information as is comfortable. The physician needs to have an understanding of what the older adult’s normal sexual patterns and interests have been and what if any changes have occurred that affect sexual functioning and intimacy such as health problems, medications, physical disabilities, or cognitive impairments.

   Older persons often have problems that are not easily detected during an office visit. A home visit either by the physician or a community agency provider such as a visiting nurse can reveal problems in the living situation, such as wandering, household and bathing hazards, social isolation and loneliness, family stress, nutrition problems, financial concerns, and even alcohol abuse. An environmental checklist that the older person or family member can use for a self-assessment can be found at the National Safety Council’s Web site (http://www.nsc.org).


6. Spirituality—Assessing an older person’s spirituality is important to understanding the overall well-being of that individual. It is important to ascertain what religion or spirituality means to the older adult and what role it plays in his or her life. The spiritual assessment should include the older
person’s concept of God or deity, religious practices, beliefs about spirit and hell, and value and meaning in life. Older adults can suffer from spiritual distress that may be expressed as depression, crying, fear of abandonment, or hopelessness, anxiety, and despair. This distress may occur after a loss of a significant other, after a family or personal disaster, or when there is a disruption in usual religious activities. Religion and spirituality are a source of comfort for patients. Inquiring into the spirituality of patients requires empathy on the part of the physician, strong interpersonal skills, and a closely established physician-patient relationship.


7. Advanced care planning—Advanced care planning is a process of planning for the medical future in which the patient’s preferences will guide the nature and intensity of future medical care, particularly if the patient is unable to make his or her own decisions. As part of the assessment of the older person it is important for the physician to learn about the patient’s goals and preferences for care (Table 39-16). This is especially important for the frail elderly, because it will ultimately influence management decisions. The process of advanced care planning helps patients identify their personal values and goals about health and medical treatment. Older adults should indicate the care they would and would not want to receive in various situations. Advanced care planning is designed to ensure that the patient’s wishes

<table>
<thead>
<tr>
<th>Steps</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Introduce the topic</td>
<td>During a wellness visit or some other time when the individual is in a good state of health, explain the purpose and nature of the discussion  &lt;br&gt; Inquire into how familiar the individual is with advanced care planning and define terms as necessary  &lt;br&gt; Be aware of the comfort level of the patient—give information and be supportive  &lt;br&gt; Suggest that family members, friends, or even members of the community explore how to manage potential burdens  &lt;br&gt; Discuss the identification of a proxy decision maker  &lt;br&gt; Encourage the patient to bring the proxy decision maker to the next visit</td>
</tr>
<tr>
<td>2. Engage in structured discussions</td>
<td>Convey commitment to patients to follow their wishes and protect patients from unwanted treatment or undertreatment  &lt;br&gt; Involve the potential proxy decision maker in discussions and planning  &lt;br&gt; Allow the patient to specify the role he or she would like the proxy to assume if the patient is incapacitated—follow patient’s explicit wishes or allow the proxy to decide according to the patient’s best interests  &lt;br&gt; Elicit the patient’s values and goals  &lt;br&gt; Use a validated advisory document available at <a href="http://www.medicaldirective.org">http://www.medicaldirective.org</a></td>
</tr>
<tr>
<td>3. Document patient preferences</td>
<td>Review advanced directives with patient and proxy for inconsistencies and misunderstandings  &lt;br&gt; Enter the advanced directives into the medical record  &lt;br&gt; Recommend statutory documents be completed by the patient that comply with state statutes  &lt;br&gt; Distribute directives to hospital, patient, proxy decision maker, family members, and all health care providers  &lt;br&gt; Include advanced directives in the care plan</td>
</tr>
<tr>
<td>4. Review and update the directive regularly</td>
<td>Most advanced directives go into effect when the patient can no longer direct his or her own medical care  &lt;br&gt; Assess the patient’s decision-making capacity  &lt;br&gt; Never assume advanced directive content without reading it thoroughly  &lt;br&gt; Advanced directives should be interpreted in view of the clinical facts of the case  &lt;br&gt; Physician and proxy decision maker will need to work together to resolve ambiguous or uncertain situations  &lt;br&gt; If disagreements between physician and proxy cannot be resolved—seek the assistance of an ethics consultant or committee</td>
</tr>
</tbody>
</table>

are known, even if the patient is unable to participate in those decisions. (For more information on advanced care planning, see Chapter 63.)


Web Sites

AGS Foundation for Health in Aging: http://www.healthinaging.org
Administration on Aging: http://www.aoa.gov
American Association of Retired Persons: http://www.aarp.org
American Geriatrics Society: http://www.americangeriatrics.org
American Medical Directors Association: http://www.amda.com
American Society of Consultant Pharmacists: http://www.ascp.com
Assisted Living Federation of America: http://www.alfa.org
Children of Aging Parents: http://www.caps4caregivers.org
CDC National Prevention Information Network: http://www.cdcnpin.org
Family Caregiver Alliance: http://www.caregiver.org
Medicare Hotline: http://www.medicare.gov
National Adult Day Services Association: http://www.nadsa.org
The syndromes of failure to thrive, pressure ulcers, and falls share features that make them particularly challenging. Their etiologies are multifactorial; they require an interdisciplinary approach to maximize care; and they often herald disability, institutionalization, and death. Small improvements in multiple domains can improve outcomes. Maintaining open communication with patients and/or caregivers is vital. Empower them to play a role in their care and keep expectations realistic. The physician can and should maintain a therapeutic relationship with the patient and the family beyond the time medical therapies are effective. Home visits enhance this relationship and often reveal opportunity for intervention.

**FAILURE TO THRIVE**

**ESSENTIALS OF DIAGNOSIS**

- Weight loss of more than 5%.
- Functional decline.
- Depression.
- Cognitive impairment.

**General Considerations**

The National Institute on Aging defined failure to thrive (FTT) as “a syndrome of weight loss, decreased appetite and poor nutrition, and inactivity, often accompanied by dehydration, depressive symptoms, impaired immune function, and low cholesterol.” Two new concepts, cachexia and sarcopenia, have enhanced our understanding of the pathophysiology of FTT and should be considered in the approach to the patient. Cachexia is the catabolic state seen in illnesses such as cancer, end-stage renal disease, lung disease, and heart failure. It is progressive and characterized by weight loss, anorexia, inflammation and insulin resistance; nutrition therapy does not alter the course. Sarcopenia is loss of muscle mass that occurs with aging. It is associated with functional decline, disability, and falls; it is mitigated by exercise.

**Clinical Findings**

**A. Symptoms and Signs**

Weight loss is an essential feature. Functional decline contributes to falls, poor grooming, depression, and cognitive decline. As in infants, FTT can occur from organic and nonorganic causes necessitating an approach that includes medical, psychological, functional, and social domains.

**B. History and Physical Examination**

The history provided by the patient and caregiver can help identify common acute triggers: change in medication, infection, constipation, pain, loss, or grief. Undiagnosed chronic diseases: endocrine, tuberculosis, dementia, depression, substance abuse, and rarely, hypoactive delirium may trigger FTT.

Assess, do not assume, medication compliance; have the patient demonstrate how he/she is taking all prescription and over-the-counter medications. Drug effects and interactions should not be underestimated. Alendronate, antiarrhythmics, antihistamines including H2 blockers, α-antagonists, benzodiazepines, β-blockers, calcium antagonists, colchicine, digoxin even within therapeutic range, diuretics, iron or zinc, metformin, metronidazole, neuroleptics, nonsteroid antiinflammatory drugs (NSAIDs), narcotics, steroids, SSRIs, tricyclic antidepressants, and xanthines have been associated with FTT. Levels are nonspecific; normal therapeutic levels can have adverse effects. Be aware of genetic and racial variation in drug metabolism.

A comprehensive physical examination should focus on those items noted in Table 40-1. Laboratory evaluations should include complete blood count (CBC), comprehensive metabolic panel (CMP), thyroid-stimulating hormone (TSH), erythrocyte sedimentation rate (ESR), total 25-OH vitamin D, B12 (if 200-400 pmol/L check a methylmalonic
and homocysteine levels.) Additional workup could include fecal occult blood, purified protein derivative, and urinalysis.

➤ Treatment

A. Assessment and Plan

Address modifiable medical conditions. Discuss risk/benefit of watchful waiting for conditions whose interventions carry high morbidity and mortality. Appetite stimulants are neither approved nor recommended and carry significant side effects. As medical interventions become more limited, palliative or hospice services should be initiated.

B. Team Approach

Simplify medications with help of a PharmD. Enlist the help of the Area Agency on Aging (AAA) [www.aoa.dhhs.gov or (800) 677–1116, "Elder Care Locater"]. Concerns about neglect or abuse should be discussed openly and nonjudgmentally; and should be reported. Home Health can supply short-term nursing, social worker, dietician, physical and occupational therapy and aide services.

Ritchie C: Geriatric nutrition: nutritional issues in older adults. UpToDate October 17, 2008.

Table 40-1. Targeted physical examination.

<table>
<thead>
<tr>
<th>Physical examination details and considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital signs: BMI &lt;21 or percentage of weight loss since last visit,</td>
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<tr>
<td>BP and HR in 2 positions, pulse for 60 seconds; abnormal if &gt;88/min</td>
</tr>
<tr>
<td>or irregular, respiratory rate/effort</td>
</tr>
<tr>
<td>Ears: hearing defects or tinnitus lead to social isolation</td>
</tr>
<tr>
<td>Eyes: cataracts/vision disturbance lead to depression &amp; isolation</td>
</tr>
<tr>
<td>Oral health: tooth or gum disease impair eating</td>
</tr>
<tr>
<td>Swallowing: aspiration and cough (ACE inhibitor) can negatively</td>
</tr>
<tr>
<td>impact eating, have patient swallow liquid in your presence if any</td>
</tr>
<tr>
<td>question of aspiration</td>
</tr>
<tr>
<td>JVD: a sensitive marker for CHF exacerbation</td>
</tr>
<tr>
<td>Breast mass: will often go unnoticed or unreported</td>
</tr>
<tr>
<td>Abdomen: masses, constipation, urinary bladder distention</td>
</tr>
<tr>
<td>Skin: sacrum and feet, axillae, panniculus and groin for breakdown/</td>
</tr>
<tr>
<td>candida/impetigo</td>
</tr>
<tr>
<td>Feet: any condition causing gait or balance disturbance</td>
</tr>
<tr>
<td>Motor: Gait: bradykinesia, consider Parkinson disease. Shoulder/</td>
</tr>
<tr>
<td>hip weakness, consider polymyalgia rheumatica</td>
</tr>
<tr>
<td>Mental status: test for variance from baseline and screen for</td>
</tr>
<tr>
<td>depression</td>
</tr>
</tbody>
</table>

PRESSURE ULCERS

ESSENTIALS OF DIAGNOSIS

➤ A skin ulcer caused by ischemia due to prolonged pressure or pressure in combination with shear and/or friction.
➤ Occur on weight bearing or bony prominences: ex: sacrum, hip, heel.
➤ Differentiate from ulcers caused by venous or arterial insufficiency.

New Considerations: Systems-Based Practice

In 2007, the Centers for Medicare and Medicaid Services (CMS) deemed pressure ulcers a “high cost, high volume” condition that was preventable. 2007 costs were estimated at $11 billion. Effective October 2008, Medicare began denying reimbursement for a stage 3 or 4 ulcer as a secondary diagnosis unless it was “present on admission (POA).” Physician documentation is required for coders to use the POA qualifier. Hospital reimbursement is not the only arena affected by physician compliance. Pressure ulcers are projected to be a Joint Commission Quality Indicator and are one of the most highly litigated medical conditions in the United States. Physicians should be familiar with the 2007 National Pressure Ulcer Advisory Panel (NPUAP) staging system and document skin status in the daily note.
Pathogenesis
Extrinsic and intrinsic factors cause pressure ulcers. Extrinsic factors are prolonged pressure, moisture, friction, and shear. Intrinsic causes are the susceptibility of aged skin (less thickness and elasticity), loss of sensation, circulatory compromise, immobility, weight loss, dehydration, malnutrition, and cognitive impairment including sedation.

Prevention
On admission and daily, document the condition of the occiput, spinous processes, scapulae, elbows, sacrum, ischia, greater trochanters, malleoli, and heels. Extra vigilance is needed in cognitively or sensory impaired elders who wear support stockings, casts, or other orthopedic devices. These should be removed for inspection when possible. The admitting nurse will also do a complete skin assessment; the physician should review, verify, and document concurrence with the findings. Table 40-2 summarizes the AHRQ (Agency for Healthcare Research and Quality) guidelines for pressure ulcer prevention. Screening scales such as Braden and Norton help quantify risk and tailor treatment plans. The downside to these scales is the misconception that low- and moderate-risk patients are not at risk. It takes them 2 hours to develop a Stage I ulcer just like the high-risk patient. Although never studied, patient repositioning every 2 hours remains a mainstay in clinical practice.

Differential Diagnosis
Among the differential diagnoses for pressure ulcers are vascular ulcers, diabetic ulcers, and cellulitis. Venous ulcers are the result of prolonged venous hypertension and are usually located over the medial malleolus. Arterial ulcers are predominantly caused by atherosclerotic vessels, and may be located between toes, over phalangeal heads, or around the lateral malleolus. Diabetic ulcers are produced by a variety of factors: micro and macrovascular injury, peripheral neuropathy, and mechanical changes in the bony architecture of the foot. These are usually located on the plantar aspect of the foot, metatarsal heads, or under the heel. Cellulitis is an acute inflammation of the dermis and subcutaneous tissue and thus blanches with palpation.

The National Pressure Ulcer Advisory Panel Classification

A. Stage I
Intact skin with non-bleanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its color may differ from the surrounding area. The area may be painful, firm, soft, warmer, or cooler as compared to adjacent tissue. Stage I may be difficult to detect in individuals with dark skin tones. May indicate “at risk” persons (a heralding sign of risk.) Preventative efforts should be intensified. Transparent films like Op-site or Tegaderm can be used; they provide barrier, prevent contamination, and reduce friction. The wound should be pressure free. Donut cushions and bunny boots worsen ulcers. Use foam or gel overlay for beds or chairs, and inflatable heel elevators to protect feet. Compared with standard hospital mattresses, these devices decrease the incidence of ulcers. [LOE A] For a Stage I, use Group 1 support surfaces. A good description of support surfaces can be found at www.wocn.org/pdfs/WOCN_Library/Fact_Sheets/medicare_part_b.pdf.

B. Stage II
Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled blister. Presents as a shiny or dry shallow ulcer without slough or bruising.¹ This stage should not be used to describe skin tears, tape burns, perineal dermatitis, maceration, or excoriation.

1. Management—Cleansing around the wound with cleanser rather than normal saline has been shown to promote healing in Stage II-IV ulcers, stage II gaining the greatest benefit in healing time. Normal saline is fine if cleanser not available. Do not use old favorites like hydrogen peroxide, povidone-iodine (Betadine), liquid detergent, acetic acid, or hypochlorite solutions. Even when diluted, they are potentially toxic to both fibroblasts and white blood cells. Occlusive or semi permeable dressing that will maintain moist wound environment should be used after cleansing. Hydrogel alone (IntraSite, Solosite) Hydrogel sheets like NuGel or hydrogel-impregnated gauze like Normlgel are appropriate. Wet/dry dressing should be avoided, as these ulcers need little

<table>
<thead>
<tr>
<th>Table 40-2. AHRQ guidelines for pressure ulcer prevention.</th>
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<tbody>
<tr>
<td>Assess risk and institute care plan within 8 h of admission.</td>
</tr>
<tr>
<td>Inspect high-risk patients daily (all vulnerable sites).</td>
</tr>
<tr>
<td>Keep skin clean with mild soap and water.</td>
</tr>
<tr>
<td>Keep clean skin dry with moisture barrier.</td>
</tr>
<tr>
<td>Minimize friction and shear with lift-sheet, bed trapeze, or both.</td>
</tr>
<tr>
<td>Post a turning schedule near patient.</td>
</tr>
<tr>
<td>Relieve heel pressure with inflatable heel elevators.</td>
</tr>
<tr>
<td>Avoid doughnut cushions.</td>
</tr>
<tr>
<td>Leave head of bed flat when possible.</td>
</tr>
<tr>
<td>Use pressure-relieving chair cushion; reposition frequently.</td>
</tr>
<tr>
<td>Maintain and promote mobility; avoid bed rest.</td>
</tr>
<tr>
<td>Address nutrition in patients who are hypoalbuminemic, anemic, or in whom BMI is abnormal.</td>
</tr>
<tr>
<td>Educate patient and family about prevention.</td>
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</tbody>
</table>

debridement. If the wound is exudating then use a dressing that will absorb the exudate such as alginate (Sorbsan or Aquacel) or NaCl-impregnated gauze (Mesalt.). If multiple stage II ulcers develop while patient is on a Group I surface for a month or more, consider a Group II device. Seventy-five percent of stage II ulcers will heal in 8 weeks.

C. Stage III

Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon, or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunneling. The depth of a stage III pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput, and malleolus do not have subcutaneous tissue and stage III ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep stage III pressure ulcers. Bone/tendon is not visible or directly palpable.

1. Management—Use a sterile Q tip while examining in order to document tunneling. Do not use this to culture the wound; it will not yield reliable results, it is not a sterile culture. If necrotic tissue or slough is present, sharp debridement is the best management. Exceptions are: heel ulcers, thrombocytopenia, or patient refusal. Other methods of debridement are pulse lavage, whirlpool, wet to dry dressings (NaCl impregnated gauze several times daily,) chemical debridement (Santyl) or autolytic debridement via an occlusive dressing (Duoderm.) Occlusive dressings are good for eschar attached to intact skin; once separated it is more easily debrided mechanically or chemically. Combinations are also effective: Santyl with pulse lavage for example.

D. Stage IV

Full thickness tissue loss with exposed bone, tendon, or muscle. Slough or eschar may be present on some parts of the wound bed. Often include undermining and tunneling.

As in Stage III, the depth of a Stage IV pressure ulcer varies by anatomical location. Stage IV ulcers can extend into muscle and/or supporting structures (eg, fascia, tendon, or joint capsule) making osteomyelitis possible. Exposed bone/tendon is visible or directly palpable.

These are bad wounds: only 62% ever heal, and only 52% heal within 1 year. They should be managed as in a Stage III. If after 14 days there is no sign of healing, consider infection: see appropriate management under the section Treatment, later.

The 2 new stages below are grouped with Stage IV because of their like severity.

E. Unstageable

Full thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, gray, green, or brown) and/or eschar (tan, brown, or black) in the wound bed.

Until enough slough and/or eschar is removed to expose the base of the wound, the true depth, and therefore stage, cannot be determined. Stable (dry, adherent, intact without erythema or fluctuance) eschar on the heels serves as “the body’s natural (biological) cover” and should not be removed.

F. Suspected Deep Tissue Injury

Purple or maroon localized area of discolored intact skin or blood-filled maroon blister due to damage of underlying soft tissue from pressure and/or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer, or cooler as compared to adjacent tissue. Deep tissue injury may be difficult to detect in individuals with dark skin tones. Evolution may include a thin blister over a dark wound bed. The wound may further evolve and become covered by thin eschar. Evolution may be rapid exposing additional layers of tissue even with optimal treatment.

Complications

The most common complications are cellulitis, osteomyelitis, and sepsis. If local erythema of 1 cm or greater occurs around the wound, topical antibiotics such as sulfasalazine or mupirocin should be used. If the erythema is rapidly expanding, there is heat, edema, or induration, the patient should be treated for cellulitis with systemic antibiotics. Use local susceptibility patterns to guide therapy. If the patient exhibits systemic symptoms: fever, rigors, delirium, or leukocytosis, draw blood cultures and obtain a sterile wound culture by needle aspiration or punch biopsy. We recommend consulting infectious diseases if any infection is suspected. Update tetanus immunity.

Osteomyelitis is another complication and should be suspected in painful and non-healing ulcers and whenever bone is visible. The technetium-99m bone scan and magnetic resonance imaging (MRI) have equal sensitivity. CT has good specificity, poor sensitivity. Needle biopsy of bone is the most useful single test, with a sensitivity of 73% and a specificity of 96%.

Sepsis is a serious consequence of infected pressure ulcers and a frequent cause of death with mortality rates as high as 48%.

Treatment

A. Management

We recommend a team approach once a stage I ulcer is identified. The wound should be checked daily and documentation of healing performed weekly. A tool to document healing has been developed by the NPUAP. The Pressure Ulcer Status for Healing (PUSH) tool measures three components—size, exudate amount, and tissue type. This tool has been validated, has good inter-rater reliability, and is sensitive to change over time.

Enlist the care of a wound team. A physical therapist will mobilize the patient. Unless contraindicated, no elder should...
be on bed rest. An occupational therapist can assist with positioning for safety and recommend devices to minimize pressure. A wound nurse will document the wound, often photograph it, and recommend appropriate dressings and support surfaces.

Nutrition is essential to healing. A dietician will assist with protein, calorie, and water recommendations as well as nutritional deficiencies. A BMI of less than 19, more than 5% weight loss in 30 days or more than 10% loss in 180 days, and a serum albumin less than 3.5 g/dL suggest malnutrition. Thirty to 40 kcal/kg body weight/day, 1.2-1.5 g protein/kg body weight/day, and minimum fluid intake of 30 mL/kg body weight/day are recommended for at-risk patients. Those with ulcers are in a catabolic state and will require a more intensive and tailored approach by a clinical dietician. While supplements of vitamin c and zinc are commonly recommended, there is no evidence they enhance wound healing unless the patient is deficient. Zinc at 100 mg daily can cause nausea and vomiting. A speech therapist and oral surgeon/dentist should be involved as needed.

Urinary and fecal incontinence must be managed on a case by case basis. The risk of Foley catheter urinary tract infection must be weighed against the projected benefit of a dry wound site. Fecal incontinence can cause skin breakdown and impair healing. Toilet ambulatory patients frequently, manage diarrhea, and use containment devices when necessary.

Attend to pain management: both physical and psychic. Patient dignity should be valued and respected. While use of sedation is associated with significantly increased risk of ulcers, pain from them must be addressed. This is especially important before dressing changes. Topical narcotics may be effective and have the added advantage of little systemic absorption, sedation, and constipation.

B. Alternative Therapies

Platelet derived growth factors were introduced in the 1990s. No study has shown improved healing in the elderly patient with multiple risk factors. No real benefits have yet been established for a number of alternate therapies including therapeutic ultrasound electromagnetic therapy, nutritional supplements, hyperbaric oxygen, infrared, UV, low energy, laser irradiation and most recently, honey.

C. Cultural Considerations

Some studies have shown higher incidence and severity of pressure ulcers in the black and Native American populations. Postulated contributing factors are dark skin color and economic factors.

D. Patient Education

Caring for a patient with pressure ulcers is demanding. Practitioners must teach caregivers to: examine the skin daily; turn and position bedridden patients; clean and dress the wounds; and recognize and report signs of infection. Help caregivers access resources such as AAA, Home Health, and support groups.

For chronically or terminally ill patients with longstanding or recurrent ulceration, aggressive treatment may not be in the best interest of the patient. Under these circumstances, maintaining patient comfort should be the primary goal rather than instituting major invasive procedures.

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**Web Sites**

- [www.ahrq.gov](http://www.ahrq.gov)
- [www.npuap.org/PDF/push3.pdf](http://www.npuap.org/PDF/push3.pdf)

**FALLS**

**ESSENTIALS OF DIAGNOSIS**

- A sudden, unintentional change in position causing an individual to land at a lower level.
- Not caused by paralysis, seizure, or trauma.
- Responsible for increased morbidity and mortality in the elderly population.
- Often multifactorial.

**General Considerations**

More than one-third of community dwelling elders will fall each year. Twenty to thirty percent will suffer moderate to severe injuries such as hip fractures and head trauma that reduce mobility and independence. Falls have psychological and social consequences such as fear of falling, anxiety, social isolation, and loss of self-confidence.

**Pathogenesis**

Most falls in older people result from the interaction of multiple intrinsic (age-related physiologic changes, medications, gait or balance disturbance, risk taking) and extrinsic factors (environmental hazards, lighting, footwear). Assessment of an acute fall-event or of patients at risk of falls warrants a
multidimensional approach incorporating (1) postural stability, (2) medical comorbidities, (3) overall function, and (4) environment.

Postural stability is maintained in three phases: input, processing, and output. Input includes vision, vestibular apparatus, and proprioception. Processing requires an intact nervous system: both central processing and competent efferent command. Output requires a motor system characterized by strength, flexibility, absence of pain, and cardiovascular endurance. Impairment of any one increases the risk for falls and the risk is cumulative. Conversely, interventions to modify any of these impairments will decrease the risk for falls.

Chronic diseases, and the medications we use to treat them, constitute the second key area of assessment. Conditions and drugs that affect the components of postural stability are suspect and there are usually more than one. Conditions to consider are: autonomic dysfunction, arrhythmia, seizure, movement disorder, central nervous system pathology including dementia, vertigo, or vision impairment. Any medication or combination can contribute to falls; these are particularly notorious: psychotropics, narcotics, benzodiazepines, antihistamines, antiarrhythmics, the cumulative effect of antihypertensives, more than any four drugs and alcohol.

Finally, the concept of functional thresholds places the data into a framework that identifies the point at which a particular patient exceeds his/her compensatory abilities. A detailed history and focused physical and performance examination will provide key information on function. For those frail elders, who most commonly fall at home, a home assessment completes the evaluation.

### Prevention

A systematic review of scientific studies has identified several evidenced-based strategies, targeting both intrinsic and environmental risk factors that are likely to be beneficial in preventing falls. The only evidence-based strategies shown to reduce fall risk are exercise programs targeting at least two areas: strength, balance, flexibility, and endurance; individually prescribed exercise programs at home; 15-week Tai Chi group exercise program; other group exercise; home hazard modification for at risk patients; withdrawal of psychotropic or sedating medications and decreasing number of medications; cardiac pacing for fallers with cardioinhibitory carotid sinus hypersensitivity; cataract surgery and vitamin D supplementation in deficient patients.

Risk reduction should also include advice on appropriate footwear (hard soled—only proven in laboratory studies not proven in clinical trials, flat, closed-toed shoes); adequate lighting for all activities; and caution with any activity that requires balance. For example, seniors should not climb stairs without a hand on the railing, stairs should be well-lit and in good repair. Climbing ladders should be discouraged. Robust elders should be cautioned about activities (skiing, skating, etc) that increase their risk for falls hence putting them at higher risk for fractures. Patients identified as having balance difficulty or who have had multiple falls will benefit from muscle strengthening and balance retraining. Assistive devices may prevent falls when used correctly within a targeted intervention. Hip protectors may be necessary to prevent serious injuries such as hip fractures. Environmental modification is of known benefit as part of an overall targeted intervention in the subgroup of older patients who are at known risk for falls.

### Clinical Findings

#### A. Signs and Symptoms

The history should elicit the exact details and circumstances surrounding the fall as precisely as possible. The clinician should ask questions regarding when the fall or near-fall occurred (what time of the day, postprandial), where the patient was (indoors, outdoors), what the patient was doing (getting up from seated position, climbing stairs, turning, reaching, stooping, micturating), how the patient fell (tripped/stumbled, lost balance, lost consciousness), whether there was pain (severe arthritis) or other symptoms (chest pain, shortness of breath, dizziness/lightheadedness, vertigo, diaphoresis, numbness and weakness of extremities, loss of consciousness), what medications were taken (prescription and over-the-counter), and whether the patient had ingested alcohol.

Pinpointing the patient’s subjective complaints is very helpful. Lightheadedness or a near-faint is consistent with cerebral ischemia and would suggest orthostasis, arrhythmias, and other cardiovascular conditions. Muscular weakness, the sense that their legs cannot hold them up, would be more consistent with deconditioning, or neuromuscular disease. Dysequilibrium or the sensation of no coordination between the legs and the walking surface is suggestive of vestibulospinal tract, proprioception, somatosensory, and cerebellar lesions. Finally, the sensation of movement within the patient or of the room spinning is true vertigo. Clinical examination in itself can provide some useful information about the events surrounding a fall, for example, wrist fractures by a fall on an outstretched hand suggest that consciousness was preserved while falling, or bilaterally damaged patellas suggest drop attacks.

#### B. Physical Examination

The physical examination should be problem-focused as noted in Table 40-3.

#### C. Performance Assessment

It is helpful to categorize the patient as frail, intermediate or robust. In general, vigorous elders will fall outside the home
COMMON GERIATRIC PROBLEMS

Table 40-3. Focused physical examination.

- **Vital signs:** Orthostatic blood pressure and heart rate, sitting and standing. Pulse for 1 minute.
- **Height:** Loss of height and kyphosis indicate osteoporosis. Intervention may reduce fracture risk.
- **Body mass index:** If below 21, patient at risk of malnutrition and/or depression. Decreased padding leads to increased injury risk.
- **Vision:** Visual acuity, field testing, pupillary size, depth perception. Visual field loss and depth perception have a much greater impact on mobility and vision function than acuity. Dark adaptation time increases with age and is contingent on pupil size, lens opacification, and duration and brightness of light aggravate the problem further. An annual ophthalmologic examination is recommended for all elders; alert the ophthalmologist to your concerns.
- **Vestibular function:** Have patient march in place with eyes closed. Abnormal response is moving more than a few degrees or moving more than a foot in any direction.
- **Neuromuscular**
  - Proximal muscle weakness suggests polymyalgia rheumatica, polymyositis, adrenal, thyroid, or parathyroid disease.
  - Distal muscle weakness more suggestive of peripheral neuropathy.
  - Peripheral neuropathy: Up to 20% of elders will have peripheral neuropathy: common causes are diabetes, alcohol, chronic lung disease, monoclonal gammopathy, neoplasm, medication (dilantin, lithium, isoniazid, vincristine), renal disease, thyroid disease, and vitamin B<sub>12</sub> deficiency. Neuropathy occurs before weakness or ataxia. Further testing includes vibratory sense: patients should be able to feel a 128 Hz tuning fork at the malleolus for 10 seconds. Absence of position sense and Achilles reflex help confirm the diagnosis.
  - Muscle tone and postural reflexes should be assessed to rule out Parkinson disease or movement disorders.
  - Range of motion: joint, neck, spine and hip, knee, and ankle should be assessed; restriction impairs reflex time and precision. Cervical spondylosis is a significant cause of falls.
  - **Feet:** In addition to peripheral neuropathy, check for deformities like bunions, callouses, ulcers, hammertoes, and nail pathology. Achilles reflex suggests peripheral neuropathy but is absent in up to 70% of normal aged individuals. Note footwear; thick, soft-soled shoes increase fall risk.
  - **Cognitive ability can be screened by three item recall, Mini-Mental Status Examination, or clock draw.**

while doing complicated activities. Frail elders generally fall at home performing activities of daily living. Interestingly, individuals who are completely immobile may have less risk of falling compared to vigorous/frail adults. Most studies show equal injury rates in both, although the frail fall more often. Gait speed is currently the best predictor of mobility problems and correlates with future disability. Another clinically relevant fact is that females tend to have a higher risk of falling compared to men.

For robust elders, have the patient tandem walk and stand on one leg with the other leg flexed for 30 seconds. If they have no problems, risk reduction counseling is all they need. If they have difficulty, focus on peripheral neuropathy as a potential and remediable culprit. Its onset is insidious, it, affects an estimated 20% of elders, and significantly increases risk of falling. Ask intermediate patients to climb stairs, step over objects, and rise from a chair with their arms folded and stand on one leg for 10 seconds. The 10-second stand is a more sensitive screen than the Romberg. Difficulty with these tasks may represent deconditioning, a neuromuscular disorder, and/or peripheral neuropathy.

For frail elders, have them perform the “Get-Up and Go” test and functional reach. The timed “Get-Up and Go” is a simple, well-validated office tool for assessing gait and balance disturbance in frail elders. The patient sits in a straight-back chair, then rises and walks 10 feet, turns, walks back, and sits on the chair. The patient may use whatever assistive device he/she normally uses and should be allowed one trial before being timed. Completion of the test in less than 10 seconds represents no risk and can be expected from non-frail elders. A score of 10-19 seconds represents minimal risk; 20-29 seconds moderate risk; and more than 30 seconds a definite risk for falling. Referral to physical therapy is warranted for 20 seconds or more.

D. Laboratory Findings

While lacking evidence the following are reasonable: complete blood count, serum electrolytes including calcium, blood urea nitrogen, vitamin B<sub>12</sub>, vitamin D, and thyroid function tests. Neuroimaging can be useful for a person with a head injury or a new neurologic deficit. Electroencephalography is rarely helpful but may be indicated if there is high suspicion of seizure. Persons with unexplained falls may benefit from ambulatory electrocardiography (Holter monitor) although this has been associated with high false positives and false negatives.

E. Environmental Assessment

A home assessment is warranted for frail elders and for anyone who has fallen at home. This may be done by the physician or occupational therapist and should include the environment itself as well as a replay of the circumstances of the fall. See Table 40-4.
Conclusion

In conclusion, falls, like other syndromes of the elderly, are multifactorial and require a multidisciplinary approach. Assessment that identifies intrinsic and extrinsic causes helps focus targeted interventions. A team approach that incorporates the patient, specialists (physiatrist, ophthalmologist, optometrist, podiatrist, orthopedist), and occupational and physical therapists will maximize outcomes.


Web Sites (For Patient Education)

American Geriatrics Society http://www.americangeriatrics.org
National Center for Injury Prevention and Control http://www.cdc.gov/ncipc/falls
National Institute on Aging http://www.niapublications.org/engagepages/falls.asp
Nice information on how to get up after a fall http://www.stritch.luc.edu/depts/injprev/Falls/adult.htm
General Considerations

Urinary incontinence is the involuntary loss of urine that is so severe as to have social or hygienic consequences. It is very common, with a prevalence in community-dwelling elderly persons as high as 35%, and significantly higher rates among institutionalized patients. Despite this high prevalence, studies have shown that about half of all incontinent persons have never discussed the problem with a physician. This is likely because of embarrassment, a belief that incontinence is normal with aging, or an assumption that nothing can be done to help. Incontinence is associated with significant medical morbidity, including infection, sepsis, pressure ulcers, and falls. It is also associated with significant psychological stress and social isolation. Incontinence causes significant caregiver burden, and is frequently cited as a reason for deciding to abandon home care efforts in favor of nursing home placement. The economic burden of incontinence is also substantial, with an estimated direct cost in the United States of $16.3 billion per year.

Because of its high prevalence, significant morbidity, and high psychosocial impact, it is important for family physicians to accurately identify, assess, and treat incontinent patients. The large majority of patients with incontinence can be diagnosed and managed effectively by family physicians in the primary care setting.

A. Physiology of Normal Urination

A basic understanding of the normal physiology of urination is important to understand the potential causes of incontinence, and the various strategies for effective treatment.

The lower urinary tract consists primarily of the bladder (detrusor muscle) and the urethra. The urethra contains two sphincters, the internal urethral sphincter (IUS), composed predominantly of smooth muscle, and the external urethral sphincter (EUS), which is primarily voluntary muscle. The detrusor muscle of the bladder is innervated predominantly by cholinergic (muscarinic) neurons from the parasympathetic nervous system, the stimulation of which leads to bladder contraction. The sympathetic nervous system innervates both the bladder and the IUS. Sympathetic innervation in the bladder is primarily β-adrenergic and leads to bladder relaxation, whereas α-adrenergic receptors predominate in the IUS, leading to sphincter contraction. Thus, in general, sympathetic stimulation of the urinary tract promotes bladder filling (relaxation of the detrusor with contraction of the sphincter), whereas parasympathetic stimulation leads to bladder emptying (detrusor contraction and sphincter relaxation).

The EUS, on the other hand, is striated muscle and primarily under voluntary (somatic) control. This allows for some ability to voluntarily postpone urination by tightening the sphincter and inhibiting the flow of urine. Additional voluntary control is provided by the central nervous system through the pontine micturition center. This allows for central inhibition of the autonomic processes previously described, and for further voluntary postponement of the need to urinate until the circumstances are more socially appropriate or until necessary facilities are available.

The physiologic factors influencing normal urination are summarized in Table 41-1 and are important considerations when discussing urinary disorders and treatment.

B. Age-Related Changes

Contrary to common perception, urinary incontinence is not inevitable with aging. Most elderly patients remain continent throughout their lifetimes, and a complaint of incontinence at any age should receive a thorough evaluation and not be dismissed as “normal for age.” Nonetheless, many common age-related changes predispose elderly patients to incontinence and increase the likelihood of its development with advancing age.

The frequency of involuntary bladder contractions (detrusor hyperactivity) increases in both men and women with aging. In addition, total bladder capacity decreases, causing the voiding urge to occur at lower volumes. Bladder contractility decreases, leading to increased postvoid residuals...
and increased sensation of urgency or fullness. Elderly patients excrete a larger percentage of their fluid volume later in the day than younger persons. This, in addition to the other changes listed, often leads to an increase in the incidence of nocturia with aging, and more frequent nighttime awakenings.

In women, menopausal estrogen decline leads to urogenital atrophy and a decrease in the sensitivity of \( \alpha \)-receptors in the IUS. In men, prostatic hypertrophy can lead to increased urethral resistance, and varying degrees of urethral obstruction.

It is important to remember that these age-related changes are found in many healthy, continent persons as well as those who develop incontinence. It is not completely understood why the predisposition to urinary problems is stronger in some patients than in others, which emphasizes the multifactorial basis of incontinence.

**Clinical Findings**

**A. Symptoms and Signs**

1. **Incontinence outside the urinary tract**—Incontinence is often classified based on whether it is related to specific urogenital pathology or to factors outside the urinary tract. Terms such as *transient versus established, acute versus persistent, and primary versus secondary* have been used to highlight this distinction. The mnemonic DIAPPERS is helpful in remembering the many causes of incontinence that occur outside the urinary tract (Table 41-2). These “extraurinary” causes are very common in the elderly, and it is important to identify or rule them out before proceeding to a more invasive search for primary urogenital etiologies.

Delirium, depression, and disorders of excessive urinary output generally require medical or behavioral management of the primary cause rather than strategies relating to the bladder. Once the primary causes are corrected, the incontinence often resolves. Urinary tract infections, although easily treated if discovered, are a relatively infrequent cause of urinary incontinence in the absence of other classic symptoms (dysuria, urgency, frequency, etc). Asymptomatic bacteriuria, which is common even in well elderly, does not cause incontinence.

Pharmaceuticals are a particularly important and very common cause of incontinence. Because of the many neural receptors involved in urination (see Table 41-1), it is easy to understand why so many medications used to treat other common problems can readily affect continence. Medications frequently associated with incontinence are listed in Table 41-3. Many of these medications are available over the counter and in combination (Table 41-4). In addition, commonly used substances such as caffeine and alcohol can contribute to incontinence by virtue of their diuretic effects or the effects they have on mental status. Because of this, some medications and substances associated with a patient’s incontinence may not be considered important or readily volunteered during a medication history unless the physician specifically asks about them.

Restricted mobility or the inability to physically get to the bathroom in time to avoid incontinence is also referred to as “functional” incontinence. The incontinence may be temporary or chronic, depending on the nature of the physical or cognitive disability involved. Physical therapy or strength and flexibility training may be helpful, as well as simple measures such as a bedside commode or urinal.

Stool impaction is very common in the elderly and may cause incontinence both through its local mass effect and by

### Table 41-1. Physiologic factors influencing normal urination.

<table>
<thead>
<tr>
<th>Bladder filling</th>
<th>Sympathetic nervous system</th>
<th>( \beta )-Adrenergic</th>
<th>Detrusor relaxation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( \alpha )-Adrenergic</td>
<td>IUS contraction</td>
</tr>
<tr>
<td>Bladder emptying</td>
<td>Parasympathetic nervous system</td>
<td>Cholinergic</td>
<td>Detrusor contraction</td>
</tr>
<tr>
<td>Voluntary control</td>
<td>Somatic nervous system</td>
<td>Striated muscle</td>
<td>EUS contraction</td>
</tr>
<tr>
<td></td>
<td>Central nervous system</td>
<td>Pontine micturition center</td>
<td>Central inhibition of urinary reflex</td>
</tr>
</tbody>
</table>

EUS, external urethral sphincter; IUS, internal urethral sphincter.

### Table 41-2. Causes of urinary incontinence without specific urogenital pathology.

<table>
<thead>
<tr>
<th>D</th>
<th>Delirium/confusional state</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Infection (symptomatic)</td>
</tr>
<tr>
<td>A</td>
<td>Atrophic urethritis/vaginitis</td>
</tr>
<tr>
<td>P</td>
<td>Pharmaceuticals</td>
</tr>
<tr>
<td>P</td>
<td>Psychiatric causes (especially depression)</td>
</tr>
<tr>
<td>E</td>
<td>Excessive urinary output (hyperglycemia, hypercalcemia, congestive heart failure)</td>
</tr>
<tr>
<td>R</td>
<td>Restricted mobility</td>
</tr>
<tr>
<td>S</td>
<td>Stool impaction</td>
</tr>
</tbody>
</table>

*Also known as transient, acute, or secondary incontinence.*
stimulation of opioid receptors in the bowel. It has been reported to be a causative factor in up to 10% of patients referred to incontinence clinics for evaluation. Continence can often be restored by a simple disimpaction.

2. Urologic causes of incontinence—Once secondary or transient causes have been investigated and ruled out, further evaluation should focus on specific urologic pathology that may be causing incontinence.

The urinary tract has two basic functions: the emptying of urine during voiding and the storage of urine between voiding. A defect in either of these basic functions can cause incontinence, and it is useful to initially classify incontinence by whether it is primarily a defect of storage or of emptying. An inability to store urine occurs when the bladder contracts too often (or at inappropriate times), or when the sphincter(s) cannot contract sufficiently to allow the bladder to store urine and keep it from leaking. Thus the bladder rarely, if ever, fills to capacity and the patient’s symptoms are generally characterized by frequent incontinent episodes of relatively small volume. An inability to empty urine occurs when the bladder is unable to contract appropriately, or when the outlet or sphincter(s) is partially obstructed (either physically or physiologically). Thus, the bladder continues to fill beyond its normal capacity and eventually overflows, causing the patient to experience abdominal distention and continual or frequent leakage.

Determining whether the primary problem is the inability to store or the inability to empty can often be done easily during the history and physical examination based on the

<table>
<thead>
<tr>
<th>Table 41-3. Pharmaceuticals contributing to incontinence.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmaceutical</strong></td>
</tr>
<tr>
<td>α-Adrenergic agonists</td>
</tr>
<tr>
<td>α-Adrenergic blockers</td>
</tr>
<tr>
<td>Anticholinergic agents</td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
<tr>
<td>Antihistamines</td>
</tr>
<tr>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Sedatives</td>
</tr>
<tr>
<td>β-Adrenergic agonists</td>
</tr>
<tr>
<td>β-Adrenergic blockers</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Narcotic analgesics</td>
</tr>
</tbody>
</table>

IUS, internal urethral sphincter.

<table>
<thead>
<tr>
<th>Table 41-4. Nonprescription agents contributing to incontinence.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>α-Agonists</td>
</tr>
<tr>
<td>Antihistamines</td>
</tr>
<tr>
<td>α-Agonist/antihistamine combinations</td>
</tr>
<tr>
<td>Caffeine</td>
</tr>
</tbody>
</table>

IUS, internal urethral sphincter.
patient’s pattern of incontinence (intermittent or continuous) and whether abdominal (bladder) distention is present. Determination of postvoid residual is also helpful in making this distinction (see section History and Physical Findings, later). This initial classification is important in narrowing down the specific etiology of the incontinence, and in ultimately deciding on the appropriate management strategy.

3. Symptomatic classification—Once it is determined whether the primary problem is with storage or with emptying, incontinence can be further classified according to the type of symptoms that it causes in the patient. The most common categories are discussed below. The first two types, urge incontinence and stress incontinence, result from an inability to store urine. The third type, overflow incontinence, results from an inability to empty urine. Because the term “overflow” has been felt by many to be confusing and imprecise, the term “incomplete bladder emptying” is now often used instead. A patient may have a single type of incontinence or a combination of more than one type (mixed incontinence).

Table 41-5 summarizes the major categories of incontinence, the underlying urodynamic findings, and the most common etiologies for each.

### Table 41-5. Types and classification of urinary incontinence.

<table>
<thead>
<tr>
<th>Underlying Defect</th>
<th>Symptomatic Classification</th>
<th>Most Common Urodynamics</th>
<th>Possible Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to store urine</td>
<td>Urge (U)</td>
<td>Detrusor hyperactivity</td>
<td>Uninhibited contractions; local irritation (cystitis, stone, tumor); central nervous system causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress (S)</td>
<td></td>
<td>Sphincter incompetence</td>
<td>Urethral hypermobility; sphincter damage (trauma, radiation, surgery)</td>
</tr>
<tr>
<td>Inability to empty urine</td>
<td>Overflow (O) (incomplete emptying)</td>
<td>Outlet obstruction</td>
<td>Physical (benign prostatic hyperplasia, tumor, stricture); neurologic lesions, medications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Detrusor hypoactivity</td>
<td>Neurogenic bladder (diabetes, alcoholism, disc disease)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Functional (F)</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>U + S, U + F</td>
<td>Immobility problems; cognitive deficits</td>
</tr>
</tbody>
</table>

A. Urge incontinence—Urge incontinence is the most common type of incontinence in the elderly. Patients complain of a strong, and often immediate, urge to void followed by an involuntary loss of urine. It is often not possible to reach the bathroom in time to avoid incontinence once the urge occurs, and patients often lose urine while rushing toward a bathroom or trying to locate one. Urge incontinence is most frequently caused by involuntary contractions of the bladder, often referred to as detrusor instability. These involuntary contractions increase in frequency with age, as does the ability to voluntarily inhibit them. Although the symptoms of urgency are a hallmark feature of this type of incontinence, detrusor instability can sometimes result in incontinence without these symptoms. Although most patients with detrusor instability are neurologically normal, uninhibited contractions can also occur as the result of neurologic disorders such as stroke, dementia, or spinal cord injury. In these cases it is often referred to as detrusor hyperreflexia. Detrusor instability and urgency can also be caused by local irritation of the bladder as with infection, bladder stones, or tumors. The term overactive bladder syndrome (OABS) is now commonly used to describe the symptoms of urgency caused by detrusor instability and to emphasize that they can occur either with or without incontinence. OABS is described by the International Continence Society as voiding eight or more times during a 24-hour period, and awakening two or more times during the night. Treatment of OABS is similar whether or not incontinence is present.

B. Stress incontinence—Stress incontinence is much more common among women than men and is defined as a loss of urine associated with increases in intra-abdominal pressure (Valsalva maneuver). Patients complain of leakage of urine (usually small amounts) during coughing, laughing, sneezing, or exercising. In women, stress incontinence is most often caused by urethral hypermobility resulting from weakness of the pelvic floor musculature, but it can also be caused by intrinsic weakness of the urethral sphincter(s), most commonly following trauma, radiation, or surgery. Stress incontinence is rare in men, unless they have suffered damage to the sphincter through surgery or trauma. In making the diagnosis of stress incontinence, it is important to ascertain that the leakage occurs exactly coincident with the stress maneuver. If the leakage occurs several seconds after the maneuver, it is more likely caused by an uninhibited bladder contraction that has been triggered by the stress maneuver, and is urodynamically more similar to urge incontinence. This is sometimes known as stress-induced detrusor instability.

C. Incomplete bladder emptying (overflow incontinence)—This is a loss of urine associated with overdistention of the bladder. Patients complain of frequent or constant
leakage or dribbling, or they may lose large amounts of urine without warning. Incomplete emptying may result either from a defect in the bladder’s ability to contract (detrusor hypoactivity) or from obstruction of the bladder outlet or urethra. Detrusor hypoactivity is most commonly the result of a neurogenic bladder secondary to diabetes mellitus, chronic alcoholism, or disc disease. It can also be caused by medications, primarily muscle relaxants and β-adrenergic blockers. Outlet obstruction can be physical (prostatic enlargement, tumor, stricture), neurologic (spinal cord lesions, pelvic surgery), or pharmacologic (α-adrenergic agonists). Because neurogenic bladder is relatively rare in the geriatric population, it is important to rule out possible causes of obstruction whenever the diagnosis of overflow incontinence is made.

D. Functional incontinence—The term functional incontinence is used to describe physical or cognitive impairments that interfere with continence even in patients with normal urinary tracts (see section Incontinence Outside the Urinary Tract, Table 41-2, and the DIAPPERS mnemonic, earlier).

E. Mixed incontinence—Mixed incontinence describes various combinations of the preceding four types. When present, it can make the diagnosis and management of incontinence more difficult. The term is most frequently used to describe patients who present with a combination of stress and urge incontinence, although other combinations are also possible. Functional incontinence, for example, can coexist with stress, urge, or overflow incontinence, further complicating the treatment of these patients. Side effects of medications being used to treat other comorbidities can also cause a mixed picture when combined with underlying incontinence of any type. Mixed stress and urge incontinence is particularly common among elderly women. When present, it is helpful to focus on the symptom that is most bothersome to the patient, and to direct the initial therapeutic interventions in that direction.

B. Screening

Screening for incontinence in all women is recommended because of its high prevalence and low degree of self-reporting by patients. Elderly women and those with neurologic diseases or diabetes are at the highest risk. Screening women for urinary incontinence is one of the 153 Quality Reporting Measures adopted by the Centers for Medicare and Medicaid Services in their 2009 Physician Quality Reporting Initiative (PQRI) Program.

C. History and Physical Findings

The history and physical examination of a patient presenting with incontinence should have the following goals:

1. To evaluate for and rule out causes of incontinence outside the urinary tract (DIAPPERS).
2. To determine whether the primary defect is an inability to store urine or an inability to empty urine.
3. To determine the type of incontinence based on the patient’s symptoms and likely etiologies.
4. To determine the pattern of incontinence episodes and its effect on the patient’s functional ability and quality of life.

1. History—A thorough medical history should include a special focus on the neurologic and genitourinary history of the patient as well as any other medical problems that may be contributing factors (see Table 41-2). Information on any previous evaluation(s) for incontinence, as well as their degree of success or failure, can be helpful in guiding the current evaluation and in determining patient expectations. A careful medication history is very important, focusing on the categories of medications listed in Table 41-3 and remembering to include nonprescription substances (see Table 41-4). Finally, the pattern of incontinence is important in helping to classify its type and in planning appropriate therapy. While many urinary symptoms (eg, dribbling, frequency, hesitancy, nocturia) may lack diagnostic specificity, symptoms of urgency (the sudden urge to void with leakage before reaching the toilet) are very sensitive and specific for the diagnosis of urge incontinence. Urine leakage with coughing or other stress maneuvers is a sensitive indicator of stress incontinence, but is less specific than urge because of overlap with other conditions. A voiding diary or bladder record can be a very useful tool in obtaining additional diagnostic information. The patient or caregiver is given a set of forms and is asked to keep a written record of each incontinent episode for several days. A sample form is shown in Table 41-6. Incontinent episodes are recorded in terms of time, estimated volume (small or large), and precipitating factors. Fluid intake, as well as any episodes of urination in the toilet, is also recorded. When completed accurately, the bladder record can often elucidate the most likely type of incontinence and provide a clue to possible precipitating factors. Continuous leakage, for example, may be more consistent with overflow incontinence, whereas multiple, large-volume episodes may be more consistent with urge. Smaller volume episodes associated with coughing or exercise may be more consistent with stress incontinence, whereas incontinence occurring only at specific times each day may suggest an association with a medication or other non-urinary tract cause. Although other information from the physical and laboratory evaluations will obviously be needed, the physician can often make significant progress toward determining the type of incontinence and possible precipitating factors from the history and voiding record alone.

2. Physical examination—In addition to a thorough search for non-urologic causes of incontinence, the physical examination should focus on the cardiovascular, abdominal, genital, and rectal areas. Cardiovascular examination should focus on signs of fluid overload. Evidence of bladder distention on abdominal examination should raise suspicion for overflow incontinence. Genital examination should include a pelvic examination in women to assess for evidence of atrophy or
mass, as well as any signs of uterine prolapse, cystocele, or rectocele. A rectal examination is helpful in ruling out stool impaction or mass, as well as in evaluating sphincter tone and perineal sensation for evidence of a neurologic deficit. A prostate examination is usually included, but several studies have demonstrated a poor correlation between prostate size and urinary obstruction. A neurologic examination focusing on the lumbosacral area is helpful in ruling out a spinal cord lesion or other neurologic deficits.

3. Special tests—Two additional tests, specific to the diagnosis of incontinence, should be added to the general physical examination.

A. Provocative stress testing—This test attempts to reproduce the symptoms of incontinence under the direct visualization of the physician and is useful in differentiating stress from urge incontinence. The patient should have a full bladder and preferably be in a standing position (although a lithotomy position is also acceptable for patients unable to stand). The patient should be told to relax, and then to cough vigorously while the physician observes for urine loss. If leakage occurs simultaneously with the cough, a diagnosis of stress incontinence is likely. A delay between the cough and the leakage is more likely caused by a reflex bladder contraction and is more consistent with urge incontinence.

B. Postvoid residual (PVR)—This measurement should be obtained for incontinent patients suspected of urinary retention and potential obstruction. This includes men with severe urinary symptoms, women with prior gynecological or pelvic surgery, persons with neurological disorders or diabetes, and those who have failed initial empiric therapy. PVR measurement is traditionally done by urinary catheterization; however, portable ultrasound scanners for this purpose are now available that also provide very accurate readings. These ultrasound devices minimize the risks of instrumentation and infection that are inherent in catheterization, especially in male patients. Prior to measurement, the patient should be asked to empty the bladder as completely as possible. Measurement of residual urine in the bladder should be made within a few minutes after emptying using

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Urinated in Toilet</th>
<th>Had a Small Incontinent Episode</th>
<th>Had a Large Incontinent Episode</th>
<th>Reason for Incontinent Episode</th>
<th>Type/Amount of Liquid Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-8 AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-10 AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-noon</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noon-2 PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4 PM</td>
<td></td>
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<tr>
<td>4-6 PM</td>
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<tr>
<td>6-8 PM</td>
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<tr>
<td>8-10 PM</td>
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<tr>
<td>10-midnight</td>
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</tr>
<tr>
<td>Overnight</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Number of pads used today: ___________________________

Number of episodes: ________________________

Comments: ________________________________
either in-and-out catheterization or ultrasound. A PVR of less than 50 mL is normal; more than 200 mL indicates inadequate bladder emptying and is consistent with overflow incontinence. PVRs between 50 and 199 mL can sometimes be normal but may also exist with overflow incontinence, and results should be interpreted in light of the clinical picture. Patients with elevated PVRs should generally be referred for further evaluation and to rule out obstruction prior to treatment of the incontinence symptoms.

C. Other diagnostic maneuvers—Other maneuvers, or “bedside urodynamics,” have often been recommended to help in the diagnosis of incontinence. The best known of these are the Q-tip test to diagnose pelvic laxity and the Bonney (Marshall) test to determine whether surgical intervention will be helpful. Although these tests may be useful in some settings, recent studies have cast doubt on their predictive value, and in the family practice setting they are unlikely to add clinically useful information to that obtained from the history and physical examination as previously described. Likewise, bedside urodynamics to assess bladder contractions and function will not likely add useful information to help in sorting out the small percentage of patients whose diagnosis remains unclear after a thorough history and physical examination.

C. Laboratory and Imaging Evaluation

Like the history and physical examination, the laboratory evaluation should be focused on ruling out the non-urologic causes of incontinence. A urinalysis is very helpful in screening for infection as well as in evaluating for hematuria, proteinuria, or glucosuria. It must be remembered, however, that asymptomatic bacteriuria is very common in the elderly and is not a cause of incontinence. Antibiotic treatment of asymptomatic bacteriuria has not been shown to reduce morbidity or to improve incontinence either in the institutionalized elderly or in ambulatory women. Thus, antibiotic treatment in the face of incontinence and bacteriuria should be reserved for patients whose incontinence is of recent onset, has recently worsened, or is accompanied by other signs of infection. Hematuria, in the absence of infection, should be referred for further evaluation to rule out carcinoma.

Additional laboratory studies that are recommended and may be helpful include measurement of renal function (blood urea nitrogen and creatinine) and evaluation for metabolic causes of polyuria (hypercalcemia, hyperglycemia). Radiologic studies are not routinely recommended in the initial evaluation of most patients with incontinence; however, a renal ultrasound study is useful in patients with obstruction to evaluate for hydronephrosis.

If non-urologic or functional causes are found as major contributors to the patient’s incontinence, treatment should be targeted at the underlying illnesses and improving any functional disability. In addition to medical management of the underlying disorder(s), physical therapy and the use of assistive devices may be helpful in improving the patient’s level of function and his or her ability to reach the bathroom prior to having an incontinent episode. For the ambulatory patient, a home visit is often useful in assessing for environmental hazards that may be contributing to functional incontinence.

Simple lifestyle modifications may be helpful in mild cases of urinary incontinence. Fluid restriction and avoidance of caffeine and alcohol, especially in the evening, can be recommended as an initial step. Weight loss can be recommended if the patient is obese, and the use of a bedside commode or urinal can also be helpful. For patients with more severe incontinence, however, including most patients with urologic causes, further treatment measures usually are necessary.

Treatment for urinary incontinence is divided into three categories: behavioral and nonpharmacologic therapies, pharmacotherapy, and surgical intervention.

A. Behavioral and Nonpharmacologic Therapies

Lifestyle measures and behavioral therapies should be the first line treatments in most patients with urge or stress incontinence, as they have the advantages of being effective in a large percentage of patients with few, if any, side effects. Lifestyle measures include limiting excessive fluid intake, avoiding caffeinated and alcoholic beverages, and attaining a healthy weight. Weight loss in overweight and obese women has been shown to be effective in reducing episodes of stress incontinence, but urge incontinence was not decreased. Behavioral therapies range from those designed to treat the underlying problem and restore continence (eg, bladder training, pelvic muscle exercises) to those designed simply to promote dryness through increased attention from a caregiver (eg, timed voiding, prompted voiding). The former category requires a motivated patient who is cognitively intact, whereas the latter...
category can be used even in patients with significant cognitive impairment.

1. **Bladder training**—This technique is designed to help patients control their voiding reflex by teaching them to void at scheduled times. The patient is asked to keep a voiding record for approximately 1 week to determine the pattern of incontinence and the interval between incontinent episodes. A voiding schedule is then developed with a scheduled voiding interval significantly shorter than the patient’s usual incontinence interval. (For example, if the usual time between incontinent episodes is 1-2 hours, the patient should be scheduled to void every 30-60 minutes.) The patient is asked to empty the bladder as completely as possible at each scheduled void whether or not an urge is felt. Patients who have the urge to void at unscheduled times should try to stop the urge through relaxation or distraction techniques until the urge passes, and then void at the next scheduled time. If the urge between scheduled voids becomes too uncomfortable, the patient should go ahead and void, but should still void again as completely as possible at the next scheduled time. As the number of incontinent episodes decreases, the scheduled voiding intervals should be gradually extended each week, until a comfortable voiding interval is reached.

Fantl and colleagues, in a well-publicized albeit relatively small trial of bladder retraining, demonstrated significant improvement in both the number of incontinent episodes and the amount of fluid lost in incontinent elderly women. Although the benefit was greatest in women with urge incontinence, women with stress incontinence also demonstrated improvement. In a later study, their group also demonstrated a significant improvement in quality of life following institution of bladder training. Studies in a family practice setting, in a home nursing program, and in a health maintenance organization also demonstrated significant benefit from a program of bladder training. The latter, a randomized controlled trial published in 2002, included patients with stress, urge, and mixed incontinence. Overall, patients had a 40% decrease in their incontinent episodes with 31% being 100% improved, 41% at least 75% improved, and 52% at least 50% improved.

2. **Pelvic muscle exercises**—These exercises, also known as Kegel exercises, are designed to strengthen the perirethral and perivaginal muscles. They are most useful in the treatment of stress incontinence but may also be effective in urge and mixed incontinence. Patients are initially taught to recognize the muscles to contract by being asked to squeeze the muscles in the genital area as if they were trying to stop the flow of urine from the urethra. While doing this, they should be sure that only the muscles in the front of the pelvis are being contracted, with minimal or no contraction of the abdominal, pelvic, or thigh muscles. Once the correct muscles are identified, patients should be taught to hold the contraction for at least 10 seconds followed by 10 seconds of relaxation. The exercises should be repeated between 30 and 80 times per day. Patients are then taught to contract their pelvic muscles before and during situations in which urinary leakage may occur to prevent their incontinent episodes from occurring.

A recent systematic review of 43 published clinical trials concluded that pelvic muscle exercises are effective for both stress and mixed incontinence, but that their effectiveness for urge incontinence remains unclear. Biofeedback has been used effectively to improve patients’ recognition and contraction of pelvic floor muscles, but the required equipment and expertise can make this impractical in a primary care setting. Weighted vaginal cones and electrical stimulation have also been used to enhance pelvic muscle exercises. These modalities are provided by many physical therapy or geriatric departments and can be considered as additional options for women who are unsuccessful with pelvic muscle exercises or who have obtained only partial improvement. The Cochrane group concluded that weighted vaginal cones, electrostimulation, and pelvic muscle exercises are probably similar in effectiveness. There was not enough evidence to conclude that the effectiveness of cones plus pelvic muscle exercises is different than either one alone. The effectiveness of pelvic muscle exercises have not been well studied in men, but have been shown to improve incontinence following prostatectomy.

3. **Timed voiding**—Timed voiding is a passive toileting assistance program that is caregiver dependent and can be used for patients who are either unable or unmotivated to participate in more active therapies. Its goal is to prevent incontinent episodes rather than to restore bladder function. The caregiver provides scheduled toileting for the patient on a fixed schedule (usually every 2-4 hours), including at night. There is no attempt to motivate the patient to delay voiding or resist the urge to void as there is in bladder training. The technique can be used both for patients who can toilet independently as well as those who require assistance. It has been used with success in both male and female patients and has achieved improvements of up to 85%. Timed voiding has also been used effectively in post-prostatectomy patients as well as in patients with neurogenic bladder.

A variation of timed voiding, known as **habit training**, uses a voiding schedule that is modified according to the patient’s usual voiding pattern rather than an arbitrarily fixed interval. The goal of habit training is to preempt incontinent episodes by scheduling the patient’s toileting interval to be shorter than the usual voiding interval. Both timed voiding and habit training are most commonly used in nursing homes but may also be used in the home if a motivated caregiver is available.

4. **Prompted voiding**—Prompted voiding is a technique that can be used for patients with or without cognitive impairment; it has been studied most frequently in the nursing home setting. Its goal is to teach patients to initiate their own toileting through requests for help and positive reinforcement from caregivers. Approximately every 2 hours, caregivers prompt the patients by asking whether they are
wet or dry and suggesting that they attempt to void. Patients are then assisted to the toilet if necessary and praised for trying to use the toilet and for staying dry. A recent systemic analysis of controlled trials of prompted voiding concluded that the evidence was suggestive, although inconclusive, that prompted voiding provided at least short-term benefit to incontinent patients. The addition of oxybutynin to a prompted voiding program may provide additional benefit for some patients. A recent nursing home trial demonstrated that prompted voiding is most effective for reducing daytime incontinence, and that routine nighttime toileting was not effective in reducing incontinent episodes during the night.

B. Pharmacotherapy

Medications may be used alone or in conjunction with behavioral therapy when degree of improvement has been insufficient. There are very few studies comparing drug therapy with behavioral therapy, but both have been found more effective than placebo. An accurate diagnosis of the type of incontinence is necessary in order to choose appropriate pharmacotherapy for each patient.

1. Urge incontinence—Anticholinergic medications are the drugs of choice for urge incontinence, and six medications in a total of eleven formulations are now available. Oxybutynin, the earliest of these medications, is now available in a transdermal patch (Oxytrol) that can be dosed twice weekly, as well as a long-acting formulation (Ditropan XL) and a gel (Gelnique) that can both be dosed once daily. It is also available in a generic formulation that is significantly less expensive, but requires dosing (2.5-5 mg) two to four times a day.

Tolterodine is also available in both short-acting (Detrol) and long-acting (Detrol LA) formulations that can be dosed either once or twice daily. No direct trial has yet been published comparing the long-acting forms of the two drugs. A study of long-acting oxybutynin versus short-acting tolterodine found oxybutynin was modestly more effective with a similar side-effect profile and cost. A meta-analysis of four comparative trials (looking mainly at the short-acting formulations) concluded that oxybutynin is superior in efficacy, but that tolterodine is better tolerated with fewer dropouts because of medication side effects. Major side effects of both drugs include dry mouth, urinary retention, and delirium. These effects are less common with tolterodine, and dry mouth seems less common with the transdermal and gel formulations of oxybutynin due to a lower production of metabolite.

Four newer anticholinergic medications have been released to compete with oxybutynin and tolterodine. Trospium (Sanctura), released in 2004, offers the advantage of fewer drug-drug interactions because it is not metabolized by the cytochrome P450 system and is cleared by the kidney. It now has an extended-release formulation available that allows once-daily dosing. Solifenacin (Vesicare) and darifenacin (Enablex), both released in 2005, are more selective for the M3 muscarinic receptors in the bladder than the more traditional agents. Both are dosed once daily. Solifenacin are found preferentially in smooth muscle, the salivary glands, and the eyes. This selectivity may lead to a lower incidence of drowsiness and dizziness in some patients, with the most common side effects being dry mouth and constipation. The industry-sponsored STAR Trial found solifenacin to be somewhat more effective than tolterodine in reducing urgency and frequency but dry mouth and constipation were more frequent with solifenacin. Fesoterodine (Toviaz), just released in 2009, is similar to Detrol LA and has the same active metabolite. It comes in a higher dose formulation (8 mg) than Detrol that may increase its efficacy but likely also its side effects.

The tricyclic antidepressant imipramine has traditionally been widely used to treat urge incontinence, but its use has now largely been supplanted by these newer agents with more favorable side-effect profiles and better documented efficacy.

2. Stress incontinence—Medical treatment is most effective for patients with mild to moderate stress incontinence and without a major anatomic abnormality. The α-agonist pseudoephedrine, at a dosage range of 15-60 mg three times a day, is the drug of choice for patients without contraindications. Side effects include nausea, dry mouth, insomnia, and restlessness. Studies using phenylpropanolamine (now removed from the market) demonstrated improvement in 19%-60% of women and cure in 9%-14%. One study indicated that a significant number of patients referred for surgical intervention could avoid surgery with α-agonist therapy.

Traditionally, estrogen therapy has been used in conjunction with α-agonists to increase α-adrenergic responsiveness and improve urethral mucosa and smooth muscle tone. However, the recent Heart and Estrogen/Progestin Replacement Study (HERS) demonstrated estrogen therapy to be less effective than placebo for symptoms of urinary incontinence, with only 20.9% of the treatment group reporting improvement and 38.8% reporting worsening of their incontinence (compared with 26% improvement and 27% worsening in the placebo group). Data from the Women's Health Initiative study indicating that patients on an estrogen-progestin combination demonstrated increased risk for heart disease, stroke, breast cancer, and pulmonary embolism also cast significant doubt on the advisability of long-term estrogen use for this indication. Although the risks and benefits of topical estrogen are not completely known, it is not currently recommended to prescribe oral estrogen for the treatment of incontinence.

3. Overflow incontinence—Overflow incontinence associated with outlet obstruction is generally not treated with medications because the primary therapy is removal of the obstruction. In men, outlet obstruction is most commonly caused by prostatic enlargement secondary to infection (prostatitis), benign prostatic hyperplasia, or prostate cancer. Prostatitis can be treated with a 2- to 4-week course of a fluoroquinolone or trimethoprim-sulfamethoxazole. Once prostate cancer has been ruled out, benign prostatic hyperplasia
may be treated with \( \alpha \)-blockers, finasteride, surgery, or transurethral microwave thermotherapy. \( \alpha \)-Blockers have been shown to be ineffective in “prostatism-like” symptoms in elderly women.

Medical treatment of overflow incontinence caused by bladder contractility problems is usually not highly efficacious. The cholinergic agonist bethanechol may be useful subcutaneously for temporary contractility problems following an overdistention injury but is generally ineffective when given orally or when used long term.

### C. Surgical Intervention

Surgical therapy may be indicated for patients with incontinence resulting from anatomic abnormalities (eg, cystocele, prolapse), with outlet obstruction resulting in urinary retention, or for patients in whom more conservative methods of treatment have not provided sufficient relief. Beyond the correction of anatomic abnormalities or obstruction, surgical therapy is most effective for stress incontinence or for mixed incontinence in which stress incontinence is a primary component. Numerous surgical options are available for the management of stress incontinence, including injection of periurethral bulking agents, transvaginal suspensions, retropubic suspensions, slings, and sphincter prostheses. Choice of procedure is based on the relative contributions of urethral hypermobility versus intrinsic sphincter deficiency, urodynamic findings, the need for other concomitant surgery, the patient’s medical condition and lifestyle, and the experience of the surgeon.

### D. Electrical Stimulation

These devices are sometimes used to treat incontinence that has been refractory to other methods. The goals are to stimulate contractions of the pelvic floor muscles and/or inhibit overactive bladder contractions. Noninvasive stimulation electrodes can be placed in either the vagina or anus. Current evidence does not support the efficacy of these methods as being better than behavioral training alone. Electrodes can also be implanted in the sacral nerve roots, the bladder, or the peripheral tibial nerve. These appear to be more effective than noninvasive stimulation, but are reserved for carefully selected patients who have been refractory to less invasive measures.

### E. Pads, Garments, Catheterization, and Pessaries

The use of absorbent pads and undergarments is extremely common among the elderly. Although they are not recommended as primary therapy before other measures have been tried, they may be useful in patients whose incontinence is infrequent and predictable, who cannot tolerate the side effects of medications, or who are not good candidates for surgical therapy. The main purpose of these pads and garments is to contain urine loss and prevent skin breakdown. However, very few studies have compared the numerous absorbent products available and their degree of success or failure in meeting these objectives. A recent Cochrane review concluded that disposable products may be more effective than nondisposable products in decreasing the incidence of skin problems, and that superabsorbent products may perform better than fluff pulp products. More comparative studies are needed in this area to assist patients and caregivers in making better-informed decisions.

Although urethral catheterization should be avoided as a general rule, it is sometimes indicated in cases of overflow incontinence or in patients for whom no other measures have been effective. External collection devices (eg, Texas catheters) are preferable to indwelling catheters, but acceptable external devices are not widely available for women and adverse reactions such as skin abrasion, necrosis, and urinary tract infection may occur. When internal catheterization is needed, intermittent or suprapubic catheterization has been shown to be preferable to indwelling catheterization in reducing the incidence of bacteriuria and its consequent complications. Indwelling urethral catheterization should be limited to very few circumstances, including comfort measures for the terminally ill, prevention of contamination of pressure ulcers, and for patients with inoperable outflow obstruction.

Pessaries are intravaginal devices used to maintain or restore the position of the pelvic organs in patients with genitourinary prolapse. Although there are few comparative data on their use in incontinence, they can sometimes be useful in patients with intractable stress incontinence who are poor candidates for, or who do not desire, surgery.

### F. Primary Care Treatment versus Referral

Once the information from the history, physical examination, voiding record, provocative stress testing, PVR measurement, and laboratory data is available, a presumptive diagnosis can be made in the large majority of patients. If the patient has uncomplicated urge or stress incontinence, referral is indicated by the family physician. If the patient has overflow incontinence, manifested by an elevated PVR, referral is indicated to rule out obstruction prior to attempting medical or behavioral management. In the minority of patients in whom the type or cause of incontinence remains unclear, referral for urodynamic testing is indicated if a specific diagnosis will be helpful in guiding therapy. Urodynamic testing in the routine evaluation of incontinence is not indicated as studies have not shown an improvement in clinical outcome between patients diagnosed by urodynamics and patients treated based on history and physical examination.

Other indications for referral include incontinence associated with recurrent symptomatic urinary tract infections, hematuria without infection, history of prior pelvic surgery or irradiation, marked pelvic prolapse, suspicion of prostate cancer, lack of correlation between symptoms and physical findings, and failure to respond to therapeutic interventions as would be expected from the presumptive diagnosis.


Elder Abuse

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Jeannette E. South-Paul, MD, FAAFP

General Considerations

As hidden as the other forms of family violence may be, domestic elder abuse is even more concealed within our society. Elder abuse was first described in the literature in 1975, when the first reports of “granny battering” appeared. Vastly under-reported, only one in four domestic elder abuse incidents (excluding the incidents of self-neglect) come to the attention of authorities.

The most common reporters of abuse are family members (17%) and social services agency staff (11%). Physicians reported only 1.4% of the cases. Although physicians are mandatory reporters in all states, many physicians feel ill-equipped to address this important social and medical problem. Health care professionals consistently underestimate the prevalence of elder abuse. Concerns for patient safety and retaliation by the caregiver, violation of the physician-patient relationship, patient autonomy, confidentiality, and trust issues are quoted as reasons for low reporting. A recent survey indicates that more than one-third of health care professionals had detected cases of elder abuse in the past year.

Family physicians are particularly well positioned to assist in identifying and managing elder abuse. Family medicine residencies focus on training residents regarding elder abuse more comprehensively than other primary care programs. Except for the primary caregivers, they may be the only ones to see an abused elderly patient. Older victims who suffer from neglect, self-neglect, or physical abuse are likely to seek care from their primary care physician or gain entry into the medical care system through an emergency department.

In the 2000 census, 35 million people in the United States were 65 years of age and older. Adults 85 years and older showed the highest percentage increase of any age group (38%), from 3.1 million to 4.2 million. As the baby boomers age, the number of elders in the United States will continue to increase. The societal cost for the identification and treatment of elder abuse is also projected to rise as the baby boomers enter the elder years.


A. Definition and Types of Abuse

Elder abuse is an all-inclusive term that describes all types of mistreatment and abusive behaviors toward older adults. The mistreatment can be either acts of commission (abuse) or acts of omission (neglect). Labeling a behavior as abusive, neglectful, or exploitative can depend on the frequency, duration, intensity, severity, consequences, and cultural context. Currently, state laws define elder abuse, and definitions vary considerably from one jurisdiction to another. Research definitions also vary, making it difficult to review comparative data.

There are three basic categories of elder abuse: (1) domestic elder abuse, (2) institutional elder abuse, and (3) self-neglect or self-abuse. The National Center on Elder Abuse (NCEA) describes seven different types of elder abuse: physical abuse, sexual abuse, emotional abuse, financial exploitation, neglect, abandonment, and self-neglect (Table 42-1).

According to the 2003 National Research Council Panel to Review Risk and Prevalence of Elder Abuse and Neglect, it is estimated that approximately one to two million elders were victims of various types of domestic elder abuse, excluding abuse due to self-neglect. More than 2%-10% of the nation's elderly may be victims of moderate to severe abuse, but because of underreporting, poor detection, and differing definitions, the true estimate of elder abuse may be far greater. It is estimated that for every one case of elder abuse, neglect, exploitation, or self-neglect reported to authorities, about five more go unreported. Current estimates put the overall reporting of financial exploitation at only 1 in 25 cases, suggesting that there may be at least five million financial abuse victims each year. In a recent survey of almost 6000, there was a 1-year prevalence of 4.6% of emotional abuse, 1.6% of physical abuse, 0.6% of sexual abuse, 5.1% of potential neglect, and 5.2% of financial abuse by a family member.

In reported cases of domestic elder abuse, 77% of the victims were white and 22% were African American. The proportions of Native Americans and Asian Americans/Pacific Islanders were each less than 1%. Neglect—the failure of a designated caregiver to meet the needs of a dependent elderly person—is the most common form of elder maltreatment in domestic settings. In almost 90% of cases the perpetrator of the abuse is known, and in two-thirds of cases the perpetrators are spouses or adult children.

Several explanations have been proposed to explain the origins of elder mistreatment. These explanations have focused on overburdened caregivers, dependent elders, mentally disturbed caregivers, a history of childhood abuse and neglect, and the marginalization of elders in society. Care setting also seems to influence risk of elder abuse. Paid home care has a relatively high rate of verbal abuse and assisted living settings have an unexpectedly high rate of neglect. Moving from paid home care to nursing homes has been shown to more than triple the odds of the elder experiencing neglect. Risk factors commonly cited for elder mistreatment are listed in Table 42-2.

From the Indicators of Abuse (IOA) screen, a profile of the abuser has been developed that can identify abuse cases 78%-85% of the time. The salient features of the profile are detailed in Table 42-3.

A typology of abusers has also been suggested to better delineate who may perpetrate abuse. Five types of offenders have been postulated:

1. Overwhelmed offenders are well intentioned and enter caregiving expecting to provide adequate care; however, when the amount of care expected exceeds their comfort level, they lash out verbally or physically. The maltreatment is usually episodic rather than chronic. This type of offender is often seen in long-term care settings.

2. Impaired offenders are well intentioned, but have problems that render them unqualified to provide adequate care. The caregiver may be of advanced age and frail, have physical or mental illness, or have developmental disabilities. This type of maltreatment is usually chronic.
and the caregiver is unable to recognize the inadequacy of the care. Neglect is frequently observed in these cases.

3. **Narcissistic offenders** are motivated by anticipated personal gain and not the desire to help others. These individuals tend to be socially sophisticated and gain a position of trust over the vulnerable elder. Maltreatment is usually in the form of neglect and financial exploitation and is chronic in nature. These offenders will also use psychological abuse and physical maltreatment to obtain their objective. This type of offender may work in a long-term care facility and become involved in stealing from the residents.

4. **Domineering or bullying offenders** are motivated by power and control and are prone to outbursts of rage, believing their actions are justified by rationalizing that the victim “deserved it.” These offenders know where and when they can get away with abuse. This abuse is chronic, multifaceted, and ongoing with frequent outbursts of temper. Abuse takes the form of physical, psychological, and even forced sexual coercion. The victims are fearful, and the abuser may lash out when confronted or attempt to manipulate those who confront them.

5. **Sadistic offenders** derive feelings of power and importance by humiliating, terrifying, and harming others. They have sociopathic personalities and inflict severe, chronic, and multifaceted abuse. Signs of this type of abuse include bite, burn, and restraint marks and other signs of physical and sexual assault. The victims are fearful and experience terror. If confronted, the abuser may attempt to charm and manipulate or intimidate and threaten the accuser in an attempt to control professionals who are trying to stop the abuse.

Several medical and social factors make the detection of elder abuse more difficult than other forms of family violence. Given the higher prevalence of chronic diseases in older adults, signs and symptoms of mistreatment may be misattributed to chronic disease, leading to “false negatives,” such as fractures that are ascribed to osteoporosis instead of physical assault. Alternatively, sequelae of many chronic diseases may be misattributed to elder mistreatment, creating “false positives,” such as weight loss because of cancer erroneously ascribed to intentional withholding of food. Another significant issue for the physician is denial that the reason for the presentation into the health care system could be attributable to abuse. Physician barriers to reporting elder abuse are listed in Table 42-4.

### A. Screening

The US Preventive Services Task Force (USPSTF) found insufficient evidence to recommend for or against routine screening of older adults or their caregivers for elder abuse.

<table>
<thead>
<tr>
<th>Personal Abusive Caregiver Characteristics</th>
<th>Interpersonal Caregiver Characteristics</th>
<th>Abused Elder Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abuses alcohol or other substance</td>
<td>Has poor relationships generally or with the elder</td>
<td>Was abused in the past</td>
</tr>
<tr>
<td>Is depressed or has a personality disorder</td>
<td>Has current marital or family conflict</td>
<td>Lacks social support</td>
</tr>
<tr>
<td>Has other mental health problems</td>
<td>Lacks empathy and understanding for the elder</td>
<td>Is financially dependent on the elder</td>
</tr>
<tr>
<td>Has behavioral problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiving inexperience or is reluctant to give care</td>
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</tbody>
</table>

**Table 42-3. Profiles of elder abusers.**


### Clinical Findings

#### Table 42-4. Physician barriers to reporting elder abuse.

<table>
<thead>
<tr>
<th>Lack of consistent definitions</th>
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<tbody>
<tr>
<td>Unfamiliarity with mandatory reporting laws</td>
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<tr>
<td>Lack of required training to recognize abuse</td>
</tr>
<tr>
<td>Time constraints</td>
</tr>
<tr>
<td>Concerns with offending patients</td>
</tr>
<tr>
<td>Lack of awareness of available resources</td>
</tr>
<tr>
<td>Subtle presentation</td>
</tr>
<tr>
<td>Reluctance/terror of confronting the abuser</td>
</tr>
<tr>
<td>Abused elder requests abuse not be reported</td>
</tr>
<tr>
<td>Cultural issues</td>
</tr>
<tr>
<td>Isolation of victims</td>
</tr>
<tr>
<td>Fear of jeopardizing relationship with hospital or nursing facility</td>
</tr>
</tbody>
</table>

The American Medical Association recommends that all older patients be asked about family violence even when evidence of such abuse does not appear to exist. A careful history is crucial to determining if suspected abuse or neglect exists. The elderly dependent patient may fear retaliation from the abuser and may be reluctant to come forward with information. The physician should interview the patient and caregiver separately and alone, and if the caregiver does not allow this, abuse potential should be considered. General questions about feeling safe at home and who prepares meals and handles finances can open the door to more specific questions about disagreements with the caregiver and how these disagreements are handled, such as the caregiver yelling, hitting, slapping, kicking, or punching; making the elder wait for meals and medications; or confining the elder to a room. It is also important to inquire about the possibility of sexual abuse (unwanted touching), financial abuse (stolen money, signing legal documents without understanding the consequences), and finally threats of institutionalization. Table 42-5 lists important questions to ask when screening for suspected abuse.

The caregiver interview should avoid confrontation and blame. The physician needs to appear sympathetic and understanding of the abuser’s perceived burden in caregiving. The physician should be alert to a caregiver who has poor knowledge of a patient’s medical problems, has excessive concerns about costs, dominates the medical interview, or is verbally aggressive either to the patient or physician during the interview. A caregiver with substance abuse or mental health problems and one who is financially dependent on the elder should also alert the physician to a greater potential for abuse. Identification of abuse is critical to the health of the elder given the fact that data demonstrate that mortality is increased dramatically once abuse is identified.

Table 42-5. Questions to elicit information about elder abuse.

<table>
<thead>
<tr>
<th>Physical Abuse</th>
<th>Psychological Abuse</th>
<th>Sexual Abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you afraid of anyone at home?</td>
<td>Do you ever feel alone?</td>
<td>Has anyone touched you without permission?</td>
</tr>
<tr>
<td>Have you been struck, slapped, or kicked?</td>
<td>Have you been threatened with punishment, deprivation, or institutionalization?</td>
<td>Neglect</td>
</tr>
<tr>
<td>Have you been tied down or locked in a room?</td>
<td>Have you received “the silent treatment”?</td>
<td>Do you lack aids such as eyeglasses, hearing aids, or false teeth?</td>
</tr>
<tr>
<td></td>
<td>Have you been forced-fed?</td>
<td>Have you been left alone for long periods?</td>
</tr>
<tr>
<td></td>
<td>Do you receive routine news or information?</td>
<td>Is your home safe?</td>
</tr>
<tr>
<td></td>
<td>What happens when you and your caregiver disagree?</td>
<td>Has anyone failed to help you care for yourself when you needed assistance?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Financial Abuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Is money stolen from you or used inappropriately?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Have you been forced to sign a power of attorney, a will, or another document against your wishes?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Have you been forced to make purchases against your wishes?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does your caregiver depend on you for shelter or financial support?</td>
</tr>
</tbody>
</table>


B. Physical Examination

A thorough physical examination is the initial invitation to recognizing and documenting elder abuse. Particular attention to the functional and cognitive status of the elder is important to understanding the degree of dependency that the elder may have on the caregiver. The primary care physician may be confronted with subtle forms of ongoing abuse or mistreatment in which neglect and psychological abuse predominate. Behavioral observations of withdrawal, a caregiver who treats the elder like a child, or a caregiver who insists on giving the history should heighten the clinician’s suspicions. Table 42-6 lists the basic features of the physical examination for assessing suspected elder mistreatment or abuse.

Detailed documentation of the physical examination is important as it may be used as evidence in a criminal trial. Documentation must be complete and legible, with accurate descriptions and annotations on sketches or, when possible, with the use of photo documentation.

▶ Intervention & Reporting

Once elder abuse is suspected, all health care providers and administrators are legally obligated to report the abuse to the appropriate authorities. Most states have anonymous reporting and Good Samaritan laws that can offer an alternative to a direct physician report if there are significant concerns for maintaining the physician-patient relationship. As previously noted, laws differ from state to state, and physicians should become familiar with the specific reporting requirements of their state. By emphasizing the diagnosis and treatment of the health consequences of the mistreatment or the abuse, the elderly patient and caregiver may feel less threatened. Reporting should be done in a caring and compassionate manner in order to protect the autonomy and self-worth of the elder while ensuring his or her continued safety.

The victim should be told that a referral will be made to Adult Protective Services (APS). Involving the caregiver in
the discussion must be carefully considered with regard to potential retaliation on the victim. The law enforcement implications of APS should be downplayed and the social support and services offered by APS should be offered as part of the medical management of the victim. Victims may deny the possibility of abuse or fail to recognize its threat to their personal safety. In the event of financial abuse the victim or the offender, or both, may not acknowledge the abuse. If the victim refuses the APS referral, the clinician may explain that he or she is bound to adhere to state laws and regulations in making the referral and that the regulations were developed to help older persons who were not receiving the care they needed for whatever reason.

The safety of the patient is the most important consideration in any case of suspected abuse. If the abuse is felt to be escalating, as may occur with physical abuse, law enforcement as well as APS should be contacted. Hospitalization of the elder may be the only temporary solution to removing the victim from the abuser.

If elders are competent and not cognitively impaired, their wishes to either accept interventions for suspected abuse or refuse those interventions must be respected. If an abused elder refuses to leave an abusive environment, the primary care physician can help by providing support and whatever interventions the older person will accept. Helping the older victim to develop a safety plan, such as when to call 911, or installing a lifeline emergency alert system may be part of the management plan. Close follow-up should be offered.

If older victims no longer retain decision-making capacity, the courts may need to appoint a guardian or conservator to make decisions about living arrangements, finances, and care. This is typically coordinated through APS. The physician’s role in these cases is to provide documentation not only of the physical findings of abuse but also of impaired decision-making capacity.

Intervention can be complicated when professionals suspect self-neglect or self-abuse. Many people are capable of understanding and accepting the consequences of their actions, but they make decisions with which their families or professionals disagree. Assessments of cognition and decision-making capacity are critical if we are to execute our mandate to assist and protect without treading upon

### Table 42-6. Physical examination and possible signs of abuse or mistreatment.

<table>
<thead>
<tr>
<th>Focus of Examination</th>
<th>Possible Signs of Abuse/Mistreatment</th>
<th>Type of Abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Hygiene, cleanliness of clothing, weight loss, dehydration</td>
<td>Neglect</td>
</tr>
<tr>
<td>Skin and mucous membranes</td>
<td>Skin turgor and signs of dehydration; multiple skin lesions in various stages of healing; bruises, welts, bite marks, burns</td>
<td>Neglect</td>
</tr>
<tr>
<td></td>
<td>Pressure ulcers</td>
<td>Physical</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Traumatic alopecia, scalp hematomas; lacerations or abrasions; poor oral hygiene</td>
<td>Physical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neglect</td>
</tr>
<tr>
<td>Trunk and extremities</td>
<td>Bruises and welts; wrist or ankle lesions suggesting restraint use; immersion burns</td>
<td>Physical</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Occult fractures, pain; observe gait</td>
<td>Physical</td>
</tr>
<tr>
<td>Genitourinary/urinary</td>
<td>Vaginal, rectal bleeding, itching, pain, or bruising; sexually transmitted disease; torn, stained, or bloody underwear</td>
<td>Sexual</td>
</tr>
<tr>
<td></td>
<td>Poor hygiene; inguinal rash, urine burns, fecal impaction</td>
<td>Neglect</td>
</tr>
<tr>
<td>Neurologic and psychiatric status</td>
<td>Thorough cognitive evaluation; look for depression and anxiety; cognitive impairment suggesting delirium or dementia that can affect decision-making capacity</td>
<td>All forms</td>
</tr>
<tr>
<td></td>
<td>Behaviors such as rocking, sucking, antisocial or borderline, or conduct disorders</td>
<td>Psychologic</td>
</tr>
<tr>
<td>Imaging/laboratory</td>
<td>As indicated from clinical examination; albumin, creatinine, blood urea nitrogen, possible toxicology screen</td>
<td></td>
</tr>
<tr>
<td>Social and financial</td>
<td>Inquire about other members of social network and who can assist and about financial resources and who handles finances</td>
<td></td>
</tr>
</tbody>
</table>

civil rights. Further complications may ensue when these individuals refuse assessment. The role of family, clergy, and other community organizations can be difficult because of HIPAA and other confidentiality guidelines. Behavioral health professionals, ethics committees, the guardianship process, and court system are invaluable in assisting families and primary care physicians with these very challenging situations.

As the growth of the elderly population in the United States continues, physicians will need to use vigilance to identify and assist patients at risk for elder abuse. Geroff and Olshaker have provided a framework to help the physician with this potentially overwhelming task. The primary care physician’s role is to recognize or suspect abuse in its various forms, treat the medical problems associated with the abuse, and provide a safe disposition for the patient. The additional evaluations, assessments, and long-term follow-up may be provided by a team of social workers, APS personnel, attorneys, and other members of the traditional health care team. The initial assessment by the primary care or emergency physician may start these crucial interventions.

Movement disorders are a cluster of motor disturbances arising from the dysfunction of basal ganglia and, in some cases, from other parts of the nervous system, for example, brainstem, cortex, spinal cord, cerebellum, and peripheral nervous system. Patients suffering from movement disorders have normal muscle strength and sensation, but their normal voluntary motor activities are influenced or impaired by the involuntary movement, alteration in muscle tone or posture, and loss of coordination or regulation—either facilitation or inhibition—of pyramidal motor activities as a result of malfunction. Movement disorders can be classified into the following categories based on their clinical manifestations: tremor, chorea and choreoathetosis, dystonia, myoclonus, tics, and ataxia. They demonstrate less movement, hypokinesia or akinesia, or excessive movement, hyperkinesia, or both. The goal of this chapter is to provide clinical information regarding the diagnosis, management, and recent findings for the most commonly encountered movement disorders. Nonmotor features of movement disorders are also discussed in an effort to improve comprehensive care and patients’ quality of life.

**PARKINSON’S DISEASE**

**ESSENTIALS OF DIAGNOSIS**

- At least two of the first three cardinal motor features, which are unilateral, and absence of a secondary cause:
  - Bradykinesia.
  - 4-6 Hz rest tremor.
  - Muscular rigidity.
  - Postural instability (late presentation).

**General Considerations**

Parkinson disease (PD) is the second most common progressive neurodegenerative disorder after Alzheimer disease but remains the only neurodegenerative disease for which symptoms can be effectively controlled medically. It affected about 340,000 individuals older than 50 years in the United States, according to the estimate of Dorsey et al (2005). In the United States, the prevalence of PD is estimated at 128 per 100,000 in individuals in their fifties, 550 per 100,000 in those in their sixties or seventies, and 958 per 100,000 in those older than 80 years. The number is expected to grow in the next 25 years, with the projected number being 610,000 in 2030 in the United States (Dorsey et al, 2007). The number of individuals with PD older than 50 years in Western Europe’s five most and the world’s 10 most populous nations was between 4.1 and 4.6 million in 2005 and will double to between 8.7 and 9.3 million by 2030 (Dorsey et al, 2007).

Numerous hypotheses, for example, environmental, genetic, inflammatory process, defects in mitochondrial function or oxidative stress, have been explored to explain the process of the neurodegeneration but without a definitive conclusion. Aging is the biggest risk factor associated with PD. About 95% of PD cases are idiopathic and occur in people older than 50 years. Recent research shows a 1.5-2 times higher incidence in males. Other risk factors include pesticides or herbicides in association with rural living and exposure to well water, and head trauma. The remaining 5% are early onset and occur in familial clusters. An individual may have a doubled risk if there is a family history in a first-degree relative. Five genes, two of which are alpha-synuclein (dominant) and parkin (autosomal recessive), have been located for familial forms of PD.

**Pathogenesis**

PD results from the loss of dopaminergic projections neurons in the substantia nigra (SN). It is a progressive and degenerative process. Patients will become symptomatic when 60%-80% of SN dopaminergic neurons are impaired or dead and there is a 20%-50% dopamine decrease in the striatum. One side of the SN is usually more severely affected than the other,
Classification of movement disorders.

- PD is no longer considered a Hyperkinetic Disorders.

Development.

- Dopaminergic neurons and in decreasing the risk of PD potential role in preventing neuroinflammatory destruction.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) may have a potential role in preventing neuroinflammatory destruction.

- Some potential protective factors have been identified in some studies, such as caffeine and smoking. Smoking, however, is not an option for obvious reasons.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) may have a potential role in preventing neuroinflammatory destruction of dopaminergic neurons and in decreasing the risk of PD development.

Prevention

The insidious onset and wide variety of possible etiologies make PD difficult to identify and to initiate effective preventive care. The role of sex hormones, such as estrogen and testosterone, as well as other hormones, such as growth hormone, in neuroprotection has been under investigation with uncertain clinical value. Based on a study by Haaxma et al, estrogen may play a role in the lower prevalence of PD, delayed and milder symptoms, and slower progression of PD in females. Some potential protective factors have been identified in some studies, such as caffeine and smoking. Smoking, however, is not an option for obvious reasons. Nonsteroidal anti-inflammatory drugs (NSAIDs) may have a potential role in preventing neuroinflammatory destruction of dopaminergic neurons and in decreasing the risk of PD development.

Clinical Findings

A. Symptoms and Signs

The diagnosis of PD is based on its characteristic cardinal motor manifestations not caused by infections or by primary visual, vestibular, cerebellar, proprioceptive, or other neurodegenerative disorders. Excellent and sustained response to dopaminergic treatment supports the diagnosis. The most common initial finding is an asymmetric resting tremor in an upper extremity. The cardinal signs may eventually become bilateral after several years but will remain more prominent on one side of the body. Early referral to PD specialists is crucial when a patient has atypical or secondary parkinsonism.

1. Cardinal motor signs—Resting tremors are the presenting symptoms in 50%-70% of patients, with hands, fingers, forearms, and feet most frequently affected. The tremors are a characteristic oscillating or pill-rolling movement of one hand at a regular rhythm (4-6 Hz). They diminish during sleep and voluntary movement. Other parts of the body such as the jaw or face may also be affected. Bradykinesia refers to slow movement or initiation of movement or the sudden stopping of movement. Patients may make short, shuffling steps with decreased arm swing or have an expressionless mask-like face, freezing gait, or difficulty turning in bed. They cannot make a rapid repetitive movement, such as tapping the fingers or heels repeatedly. Rigidity or increased muscle tone in the affected limb manifests as a “lead pipe” with continuous resistance or “cogwheel type” movement with passive flexion or extension of the elbow. Patients with PD may experience impaired balance and postural reflexes with standing, known as postural instability, which will increase the risk of falls. Other clinical presentations include hypophonia, difficulty swallowing, muscle spasm, and micrographia.

2. Nonmotor symptoms—PD is no longer considered a pure motor disorder. The nonmotor symptoms may begin unnoticeably long before the motor signs start. When treating the cardinal motor symptoms, we need to be attentive to the nonmotor symptoms affecting patients’ emotional, cognitive, behavioral, and general health. Clinical evidence shows that nonmotor symptoms may precede motor signs by 4-20 years. Recognizing these premotor symptoms may aid in early diagnosis of PD so preventive measures and treatment can be started early to achieve more favorable results. The major nonmotor/premotor features are listed in Table 43-2. The significance of these nonmotor features in early diagnosis of PD requires further investigation.

Some research has shown that olfactory impairment precedes motor features of PD and may be used to identify people either at risk for developing PD or in a presymptomatic stage of PD. Depression is commonly seen in PD patients. According to some studies, depression may precede PD by decades; patients who have depression also are at higher risk of developing PD.
3. Cognitive and psychiatric symptoms—Psychosis happens late (10 years after the diagnosis) in the disease process. These symptoms are often the side effects of antiparkinsonian medications. Both dopaminergic and dopamine receptor agonists (higher risks) can cause psychosis, which is independent of dosage and treatment duration. Other underlying disease processes, for example, normal-pressure hydrocephalus (NPH) and vascular or other causes of parkinsonism. Positron emission tomography (PET) or single photon emission computed tomography (SPECT), functional MRI, and other MRI modalities may have a role in early detection of preclinical PD and in monitoring disease progression. SPECT is useful in differentiating PD from essential tremors when they appear asymmetrically and at rest. Transcranial sonography (TCS) can differentiate PD from progressive supranuclear palsy (PSP) and multisystem atrophy (MSA) by detecting hyperechogenicity of the substantia nigra.

### Differential Diagnosis

It is important to differentiate PD from other parkinsonian syndromes (see Table 43-1) in order to effect a favorable response to antiparkinsonian treatment. An imaging study of the brain is usually required to rule out other parkinsonian syndromes if a patient has an atypical presentation, such as being unresponsive to levodopa, early falls in the disease course, symmetric signs without tremor, rapid disease process, and early dysautonomia. Patients with secondary parkinsonism may have a positive medication or medical history. Parkinson-plus syndromes underlying neurodegenerative conditions are relatively uncommon and have characteristic clinical presentations and different neurologic imaging findings. PSP is the most common Parkinson-plus syndrome. It is characterized by a downgaze palsy, minimal tremor, and severe postural instability with frequent falls starting during the first year of the disease process. Corticobasal ganglionic degeneration (CBGD) demonstrates asymmetric symptoms but also severe limb apraxia and dystonia. The detailed clinical presentation of Parkinson-plus syndromes is not discussed in this chapter.

### Complications

Both motor and nonmotor clinical features of PD cause progressive disability that interferes with daily activities in all age groups and at all stages of the illness. Examples include falls and injuries, weight loss, malnutrition and risk of aspiration, cognitive deterioration and depression, speech, worsening of vision, and loss of smell. The risk of osteoporosis may double in PD. Table 43-2 lists common clinical complications.

Motor complications, dyskinesias, and motor fluctuations usually start 4-6 years after initiation of treatment. They are thought to be induced by pulsatile plasma levodopa levels. Dyskinesias are involuntary movements that can present as choreiform movements, dystonia, and myoclonus. Patients with motor fluctuations may experience a sudden loss of levodopa effects and switch from an “on” symptom-controlled period to an “off” symptomatic period, an end-dose “wearing-off” effect, and “freezing” during “on” periods.

### Treatment

Treatment of PD is aimed at cardinal symptom control, disease process modification, nonmotor manifestation treatment,
and management of motor and nonmotor complications in late stages of PD. Although no treatment has been shown conclusively to slow progression of the disease, several pharmacologic and surgical therapies are available to control patients’ symptoms.

The goals of treatment vary, depending on the disease stage. In early PD, treatment goals are to modify the disease process, to delay the onset of and control motor symptoms, and to maintain patients’ independent functions; in more advanced PD, the goals are to maximize medication effectiveness, to manage motor complications from levodopa, and to control complications due to PD progression. Nonmotor symptom treatment should be started early and monitored throughout the disease process.

A. Pharmacotherapy

When to start PD therapy is a collaborative decision relying on effective communication among physician, patient, and family. A variety of factors will be considered, such as the degree of impairment and its effect on the patient’s daily life and employment, the patient’s understanding of PD, and the patient’s attitude toward medications. The traditional wait and watch approach, to start treatment when the patient begins to experience functional impairment, has been challenged. Recent research shows the beneficial effects of starting neuroprotective treatment as soon as the diagnosis has been made. This approach may protect dopaminergic neurons and slow disease progression.

1. Motor symptom therapy—Levodopa is the most effective medication for PD symptom control and has a more favorable safety profile compared with other regimens, especially in older patients. However, the motor complications appearing several years after initiation of levodopa can compromise its effects and limit its long-term use. Strategies to extend levodopa treatment and minimize motor complications have been explored, such as continuous administration of intravenous levodopa or administration via duodenal infusion (effective but not clinically applicable). Sustained-release levodopa has not been shown to decrease motor complications. Adding a catechol-O-methyltransferase (COMT) inhibitor to levodopa reduces “off” periods by limiting dopamine metabolism and prolonging levodopa half-life. Dopamine agonists can be used as the first-line PD treatment preferably in patients younger than 65 years, who can better tolerate their psychiatric side effects. Together with levodopa, they increase dopamine levels in the brain and reduce motor fluctuation. Compared with bromocriptine, a dopamine agonist, levodopa has a demonstrated advantage in motor function, better cognitive function and less dementia, and overall quality of life. Both drugs have similar mortality rates and effects on motor fluctuation. Many patients have benefited from the irreversible monoamine oxidase (MAO)-B inhibitors selegiline and rasagiline. In some laboratory experiments, they have shown potential cognitive enhancement and neuroprotective features. The extended MAO-B blockade from selegiline may make daily dosing of selegiline unnecessary for motor symptom control. MAO-B inhibitors, alone or together with a dopamine agonist, are preferred by some physicians to initiate PD treatment, but they have demonstrated conflicting effectiveness on motor fluctuation. The fear of motor complications may delay the use of levodopa and result in under-treatment of PD. Table 43-3 lists the common antiparkinsonian medications.

Pergolide was withdrawn from the market in 2007 owing to its potential serious side effect of heart valve damage. The rotigotine patch was recalled in the United States in April 2008 secondary to the formation of rotigotine crystals, which decrease the delivery and thus the efficacy of the medication.

2. Neuroprotective/disease-modifying therapy—Neuroprotective treatment should be the final goal of PD treatment. Ideally, it should be started as soon as the diagnosis of PD has been made or even before that when some nonmotor or premotor symptoms are identified. The MAO-B inhibitors selegiline and rasagiline, levodopa, and coenzyme Q10 may possess neuroprotective properties, but more evidence is needed. Antioxidant (vitamin E) has not shown protective effects. How to identify at-risk patients and diagnose PD early to start preventive or protective treatment also need to be addressed.

3. Nonmotor symptom therapy—Medications and other management methods are chosen based on each specific symptom or problem, such as SSRI antidepressants for depression and baclofen for pain and spasm control.

For patients with cognitive impairment, antiparkinsonian medications such as anticholinergics, dopamine agonists, amantadine, and selegiline may need to be decreased or discontinued. Cholinesterase inhibitors may be considered for dementia and fludrocortisone or midodrine for orthostatic hypotension. To adjust levodopa dosage, discontinue nighttime use of antiparkinsonian drugs, or discontinue dopamine agonists for sleep disturbance. Clonazepam may be started. Methylphenidate may help improve gait and decrease the risk of falls.

The first step in controlling psychosis is to decrease the dosage of antiparkinsonian medication or gradually remove some medications in the order of anticholinergics, selegiline, amantadine, dopamine receptor agonists, COMT, and lastly levodopa (switch to short acting). Antipsychotic agents are considered if the patient still has symptoms. The atypical antipsychotic agents clozapine and quetiapine have fewer extrapyramidal and prolactin-elevating adverse effects. Other second-generation antipsychotic medications, such as ziprasidone, risperidone, and olanzapine, and the third-generation antipsychotic aripiprazole are not recommended because they may not be as effective or have worse extrapyramidal adverse effects. Cholinesterase inhibitors (except rivastigmine), for example, donepezil, galantamine, and tacrine, have shown inconsistent results and may worsen PD or have other side effects. Electroconvulsive therapy (ECT) should be used as the last resort for psychiatric disorders or depression when
medications are not effective. By stimulating the D₂ dopamine receptors in the mesolimbic pathways, ropinirole has been shown to control motor symptoms and mood fluctuation including depression and anxiety in patients with motor fluctuations.

B. Surgical Intervention

Surgery is an effective treatment option in more advanced PD. Subthalamic nucleus (STN) deep brain stimulation (DBS) is effective in improving motor function and alleviating motor complications. Potential neurorestoration with dopaminergic or stem cell replacement may also bring hope in controlling dopamine deficiency-related disabilities. Other options such as thalamotomy and pallidotomy are effective in controlling motor complications but can cause destructive lesions.

C. Ancillary Treatment and Supportive Measures

Psychological counseling and therapy, such as cognitive-behavioral therapy, supportive therapy, and coping skill development may help patients with psychiatric manifestations.

Supportive treatment is important in terms of maintaining function and general health. It includes allied health

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Table 43-3. Pharmacotherapy for Parkinson disease.

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>Usual Daily Dosage</th>
<th>Clinical Use and Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopaminergic drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precursor amino acid:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levodopa</td>
<td>10/100, 25/100, 25/250, 200/2000 mg/d three times a day</td>
<td>Nausea, dyskinesia, motor fluctuations, somnolence, compulsive behaviors, psychosis, hypotension, peripheral edema, melanoma, weight loss. Increase by one tablet every day or every other day to a maximum of eight tablets per day. Increase by one tablet every 3 days to a maximum of eight tablets per day.</td>
</tr>
<tr>
<td>Carbidopa/levodopa (Sinemet)</td>
<td>25/100, 50/200, 200-1400 mg/d two times a day</td>
<td></td>
</tr>
<tr>
<td>Controlled release (Sinemet CR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbidopa/levodopa/entacapone (Stalevo)</td>
<td>12.5/50/200 mg twice daily</td>
<td>Used when other medications become less effective. Increase slowly to a maximum of eight tablets per day.</td>
</tr>
<tr>
<td><strong>Dopamine agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Initially, 1.25 mg twice daily 100 mg/d maximum</td>
<td>Somnolence, hallucinations, orthostatic hypotension, edema, vomiting, dizziness, sleepiness (caution with driving), confusion. Higher risk in older patients. Adjust every 2-4 wk.</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>0.125 mg three times daily</td>
<td></td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Initially, 0.25 mg three times daily or once daily</td>
<td></td>
</tr>
<tr>
<td>Apomorphine</td>
<td>2-6 mg/d SC approved in the United States</td>
<td>For rescue therapy for “off” episodes. Nausea (requires trimethobenzamide initially), hypotension.</td>
</tr>
<tr>
<td><strong>Monamine oxidase B (MAO-B) inhibitor</strong></td>
<td>1.25-2.5 mg daily 0.5-1 mg/d</td>
<td>Sleep disturbance, lightheadedness, nausea, abdominal pain, confusion, hallucinations. Avoid tyramine-containing food (cause uncontrolled hypertension); be aware of drug interactions. No dose titration required. Possible neuroprotective.</td>
</tr>
<tr>
<td>Selegiline</td>
<td></td>
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<tr>
<td>Rasagiline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-methyl-D-aspartate (NMDA) receptor inhibitor</td>
<td>100-300 mg/d</td>
<td>Hallucinations, dry mouth, livedo reticularis, ankle swelling, myoclonic encephalopathy in setting of renal failure. Avoid in cognitive impairment.</td>
</tr>
<tr>
<td>Amantadine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Catechol-O-methyl transferase inhibitor (COMT)</strong></td>
<td>100 or 200 mg three times a day 200 mg, 2-8 times per day with each dose of carbidopa/levodopa</td>
<td>Effective only with levodopa. Worsening of levodopa-induced dyskinesias (improve with decreasing levodopa dosage); diarrhea, nausea, vivid dreams, visual hallucinations, sleep disturbances, daytime drowsiness, headache, hepatotoxicity. No hepatotoxicity.</td>
</tr>
<tr>
<td>Tolcapone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entacapone</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>2-15 mg/d</td>
<td>Confusion, sleepiness, blurred vision, constipation. May worsen motor symptoms on discontinuation; tapering needed.</td>
</tr>
<tr>
<td>Biperidine</td>
<td>1-8 mg/d</td>
<td></td>
</tr>
</tbody>
</table>
interventions; occupational therapy; physical therapy; and speech, swallowing, and voice therapy. Support for family and caregivers is also crucial. Information regarding PD and other resources should be provided to caregivers. Patients and their families can be referred to various support groups, including the American Parkinson Disease Association (http://www.apdaparkinson.com), the National Parkinson Foundation (http://www.parkinson.org), and the Michael J. Fox Foundation for Parkinson Research (http://www.michaeljfox.com). Other Web sites providing PD information include the Worldwide Education and Awareness for Movement Disorder (http://www.wemove.org/) and the Movement Disorder Society (http://www.movementdisorders.org/).

**TREMOR**

Tremor is a rhythmic oscillation of one part of the body from regular contractions of reciprocally innervated antagonistic muscles. It is the most common movement disorder. Tremor can occur at rest, when body parts are held in a fixed posture (postural), or during certain actions (intentional). Table 43-4 lists different types of tremor due to different physiologic or pathologic etiologies.

### ESSENTIAL TREMOR

**ESSENTIALS OF DIAGNOSIS**

**Core Criteria:**
- Postural or kinetic tremor of the hands and forearms or at least one arm.
- Head tremor with no signs of dystonia.
- Absence of other etiologic factors and neurologic signs: medications, alcohol, parkinsonism, dystonia, hyperthyroidism.

**Additional diagnostic criteria (not consistently applied):**
- Bilateral.
- Duration (>1 year to longstanding).
- Severity (interferes with activities of daily living, handwriting, vocalization).
- Positive family history.
- Beneficial effect of alcohol.

**General Considerations**

Essential tremor (ET) is the most common movement disorder. It starts at a mean age of 45 years and affects about 4% of those older than 40 years, and the prevalence increases with aging. The prevalence of ET varies widely among studies because of different criteria used in making the diagnosis. It affects both males and females. ET is a chronic and slowly progressive disorder with both upper extremities most commonly affected. It is postural and kinetic in nature and can be disabling and affect the quality of life. Family aggregation is noted in more than half of the patients and seems to follow an autosomal dominant pattern of inheritance. Linkage of genes on chromosomes 3q13 (ETM1) and 2p24.1 (ETM2) to ET and their clinical significance need to be further investigated. Environmental factors such as β-carboline alkaloids—harmine and harmamine, may also play a role in the development of ET.

**Clinical Findings**

**A. Symptoms and Signs**

ET is diagnosed based on its clinical features collected through a detailed medical history regarding tremor, family...
history, social history (alcohol, caffeine, and drug use), and medications (eg, β-agonists, corticosteroids, valproic acid, amphetamines, thyroid hormones, lithium, neuroleptic agents, tricyclic antidepressants), as well as a thorough physical examination. The tremor typically starts from either hands or forearms (about 95%) or less commonly from one hand (usually dominant) in 10%-15% of cases with upper extremity involvement as the initial presentation. The tremor can be postural, occurring with outstretched arms, or kinetic, occurring during action such as finger-to-nose movement, pouring and drinking water from a cup, writing, or drawing Archimedean spirals. With more advanced age, the tremor will be slower but have bigger amplitude, which can be more disabling. Other parts of the body can be affected in isolation or concomitantly with hand tremor, such as head (34%), legs (30%), voice (12%), chin, tongue, or trunk. The patient may present with head shaking (no-no) or nodding (yes-yes), a shaky or trembling voice, or an unsteady gait (eg, tandem gait disturbance). Many tremor scales are available for assessing severity, for example, the tremor rating scale from the Washington Heights–Inwood Genetic Study of Essential Tremor (score 0-5) and the Fahn-Tolosa-Marin tremor rating scale (score 0-40). In Table 43-5, the classic phenomena of essential tremor are described and contrasted with features of tremor resulting from other physiologic and pathologic causes.

**B. Laboratory and Other Tests**

Routine laboratory tests such as thyroid function; liver function; electrolytes including calcium, magnesium, and phosphorous; and blood glucose level may be ordered.

<table>
<thead>
<tr>
<th>Category</th>
<th>Tremor Characteristics</th>
<th>Medical Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action tremor</td>
<td>Occurs when a body part (limb) is maintaining a posture against the force of gravity (4-12 Hz)*</td>
<td>(Enhanced) physiologic tremor (most common tremor)</td>
</tr>
<tr>
<td>Postural tremor</td>
<td>Occurs with voluntary but non-target-directed movement of extremities (eg, pronation-supination or flexion-extension wrist movement) (3-10 Hz)</td>
<td>Essential tremor (second most common)</td>
</tr>
<tr>
<td>Kinetic:</td>
<td></td>
<td>Orthostatic tremor</td>
</tr>
<tr>
<td>Simple kinetic tremor</td>
<td>Occurs with voluntary but non-target-directed movement of extremities (eg, pronation-supination or flexion-extension wrist movement) (3-10 Hz)</td>
<td>Writing tremor</td>
</tr>
<tr>
<td>Intentional tremor</td>
<td>Occurs with target-directed movement (finger-to-nose) (&lt;5 Hz)</td>
<td>Musician's tremor</td>
</tr>
<tr>
<td>Task-specific intention tremor</td>
<td>Involves task-specific, skilled, highly learned motor acts (eg, writing, sewing, playing musical instruments) (5-7 Hz)</td>
<td>Primary writing tremor</td>
</tr>
<tr>
<td>Isometric tremor</td>
<td>Occurs with muscle contraction against a stationary object (eg, squeezing examiner's fingers) (4-6 Hz)</td>
<td>Musician's tremor</td>
</tr>
<tr>
<td>Resting tremor</td>
<td>Frequency: low to medium (3-6 Hz)</td>
<td>Parkinsonism (third most common)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td>Rubral (midbrain) tremor</td>
</tr>
</tbody>
</table>

*Hz, the number of tremor cycles per second.
Other lab tests or imaging studies should be ordered based on each clinical scenario. In patients with tremor started before age 40 years, blood and urine should be checked to rule out Wilson disease. Physiologic studies such as electromyography and accelerometry are available in specialized labs. They are not part of the routine evaluation but can assist with atypical tremor diagnosis and measure tremor severity and its influence on patients by assessing frequency, rhythmicity, and amplitude of the tremor.

### Nonmotor Complications

ET is not as benign as once thought. It can cause substantial physical, cognitive, and psychosocial disability. Patients may lose or have to quit their jobs owing to the uncontrollable tremor and memory and other cognitive impairments.

Activities of daily living, as simple as drinking and eating, are significantly affected. The impact of ET on the patient's physical, psychologic, and social health status needs to be assessed from the patient's point of view. The health-related quality of life (QoL) evaluation for ADL abilities is also essential to management.

Nonmotor, cognitive-neuropsychological presentations of ET also contribute to the health status and may influence functional disability. Depression, anxiety, low vigor, mild executive dysfunction, possible mild cognitive impairment, and personality changes are some of the nonmotor manifestations of ET. Patients with late onset are more likely to have dementia. A disease-specific questionnaire, for example, the Quality of Life in Essential Tremor Questionnaire, will assist in a comprehensive evaluation of ET to improve management and QoL.

---

**Table 43-5. Clinical and differential diagnosis of tremors.**

<table>
<thead>
<tr>
<th>Tremor</th>
<th>Clinical Features</th>
<th>Diagnostic Tests and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential tremor</td>
<td>An 8-12-Hz tremor is seen in young adults and a 6-8-Hz tremor in elderly people. There are negative neurologic signs with normal muscle tone and coordination, worsening with stress, fatigue, and voluntary movement. Improves with alcohol ingestion.</td>
<td>Only for differential diagnosis or atypical presentations.</td>
</tr>
<tr>
<td>Enhanced physiologic tremor</td>
<td>High frequency 10-12 Hz, lower amplitude. Involves hands; occurs under various conditions, eg, stress, fatigue, hypoglycemia, thyroid and adrenal gland disorders, alcohol withdrawal, and medication use. No other neurologic signs. Responsive to offending medication or toxin reduction or removal, treatment of endocrine disorders, and stress management.</td>
<td>Chemistry profile (glucose, liver function tests); thyroid function tests; review of medications. Propranolol prior to stressful events may help.</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Late age onset; asymmetric; slow (4-6 Hz), high amplitude, rest tremor bimanual; pill-rolling; possible action tremor; worse under stress, better with voluntary movement; unaffected by alcohol; onset in hands or legs; additional parkinsonian symptoms.</td>
<td>See text.</td>
</tr>
<tr>
<td>Cerebellar tremor</td>
<td>Intentional tremor on the ipsilateral side of the body; 3-4 Hz; positive ataxia; dysmetria; nystagmus; other cerebellar signs.</td>
<td>Appropriate imaging and other tests.</td>
</tr>
<tr>
<td>Orthostatic tremor</td>
<td>Occurs exclusively while standing (13-18 Hz); late onset; rare family history; tremor limited to legs and paraspinal muscles.</td>
<td>Response to gabapentin, pramipexole, and clonazepam.</td>
</tr>
<tr>
<td>Neuropathic tremor</td>
<td>Associated with peripheral nerve pathology, eg, hereditary neuropathies, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy. Not responsive to propranolol or other therapy.</td>
<td></td>
</tr>
<tr>
<td>Psychogenic tremor</td>
<td>Variable tremor; intermittent; somatization in past history. Tremor changes with voluntary movement of contralateral limb.</td>
<td>Electrophysiologic testing.</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Postural or intentional, wing-beating tremor (4-6 Hz); ascites, jaundice, signs of hepatic disease; intracorneal ring-shaped pigmentation; rigidity, muscle spasms; mental symptoms.</td>
<td>Liver function tests; serum ceruloplasmin; urine copper; slit-lamp examination for Kayser-Fleischer rings.</td>
</tr>
<tr>
<td>Task-specific intention tremors</td>
<td>Involves skilled, highly learned motor acts, eg, writing, sewing, playing musical instrument (5-7 Hz).</td>
<td>Treatment: Botulinum toxin injection; surgery effective; oral medicine less effective.</td>
</tr>
</tbody>
</table>
Treatment

The goal of ET treatment is to decrease functional disability and improve patient’s health status and QoL. Treatment may be initiated when symptoms are present. Both pharmacologic and surgical approaches are available. The response to medical treatment varies; some patients may not benefit from any medications or have only a partial response. Propranolol and primidone are the mostly commonly used medications for ET, either alone or in combination (Table 43-6). Ethanol reduces tremor in two-thirds of cases with prompt improvement within 15 minutes. But it may cause rebound worsening of tremor, and the risk of alcohol abuse remains controversial. In recent studies, the anticonvulsants zonisamide and levetiracetam have demonstrated promising treatment effects, but further investigations are needed. In medically refractory cases, deep brain stimulation (DBS) of the thalamus and unilateral thalamotomy (level B) have shown moderate to marked improvement of tremor in most patients. DBS has fewer adverse events than thalamotomy and the flexibility for adjustment but is more expensive.

Physical or occupational therapy with light-weight training of wrists may help improve hand stability and function.

Prognosis

ET is a slowly progressive disorder with a potential 7% increase in tremor amplitude each year. More than two-thirds of patients report significant changes in their daily living and socializing, and about 15% are seriously disabled. Mortality increased, more notably in men, in a recent longitudinal, prospective study. Complications, such as falls and pneumonia, owing to difficulty ambulating, and other functional disabilities may have contributed to the increased mortality.

Table 43-6. Pharmacotherapy for essential tremor.

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>Usual Daily Dosage</th>
<th>Clinical Use and Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Adrenergic blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>Start: 10 mg/d</td>
<td>50% improvement</td>
</tr>
<tr>
<td></td>
<td>Optimal: 160-320 mg/d (divided tid)</td>
<td>Well tolerated; titrate every 3-7 d</td>
</tr>
<tr>
<td></td>
<td>Long-acting: 80-320 mg/d</td>
<td>Fatigue, bradycardia, mild-to-moderate reduced heart rate, exertional dyspnea, depression</td>
</tr>
<tr>
<td>Atenolol</td>
<td>50-150 mg/d</td>
<td>25%-37% improvement</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GABA receptor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td>50-1000 mg/d (divided tid)</td>
<td>50% improvement</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Start: 300 mg/d</td>
<td>Tolerance may develop</td>
</tr>
<tr>
<td></td>
<td>1200-3600 mg/d</td>
<td>Sedation, fatigue, unsteadiness, vomiting, acute toxic reaction, ataxia, vertigo</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Start: 25 mg/d</td>
<td>33%-77% improvement</td>
</tr>
<tr>
<td></td>
<td>200-400 mg/d</td>
<td>Drowsiness, nausea, dizziness, unsteadiness</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GABA receptor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.75-2.75 mg/d</td>
<td>Sedation and cognitive slowing; potential for abuse</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>1-3 mg/d</td>
<td>25%-35% improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be as effective as propranolol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Efficacy varies; 26%-71% improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withdrawal following abrupt discontinuance</td>
</tr>
<tr>
<td><strong>Botulinum toxin injection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For hand tremor</td>
<td>50-100 units per arm</td>
<td>Produces focal weakness; reduces tremor effectively but may not improve function; postinjection pain</td>
</tr>
<tr>
<td>For head tremor</td>
<td>40-400 units</td>
<td>20%-27% improvement</td>
</tr>
<tr>
<td>For voice tremor</td>
<td>0.6-15 units (uni- or bilateral)</td>
<td>Significant clinical improvement but no statistical significance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22%-30% improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difficulty swallowing</td>
</tr>
</tbody>
</table>
Tic Disorders

Tics are sudden, brief (0.5-1 second), repetitive, nonrhythmic, stereotyped, and purposeless movements (motor tics) or vocalizations (vocal tics). Tics can be either simple, such as blinking, grimacing, head jerking, shoulder shrugging, and throat clearing or other meaningless utterances/noises, or more coordinated and purposeful complex features, such as jumping, kicking, abdomen thrusting, stuttering, echolalia (copying others’ words), echopraxia (imitating others’ gestures), and coprolalia (speaking obscenities). An antecedent sense of inner tension or sensation of burning, tingling, itching, or pain may precede many tics, leading to the irresistible but partly controllable “urges” to tic. Patients are able to transiently suppress the urges and subsequently the tics, but the urges will escalate until they are “relieved” by tics. They may improve when the patient is focused, distracted, or relaxed (eg, playing video games) and exaggerate when the patient is stressed, tired, or worried (about the tics). Tics typically start early at 3-5 years of age and peak around 9-12 years; the severity improves at the end of adolescence. Simple and transient tics are common in children, with 6%-20% affected. Tourette syndrome, one of the most common tics, is discussed below.

Tourette Syndrome

**Essentials of Diagnosis**

- Multiple motor tics and one or more vocal tics are present (not necessarily concurrent).
- The tics occur many times a day nearly every day or intermittently over more than 1 year without a tic-free period of more than 3 consecutive months.
- Disease onset before age 18 years.
- Other causes of tics ruled out (eg, stimulants, Huntington disease, CNS infection, stroke).

**General Considerations**

Tourette syndrome (TS) is a serious, chronic neuropsychiatric disorder. It affects 4-6 per 1000 children and males four to five times more than females. Both genetic and environmental factors (eg, stress, postinfection autoimmune disease, intrauterine exposure) play a role in the development of TS.

**Clinical Findings**

**A. Symptoms and Signs**

Tics are the only positive findings on neurologic examination in TS. They usually start in the upper body, especially the eyes or other parts of the face in the form of simple motor or vocal tics. As TS gradually progresses, the tics can involve other parts of the body such as extremities and torso, they will become complex in nature, and vary in type and combination, severity, and location. The phenotype of TS involves not only tics but also behavioral components and commonly associated comorbidities (Table 43-7). Frustrated or embarrassed by the involuntary and sometimes disabling tics, together with the misconception of family and others that tics can be controlled, patients may develop anxiety, depression, or even social withdrawal, which impair academic and social performance. Comorbid conditions include obsessions such as repeatedly counting, hand washing, or touching, and the need to scratch out a word. Comorbid ADHD may result in relationship problems at school or home. A comprehensive physiopsychosocial evaluation is necessary for children with tics. It should include a detailed history of the tics as well as the impact of TS on the patient’s school performance, daily life, and social interactions. Coping strategies for the patient, family, and teachers need to be explored.

**Table 43-7.** Tourette syndrome phenotype and comorbidities.

<table>
<thead>
<tr>
<th>Tic Component</th>
<th>Simple or Complex Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Socially inappropriate behaviors</td>
<td>Coprophenomena (coprolalia, mental coprolalia, copropraxia)</td>
</tr>
<tr>
<td>Echophenomena (echolalia, echopraxia)</td>
<td></td>
</tr>
<tr>
<td>Paliphenomena (palilalia, palipraxia)</td>
<td></td>
</tr>
<tr>
<td>spitting, hitting and kicking, self-injury</td>
<td></td>
</tr>
<tr>
<td>Compulsive behaviors</td>
<td>Forced touching, repetitive looking at objects, other ritualized behaviors</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>ADHD (60%)^a</td>
</tr>
<tr>
<td>OCD (50%^a)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
</tr>
<tr>
<td>Learning disability (20%^a)</td>
<td></td>
</tr>
<tr>
<td>Problems with executive planning, organization, and social problem solving</td>
<td></td>
</tr>
</tbody>
</table>

ADHD, attention deficit hyperactivity behaviour; OCD, obsessive-compulsive disorder.

^aPercentage of the comorbidity in patients diagnosed with TS.
B. Laboratory and Other Test Findings

TS is a clinical diagnosis based on a thorough personal and family history, physical examination, and close observation of the disease process. Laboratory tests and brain imaging studies (CT, MRI, or PET) may be considered to rule out infections or other neurologic conditions that can either cause tics or mimic tics. Psychological testing may be employed when learning disability is suspected. A QoL questionnaire will help define the influence of TS on the patient’s life.

Differential Diagnosis

Other medical conditions that may cause tics or be misdiagnosed as tics need to be ruled out before starting treatment. Tics may be mistaken for other hyperkinetic movement disorders such as chorea, myoclonus, dystonia, tardive dyskinesia, seizure, periodic limb movements of sleep, and restless legs syndrome. Tics can also be caused by other medical conditions such as stroke, infections, dystonia, essential tremor, and dementia.

Treatment

The goal of TS treatment is to control disabling symptoms and comorbidities, improve academic, occupational, or social performance and quality of life, and to support patient and family. It is important to prioritize treatment to the most bothersome symptoms and to achieve symptom control to the level at which the patient can function. Patients and families need to realize that complete resolution of symptoms is difficult to achieve. TS with mild symptoms that do not interfere with the patient’s daily functioning can be followed clinically without medical treatment.

A. Medical Treatment (Table 43-8)

\(\alpha_2\)-Agonists may help reduce tics by around 30% and can improve comorbid ADHD symptoms. They are preferred to antipsychotics because they do not cause tardive dyskinesia or weight gain. Neuroleptics (haloperidol, pimozide, fluphenazine, and risperidone) are usually reserved for moderate to severe TS that did not respond to other forms of treatment, and can reduce the severity of tics by 25%-50%. They should be started at a low dose and titrated slowly because of possible severe side effects. Acute dystonic reactions may occur with initiation of these agents. Anticholinergics can be added to decrease their risk. Tardive dyskinesia may develop during neuroleptic treatment and is not always reversible after treatment is discontinued. Many agents have been under investigation, such as metoclopramide and

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>Usual Daily Dosage</th>
<th>Clinical Use and Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha_2)-Agonists</td>
<td></td>
<td>First-line agents</td>
</tr>
<tr>
<td>Clonidine (oral, transdermal)</td>
<td>0.05 mg at bedtime, increased by 0.05 mg every few days to a maximum of 0.2 mg three times daily</td>
<td>Initial treatment of TS Sedation, orthostatic hypotension and constipation Withdrawal: taper over 7-10 d</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>0.5 mg at bedtime; maximum 1 mg three times daily</td>
<td>Fewer side effects; well tolerated</td>
</tr>
<tr>
<td>Antipsychotics (dopamine receptor blockers)</td>
<td></td>
<td>Second-line agents; may be added to (\alpha_2)-agonist or monotherapy First-line agents: for patients with severe tics Acute dystonic reaction</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.25 mg at bedtime; maximum 2 mg twice daily</td>
<td>Sedation and weight gain Less risk of tardive dyskinesia</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1.25 mg at bedtime; maximum 5 mg twice daily</td>
<td>Similar to risperidone</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.25-2 mg/d</td>
<td>Used when atypical antipsychotics listed above are ineffective Tardive dyskinesia</td>
</tr>
<tr>
<td>Pimozide</td>
<td>0.5 mg at bedtime; maximum 3 mg twice daily</td>
<td>Prolonged QTc interval, ventricular arrhythmia</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>0.5 mg at bedtime; maximum 3 mg three times daily</td>
<td>Safer than haloperidol; more controlled studies needed</td>
</tr>
<tr>
<td>Other drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baclofen</td>
<td>5 mg daily; maximum 20 mg three times daily</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>25 mg at bedtime; maximum 200 mg daily</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.25 mg at bedtime; maximum 1 mg three times daily</td>
<td></td>
</tr>
</tbody>
</table>

Table 43-8. Pharmacotherapy for Tourette syndrome.
pergolide, and have shown promising effects. Stimulants or SSRIs may be started for attention-deficit hyperactivity behaviour (ADHD), obsessive compulsive disorder (OCD), and other comorbidities.

B. Behavioral Therapy and Counseling

Awareness training, assertiveness training, cognitive therapy, relaxation therapy, and habit reversal therapy are widely used to improve patients’ social functioning and the undesirable behaviors associated with tics. Education should be provided to the family and at school to create a supportive and understanding environment and decrease misconceptions and intolerance.

C. Other Therapies

Botulinum toxin injection and deep brain stimulation are available for medically refractory tics.

Prognosis

Tics typically wax and wane and peak during the second decade of life. Many patients will have significant improvement by the end of adolescence. However, if tics persist into adulthood, TS can cause severe behavioral and social dysfunction.


Restless legs syndrome (RLS) is a chronic neurologic movement disorder with a prevalence of 5%-10% in the adult population and affects about 2% of children aged 8-17 years. It affects 12 million people in the United States with females twice as often affected as males, and it is more severe in females. Primary RLS is idiopathic and occurs sporadically, but it demonstrates a strong genetic component with familial inheritance. Secondary RLS can be associated with other medical conditions such as anemia, thyroid problems, diabetes, kidney failure, peripheral neuropathy, ADHD, fibromyalgia, rheumatoid arthritis, Sjögren’s syndrome, cyanocobalamin deficiency, folic acid deficiency, and pregnancy. Medications that can aggravate RLS symptoms include anti-nausea drugs (prochlorperazine, metoclopramide), anticonvulsants (phenytoin, droperidol), antipsychotic drugs (haloperidol), tricyclic and SSRI antidepressants, and over-the-counter cold and allergy medications. The etiology of RLS is thought to involve the subcortical dopaminergic system, iron homeostasis, and genetics (autosomal recessive and dominant).

General Considerations

RLS is diagnosed based on a detailed history including symptoms, medications, and family history, and a thorough neurologic evaluation. Its typical presentation is unpleasant sensations due to paresthesias and dyesthesias (burning, itching, tingling, cramping, or aching) deep in the legs (calves), which subside only with voluntary movement of the legs. The sensation may present only on one side of the body and may move to another part of the body. The motor restlessness occurs with the urge to relieve the sensation, and the patient may move voluntarily with repetitive stereotypical movements such as pacing, rocking, and stretching. Patients

- The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
- The urge to move or unpleasant sensations are worse or only occur in the evening or night (6 PM to 4 AM).
- Supportive features
  - Family history of restless legs syndrome.
  - Positive response to dopaminergic therapy.
  - Occurrence of periodic leg movements (PLMs) in sleep (PLMS) or during wakefulness (PLMW).
  - Additional diagnostic criteria for children 2-12 years of age
  - Children must express leg discomfort in their own words, for example, tickle, bugs, shaky, or
  - Have two of the following: sleep disturbance, parent with definite RLS, and elevated periodic limb movement index on polysomnography.

Clinical Findings

A. Symptoms and Signs

RLS is diagnosed based on a detailed history including symptoms, medications, and family history, and a thorough neurologic evaluation. Its typical presentation is unpleasant sensations due to paresthesias and dyesthesias (burning, itching, tingling, cramping, or aching) deep in the legs (calves), which subside only with voluntary movement of the legs. The sensation may present only on one side of the body and may move to another part of the body. The motor restlessness occurs with the urge to relieve the sensation, and the patient may move voluntarily with repetitive stereotypical movements such as pacing, rocking, and stretching. Patients

- An urge to move the legs, usually caused by uncomfortable and unpleasant sensations in the legs.
- The urge to move or unpleasant sensations beginning or worsening during periods of rest or inactivity such as lying or sitting.

Web Sites

http://www.wemove.org hppt://www.tsa-usa.org
with RLS usually have sleep disturbances, such as difficulty falling asleep or maintaining sleep, leg movement during sleep, and daytime fatigue. PLMS and PLMW are stereotyped, repetitive movements with dorsiflexion of ankles or big toes. Abnormal physical findings and positive test results may be due to associated conditions in secondary RLS. Smoking, alcohol consumption, poor sleep hygiene, and fatigue may aggravate symptoms of RLS.

B. Laboratory and Other Test Findings

A complete blood count, ferritin iron level, electrolytes, glucose level, thyroid hormone, and kidney function should be ordered. PLMS can be monitored through an ambulatory monitor. Polysomnography is not routinely ordered. It may be considered when the presentation is not diagnostic for RLS, there is suboptimal response to treatment, or other nocturnal conditions such as sleep apnea are suspected.

▶ Differential Diagnosis

Among the many medical conditions that need to be differentiated from RLS, polyneuropathy is the most commonly encountered. The sensory symptoms of polyneuropathy do not improve with movement, and there will be positive findings from the neurologic examination, nerve biopsy, and neurophysiologic examination. Examples of differentials are nocturnal leg cramps, obstructive sleep apnea syndrome, intermittent claudication, pathophysiologic insomnia, Tourette syndrome, and orthostatic tremor.

▶ Treatment

The goal of RLS treatment is to minimize the unpleasant sensations and motor restlessness, reduce sleep disturbance, and improve quality of life.

A. Nonpharmacotherapy

Identify any conditions that may cause or aggravate RLS, such as offensive medications, smoking, and excessive alcohol consumption. Give iron supplementation when ferritin is low and vitamin supplementation. Monitor kidney function. A healthy lifestyle will help alleviate RLS with moderate daily exercise, leg movement and massage, and hot baths.

B. Pharmacotherapy

Medications should be started when patients are experiencing daily symptoms that are affecting their quality of life. The nonergot dopamine agonists ropinirole and pramipexole are the medications of choice in primary RLS. They can be administered 1-3 hours before the onset of symptoms, and their effect is immediate. Adverse effects include nausea, peripheral edema, daytime somnolence, and impulsivity. Dopaminergic medications, short- or long-acting agents, are effective in abating RLS symptoms. Levodopa is fast acting and can be taken 1-2 hours before symptoms start. However, augmentation may develop with long-term use or high doses (>200 mg) of dopaminergic medications, especially carbidopa/levodopa. The symptoms of RLS are more intense with earlier onset (2 hours) and with spread to additional limbs. Rebound is another treatment complication of levodopa. RLS symptoms worsen when levodopa effects wear off. Because of the complications and short- and fast-acting features of levodopa, it is recommended for treatment of intermittent RLS. Benzodiazepines such as clonazepam, temazepam, diazepam, and triazolam are effective in improving sleep quality but not on PLMs. Anticonvulsants such as gabapentin, valproate, and lamotrigine have been found to improve RLS symptoms. Other medications such as baclofen, clonidine, and amantadine have also been shown to improve patient performance on RLS rating scales.


Web Site

http://www.wemove.org

CHOREA

Chorea is an irregular, rapid, involuntary jerky movement that flows randomly to any part of the body. Multiple etiologies, such as Huntington disease (see next section), vascular disorders, electrolyte imbalance, medications (antiparkinsonian, anticonvulsants, cocaine, neuroleptics), infection (HIV, encephalitis), autoimmune disorders (SLE, Sydenham chorea), have been identified as causing chorea by affecting the basal ganglia. Chorea usually affects hands, feet, face (eg, nose wrinkling), and trunk. Laboratory tests may be ordered to differentiate the causes, such as throat culture and streptococcal blood antigen for Sydenham chorea, liver function tests, complement levels, ANA, antiphospholipid antibody titers, TSH, and electrolytes. Brain CT, MRI, and PET scan may also aid in diagnosis.

1. Huntington Disease

Huntington’s disease (HD) is an adult-onset (35-50 years), autosomal dominant progressive neurodegenerative disorder caused by a mutation with CAG repeats in the IT15 gene on chromosome 4. It affects approximately 1 per 10,000 people. The diagnosis is based on clinical features and neurologic examination with findings of chorea, gait disturbance, dysarthria and dysphagia, eye movement disorders, and associated cognitive and behavioral disorders (dementia, depression, OCD, suicidal ideation). Imaging studies may show abnormalities such as putamen atrophy on MRI, enlarged ventricles on CT, and decreased glucose and oxygen metabolism in caudate...
nuclei on PET. Genetic confirmatory testing may be offered to patients with clear symptoms of HD and a family history of HD. Testing for fatal HD in individuals without symptoms but with a documented family history can cause enormous stress and emotional concerns. Genetic counseling before and after the test regarding implications of possible results and potential family, social, and ethical issues is important for informed decision making and patient and family support. Individuals who have a positive test result will experience a gradually increasing sense of hopelessness as the onset of the disease approaches. Some will suffer severe depression with suicidal ideation. They will demonstrate increased avoidance behaviors, and a close monitoring is warranted.

Treatment is mainly symptomatic to control chorea, behavioral comorbidities (by means of antidepressants), and potential complications (rhabdomyolysis, local trauma, aspiration pneumonia). Chorea and psychiatric symptoms may respond to dopamine receptor antagonists (eg, haloperidol), benzodiazepines (clonazepam), or monoamine-depleting agents (eg, reserpine, tetrabenazine). However, the response is only temporary, and these medications may exacerbate parkinsonism, which is a late presentation of HD. Supportive management and a multidisciplinary approach, including speech and physical and occupational therapy, are important in maintaining patients’ quality of life. Patients can be referred to several national support groups and organizations, including the Huntington Disease Society of America (http://www.hdsa.org) and the Hereditary Disease Foundation (http://www.hdfoundation.org/home.php).

Web Sites
http://www.wemove.org
http://www.hdsa.org
http://www.hdfoundation.org/home.php

OTHER MOVEMENT DISORDERS

1. Dystonia

Dystonia is characterized by sustained, directional, uncoordinated, or simultaneous agonist and antagonist muscle contractions, which result in repetitive twisting movements or abnormal postures. The same group of muscles are repeatedly involved. The excessive random movements are worsened with intentional movements and improve at rest. Dystonic movements can be triggered by specific actions such as hand cramps with writing, called task-specific dystonia; they can be activated by actions in remote parts of the body such as leg dystonia while writing, called overflow dystonia; in a more severe form than action dystonia, they can occur at rest, called rest dystonia; and finally, the movements become fixed postures or positions, referred to as permanent contractures. A sensory trick (“geste antagonistique”) is a phenomenon of dystonic movements. Patients may suppress dystonic movements by touching affected or adjunctive body parts. Primary dystonia has dystonia as the only neurologic abnormal finding and is associated with a genetic cause in autosomal dominant fashion. Early onset (<26 years) primary dystonia usually affects an extremity. Late-onset (>26 years) primary dystonia affects the neck or cranial muscles and tends to remain focal. Secondary dystonia is associated with an exogenous etiology such as drug use, head trauma, infection, and hypoxia. Other abnormal neurologic examination findings are present, for example, HD, PD, neurodegeneration, Wilson disease, CNS tumor, and stroke. Dopa-responsive dystonia (DRD, Segawa syndrome) is a childhood-onset dystonia plus parkinsonism that responds to levodopa.

The diagnosis of dystonia is based on history, typical clinical presentation, and neurologic examination. MRI of the brain and appropriate laboratory investigations (eg, serum ceruloplasmin, CSF analysis, ANA, ESR, and metabolic panels) can help assess secondary dystonia. Genetic testing for early-onset dystonia can be done but has limited sensitivity. Genetic counseling should be provided to patients and family before and after the testing.

Treatment of dystonia is aimed at underlying causes and symptom control with oral medication (benzodiazepines, dopamine agonists or dopaminergic agents, anticholinergics, or baclofen); botulinum toxin injection; and surgery in severe, unresponsive cases (thalamotomy, pallidotomy, deep brain stimulation, peripheral denervation). Early onset dystonia should have a trial of levodopa for possible DRD. Physical therapy such as stretching exercises and sensory tricks may be used to help maintain range of motion or interrupt muscle twisting.

Web Sites
http://www.wemove.org

2. Myoclonus

Myoclonus refers to sudden, quick, shock-like, involuntary jerk movements of a muscle or a group of muscles. Positive myoclonus is due to involuntary muscular contractions; negative myoclonus (asterixis) to sudden brief loss of muscle
tone. Based on etiology, myoclonus can be classified into four categories. **Physiologic myoclonus** is a normal and benign movement that occurs commonly, such as hiccups, sleep jerks, and benign infantile myoclonus with feeding. The movements are usually self-limited and not disabling. **Essential myoclonus** is a multifocal movement disorder, which can be sporadic or hereditary in an autosomal dominant pattern (associated with dystonia). Even though myoclonic movements are the one abnormal clinical finding on neurologic examination, they occur more frequently at any time, affecting patients’ daily life. **Epileptic myoclonus** occurs with seizure activities and demonstrates EEG and electromyographic changes. **Secondary (symptomatic) myoclonus** is the most common type of myoclonus (about 70%) and occurs as the result of central or peripheral nervous system insult or damage from a wide variety of medical conditions, which can be metabolic (inborn errors of metabolism, Hashimoto encephalopathy) or neurodegenerative (PD, HD) or due to trauma or infection at the level of brain, spinal cord, or peripheral nervous system; medications (eg, anesthetic agents, opiates, and anticonvulsants), or toxin exposure (pesticides, gases). Laboratory investigations, imaging studies (MRI of brain or spinal cord), other tests (EEG, EMG), and genetic testing should be ordered based on suspected underlying conditions. Treatment of myoclonus is aimed at the secondary causes. Levetiracetam, clonazepam, valproic acid, and primidone can be used to provide symptomatic control of disabling myoclonus.


**Web Site**

http://www.wemove.org
Family physicians are keenly aware of the joy that comes from interacting with the world around them. Many elderly patients are deprived of parts of this world because of hearing and vision impairment. Sensory impairment affects up to two-thirds of the geriatric population. Identification, evaluation, and treatment of these conditions (Table 44-1) may improve patients’ quality and quantity of life.

The impact of sensory impairments is significant. The same objective level of sensory function can result in different levels of disability, depending on the needs and expectations of patients. Vision and hearing impairments have been linked with the wish to die in elderly patients. Poor hearing is associated with depression as well as decreased quality of life, mental health, and physical, social, and cognitive functioning. Vision impairment increases the risk of death and is associated with an elevated risk of falling and hip fracture, depression, medication errors, and problems with driving.

Given the functional impact of undetected and untreated sensory impairments, many arguments have been made for population-based screening. Research has yet to demonstrate that community-based screening of asymptomatic older people results in improvements in vision or hearing. The US Preventive Services Task Force (USPSTF) and the American Academy of Family Physicians (AAFP) recommend screening for hearing difficulties by questioning elderly adults about hearing impairment and counseling them regarding the availability of treatment, when appropriate. Although, in 2009 update, AAFP and USPSTF concluded that there is inadequate direct evidence that screening for impairment of visual acuity by primary care physicians improve functional outcomes in elderly, they found adequate evidence that early treatment of refractive error, cataracts, and AMD improves or prevents loss of visual acuity.
Table 44-1. Differential diagnosis of geriatric hearing and vision impairment.

<table>
<thead>
<tr>
<th>Hearing Impairment</th>
<th>Vision Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presbycusis</td>
<td>Presbyopia</td>
</tr>
<tr>
<td>Cerumen impaction</td>
<td>Age-related macular degeneration</td>
</tr>
<tr>
<td>Noise-induced hearing loss</td>
<td>Glaucoma</td>
</tr>
<tr>
<td>Central auditory processing disorder</td>
<td>Senile cataract</td>
</tr>
<tr>
<td>Otosclerosis</td>
<td>Diabetic retinopathy</td>
</tr>
<tr>
<td>Chronic otitis media</td>
<td>Central retinal artery or vein occlusion</td>
</tr>
<tr>
<td>Glomus tumor or vascular anomaly</td>
<td>Posterior vitreous or retinal detachment</td>
</tr>
<tr>
<td>Cholesteatoma</td>
<td>Vitreous hemorrhage</td>
</tr>
<tr>
<td>Autoimmune hearing loss</td>
<td>Temporal arteritis</td>
</tr>
<tr>
<td>Perilymph fistula</td>
<td>Optic neuritis</td>
</tr>
<tr>
<td>Ménière disease</td>
<td>Corneal pathology</td>
</tr>
<tr>
<td>Acoustic neuroma</td>
<td>Iritis</td>
</tr>
</tbody>
</table>

The most common causes are indicated in bold type.

Clinical Findings

Patients with this disorder may present with a chief complaint of hearing loss and difficulty understanding speech. However, presbycusis is often diagnosed only after complaints are raised by close patient contacts, or hearing loss is noted on routine screening in a patient without hearing-related complaints. The Hearing Handicap Inventory of the Elderly Screening Version (HHIE-S) is a widely accepted subjective screening tool for hearing disability. Abnormalities of the whisper test are found as the level of hearing loss increases. Results of the Weber tuning-fork test remain normal as long as the hearing loss is symmetric. Results of Rinne testing are normal, because presbycusis is a sensorineural hearing loss and not a conductive one.

An audiogram of a patient with presbycusis typically shows bilaterally symmetric high-frequency hearing loss.

Treatment

The treatment of presbycusis consists of hearing rehabilitation, which often involves fitting for binaural hearing aids. Patients are more likely to perceive benefit from hearing aids if they view their hearing loss as a problem. Cochlear implantation is reserved for patients with profound hearing loss that is unresponsive to hearing aids. Additional tools include lip-reading classes; television closed captionings; sound-enhancing devices for concerts, church, or other public gatherings; and telephone amplifiers. A combined approach involving the patient, hearing loss specialist, family physician, and close contacts of the patient is likely to produce the best overall treatment plan.

Suggested topics for patient education include patient self-advocation as well as the proper use of hearing aids and other assistive devices.

Prognosis

The expectation of slow progression of this hearing loss should be communicated to the patient. Complete deafness, however, is not typical of presbycusis.

NOISE-INDUCED HEARING LOSS

ESSENTIALS OF DIAGNOSIS

- History of occupational or recreational noise exposure.
- Bilateral notch of sensorineural hearing loss between 3000 and 6000 Hz on audiogram.
- Problems with tinnitus, speech discrimination, and hearing in the presence of background noise.

General Considerations

Noise-induced hearing loss is the second most common sensorineural hearing loss (Table 44-2) after presbycusis. Up to one-third of patients with hearing loss have some component of their deficit that is noise induced. The degree of hearing loss is related to the level of noise and the duration of exposure. Excessive shear force from loud sounds or long exposure results in cell damage, cell death, and subsequent hearing loss.

Table 44-2. Causes of hearing loss.

<table>
<thead>
<tr>
<th>Conductive Hearing Loss</th>
<th>Sensorineural Hearing Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outer ear</td>
<td>Inner ear</td>
</tr>
<tr>
<td>Otitis externa</td>
<td>Presbycusis</td>
</tr>
<tr>
<td>Trauma</td>
<td>Noise exposure</td>
</tr>
<tr>
<td>Cerumen</td>
<td>Ménière disease</td>
</tr>
<tr>
<td>Osteoma</td>
<td>Ototoxic drugs</td>
</tr>
<tr>
<td>Exostosis</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>Viral cochleitis</td>
</tr>
<tr>
<td>Middle ear</td>
<td>Barotraumas</td>
</tr>
<tr>
<td>Otitis media</td>
<td>Acoustic neuroma</td>
</tr>
<tr>
<td>Tympanic membrane perforation</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Cholesteatoma</td>
<td>Vascular disease</td>
</tr>
<tr>
<td>Otosclerosis</td>
<td>Meningioma</td>
</tr>
<tr>
<td>Glomus tumors</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Temporal bone trauma</td>
<td>Meningioma</td>
</tr>
<tr>
<td>Paget disease</td>
<td>Multiple sclerosis</td>
</tr>
</tbody>
</table>
**Prevention**

Hearing protection programs are prevalent in industrial settings and typically include the use of earplugs, intermittent audiograms, and limiting exposure. Patient commitment to the use of hearing protection is critical for the success of prevention programs.

**Clinical Findings**

Patients may present with tinnitus, decreased speech discrimination, and difficulty hearing when background noise is present. Patients identified through hearing protection programs may be asymptomatic. Results of the whisper test or office-based pure-tone audiometry may be normal or abnormal, depending on the degree of hearing loss.

Audometric evaluation of noise-induced hearing loss reveals a bilateral notch of sensorineural hearing loss between 3000 and 6000 Hz.

**Treatment**

When prevention fails, treatment involves hearing rehabilitation, as previously outlined in the treatment of presbycusis. Education about the risks of loud noise exposure should begin when patients are young, because hearing loss can occur from significant recreational noise. The importance of adhering to hearing protection programs should also be emphasized.

**Prognosis**

Nothing can be done to reverse cell death from noise-induced hearing loss; however, some patients exposed to brief episodes of loud noise exhibit only hair cell injury and may recover hearing over time. These patients are more susceptible to noise-induced hearing loss on reexposure.

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**CERUMEN IMPACTION**

**ESSENTIALS OF DIAGNOSIS**

- Mild, reversible conductive hearing loss.
- Cerumen buildup in ear canal, limiting sound transmission.
- Direct visualization of wax plug confirms diagnosis.

**General Considerations**

Impaction of wax in the external auditory canal is a common, frequently overlooked problem in the elderly. Removal of cerumen has been shown to significantly improve hearing ability. The incidence of cerumen impactions increases in the elderly population. Chronic skin changes lead to loss of normal migration of skin epithelium leading to exfoliated cell debris accumulation. Cerumen gland atrophy results in drier wax that is more likely to become trapped by the large tragi hairs in the external ear canal. The likelihood of impaction is increased by hearing aid or earplug use.

**Prevention**

Cerumen impactions may be prevented by the regular use of agents that soften wax. Readily available household agents such as water, mineral oil, cooking oils, hydrogen peroxide, or glycerin may be used. Commercially available ceruminolytic compounds, such as carbamide peroxide, triethanolamine polypeptide, and docusate sodium liquid are also efficacious, but not more so than less-expensive options.

**Clinical Findings**

Patients presenting with cerumen impaction may complain of sudden or gradual hearing loss, tinnitus affecting one or both the ears and interference with hearing aids. Examination of the external canal reveals partial or complete occlusion of the ear canal with cerumen.

**Complications**

Various removal methods are associated with ear discomfort and potential for ear canal trauma. Canal trauma can result in bleeding, canal swelling, or infection. Warm water should be used for ear irrigation, because cold water can induce vertigo.

**Treatment**

The management of impactions may be approached in a variety of ways. When the wax is soft, gentle irrigation of the canal with warm water may be sufficient to remove the offending material. In the case of firmer wax, ceruminolytic agents may be applied, followed by irrigation. Any cerumen remaining after these maneuvers may be removed using a curette in combination with an otoscope for direct visualization. The patient may experience an improvement of symptoms even with partial removal of the impaction. Patients should be instructed about ear cleaning techniques and home use of ceruminolytics.

**Prognosis**

Cerumen impaction has an excellent prognosis, and hearing can be dramatically improved with relatively simple interventions. However, recurrence of impaction is common.

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**CENTRAL AUDITORY PROCESSING DISORDER**

**ESSENTIALS OF DIAGNOSIS**

- Hearing impairment due to insult to central nervous system.
- Reduction in speech discrimination exceeds hearing loss.
General Considerations

Central auditory processing disorder (CAPD) is the general term for hearing impairment that results from central nervous system (CNS) dysfunction. Any insult to the nervous system such as stroke or dementia can cause CAPD. The disorder is characterized by a loss of speech discrimination that is more profound than the associated loss in hearing.

Prevention

It may be postulated that the protection of the CNS provided by aspirin therapy and hypertension control could reduce the incidence of CAPD.

Clinical Findings

Patients with CAPD have difficulty understanding spoken language but may be able to hear sounds well. A patient may have difficulty following verbal instructions but understand written ones. There are no specific physical findings of CAPD, but patients may have other evidence of neurologic abnormalities.

Treatment

Treatment of CAPD is limited. If CNS dysfunction is caused by a reversible entity, then treatment for the underlying cause should be initiated. Identifying and treating other causes of sensory impairment may improve the patient’s level of disability; however, CAPD may decrease the effectiveness of auditory rehabilitation. Patient education efforts should focus on educating friends and family about the disorder and options for hearing rehabilitation. The prognosis for patients with CAPD is determined by the underlying disorder.

Web Sites

National Institute on Deafness and Other Communication Disorders (patient education materials on a wide variety of hearing impairment-related topics including presbycusis and hearing aids):

National Institute on Aging (patient education handout on the hearing loss):
http://www.niapublications.org/engagepages/hearing.asp

Common Causes of Vision Impairment in the Elderly

Visual impairment is defined as binocular acuity of 20/40 or worse. Legal blindness is when acuity is worse than 20/200. Older adults with good visual acuity show problems with visual function in real life situations as testing is usually done in an optimum condition with maximum contrast and illumination with minimal glare. Testing for visual problems with decreased contrast sensitivity, decreased illumination, and increased glare is not practical for primary care provider and hence it is important that they ask questions routinely to screen for performance under these circumstances. Educating the patient about simple measures to improve the environment may help with their quality of life.

Presbyopia

Essentials of Diagnosis

Age-related decrease in near vision.
Distance vision remains unaffected.

General Considerations

Presbyopia is an age-associated progressive loss of the focusing power of the lens. Its incidence increases with age. The cause of this disorder is the ongoing increase in the diameter of the lens as the result of continued growth of the lens fibers with aging. This thickened lens accommodates less responsively to the contraction of muscles in the ciliary body, limiting its ability to focus on near objects.

Clinical Findings

Patients presenting with this disorder frequently complain of eye strain or of blurring of their vision when they quickly change from looking at a nearby object to one that is far away. On examination, the only abnormality noted is a decrease in near vision.

Treatment

Because presbyopia is due to normal age-related changes of the eye, there is no proven prevention. In patients with normal distance vision, treatment for this disorder is as simple as purchasing reading glasses. For patients requiring correction of their distance vision, options include spectacle correction with bifocal or trifocal lenses, monovision contact lenses in which one eye is corrected for distance vision and the other eye for near vision, or contact lens correction of distance vision and simple reading glasses for near vision. Surgical treatment of presbyopia is an evolving science.
Prognosis

All patients should be educated to anticipate a decline in near vision with aging. When left uncorrected, problems may occur with reading, driving, or other activities of daily living.

**AGE-RELATED MACULAR DEGENERATION**

**ESSENTIALS OF DIAGNOSIS**

- Slowly progressive central vision loss with intact peripheral vision.
- Drusen located in the macula of the retina.

**General Considerations**

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in older Americans. It is characterized by atrophy of cells in the central macular region of the retinal pigment epithelium resulting in the loss of central vision. Peripheral vision generally remains intact. AMD is typically classified as early and intermediate (usually dry type) or advanced/late AMD which is divided into atrophic or non-neovascular (dry) or exudative or neovascular (wet) forms. The exudative form occurs in only 10% of patients with AMD, but it is responsible for the majority of severe vision loss related to the disease.

**Prevention**

Multiple risk factors for this disorder have been studied including genetic factors, white race, and obesity; only increasing age and tobacco abuse have consistently been associated with AMD. Because smoking has been strongly implicated as a risk factor and continued tobacco use is associated with a worse response to laser photocoagulation, tobacco avoidance and smoking cessation should be highly recommended to all patients. Hypertension has also been linked to a worse response to laser therapy; thus, effective blood pressure control is desirable, as well. Finally, antioxidants play a role in tertiary prevention: Patients with intermediate AMD or unilateral advanced AMD had about a 25% reduction of their risk for developing advanced AMD if treated with a high-dose combination of vitamin C, vitamin E, β-carotene, and zinc. Patients with early or no AMD did not have the same benefit.

**Clinical Findings**

**A. Symptoms and Signs**

Patients may report onset of blurred central vision that is either gradual or acute. Wavy or distorted central vision, known as metamorphopsia; intermittent shimmering lights; and central blind spots, termed scotoma, may all occur. Clinical findings include decreased visual acuity, Amsler grid distortion (Figure 44-1), and characteristic abnormalities on dilated funduscopic examination. In early disease, the most common findings are drusen: yellowish-colored deposits deep in the retina. In late disease of the atrophic type, areas of depigmentation are seen in the macula. In the exudative form, abnormal vessels (subretinal neovascularization) leak fluid and blood beneath the macula.

**B. Special Examinations**

Fluorescein angiography may be used by a specialist to confirm the diagnosis and to help determine if a patient has atrophic or exudative AMD.

**Treatment**

**A. Referral**

An ophthalmologist will play a critical role in care of the patient with known or suspected AMD. Urgent referral to an eye specialist should occur if a patient with suspected or known AMD presents with acute visual changes. Treatment of exudative AMD is a rapidly advancing field with many ongoing clinical trials of surgical and pharmaceutical interventions. Current treatment options include laser photocoagulation, photodynamic therapy, and intravitreal antiangiogenic therapy. No effective treatments exist for patient with dry AMD.

Vision rehabilitation is the cornerstone to helping patients maximize their remaining vision and maintain their level of function for as long as possible. Low-vision professionals along with social workers can be of great assistance in recommending optical aids and devices and accessing local, state, and federal resources for the visually impaired. Direct illuminating devices, magnifiers, high-power reading glasses,
telescopes, closed-circuit television, large-print publications, and bold-lined paper are some of the many devices that can be employed.

B. Patient Education

Patient education topics include the importance of regular eye examinations, smoking cessation, and routine monitoring for central vision changes. Daily Amsler grid testing is an effective tool for detecting progression. Its use is described at http://www.amd.org.

Prognosis

Many patients with mild dry AMD will not experience significant worsening of their vision. It is difficult to predict which patients will develop advancing disease and further loss of central vision. This condition is generally progressive but is not completely blinding. Peripheral vision should not be affected by AMD.

Ref Jager RD et al: Age-related macular degeneration. NEJM 2008;358;(24);2606-17. [PMID 18550876]

GLAUCOMA

ESSENTIALS OF DIAGNOSIS

Optic neuropathy with variably progressive vision loss.
Intraocular pressure (IOP) is often elevated but may be normal.

General Considerations

Glaucoma is the second leading cause of blindness in the United States. Although glaucoma is most often associated with elevated IOP, it is the optic neuropathy that defines the disease. Normal IOP is generally accepted to be between 10 and 21 mm Hg. The majority of patients with an IOP greater than 21 mm Hg will not develop glaucoma and 30%-50% of patients with glaucoma will have an IOP of less than 21 mm Hg. Despite these facts, it has been clearly shown that as IOP increases, so does the risk of developing glaucoma. Other identified risk factors for glaucoma include family history and advancing age and black race. Additional possible risk factors include diabetes mellitus, hypertension, and myopia.

Prevention

The AAFP and the USPTF do not recommend screening for glaucoma, citing insufficient evidence to recommend for or against routine screening by primary care clinicians for elevated IOP or early glaucoma. The American Academy of Ophthalmology recommends screening for glaucoma by an ophthalmologist every 1-2 years after age 65.

Clinical Findings

A. Symptoms and Signs

Patients with acute angle-closure glaucoma typically present with unilateral intense pain and blurred vision. Patients may report seeing halos around light sources and complain of photophobia, headache, nausea, and vomiting. Physical examination shows a mid-dilated pupil, conjunctival injection, and lid edema. Patients generally have markedly elevated IOP, usually between 60 and 80 mm Hg.

Primary open angle glaucoma is a more insidious disease with a long asymptomatic phase. Patients may notice a gradual loss of peripheral vision. Examination may reveal diminished visual fields, elevated IOP, and abnormalities of the optic disc on direct ophthalmoscopy (symmetrically enlarged cup-to-disc ratio, cup-to-disc ratio asymmetry between the two eyes, or a highly asymmetric cup in one eye).

B. Special Tests

IOP may be measured using a variety of tools. The most readily available tool is the physician's hand. Palpation of the globe through a lightly closed lid can reveal asymmetric hardness or bilaterally firm eyeballs and provide a very gross measure of IOP. More accurate tools include tono-pen, Goldmann applanation tonometry, and pneumotonometry (puff test).

Treatment

Patients with significant risk factors or physical findings that raise concern for glaucoma should be referred to an ophthalmologist for further evaluation and confirmation of diagnosis.

A. Acute Angle-Closure Glaucoma

Acute angle-closure glaucoma is a medical emergency that requires immediate referral and treatment.

B. Primary Open-Angle Glaucoma

The treatment of primary open-angle glaucoma consists of pharmacologic and surgical interventions aimed at decreasing the IOP. Although elevated IOP is not required for the diagnosis of glaucoma, it has been shown that reduction of IOP in patients with glaucoma slows the progression of disease. Even patients with normal pressures can benefit from reduction in IOP.

1. Pharmacotherapy—Topical eye drops or oral medications aimed at decreasing aqueous humor production or increasing outflow are used. Topical agents like β-blockers and prostaglandin analogs are first line of therapy and α-adrenergic agents and carbonic anhydrase inhibitors are second line of
therapy. Topical miotics and epinephrine compounds are now infrequently used. Oral medications include carbonic anhydrase inhibitors such as acetazolamide. Topical glaucoma agents have varying degrees of systemic absorption and are capable of producing systemic side effects and drug-drug interactions. Patients should be educated on the importance of routine eye care and of taking medications as prescribed.

2. Surgical intervention—When medical management is unsuccessful, surgical intervention is considered. Laser trabeculoplasty and laser or conventional trabeculectomy are the most commonly performed procedures.

Prognosis

Untreated glaucoma can result in blindness. Rapid treatment of acute angle-closure glaucoma may preserve vision. Treatment of primary open-angle glaucoma can prevent further loss of vision, but typically does not restore lost vision.

CATARACTS

ESSENTIALS OF DIAGNOSIS

Opacity or cloudiness of the crystalline lens.

General Considerations

Any opacification of the lens is termed a cataract. Cataract disease is the most common cause of blindness worldwide and the most common eye abnormality in the elderly. Risk factors for cataracts include advancing age, exposure to ultraviolet (UV) B light, glaucoma, smoking, alcohol abuse, diabetes, and chronic steroid use. Diet and vitamins do not play a role in development or progression of the disease. Because cataracts tend to develop slowly, the patient may not be fully aware of the degree of vision impairment.

Prevention

Prevention of cataracts is aimed at the modifiable risk factors. Physicians should use steroids at as low a dose as is therapeutic and discontinue them when possible. Patients should be advised on how to minimize UV light exposure as well as the benefits of smoking cessation and control of chronic diseases.

Clinical Findings

Patients may report blurring of vision, “ghosting” of images, difficulty seeing in oncoming lights (glare) and difficulty with night driving, and monocular diplopia. The patient may also complain of a decrease in color perception and even note “second sight,” which is an improvement in near vision with a nuclear cataract. Examination of the eye reveals the opacification of the lens. Cataracts may be easier to see with dilation of the eye and a direct ophthalmoscope at +5 diopters setting held 6 in from the patient’s eye.

Treatment

The treatment of cataracts is predominantly surgical. Although small cataracts may be treated by an updated eyeglass prescription, most patients with significant symptoms from a cataract benefit from surgical removal and replacement of the lens. Factors influencing the timing of surgery include life expectancy, current level of disability, status of other medical illnesses, family and social situations, and patient expectations.

Family physicians may aid patients in understanding the surgery and in assisting with preoperative management. Cataract surgery is a low-risk procedure. Routine use of laboratory testing and electrocardiogram screening has not improved surgical outcome. Individuals should receive a history and physical examination prior to undergoing surgery. Additional testing is recommended only if findings are abnormal. Cataract surgery is often accomplished under local anesthesia with minimally invasive techniques. In this case, there is no need to discontinue anticoagulation for the procedure. Surgeons should be made aware if patients are taking α-blockers as it is associated with a complication called intraoperative floppy iris syndrome.

Prognosis

Cataracts do not resolve and may progress without treatment. The prognosis with surgical treatment is excellent, and up to 95% of patients obtain improved vision after surgery.

DIABETIC RETINOPATHY

ESSENTIALS OF DIAGNOSIS

Asymptomatic, gradual vision loss or sudden vision loss in a diabetic patient.

Characteristic funduscopic findings of microaneurysms, flame hemorrhages, exudates, macular edema, and neovascularization.

General Considerations

Diabetic retinopathy (DR) is the leading cause of blindness in adults in the United States. It is important to consider
diabetic retinopathy as a disease of the aging eye because prevalence increases with duration of diabetes mellitus. The risk of blindness attributable to this disorder is greatest after 30 years of illness. DR is divided into two major forms: nonproliferative (NPDR) and proliferative (PDR), named for the absence or presence of abnormal new blood vessels emanating from the retina, respectively. NPDR can be further classified into mild, moderate, severe, and very severe categories depending on the extent of nerve-fiber layer infarcts (cotton-wool spots), intraretinal hemorrhages, and hard exudates, and microvascular abnormalities. The severity of proliferative retinopathy can be classified as early, high risk, and severe depending on the severity and extent of neovascularization.

**Prevention**

Patients with diabetes mellitus type 2 should have a comprehensive eye examination by an ophthalmologist shortly after diagnosis to screen for signs of retinopathy. Meticulous glycemic control decreases the risk of development and progression of retinopathy in all patients with diabetes. In addition, tight control of blood pressure also significantly reduces a patient’s risk of developing retinopathy.

**Clinical Findings**

Many patients presenting with diabetic retinopathy are free of symptoms; even those with the severe proliferative form may have 20/20 visual acuity. Others may report decreased vision that has occurred slowly or suddenly, unilaterally or bilaterally. Scotomata or floaters may also be reported. Funduscopic examination reveals any or all of the following: microaneurysms, dot and blot intraretinal hemorrhages, hard exudates, cotton-wool spots, boat-shaped preretinal hemorrhages, neovascularization, and venous beading.

Fluorescein angiography may be performed by an ophthalmologist to further assess the degree of disease.

**Treatment**

Untreated proliferative retinopathy is relentlessly progressive, leading to significant vision impairment and blindness. In addition to maximizing glucose and blood pressure control, laser photocoagulation surgery (focal and scatter) or vitrectomy is the mainstay of acute and chronic treatment and may preserve vision in certain patients. When vision loss has occurred, vision rehabilitation should be initiated, as described earlier in the discussion of AMD. Topics to review with patients include the importance of an annual, comprehensive eye examination, glycemic control, and hypertension management.

**Prognosis**

Early diagnosis and treatment, as well as tight glycemic control, improve prognosis.


**Web Sites**

Lighthouse International (health information on vision disorders, treatment, and rehabilitation services):
http://www.lighthouse.org

National Institute on Aging (patient education handout on the aging eye and hearing loss):
http://www.niapublications.org/engagepages/eyes.asp
Although the nation’s oral health is believed to be the best it has ever been, oral diseases remain common in the United States. In May 2000, the first report on oral health from the US Surgeon General, *Oral Health in America: A Report of the Surgeon General*, called attention to a largely overlooked epidemic of oral diseases that is disproportionately shared by Americans: This epidemic strikes in particular the poor, young, and elderly. The report stated that although there are safe and effective measures for preventing oral diseases, these measures are underused. The report called for improved education about oral health, for a renewed understanding of the relationship between oral health and overall health, and for an interdisciplinary approach to oral health that would involve primary care providers.

### DENTAL ANATOMY & TOOTH ERUPTION PATTERN

In utero, the 20 primary teeth evolve from the expansion and development of ectodermal and mesodermal tissue at approximately 6 weeks of gestation. The ectoderm forms the dental enamel and the mesoderm forms the pulp and dentin. As the tooth bud evolves, each unit develops a dental lamina that is responsible for the development of the future permanent tooth. The adult dentition is composed of 32 permanent teeth. Figure 45-1 shows the anatomy of the tooth and supporting structures. Table 45-1 outlines the eruption pattern of the teeth.

### DENTAL CARIES

#### General Considerations

Dental caries (tooth decay) is the single most common chronic childhood disease, five times more common than asthma and seven times more common than hayfever among children 5-7 years of age. Minority and low-income children are disproportionately affected. According to the Centers for Disease Control and Prevention (CDC), among children aged 2-11 years, 21% have had untreated tooth decay in primary teeth, and of these, 32% are Mexican American, 27% are African American, and 18% are white. In addition, one-third of persons of all ages have untreated decay, 8% of adults older than 20 years of age have lost at least one permanent tooth to dental caries, and many older adults suffer from root caries.

#### Pathogenesis

Dental caries is a multifactorial, infectious, communicable disease caused by the demineralization of tooth enamel in the presence of a sugar substrate and of acid-forming cariogenic bacteria that are found in the soft gelatinous biofilm plaque (Figure 45-2). Thus, the development of caries requires a susceptible host, an appropriate substrate (sucrose), and the cariogenic bacteria found in plaque. *Streptococcus mutans* (also known as mutans streptococci [MS]) is considered to be the primary strain causing decay. Additionally, when plaque is not regularly removed, it may calcify to form calculus (tartar) and cause destructive gum disease.

Finally, the development of caries is a dynamic process that involves an imbalance between demineralization and remineralization of enamel. When such an imbalance is caused by environmental factors such as low pH or inadequate formation of saliva, dissolution of enamel occurs and caries result.

#### Clinical Findings

### A. Symptoms and Signs

When enamel is repeatedly exposed to the acid formed by the fermentation of sugars in plaque, demineralized areas develop on the tooth surfaces, between teeth, and on pits and fissures. These areas are painless and appear clinically as...
opaque or brown spots (Figures 45-3, 45-4, and 45-5). If infection is allowed to progress, a cavity forms that can spread to and through the dentin (the component of the tooth located below the enamel) and to the pulp (composed of nerves and blood vessels; an infection of the pulp is called *pulpitis*), causing pain, necrosis, and, perhaps, an abscess.

**B. Diagnosis**

Carious lesions progress at various rates and occur at many different locations on the tooth, including the sites of previous restorations. Demineralized lesions (white or brown spots) generally occur at the margins of the gingiva and can be detected visually; they may not be seen on radiographs. Advanced carious lesions such as those spread through dentin can be detected clinically or, if they occur between the teeth, by radiographs. Root caries, commonly seen in older adults, occur in areas from which the gingiva has receded.

Dental professionals use a dental explorer to detect early caries in the grooves and fissures of posterior teeth. To diagnose secondary caries (caries formed at the site of restorations), dental professionals use digitally acquired and post-processed images.

### Risk Assessment

Caries can develop at any time after tooth eruption. Early teeth are principally susceptible to caries caused by the transmission of MS from the mouth of the caregiver to the mouth of the infant or toddler. This type of caries is called *early childhood caries* (ECC) or *baby bottle tooth decay* (BBTD). According to the American Academy of Pediatric Dentistry, ECC “is defined as ‘the presence of one or more decayed (noncavitated or cavitated lesions), missing (due to caries), or filled tooth surfaces’ in any primary tooth in a child 71 months of age or younger.” In children younger than 3 years, any sign of smooth-surface caries is called *severe early childhood caries* (S-ECC). Children with a history of ECC or S-ECC are at a much higher risk of subsequent caries in primary and permanent teeth. Risk factors for caries development are shown in Table 45-2.

ECC contributes to other health problems, including chronic pain, poor nutritional practices, and low self-esteem, which may lead to lack of self-esteem among older children and a great reduction in their ability to succeed in life.

The risk factors for adult caries are similar to those for childhood caries, including those listed in Table 45-2.

### Prevention & Treatment

Fluoride, the ionic form of the element fluorine, is widely accepted as a safe and effective practice for the primary prevention of dental caries. Fluoride slows or reverses the progression of existing tooth decay by (1) being incorporated into the enamel before tooth eruption, (2) inhibiting demineralization, (3) enhancing remineralization, and (4) inhibiting
bacterial activity in plaque. Unfortunately, only 57% of the US population has access to community water fluoridation, according to the CDC fluoridation census in 2000. Systemic fluoride supplements (tablets, drops, lozenges) are recommended for children older than 6 months who are at high risk of the development of caries, for infants with ECC, to children living in non-fluoridated water areas between 6 months and 16 years and for adults whose water is not fluoridated or who have diseases that produce a decrease in salivary flow, receding gums, or mental or physical disabilities. A supplemental fluoride dosage schedule is shown in Table 45-3. Topical fluoride supplements such as gels and varnishes are highly concentrated fluoride products that are professionally applied by a dental health provider or a parent (for gels). Varnishes, which are less toxic than gels and more effective than mouth rinses, are applied three times a week, once a year by disposable brushes, cotton-tipped applicators, or cotton pellets. To learn more about fluoride varnish application visit the Smiles for Life Web site, www.smilesfororalhealth.org.

Before prescribing supplemental fluoride, the primary care provider must determine the fluoride concentration in the child’s primary source of drinking water. Natural sources of fluoride include well water exposed to fluorite minerals, certain fruits and vegetables grown in soil irrigated with fluoridated water, and foods such as meats or poultry which may contain 6%-7% of total dietary fluoride. Although fluoride supplementation is not recommended for persons who live in communities whose water is optimally fluoridated (0.7-1.2 ppm or > 0.6 mg/L), the bottled water used by many

▲Figure 45-2. Dental caries due to plaque.

▲Figure 45-3. Brown spots indicating demineralized areas in enamel.

▲Figure 45-4. Opaque areas indicating demineralized areas in enamel.
families may contain low levels of fluoride. Parents and caregivers should be educated about the benefits of fluoride and the possible side effects of too much fluoride, a condition called fluorosis. Fluorosis results when too much fluoride is obtained from any source when the permanent tooth is forming (Figure 45-6). Thirty-two percent of children and adolescents aged 6-19 years have very mild or greater fluorosis. The benefits and side effects of fluoride use should be weighed against the risk of tooth decay among children at high risk of caries.

A second method of preventing dental caries is proper oral hygiene. Before the teeth erupt, a parent may use a washcloth or cotton gauze to clean an infant’s mouth and to transition the child to tooth brushing. Parents should supervise brushing and should discourage children younger than 6 years of age from using fluoridated dentifrices because of the risk that toothpaste may be swallowed during brushing. A pea-sized amount of toothpaste is recommended for brushing. Generally speaking, children younger than 2 years should avoid fluoride toothpaste.

Dental sealants, first introduced in the 1960s, are plastic films that coat the chewing surfaces of primary or permanent teeth. Sealants prevent decay from developing in the pits and fissures of teeth. Dental professionals often use sealants in combination with topical fluorides (Figure 45-7).

Older children and adults should avoid frequent consumption of drinks and snack foods containing sugars. Chewing sugar-free gum or cheese after meals has a saliva buffer effect that may counter plaque acids.

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**Table 45-2.** Risk factors for childhood and adult caries.

<table>
<thead>
<tr>
<th>Risk Factors for Childhood Caries</th>
<th>Risk Factors for Adult Caries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary practices: frequent consumption of foods and beverages containing sugars (juice, milk, formula, soda) and sticky foods</td>
<td>Physical and medical disabilities</td>
</tr>
<tr>
<td>Frequent bottle- and breastfeeding on demand</td>
<td>Existing restorations or oral appliances</td>
</tr>
<tr>
<td>Maternal or sibling caries</td>
<td>Inadequate salivary flow</td>
</tr>
<tr>
<td>Repetitive use of a “sippy cup”</td>
<td>Medications that produce dry mouth</td>
</tr>
<tr>
<td>Poor oral hygiene</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Inadequate fluoridation</td>
<td>Low socioeconomic status</td>
</tr>
</tbody>
</table>

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**Table 45-3.** Supplemental fluoride dosage schedule.

<table>
<thead>
<tr>
<th>Fluoride ion level in drinking water (ppm)</th>
<th>Age</th>
<th>&lt;0.3 ppm</th>
<th>0.3-0.6 ppm</th>
<th>&gt;0.6 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth-6 mo</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>6 mo-3 y</td>
<td>0.25 mg/d</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>3-6 y</td>
<td>0.50 mg/d</td>
<td>0.25 mg/d</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>6-16 y</td>
<td>1.0 mg/d</td>
<td>0.50 mg/d</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

*a 1 ppm = 1 mg/L. 
*b 2.2 mg sodium fluoride contains 1 mg fluoride ion. 

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**Figure 45-5.** Dental caries.

**Figure 45-6.** Fluorosis.

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**Figure 45-7.** Fluorosis.

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PERIODONTAL DISEASE

General Considerations

Periodontal disease is the most common oral disease in adults. Three forms exist: gingivitis, chronic periodontitis, and aggressive periodontitis. It is uncommon among young children, affecting less than 1%; however in some studies, up to 25% of Hispanic children between 12 and 17 years of age were affected. Like dental caries, periodontal diseases are caused by bacteria in dental plaque that create an inflammatory response in gingival tissues (gingivitis) or in the soft tissue and bone supporting the teeth (periodontitis). Risk factors that contribute to the development of periodontal disease include poor oral hygiene, environmental factors such as crowded teeth and mouth breathing, steroid hormones, smoking, comorbid conditions such as weakened immune status or diabetes, and low income.

Severe gum disease is defined as a 6-mm loss of attachment of the tooth to the adjacent gum tissue. Severe gum disease affects approximately 14% of adults aged 45-54 years and 23% of those aged 65-74 years. Approximately 25% of adults 65 years of age or older no longer have any natural teeth. The severity of periodontal disease does not increase with age. Rather, the disease is believed to occur in random bursts after periods of quiescence.

Pathogenesis

A. Gingivitis

Gingivitis is caused by a reversible inflammatory process that occurs as the result of prolonged exposure of the gingival tissues to plaque. Gingivitis may develop as a result of steroid hormones, which encourage the growth of certain bacteria in plaque during puberty and pregnancy and in women taking oral contraceptive pills.

No special tests are needed to diagnose gingivitis; rather, the disease is diagnosed by clinical assessment. Simple or marginal gingivitis may be painless and is treated by good oral hygiene practices such as tooth brushing and flossing. This type of gingivitis occurs in 50% of the population aged 4 years or older. The inflammation worsens as mineralized plaque forms calculus (tartar) at and below the gum surface (sulcus). Gingivitis may persist for months or years without progressing to periodontitis; this fact suggests that host susceptibility plays an important role in the development of periodontitis. Additionally, gingivitis (Figure 45-8) can be either acute or chronic. A severe form, acute necrotizing ulcerative gingivitis (ANUG), also known as Vincent disease or trench mouth, is associated with anaerobic fusiform bacteria and spirochetes. ANUG (Figure 45-9) is painful, ulcerative, and edematous and produces halitosis and bleeding gingival tissue. Predisposing factors include conditions that contribute to a weakened immune status, such as HIV infection, smoking, malnutrition, viral infections, and, possibly, stress. Chronic gingivitis affects more than 90% of the population and results in gingival enlargement or hyperplasia.
that resolves when adequate plaque control is instituted. Generalized gingival enlargement or swelling (gingiva hyperplasia) may be caused by drugs such as calcium channel blockers, phenytoin, and cyclosporin (Figure 45-10); by pregnancy; or by systemic diseases such as leukemia, sarcoidosis, and Crohn disease.

**B. Periodontitis**

Chronic periodontitis (CP) is caused by chronic inflammation of gingival soft tissue and supporting structures by plaque microorganisms, specifically gram-negative bacteria that affect gingival soft tissues and supporting structures, with resultant loss of periodontal attachment and bony destruction. CP is common in adults, affecting more than 50% of the population. Adult-onset periodontitis begins in adolescence and is reversible if treated in its early stages, when minimal pockets (gaps) have formed between the tooth and the periodontal attachment. Severe periodontitis is characterized by a 6-mm loss of tooth attachment as detected by the dental health professional by means of dental probes.

If periodontitis is found in children or young adults or if it progresses rapidly, the primary care provider should be alert to the possibility of a systemic cause such as diabetes mellitus, Down syndrome, hypophosphatasia, neutropenia, leukemia, leukocyte adhesion deficiency, or histiocytosis. A less common, rapidly progressing form of adult periodontitis begins in the third or fourth decade of life and is associated with severe gingivitis and rapid bone loss. Several systemic diseases, including diabetes, HIV infection, Down syndrome, and Papillon-Lefèvre syndrome, have been associated with this rare form of periodontitis. Localized juvenile periodontitis (LJP) and localized prepubertal periodontitis (LPP) are forms of early onset periodontitis seen in young children and teenagers, respectively, without evidence of systemic disease. LJP is more common among African American children. It affects the first molars and incisors, with rapid destruction of bone. Although there is some evidence for autosomal transmission, it is likely heterogenous. Both LJP and LPP are believed to be the result of a bacterial infection (specifically implicated is *Actinobacillus actinomycetemcomitans*) and, possibly, host immunologic deficits.

** Clinical Findings**

**A. Symptoms and Signs**

Clinical signs of gingivitis and periodontitis include interdental papillae edema, erythema, and bleeding on contact during tooth brushing or dental probing (Figure 45-11). The amount of gingival inflammation and bleeding and the probing depth of gingival pockets determine the severity of periodontal disease. Tartar, gum recession, and loose teeth are characteristics of severe periodontal disease. For children younger than 4 years of age, loss of primary teeth may be the first clinical sign of periodontal disease and the systemic manifestation of hypophosphatasia. Dental probing by the dental health professional will detect sulcus depth.

**B. Imaging Studies**

Bone loss can be detected by radiographs and bone density scans.

**Periodontal Health & Systemic Disease**

Emerging evidence, particularly from the dental literature, suggests that periodontal disease may be a risk factor for systemic conditions such as cardiovascular disease, diabetes mellitus, and adverse pregnancy outcomes of preterm labor and low birth weight. Current evidence supports a bidirectional relationship between diabetes and periodontal disease. Periodontal disease is a risk factor for poor glycemic control among diabetic patients, and diabetes is associated with increased severity of periodontal disease. Studies showing the relationship between periodontal disease and cardiovascular disease have proposed that patients with chronic bacterial infection or periodontitis may have (1) a bacteria-induced platelet-aggregation defect that contributes to acute thrombolic...
events, (2) injury to vascular tissue by bacterial toxins, or (3) vascular injury resulting from a host inflammatory response that predisposes the patient to a systemic disorder such as atherosclerosis. Additionally, the link between periodontal disease and preterm labor has several proposed biological mechanisms, one of which is the infection that is mediated by prostaglandins and cytokines among patients with severe periodontitis. This infection causes decreased fetal growth and premature labor.

**Prevention & Treatment**

Good oral hygiene is essential for the prevention and control of periodontal diseases. Gingivitis, the mildest form of periodontal disease, is reversible with regular tooth brushing and flossing. An added benefit is provided by over-the-counter and prescription antimicrobial mouth rinses, such as a 0.1%-0.2% chlorhexidine gluconate aqueous mouthwash used twice a day. Caution is advised when chlorhexidine is used because it causes superficial staining of the teeth of patients who drink tea, coffee, or red wine. The treatment of periodontitis includes professional care to remove tartar and may require periodontal surgery.

Because tobacco use is an important risk factor for the development and progression of periodontal disease, patients should be counseled about tobacco cessation. Systemic diseases such as diabetes that may contribute to periodontal disease should be well controlled.


**ORAL & OROPHARYNGEAL CANCERS**

**General Considerations**

In the United States, cancers of the oral cavity and oropharynx comprise approximately 3% of all cancers among men (the ninth most common cancer among men) and 2% of all cancers among women. The prevalence of these cancers increases with age. Since the 1970s, the incidence of these cancers and the death rates associated with them have been slowly decreasing, except among African American men, for whom the incidence and 5-year mortality rates are nearly twice as high as for white men.

The overall survival rate for patients with oral and oropharyngeal cancers is only about 51% and has not changed substantially over the past 20 years. However, the 5-year survival estimate for patients with lip carcinoma is more than 90%; this high survival rate is due in part to early detection. Most oral and oropharyngeal cancers are squamous cell carcinomas that arise from the lining of the oral mucosa. These cancers occur most commonly (in order of frequency) on the tongue, the lips, and the floor of the mouth. Sixty percent of oral cancers are advanced by the time they are detected, and about 15% of patients have another cancer in a nearby area such as the larynx, esophagus, or lungs. Early diagnosis, which has been shown to increase survival rates, depends on the discerning clinician who recognizes risk factors and suspicious symptoms and can identify a lesion at an early stage.

Table 45-4 shows the risk factors associated with oral and oropharyngeal cancers. Tobacco use and heavy alcohol consumption are the two principal risk factors responsible for 75% of oral cancers. The incidence of oral cancer is higher among persons who smoke or drink heavily than among those who do not.

**Prevention**

All forms of tobacco, including cigarette, pipe, chewing, and smokeless, have been shown to be carcinogenic in the susceptible host. Alcohol has been identified as another important risk factor for oral cancer, both independently and synergistically when heavy consumers of alcohol also smoke. Therefore, primary prevention in the form of reducing or eliminating the use of tobacco and alcohol has been strongly recommended. The US Preventive Services Task Force (USPSTF) has not endorsed annual screening (secondary prevention) for asymptomatic patients, stating, “there is insufficient evidence to recommend for or against routine screening” and “clinicians may wish to include an examination for cancerous and precancerous lesions of the oral cavity in the periodic health examination of persons who chew or smoke tobacco (or did so previously), older persons who drink regularly, and anyone with suspicious symptoms or lesions detected through self-examination.” However, the American Cancer Society and the National Cancer Institute’s Dental and Craniofacial Research Group support efforts that promote early detection of oral cancers. The American Cancer Society recommends annual oral cancer examinations for persons aged 40 years or older.

<table>
<thead>
<tr>
<th>Table 45-4. Risk factors associated with oral and oropharyngeal cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco use (smoking or using smokeless tobacco or snuff)</td>
</tr>
<tr>
<td>Excessive consumption of alcohol</td>
</tr>
<tr>
<td>Viral infections (HSV, HIV, EBV)</td>
</tr>
<tr>
<td>Chronic actinic exposure</td>
</tr>
<tr>
<td>Betel quid use</td>
</tr>
<tr>
<td>Lichen planus</td>
</tr>
<tr>
<td>Plummer-Vinson or Paterson-Kelly syndrome</td>
</tr>
<tr>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Dietary factors (low intake of fruits and vegetables)</td>
</tr>
</tbody>
</table>

HSV, herpes simplex virus; HIV, human immunodeficiency virus; EBV, Epstein–Barr virus.
Because primary care providers are more likely than dentists to see patients at high risk of oral and oropharyngeal cancers, providers need to be able to counsel patients about their behaviors and to be knowledgeable about performing oral cancer examinations. The primary screening test for oral cancer is the oral cancer examination, which includes inspection and palpation of extraoral and intraoral tissues (Table 45-5).

### Clinical Findings

#### A. Symptoms and Signs

Early oral cancer and the more common precancerous lesions (leukoplakia) are subtle and asymptomatic. They begin as a white or red patch, progress to a superficial ulceration of the mucosal surface, and later become an endophytic or exophytic growth. Some lesions are solitary lumps. Larger, advanced cancers may be painful and may erode underlying tissue.

According to the definition of the World Health Organization, leukoplakia is “a white patch or plaque that cannot be characterized clinically or pathologically as any other disease.” The lesions may be white, red, or a combination of red and white (called speckled leukoplakia or erythroleukoplakia). Multiple studies have shown that these lesions undergo malignant transformation. Biopsies have shown that erythroplakia and speckled leukoplakia are more likely than other types of leukoplakia to undergo malignant transformation with more severe epithelial dysplasia. Figures 45-12 and 45-13 show leukoplakia.

Oropharyngeal carcinomas can be found in the intraoral cavity, the oral cavity proper, and the oropharyngeal sites. The most common intraoral site is the tongue; lesions frequently develop on its posterior lateral border. Lesions also occur on the floor of the mouth and, less commonly, on the gingiva, buccal mucosa, labial mucosa, or hard palate.

A common cancer of the oral cavity proper is lower lip vermilion carcinoma. These lesions arise from a precancerous lesion called actinic cheilosis, which is similar to an actinic keratosis of the skin. Dry, scaly changes appear first and later progress to form a healing ulcer, which is sometimes mistaken for a cold sore or fever blister. Figure 45-14 shows actinic cheilosis.

Oropharyngeal carcinomas commonly arise on the lateral soft palate and the base of the tongue. Presenting symptoms may include dysphagia, painful swallowing (odynophagia), and referred pain to the ear (otalgia). These tumors are often advanced at the time of diagnosis. Oral cancer metastasizes regionally to the contralateral or bilateral cervical and
submental lymph nodes. Distant metastases are commonly found in the lungs, but oral cancer may metastasize to any other organ.

B. Diagnosis

All patients whose behaviors put them at risk of oral cancer should undergo a thorough oral examination that involves visual and tactile examination of the mouth, full protrusion of the tongue with the aid of a gauze wipe, and palpation of the tongue, the floor of the mouth, and the lymph nodes in the neck. Because oral cancer and precancerous lesions are asymptomatic, primary care providers need to carefully examine patients who are at risk of oral or oropharyngeal carcinomas. Using a scalpel or small biopsy forceps, the primary care physician should perform a biopsy of any non-healing white or red lesion that persists for more than 2 weeks. Alternatively, the patient may be referred to a dentist, an oral surgeon, or a head and neck specialist, who can perform the biopsy. Patients with large lesions or advanced disease should undergo a complete head and neck examination, because 15% of these patients will have a second primary cancer at the time of diagnosis. Neck nodules with no identifiable primary tumor may be evaluated by fine-needle aspiration.

C. Imaging Studies

Imaging studies such as computed tomography with contrast and magnetic resonance imaging of the head and neck are used to determine the extent of disease and involvement of the cervical lymph nodes for the purposes of staging.

Treatment

Treatment for oral and lip cancers includes chemotherapy, surgery, radiation, or some combination of these therapies, depending on the extent of the disease. These treatments can cause severe stomatitis (inflammation of the mouth), xerostomia (dry mouth), disfigurement, altered speech and mastication, loss of appetite, and increased susceptibility to oral infection. The management of these complications requires a multidisciplinary team approach by the clinician, oral surgeon, oncologist, and speech therapist. Early diagnosis allows better treatment, cosmetic appearance, and functional outcome and increases the probability of survival. Patients should be encouraged to visit their dental health provider before beginning cancer therapy so that existing health problems can be treated and some complications can be prevented.

Silverman S Jr: Demographics and occurrence of oral and pharyngeal cancers. The outcomes, the trends, the challenge. J Am Dent Assoc 2001;132;7S. [PMID: 11803655]

Oral effects of Medications

Medications used to treat certain systemic conditions may have oral manifestations. Most commonly these include xerostomia (dry mouth), gingival hyperplasia, dental caries and erosions, and osteonecrosis of the jaw.

Xerostomia, commonly seen in the elderly, is caused by hypofunction of the salivary gland, but has also been caused by antihypertensives, antidepressants, protease inhibitors, antihistamines, and diuretics. Xerostomia increases the risk of denture sore and caries, since saliva is a lubricant with antimicrobial properties. Symptoms include a sensation of dry mouth. Treatment is avoidance of medications known to cause xerostomia and careogenic foods, good oral hygiene, and salivary substitutes or stimulants.

Gingiva hyperplasia has been associated with calcium channel blockers, methotrexate, cyclosporine, and phenytoin. Dental caries maybe caused by syrups such as cough medicines, and dental erosions may follow use of β-blockers, calcium channel blockers, nitrates, and progesterone. Treatment is avoidance of medications associated with gingiva hyperplasia.

Avascular osteonecrosis of the mandible and maxilla have been associated with bisphosphonates. Symptoms include swelling and pain, difficulty eating, bleeding, lower lip paresthesia, and loose and mobile teeth. Since radiographs are nonspecific, lesions should be biopsied for definitive diagnosis. Risk factors include IV bisphosphates, cancer, invasive dental procedures, smoking, steroid use, radiation therapy, and poor dental hygiene. Patients should be advised to avoid dental procedures while taking these medications.


Global References for Oral Health


Web Sites

Academy of General Dentistry: http://www.agd.org
American Association of Public Health Dentistry: http://www.aaphd.org
American Dental Association: http://www.ada.org
Children’s Dental Health Project: http://www.childdent.org
Health Resources and Services Administration (HRSA) Oral Health Initiative: http://www.hrsa.gov/oralhealth
Smiles for Life: http://www.smilesfororalhealth.org
Medication therapy is an integral element of health care interventions. In 2005, approximately 2.5 billion prescriptions were dispensed in the United States. Two-thirds of physician office visits result in a prescription. Medication use is often supported by “hard science” and evidence; clinical practice often shifts to the “soft science” of medicine, trying to understand patients, their histories, personalities, medication adherence, and a way to provide the best possible care.


Of the billions of prescriptions filled, it is estimated that half are taken improperly. Achieving a balance between “hard” and “soft” sciences—by providing evidence-based medication therapy that patients will adhere to—becomes paramount. This chapter explores patient adherence; provider’s considerations such as evidence, pharmacokinetics/pharmacodynamics, and safety; and health care system factors such as formulary systems/resources.


**TAKING A MEDICATION HISTORY**

Discrepancies among documented medication therapy records and actual patient use of medications are common and occur with all classes of medications. Therefore, the first step for the provider in determining optimal medication therapy is to understand what medications the patient is actually taking and how they are taking them. The physician must also inquire in a nonjudgmental manner whether patients are taking any over-the-counter (OTC) medications, herbal, or vitamin products. Over 12% of the population take herbals on a yearly basis, but only 38.5% of these patients report this to their physician. Table 46-1 lists five concise steps to a medication review. To obtain an accurate medication history, the physician should start by asking open-ended questions; for example, “What medications are you taking?” This approach avoids the common mistake of assuming the patient is taking all their medications as prescribed. Although conducting an open-ended medication history may take more time up front, it may ultimately prevent over- or underprescribing and may also improve patient relationships. *Polyparmacy* is defined as the concurrent use of multiple medications or the prescribing of more medications than are clinically indicated. Polypharmacy can be minimized by a thorough medication regimen review.


**Evaluation & Change**

A thorough medication history and safety assessment begins to clarify many aspects of a patient’s medication regimen and, paired with evidence, can help the clinician make a solid patient-specific decision about a regimen. *Evidence-based*
**Table 46-1.** Reviewing a medication regimen.

1. Match the medication with the diagnosis  
2. Review the regimen for duplication of therapy  
3. Elicit from the patient if they are taking the medicine  
4. Review laboratory results and patient history for efficacy/toxicity of the regimen  
5. Strive to remove any unnecessary agents from the regimen

**Table 46-2.** EBM sources.

### Clinical Information Internet Sources
- Agency for HealthCare Research and Quality  
  - [http://www.ahrq.gov](http://www.ahrq.gov)  
- Bandolier  
  - [http://www.jr2.ox.ac.uk/Bandolier/index.html](http://www.jr2.ox.ac.uk/Bandolier/index.html)  
- Centre for EBM  
  - [http://www.cebm.net/](http://www.cebm.net/)  
- The Cochrane Library  
  - [http://www.cochrane.org](http://www.cochrane.org)  
- Journal of Family Practice POEMS  
  - [http://www.jfponline.com](http://www.jfponline.com) or [http://www.medicalinfo retriever.com](http://www.medicalinfo retriever.com)

### Evidence-Based Guideline Web Sites
- Agency for HealthCare Research and Quality  
  - [http://www.ahrq.gov/clinic](http://www.ahrq.gov/clinic)  
- Clinical Evidence, BMJ Publishing Group  
  - [http://www.clinicalevidence.org](http://www.clinicalevidence.org)  
- Health Web  
- Institute for Clinical Systems Improvement  
  - [http://www.ICSI.org](http://www.ICSI.org)  
- Medical Matrix  
  - [http://medmatrix.org](http://medmatrix.org)  
- National Guideline Clearinghouse  
- Primary Care Clinical Practice Guidelines  
  - [http://medicine.ucsf.edu/resources/guidelines](http://medicine.ucsf.edu/resources/guidelines)

**EXPLORING THE EVIDENCE: USE OF GUIDELINES & FORMULARIES**

Formulary systems using evidence-based guidelines and principles have been developed by health care systems as a result of the information era in efforts to provide evidence-based, cost-effective medication management. Drug formularies may be defined as “a continuously revised list of medications that are readily available for use within an institution and reflect the current clinical judgment of the medical staff.” These systems provide an organized, evidence-based approach to care and have beneficial effects in improving the process of care, patient outcomes, promoting cost containment, cost-effective care, or both, and are recommended by the US Presidents’ Advisory Commission on Consumer Protection and Quality.


Evidence-based guidelines are an example of providing high “usefulness” in literature review and application. A guideline is defined by the Institute of Medicine as “systematically developed statement to assist physicians in patient decisions about appropriate health care for specific clinical circumstances.” Several types of evidence-based guidelines exist, and the strength of evidence varies. Evidence-based clinical practice guidelines incorporate recent literature regarding the effectiveness of therapy and clinical experience. Expert consensus guidelines may be the simplest type of guideline; however, limitations to this approach are inherent author bias and limited evidence-based sources. Outcomes-based guidelines incorporate measures of effectiveness to validate a positive impact on patient care.

The Cochrane Collaboration is an example of a system to provide sound clinical practice guidelines. Currently, the Cochrane Collaboration provides systematic reviews, maintains a registry of trials, and is a leading provider of evidence-based guidelines. Cochrane reviews may be located in the Cochrane Library, Cochrane Collaboration, or Cochrane Reviews’ Handbook at the following site: http://www.cochrane.org. In addition to the Cochrane Collaboration, many medical/professional societies, health maintenance organizations, and the Agency for Health Care Policy and Research provide practice guidelines and Internet links to the guidelines.


As the demand for published, evidence-based guidelines grows, so does the need for outcomes-focused formularies that consider effectiveness, safety, and cost implications to practice. Drug formulary systems are fundamental tools of hospitals, health systems, and managed care organizations to designate preferred products and provide rational, cost-effective prescribing decisions. Traditional formulary decisions are based on comparative efficacy, safety, drug interactions, dosing, pharmacology, pharmacokinetics, and cost. Pharmacy and Therapeutics (P&T) Committees represent all major disciplines of practice and guide the formulary decision process with a goal of providing high-quality, safe, and cost-effective prescribing.

Johnson N: Creating and outcomes-focused formulary: resources to assist in determining drugs’ value. Formulary 2001;36:807-810.

BALANCING THE EVIDENCE WITH THE PATIENT

Medication Adherence

“Drugs don’t work in patients who don’t take them”—E. Coop, MD, former US Surgeon General. Poor adherence to medication is a national concern and a significant barrier in optimal medication management. Adherence to medication is defined as the extent to which a person’s behavior coincides with his medical advice. Medication nonadherence is estimated to result in 125,000 deaths/y in the United States and is responsible for 10% of hospital and 23% of nursing home admissions. The average rate of medication adherence is approximately 50% to 65%. There are no significant predictors of patient nonadherence and the reason why patients do not adhere to their regimen widely varies between patients and depends on the nature of the illness, patient’s involvement in the health care decisions, and gender.


Because it is difficult to predict patient adherence behavior, it is critical to identify barriers to adherence that may be controlled or modified. The most common reason for medication nonadherence is that the patient forgot. Other reasons include: other priorities, decision to omit dose, lack of information, and emotional factors. No one intervention has been proven to consistently improve adherence; therefore, a combination of interventions is often required.


Morisky and colleagues developed a validated four-question assessment to gauge patient adherence behaviors. Patients are asked:
1. Do you ever forget to take your medications?
2. Are you careless at times about taking your medications?
3. When you are feeling better, do you sometimes stop taking your medications?
4. Sometimes if you feel worse, do you stop taking your medications?
5. Do you ever forget to take your medications?
6. Keep medication regimens as simple as possible.
7. Troubleshoot potential obstacles (ask the patient if they foresee any problems).
8. Build reminders into the treatment plan.
9. Include a plan to monitor adherence.
10. Ask patients how they are doing.


If nonadherence to a medication regimen is identified, consider assisting the patient by helping them to create a medication list or calendar, provide refill reminders, use a pill organizer, develop a medication reminder chart, or consider electronic devices and compliance services. Additionally, consider referring the patient to their pharmacist for support.

Managing Medication Cost

In 2008, the average price of a single prescription was $71.69. In the United States, a total of $253.6 billion was spent on drug therapy during that same year. Although the elderly comprise 13% of the US population, they account for 34% of all prescriptions filled or 41% of prescription costs. If the cost of the medication is a factor to nonadherence, several steps can be taken.

First, determine whether the patient has insurance. If the patient has prescription insurance coverage, an attempt should be made to prescribe within the formulary to aid in decreasing the patient’s copayment. Often patients with insurance may complain their copayments are too high; if they already have insurance, there are few other funding options. In such cases, a thorough medication regimen review with the intention of decreasing numbers of medications, if medically appropriate, can improve safety and decrease cost of medication regimens.


For patients who do not have insurance, a few options can be pursued to help them obtain medications at a reduced cost.

1. If the patient is 65 years of age or older, he or she can apply for drug coverage through Medicare Part D. To determine which plans the patient is eligible for, and associated costs, visit www.medicare.gov.
2. Determine if your patient qualifies for any federal, state, or military operated program. Income requirements apply.
3. Have contact information available for state Medicaid programs.
4. Consider applying for medication assistance programs sponsored by pharmaceutical manufacturers. Pharmaceutical manufacturers supplied free or low-cost medications to over 5 million people in the United States. Several Internet sites are available to aid in obtaining information on how to use these programs, including www.needymeds.com, www.rxhope.com, and www.themedicineprogram.com.
ENSURING MEDICATION SAFETY

The majority of adverse drug reactions (ADRs) are “dose dependent” and potentially preventable. With the direct costs of ADRs estimated to be between $1.6 and $4 billion and the estimation of ADRs being the fourth to sixth leading cause of death, there is a significant need for a greater understanding of the mechanisms of these reactions. Patients at the highest risk of experiencing ADRs include those on five or more medications; those hospitalized or in nursing home facilities; and those with diabetes, cancer, and renal or hepatic impairment. The classes of drugs most commonly associated with ADRs include nonopioid and opioid analgesics, antibiotics, cardiovascular agents, anticoagulants, and diuretics. Obtaining a thorough patient history, proactive assessment and monitoring of drug safety, ensuring proper indication of individual medications, and patient counseling can all help to reduce potential ADRs.

Some basic inquiries, as listed in Table 46-3, can assist the physician in determining if an ADR is truly linked to a particular drug. During premarketing trials, if 1500 patients or more are exposed to a drug, the most common ADRs will be detected. However, more than 30,000 patients must be exposed to the drug in the postmarketing period to detect an ADR in one patient with a power of 0.95 to discover an incidence of 1 in 10,000. Two simple ways by which physicians can anonymously report ADRs are (1) by logging on to www.fda.gov/MEDWATCH or calling 800-FDA-1088, or (2) if in a hospital or nursing home setting, by contacting the pharmacy or local drug information center.

Table 46-3. Identifying ADRs.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there any previous reports of an ADR occurring with this agent?</td>
<td></td>
</tr>
<tr>
<td>2. Consider the timing of the ADR. Does it match the drug’s pharmacokinetic profile for onset of effect?</td>
<td></td>
</tr>
<tr>
<td>3. Was their a recent dosage increase or decrease?</td>
<td></td>
</tr>
<tr>
<td>4. Was a new medication recently added to or removed from the regimen?</td>
<td></td>
</tr>
<tr>
<td>5. If serum drug levels were available, were they in the supratherapeutic range?</td>
<td></td>
</tr>
<tr>
<td>6. Has the patient had a similar reaction to medications in the past, especially those of the same class?</td>
<td></td>
</tr>
<tr>
<td>7. Are there other drugs or disease conditions that could also cause the symptoms of the event?</td>
<td></td>
</tr>
<tr>
<td>8. When the drug was discontinued, did the symptoms resolve?</td>
<td></td>
</tr>
</tbody>
</table>

MATCH THE PATIENT & THE DRUG: PHARMACOKINETIC AND PHARMACODYNAMIC PRINCIPLES

Although a subset of ADRs is unpredictable, those that are preventable include drug-drug interactions. A grasp of basic pharmacokinetic/pharmacodynamic principles is needed to prevent interactions. Pharmacokinetics characterizes the rate and extent of absorption, distribution, metabolism, and elimination of a drug. Pharmacodynamics is the study of the relationship between the drug concentration at the site of action and the patient response. In reviewing the patient history, consider the following characteristics in relation to drug pharmacokinetics:

- **Age**: Most drugs were studied in adult patients and recommended dosages may vary in different age groups.
- **Sex**: Although data are limited, male and female patients can metabolize and eliminate drugs differently, so the optimal drug dosages may differ.
- **Weight**: For patients who are obese or cachectic, changes in drug clearance or volume of distribution often necessitate dosage adjustments.
- **Disease conditions**: Three conditions that must be approached with special caution when prescribing any drug are heart failure (HF), renal disease, and hepatic failure. As HF progresses, bodily organ blood flow declines; the ensuing drug clearance decline necessitates lower dosages.


for many agents. As kidney or liver function declines, the renal and hepatic elimination of drugs decreases, leading to lower dosage requirements for renally and hepatically cleared agents, respectively.

- **Genetics:** Pharmacogenomics is the study of the relationship of genetics in drug metabolism and ADRs. In a systematic review by Phillips and colleagues, of 27 drugs known to frequently cause ADRs, 59% were known to be influenced by individual patient genetic characteristics.

- **Inhibitor:** Drug(s) competes with another drug(s) for a specific isozyme-binding site, rendering the isozyme inactive.


A review of the patient’s medication list may reveal drugs that compete or use the same enzyme system. A change in drug selection may prevent a drug interaction. Physicians may check if a drug is a CYP substrate, inducer, or inhibitor at the web site: http://medicine.iupui.edu/clinpharm/ddis/table.asp.

**KEEPING UP WITH THE LITERATURE:**

Subscribing to survey services is one way to stay current with the pertinent literature, while decreasing the amount of work and time required. Survey services provide an efficient means of reviewing a plethora of medical journals and articles; however, there may be a tendency to overemphasize positive conclusions or draw conclusions that are not fully supported by the data. The conclusions and recommendations presented by such services should be evaluated before incorporating the information to practice.


Three basic categories of survey services exist: (1) abstracting services; (2) review services; and (3) true newsletters. Abstracting services for family medicine practitioners include, but are not limited to, the ACP Journal Club, the Journal of Family Practice, and Journal Watch Online. All have a goal of providing relevant information in a timely manner. ACP Journal Club (http://www.acpjoc.org) is published by the American College of Physicians-American Society of Internal Medicine. This service provides brief, high level summaries of current original articles and systematic reviews in a structured abstract format. The ACP Journal Club reviews over 100 journals and uses prestated criteria to select and evaluate data. Pertinent information summaries are provided to subscribers on a bimonthly bases. The Journal of Family Practice (http://www.jfponline.com) provides family practice physicians with timely, reliable information supplemented by expert commentary on clinically applicable topics. Journal Watch Online
(http://www.jwatch.org) is supported by the publishers of the New England Journal of Medicine. This service, similar to the others, provides current summaries of the most important research. An editorial board, composed of physicians from many specialty areas reviews, analyzes, and summarizes 55-60 critically important articles. The summaries are published on a bimonthly basis. In addition, this service features Clinical Practice Guidelines Watch and editorials of the year’s top medical stories.


Review Services provide a concise summary of the specific topic areas, rather than a survey of the literature. One example of a review service is The Medical Letter (http://www.medletter.com). The Medical Letter is published by an independent nonprofit organization and provides critical appraisals of new medications or uses for medications in a clinical context, comparing and contrasting the new medications to similar established agents. This concise publication is printed bimonthly. Another example of a review service is Primary Care Reports (http://www.ahcpub.com/ahc_root_html/products/newsletters/pcr.html). This service is printed bimonthly and is intended to provide review articles on critical issues in primary care; treatment recommendations are provided with each review.


True newsletters provide concise reviews of current literature with topics from news media and other sources. Examples of this type of newsletter include The Drug and Therapeutics Bulletin and Therapeutics Letter, The Drug and Therapeutics Bulletin (http://www.dtb.bmj.com) is a concise monthly bulletin that provides evaluations of medications and summarizes randomized, controlled, clinical trials, and consensus statements. This service provides informed and unbiased assessments of medications and their overall place in therapy. The Therapeutics Letter (http://www.ti.ubc.ca/en/therapeuticsletters) is a bimonthly newsletter that targets problematic therapeutic issues and provides evidence-based reviews written and edited by a team of specialists and working groups of the International Society of Drug Bulletins.


It is recommended that physicians use these services as a scanning system to determine which primary literature articles are critical to read in-depth. Survey services provide the information, but it is the clinician’s responsibility to analyze, interpret, and apply this information to provide optimal patient care decisions. The goal of information sourcing is to maximize the usefulness score: increase validity and relevance while minimizing the workload.

**DRUG INFORMATION/PHARMACOTHERAPY TEXTBOOKS:**

Textbooks are among the most common sources of information used by medical professionals. Because drug inquiries are frequent topics of clinical questions, it is important to review drug information textbooks. Despite the ease and convenience of use, textbooks have inherent limitations, including the currency of information, insufficient detail, potential bias with regard to the subject matter, lack of expertise of the author regarding the content, and errors in transcription or incorrect interpretation by the author or during the publication process.


There are a number of drug information textbooks and resources available to address general or specific pharmaceutical categories (eg, ADRs, drug interactions, therapeutic use, dosing). Commonly used drug information resources include, but are not limited to, the Physicians’ Desk Reference (PDR), American Hospital Formulary Services (AHFS), MICROMEDEX, Drug Facts and Comparisons (Facts & Comparisons), and the Drug Information Handbook.

The most common drug information resource used by family medicine practitioners is the Physicians’ Desk Reference (PDR). The PDR is a compilation of drug information from manufacturer product information. AHFS contains drug monographs with information similar to that found in the PDR with additional detailed therapeutic information, including off-label indications and dosing, and ADR summaries, often providing cautionary guidance and recommendations. MICROMEDEX is a computerized drug information resource that contains facts from the DRUGDEX Information System. This is a well-referenced, easily searchable, expansive drug information reference, housing information on prescription, nonprescription, and herbal products. Facts & Comparisons contains information on prescription and nonprescription medications. Medications are listed by category with summary sections that provide tables and comparative drug class data. The Drug Information Handbook is a pocket-sized reference that includes referenced
Table 46-4. Credible sources of natural product information.

- The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines
- Herbal Companion to AHFS DI, 2001
- Micromedex AltCareDex
- Natural Medicines Comprehensive Database (recommended)
- The Natural Pharmacist (recommended)
- PDR for Herbal Medicines, 1st ed.
- The Review of Natural Products


Textbooks focusing on herbal and dietary supplements are increasingly important, as their use is widespread. The Natural Medicines Comprehensive Database and the National Library of Medicine are two electronic references that consistently provide valid natural production information. Table 46-4 lists other credible sources of natural product information.


With the Internet connectivity of handheld systems, updated evidence-based medication information is easily accessible. For example, the National Library of Medicine has customized PubMed (http://ncbi.nlm.nih.gov/entrez/query/Books.live/hHelp/mobile.html) for handheld computers. ePocrates Rx (www.epocrates.com) has been advocated by insurance companies and government agencies to enhance clinical management and decrease medication errors.

An important feature of the handheld technology to the medical professional is the medical-/pharmacy-related software, and the flexibility, accessibility, and usability of these systems. Several drug information sources are available; therefore, when evaluating drug information sources, consider accuracy, comprehensiveness, and time interval of updates among other items. A study evaluated the core and supplemental drug information databases available for use with PDAs, and the best overall performers (in order of total scores) were LexiDrugs Platinum, Tarascon Pocket Pharmacopeia, ePocrates RxPro, and Clinical Pharmacology OnHand.


Oxman AD et al: Users guides to the medical literature VI. How to use an overview. JAMA 1994;272:1367-1371. [PMID: 7933399]
Medical Economics Staff, Micromedex. USP DI. The United States Pharmacopeial Convention, Inc, 1998.
Shaughnessy AF, Slawson DC: Are we providing doctors with the training and tools for lifelong learning? BMJ 1999;319:1280.
Gillespie G: PDAs are willing, but will they be able? Health Data Manag 2002;10(12):21-28. [PMID: 12528640]
A common misconception in the medical community is that genetic disorders consist of a collection of extremely rare conditions not often relevant to day-to-day clinical practice. In fact, essentially every medical condition affecting mankind has at least some genetic component to its etiology. The study of how mutations in single genes cause rare disease (genetics) is gradually being eclipsed by research on how mutations in multiple genes interact with each other and the environment to result in health and disease (genomics). Knowledge derived from genomic discoveries is reshaping the underpinnings of much of medical practice, and will continue to do so for decades to come. At a practical level, recent advances have taught us a tremendous amount about the basis of common conditions like diabetes, heart disease, and cancer. This new knowledge is being rapidly translated into approaches for disease risk assessment, prevention, and treatment. Likewise, the study of how genes affect drug metabolism (pharmacogenetics) is being increasingly used to inform drug prescribing (see Chapter 48). Importantly, primary care physicians should not lose sight of the fact that so-called rare single-gene disorders collectively comprise a significant proportion of pediatric and adult illnesses.

Obtaining a medical family history provides the most effective current method to rapidly determine if an individual is at genetic risk of developing common disorders. Additionally, for most individuals family history captures at least some of the environmental and cultural contributors to disease risk. For many common diseases patient reported
family history of disease in first-degree relatives is highly sensitive and specific. Importantly, common disorders often have modifiable risk factors that can be addressed or for which screening interventions can be instituted (Table 47-1). Family history evaluation can also be useful in identifying rare conditions that may not otherwise be considered in a differential diagnosis. For example, a child with developmental delay may have other family members who have had developmental delays or more severe congenital abnormalities. The Office of the U.S. Surgeon General provides an excellent free patient-focused, web-based tool for family history collection called My Family Health Portrait.

Sometimes specific questions will suffice when screening for a particular disease. However, recording family medical history in the form of a pedigree (Figure 47-1) can provide a concise visual tool for recording and interpreting medical information. When obtaining or updating a pedigree, the following general information may be recorded: patient name; date recorded or updated; consanguinity (note relationship); ethnic background of each grandparent, if known; and name and credentials of the person who recorded the pedigree. It is often helpful to include a key that explains symbols used in the pedigree (see Figure 47-1). Specific information such as age, relevant health information, age at diagnosis, age at death (with year, if known), cause of death, infertility (if known), and information about pregnancies (including miscarriages, stillbirths, and pregnancy terminations, along with gestational ages of family members or their partners) is then obtained for each listed family member.

Open-ended questions, such as “describe any medical conditions that affect your mother,” provide the most information when obtaining a medical family history. It is often more efficient for patients to begin to generate their own family history at home, and several family history tools have been developed for use by patients. Family medical history may also be confirmed through medical record documentation.

### Inheritance Patterns

A pedigree can help to identify a pattern of inheritance for a particular disorder, which can be useful in establishing a diagnosis. For example, if mental retardation is present in more than one generation in a family and only male family members are affected, an X-linked disorder should be considered. Table 47-2 reviews clues to determine patterns of inheritance. Unfortunately, limited collection of family history data, small family size, nonpaternity, delayed age of onset of symptoms, mild expression of disease symptoms, and sex-limited expression of disease symptoms (eg, a woman with a healthy father whose sisters have breast and ovarian cancer) can complicate the identification of patterns of inheritance.

### Medical History “Red Flags”

In addition to family history, there are certain clinical clues derived from the patient that should alert a clinician to consider a genetic cause for a medical condition (Table 47-3). Important issues to consider in all age groups are multiple congenital anomalies, earlier-than-usual onset of common conditions, extreme pathology (eg, rare tumors or multiple primary cancers), developmental delay or degeneration, and extreme laboratory values (eg, extremely high cholesterol level).

<table>
<thead>
<tr>
<th>Anemia</th>
<th>Breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy</td>
<td>Colon cancer</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Developmental delay</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Emphysema</td>
<td>Gastric cancer</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Hip dysplasia</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>Liver cancer</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Syncope</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>Thyroid cancer</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Visual impairment</td>
<td></td>
</tr>
</tbody>
</table>

Source: Adapted, courtesy of National Human Genome Research Institute, National Institutes of Health, Bethesda, MD.
Figure 47-1. Standard pedigree symbols and sample pedigree.
Family medical history or clinical clues may lead a clinician to consider genetic testing. Many primary care providers may be unfamiliar with a particular genetic disorder or the availability of genetic testing for a disorder. GeneTests (http://www.genetests.org) is a web-based resource that contains concise reviews and information on genetic testing availability for many genetic disorders. This web site also provides information regarding access to genetic specialists, including medical geneticists (physicians who have residency training in genetics), genetic counselors (individuals with masters degree–level training in genetics), and PhD-qualified individuals with formal clinical genetics training.

**Table 47-2. Clues to determine patterns of inheritance.**

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Diagnostic Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant</td>
<td>Males and females equally affected&lt;br&gt;Transmission passes from one generation to another (vertical inheritance)&lt;br&gt;50% risk for each offspring to be affected&lt;br&gt;Variable expressivity: affected individuals in the same family may demonstrate varying degrees of phenotypic expression (severity)&lt;br&gt;Reduced penetrance: some individuals who have inherited a genetic mutation may not express the phenotype (“skipped generations” may be seen)</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>Males and females equally affected&lt;br&gt;Multiple affected offspring and unaffected parents (horizontal inheritance)&lt;br&gt;25% risk for each offspring to parents with an affected child</td>
</tr>
<tr>
<td>X-linked recessive</td>
<td>Affects more males than females&lt;br&gt;Heterozygous females are usually normal or have mild manifestations&lt;br&gt;Inheritance is through maternal side of the family (diagonal inheritance)&lt;br&gt;Female carriers have a 50% risk for each daughter to be a carrier and a 50% risk for each son to be affected&lt;br&gt;All daughters of an affected male are carriers, and none of his sons are affected</td>
</tr>
<tr>
<td>Multifactorial or complex</td>
<td>Risk highest for closest relatives to affected individuals&lt;br&gt;Multiple genes and environmental factors may contribute to risk&lt;br&gt;No well-defined pattern of inheritance in pedigree, “runs in the family”</td>
</tr>
</tbody>
</table>

*For more complex patterns of inheritance, see Korf B. Basic genetics. Prim Care Clin Office Pract 2004;31:461.

**GENETIC TESTING**

**Table 47-3. Genetic “red flags.”**

<table>
<thead>
<tr>
<th>Preconceptual/Prenatal</th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal or family history of known or suspected genetic disorder or congenital abnormality</td>
<td>One or more major malformations or dysmorphic features&lt;br&gt;Abnormal newborn screening&lt;br&gt;Abnormal development&lt;br&gt;Congenital hearing loss&lt;br&gt;Congenital blindness or cataracts&lt;br&gt;Constellation of features suggestive of genetic disorder or chromosome abnormality&lt;br&gt;Family history of known or suspected genetic disorder&lt;br&gt;Personal or family history of hereditary cancers&lt;br&gt;Development of degenerative neurologic disorder or unexplained seizures</td>
<td>Family history of known or suspected genetic disorder&lt;br&gt;Diagnosis of common disorder with earlier age of onset than typical, especially if multiple family members are affected (eg, cancer, heart disease, stroke, diabetes mellitus, hearing or vision loss, degenerative neurologic disorder), unusual manifestation of disease (eg, male breast cancer, multiple primary cancers)&lt;br&gt;Pediatric indications that have not yet been evaluated</td>
</tr>
</tbody>
</table>
Overview of Genetics

Human genetic information is contained in DNA and is present in nearly every cell in the human body. DNA consists of two long, paired strands of chemical bases called nucleotides. When cells divide, the DNA is compacted into complex structures composed of DNA and proteins called chromosomes; somatic cells have 46 chromosomes that are arranged in 23 pairs. The first 22 pairs, called autosomes, contain the genetic information for both men and women. The chromosomes that determine sex (X and Y) are paired as XX for females and XY for males. One chromosome from each pair is inherited from the mother and the other from the father. The germ cells or gametes (sperm and egg cells) contain only 23 chromosomes.

Chromosomes contain the thousands of genes that are the basis of inheritance. It is estimated that the human genome consists of about 20,000 protein coding genes. Genes consist of short segments of DNA along each chromosome that encode the blueprint for a protein or RNA molecule along with sequences of DNA that are likely involved in the control of gene expression. Each gene comes in a pair; one copy of each gene is inherited from an individual’s father and the other from his or her mother. The coding region of each gene specifies the instructions for a particular protein or RNA molecule according to the order in which the nucleotides are arranged. Proteins are responsible for the development and functioning of our bodies. RNA molecules play important roles. During cell replication and division, errors can occur in the DNA sequence (mutations), resulting in a protein that does not function properly or is present in insufficient amounts. Occasionally errors such as large deletions or rearrangements of chromosome structure occur that affect the function of multiple genes.

Methods of Genetic Testing

It is difficult to define what constitutes a “genetic” test. A test involving DNA or chromosome studies may be considered a genetic test but may not provide information about a person’s inherited genetic identity. An example of this type of “genetic” testing is the use of chromosome studies in the subclassification of leukemia. Conversely, tests that are considered routine, and not necessarily “genetic,” such as a cholesterol panel, have the potential to reveal genetic information about individuals and their family members (Table 47-4).

The test method used to detect a genetic disorder depends on what the genetic change associated with a particular condition primarily affects (eg, in the chromosomes, genes, or proteins [gene products]). The primary laboratory methods used are cytogenetic analysis, direct DNA testing, biochemical tests, and linkage analysis.

### A. Cytogenetic Analysis

Classic cytogenetic analysis is a microscopic study of chromosomes that is used to identify abnormalities in their number, size, or structure. Chemicals and tissue stains are used to produce a chromosome spread (karyotype). Fluorescent in situ hybridization (FISH) is a cytogenetic technique that uses synthetic DNA probes to evaluate whole chromosomes to rapidly detect missing or extra copies of chromosomes such as X, Y, 13, 18, and 21 in the prenatal setting or to detect submicroscopic deletions or duplications associated with specific genetic syndromes (eg, Prader-Willi, Angelman, DiGeorge). Recently classic cytogenetic testing as well as FISH is being

<table>
<thead>
<tr>
<th>Category</th>
<th>Disorder</th>
</tr>
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<tbody>
<tr>
<td>Hematologic</td>
<td>Anemias, Thrombophilias</td>
</tr>
<tr>
<td>Oncologic</td>
<td>Breast cancer, Colon cancer, Leukemia, Lymphoma, Skin cancer, Thyroid cancer</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Dementia, Headache, Movement disorders, Seizures, Stroke</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Depression, Schizophrenia</td>
</tr>
<tr>
<td>Endocrinologic</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Aneurysms, Cardiomyopathy, Hyperlipidemia, Hypertension, Sudden death</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Asthma, Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Renal</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>Glaucoma, Sudden vision loss</td>
</tr>
</tbody>
</table>

*For some of the listed disorders, only a small proportion of individuals are affected with inherited versions of the disease. Not all of the “genetic” tests for these disorders are DNA based. Some of the testing for these disorders is related to therapy and not necessarily to disease diagnosis or prognosis, and/or is not yet widely available clinically.
supplanted by gene-chip–based technologies such as array comparative genomic hybridization (CGH) that have very good sensitivity for small structural alterations in DNA.

1. Indications—Cytogenetic analysis is commonly ordered when patients are suspected of having a recognizable chromosome syndrome, in newborns with ambiguous genitalia or multiple malformations of unknown etiology, or after stillbirth of an infant with or without multiple malformations of unknown etiology. Other indications include patients with mental retardation, with or without congenital malformation; those with abnormal or delayed sexual development; couples with more than two unexplained spontaneous miscarriages; relatives of known balanced translocation or inversion carriers; and individuals with acquired chromosome abnormalities such as Philadelphia chromosome in chronic myelogenous leukemia.

2. Testable specimens—Suitable specimens for testing may be obtained from blood, fibroblasts,chorionic villi, amniocytes, or the products of conception.

3. Limitations—Cytogenetic testing may fail to identify an abnormality if it is not microscopically visible at the resolution for standard cytogenetic analysis. However, recent advances in array CGH have improved resolution. In addition, in patients with mosaicism, the abnormality may not be present in the cell type being analyzed.

B. Direct DNA Testing

Several methods are used to detect single-gene mutations. These include Southern blot analysis, multiplex polymerase chain reaction analysis, allele-specific oligonucleotide hybridization, gene-chip technologies, and direct gene sequencing. When a particular gene has not been discovered for a condition in a family, indirect methods such as linkage analysis are employed; this is typically used for rare conditions.

1. Indications—Direct DNA testing may be indicated for patients affected by or predisposed to a condition for which the gene change(s) that cause the condition have been identified (eg, cystic fibrosis, thrombophilia, hereditary breast and ovarian cancer syndrome). It may also be indicated in the setting of prescribing certain medications in order to avoid side effects (eg, abacavir hypersensitivity in human immunodeficiency virus [HIV] therapy) or to select appropriate therapies for patients (eg, KRAS testing prior to using cetuximab in colorectal cancer).

2. Testable specimens—Specimens may be obtained from blood, fibroblasts, chorionic villi, amniocytes, tumor tissue samples, or the products of conception.

3. Limitations—A negative test result may not rule out the condition. Some disorders are caused by numerous mutations within a gene (allelic heterogeneity), not all of which may be detected by a particular molecular method. Other disorders are caused by more than one gene, all of which may not be known (locus heterogeneity). Likewise, a positive test result does not always mean that the patient will develop the condition (eg, the patient may have reduced penetrance, a mutation of unknown clinical significance, or not be exposed to a critical environmental factor).

C. Biochemical Tests

Techniques such as metabolite testing, organic acid analysis, amino acid analysis, and assays of specific enzymes or proteins are used to identify or quantify absent or accumulated metabolites or measure the activity of a specific enzyme.

1. Indications—Biochemical tests are commonly used to help diagnose and monitor disorders such as hemochromatosis, familial hyperlipidemia, cancers, and the thrombophilias. Classically, biochemical tests are used to confirm the diagnosis of an inborn error of metabolism (eg, phenylketonuria, Tay-Sachs disease, Hurler syndrome).

2. Testable specimens—Blood, urine, fibroblasts, or specimens from muscle, tumor, or organ biopsies may be used.

3. Limitations—Specimens for biochemical testing may require special collection, handling, and shipping. These tests are sometimes performed by specialized laboratories and may require expertise for adequate interpretation.

D. Expression Profiling

Expression profiling measures the levels of multiple RNA or proteins present in a sample as measure of gene expression activity. Most commonly this is done by harvesting RNA from a clinical sample, converting it to complementary DNA (cDNA) and measuring cDNA levels.

1. Indications—Expression profiling is often used to determine gene expression levels in cancers. This information can help in establishing a diagnosis, providing an accurate prognosis, and can guide treatment selection.

2. Testable specimens—Blood and tumor tissue samples may be used.

3. Limitations—RNA is unstable and degrades rapidly; improper sample handling and preparation can adversely affect the accuracy of results.

E. Regulation of Laboratory Testing

Physicians should be aware that US laboratories performing clinical tests are subject to regulation by the Clinical Laboratories Improvement Act (CLIA); however, research laboratories are not. It should also be noted that some research laboratories do not provide test results to patients or their physicians; others provide their results to a clinical laboratory to be confirmed so that a formal report can be issued. While genetic tests packaged as kits to be used by third parties are regulated by the US Food and Drug
Administration (FDA), many genetic tests are developed and used in a single laboratory. Very few of these types of tests are regulated by the FDA. Currently, there is no US federal oversight regarding the value any individual test brings to patient care. Several US states have laws related to oversight of genetic testing.

What a Genetic Test Can Reveal

Before ordering testing for heritable disorders, clinicians should carefully consider the relevance and the implications of the testing for their patient. Genetic testing is typically considered to fall into several major categories, which help to determine how the test can be used for clinical decision making for a patient or his or her family members. Diagnostic testing is used to confirm or identify a known or suspected genetic disorder in a symptomatic individual. This type of testing may also include assays that help to inform prognosis and treatment decisions in someone with an established disease diagnosis. Predictive testing is offered to an asymptomatic individual with or without a family history of a genetic disorder to better define their risk of developing a given condition. Patients are further defined as “presymptomatic” if eventual development of symptoms is certain (eg, Huntington disease) or “predispositional” if eventual development of symptoms is likely but not certain (ie, colon cancer). Carrier testing is offered to appropriate individuals who have a family member with an autosomal-recessive or X-linked condition (eg, the sister of a boy with Duchenne muscular dystrophy) or individuals in an ethnic group known to have a high carrier rate for a particular disorder (eg, sickle cell anemia in the African American population). Pharmacogenetic testing is used to help guide selection and dosing of medications for drug therapy.

Prenatal testing is performed during a pregnancy and is offered when there is an increased risk of having a child with a genetic condition. Multiple marker screens, fetal ultrasound, amniocentesis, chorionic villus sampling, and periumbilical blood sampling are all used for prenatal testing. Preimplantation testing is performed on early embryos during in vitro fertilization and offered to couples who are at increased risk of having a child with a genetic condition. Newborn screening is performed during the newborn period and identifies children who may have an increased risk of a specific genetic disorder so that further evaluation and treatment can be initiated as soon as possible.

Table 47-5 summarizes points to consider with each type of genetic testing.

Genetic Counseling

The current standard of care dictates that genetic counseling be provided to patients prior to initiating DNA-based, clinically driven genetic testing. However, this model is impractical for certain commonly ordered tests in primary care (eg, thrombophilia testing), and will be increasingly problematic as more single platform tests for predisposition for multiple common conditions become available. Depending on the primary care provider’s level of comfort with the disorder to be tested for and the testing modality being offered, counseling might best be delivered by that provider or by a genetic specialist. Appropriate counseling, no matter who provides the service, has several key elements. Pretest counseling should involve discussion of the mode of inheritance and risk of the condition for the patient and family members; the natural history of the condition; prognosis; presentation of appropriate testing options and interventions, including their risks, benefits, and limitations; discussion of the voluntary nature of genetic testing; and exploration of the social and familial implications of testing. These issues comprise the basis for informed consent, which should be documented before initiating DNA testing.

Posttest counseling involves the proper interpretation of results to the patient, including implications for further testing, management, and risks for other family members. It also may involve continued emotional support and referral to mental health professionals or disease-specific support groups, even for those who have tested negative for a particular disorder that may run in their family, due to feelings of guilt or sadness.

Ethical, Legal, & Social Issues

Many issues can arise when individuals are faced with the diagnosis of or susceptibility to a genetic disorder. Critical issues to consider include, but certainly are not limited to,

• Privacy (the rights of individuals to control access to information about themselves).
• Informed consent (giving permission to do genetic testing with the knowledge of the risks, benefits, effectiveness, and alternatives to testing).
• Confidentiality (acknowledgment that genetic information is sensitive, and that access should be limited to those authorized to receive it).
• Insurance and employment discrimination: In 2008 the Genetic Information Nondiscrimination Act (GINA) became law, providing baseline national protections in the United States that prohibit the use of genetic test results (including family history) to discriminate for employment or health insurance purposes in asymptomatic individuals. It does not prevent the use of such information in life, long-term care, or disability insurance underwriting. Several states have enacted laws to protect individuals from genetic discrimination by insurance companies or in the workplace. The Health Insurance Portability and Accountability Act (HIPAA) also provides some protection from discrimination.
• Nonpaternity or unknown adoption: This information can be unexpectedly revealed through genetic testing.
• Duty to warn (the obligation to disclose information to at-risk relatives if they are in clear and imminent danger): On
rare occasions, this duty may require a health care professional to consider breaching patient confidentiality.

• Patient autonomy (the obligation to respect the decision-making capacities of patients who have been fully informed with accurate and unbiased information).

• Professional limitations (the duty of clinicians to realize the extent of their knowledge, skills, attitude, or behavior as they pertain to their practice and the laws, rules, regulations, and standards of care).


Table 47-5. Considerations in the use of genetic testing.

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic</td>
<td>Confirming a diagnosis may alter medical management&lt;br&gt;Genetic testing may yield diagnostic information at a lower cost and with less risk than other procedures&lt;br&gt;May have reproductive or psychosocial implications for patient and other family members&lt;br&gt;Negative result requires further testing or follow-up&lt;br&gt;May be used to provide prognosis.</td>
</tr>
<tr>
<td>Predictive</td>
<td>Indicated if early diagnosis allows interventions that reduce morbidity or mortality&lt;br&gt;When possible and appropriate, identification of the specific genetic mutation should be established in an affected relative first&lt;br&gt;Likelihood of showing disease symptoms is increased but is frequently considerably less than 100%&lt;br&gt;Can have psychosocial implications and can influence life&lt;br&gt;Testing of asymptomatic children at risk for adult-onset disorders is strongly discouraged when no medical intervention is available (ACMG policy statement)</td>
</tr>
<tr>
<td>Pharmacogenetic</td>
<td>Testing for metabolism of one drug may have implications for other drugs&lt;br&gt;Relatively unlikely to have psychosocial implications</td>
</tr>
<tr>
<td>Carrier</td>
<td>Identification of the specific genetic mutation in an affected family member may be required&lt;br&gt;May have reproductive or psychosocial implications&lt;br&gt;Can improve risk assessment for members of ethnic groups that are more likely to be carriers for certain genetic disorders</td>
</tr>
<tr>
<td>Prenatal</td>
<td>Invasive prenatal diagnostic procedures (eg, amniocentesis, CVS) have an associated risk to the fetus&lt;br&gt;In most cases, a specific genetic mutation must be known in an affected relative (eg, mother with myotonic dystrophy)&lt;br&gt;Prenatal testing for adult-onset disorders is controversial, and parents should receive a complete discussion of the issue</td>
</tr>
<tr>
<td>Preimplantation</td>
<td>Only performed at a few centers and available for a limited number of disorders&lt;br&gt;Because of possible errors in preimplantation procedures and DNA analysis, traditional prenatal diagnostic procedures (amniocentesis, CVS) are recommended&lt;br&gt;Cost is very high and may not be covered by insurance</td>
</tr>
<tr>
<td>Newborn screening</td>
<td>Usually legally mandated and varies by state&lt;br&gt;Not designed to be diagnostic&lt;br&gt;Further clinical evaluation and patient education is necessary with positive screening results&lt;br&gt;Parents may not realize that testing was done</td>
</tr>
</tbody>
</table>

ACMG, American College of Medical Genetics; CVS, chorionic villus sampling.

Web Sites
Genetics and Public Policy Center, Johns Hopkins University: http://www.dnapolicy.org/<br>National Human Genome Research Institute: http://www.genome.gov/PolicyEthics/

EXAMPLES IN PRACTICE

Case 1
Ms Smith, a healthy 33-year-old woman, presents to your office for routine health maintenance. On discussing her family history, you discover that her deceased maternal grandfather had colon cancer at age 45, her maternal aunt had colon cancer at age 45, and her mother had a hysterectomy at age 36 for uterine cancer. She asks you if, aside from having her annual Pap smear, she should have any additional cancer screening at her age.
Ms Smith’s family history is suggestive of a disorder, known as hereditary nonpolyposis colorectal cancer syndrome (HNPCC) or Lynch syndrome. Affecting about 1 in 800 individuals, HNPCC is more prevalent than familial adenomatous polyposis (FAP) and is thought to cause about 5% of all colon cancer cases. Affected individuals have an approximately 80% lifetime risk of colon cancer, as well as increased risks of several other cancers, including uterine, ovarian, urinary, stomach, biliary tract, brain, and small intestine. Unlike individuals with FAP, those with HNPCC have relatively few colon polyps which, when they do occur, tend to be located in the right colon and occur at a slightly older age.

HNPCC is inherited in an autosomal-dominant manner. It results from a mutation in one of at least five different members of a family of genes involved in DNA mismatch repair, with changes in the MLH1, MSH2, and MSH6 genes being the most common. These tumor-suppressor genes are thought to encode for proteins that play a role in DNA repair.

The selection of patients suspected of having HNPCC for germline mutation testing is largely based on clinical criteria that rely on both patient and family history. The most commonly used guidelines include the Amsterdam I and II criteria as well as the Bethesda criteria. Unfortunately, these criteria are a bit cumbersome to recall in the primary care setting. A good general rule would be to think of this diagnosis in families dealing with high burdens of the previously mentioned cancers, or cases of early-onset (age <50 years) colon cancer. Table 47-6 provides clues for determining if individuals are at hereditary risk of cancer.

Given that Ms Smith’s family history is suggestive of HNPCC, an appropriate course of action would be to provide her with a referral to either a gastroenterologist familiar with the hereditary colon cancer syndromes or to a genetics clinic for further discussion. If Ms Smith then wished to proceed with testing for HNPCC, contacting her mother or aunt would be the next step. This is because testing an affected individual is the most informative approach to determine if a mutation in the MLH1, MSH2, or MSH6 genes is present in the family. If an affected relative is found to have a mutation, and the patient subsequently tests positive for the same gene mutation, she would be a candidate for intense early screening for colon cancer (colonoscopy every 1-2 years starting at age 20-25 years or 10 years prior to the youngest age of cancer diagnosis in the family), gastric and duodenal cancer (possible upper endoscopy every 1-3 years starting at age 25-30 years and every 1-2 years thereafter), endometrial cancer (by annual endometrial biopsy, starting at 30–35 years or 5-10 years prior to the youngest age of cancer diagnosis in the family), and ovarian cancer (concurrent screening with transvaginal ultrasound and the tumor marker, CA-125). Surveillance for urothelial and CNS cancers as well as risk-reducing surgical and chemoprevention options might also be considered.

### Table 47-6. Indicators of hereditary cancer susceptibility in a family.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td>Cancer in two or more first-degree relatives</td>
<td></td>
</tr>
<tr>
<td>Multiple cancers in multiple generations</td>
<td></td>
</tr>
<tr>
<td>Early age of onset (ie, &lt; 50 y for adult-onset cancers)</td>
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<tr>
<td>Multiple cancers in a single individual</td>
<td></td>
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<tr>
<td>Bilateral cancer in a paired organ such as breasts, kidneys, or ovaries</td>
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</tr>
<tr>
<td>Presence of rare cancers in family (eg, male breast cancer)</td>
<td></td>
</tr>
<tr>
<td>Recognition of a known association between etiologically related cancers</td>
<td></td>
</tr>
<tr>
<td>in the family, such as breast and ovarian cancer (HBOC) or adrenocortical</td>
<td></td>
</tr>
<tr>
<td>carcinoma and breast cancer (Li-Fraumeni syndrome)</td>
<td></td>
</tr>
<tr>
<td>Presence of congenital anomalies associated with an increased cancer risk</td>
<td></td>
</tr>
<tr>
<td>Presence of precursor lesions known to be associated with cancers</td>
<td>(atypical nevi and risk of malignant melanoma)</td>
</tr>
<tr>
<td>Recognizable pattern of inheritance</td>
<td></td>
</tr>
</tbody>
</table>

HBOC, hereditary breast-ovarian cancer.


### Case 2

Mr Jones, a 45-year-old man, presented with a 1-year history of gradually worsening fatigue and diffuse arthralgias. His friends frequently compliment him on his healthy tan. Laboratory testing showed mildly elevated liver transaminases, despite his lack of recreational sun exposure. Testing for viral hepatitis was negative, but his ferritin level was elevated. Further testing revealed a markedly elevated fasting transferrin iron saturation. Genetic testing confirmed hereditary hemochromatosis.

Hemochromatosis is a disorder of iron metabolism in which toxic iron overload occurs. It can be inherited or acquired. The most common genetic form has a prevalence of about 1 in 300 in Caucasian populations and is inherited in an autosomal-recessive manner. The disorder becomes symptomatic in the fourth or fifth decade of life in men and about a decade later in women. Typical symptoms and signs include arthralgias, fatigue, abdominal pain, and bronzing of the skin. The classic triad of symptoms includes bronze skin, diabetes, and cirrhosis, but this is probably an uncommon presentation. Untreated, the disease can progress to liver cirrhosis or cardiomyopathy, either of which can be fatal. Diagnosis can be made without gene testing by measuring serum transferrin and iron saturation levels, with confirmatory liver biopsy showing elevated iron stores. Early, repeated...
phlebotomy to decrease body iron stores is very effective in treating the disease.

In the past decade, a handful of specific mutations in the HFE gene have been shown to cause a majority of the genetic cases of hemochromatosis. Most individuals are either homozygous for the C282Y mutation (85%) or compound heterozygotes for the mutations C282Y and H63D (<10%) in the HFE gene. This gene encodes a protein that regulates cellular iron uptake. Although genetic testing is available for this disorder, population screening in asymptomatic individuals is not currently recommended. Less common forms caused by gene mutations at other loci exist, including a rather severe juvenile form.


Web Site

U.S. Preventive Services Task Force, Screening for Hemochromatosis: http://www.ahrq.gov/CLINIC/USPSTF/uspshemoch.htm

Case 3

Baby girl Miller had a normal newborn examination in the hospital after birth. A week after discharge, you receive a call from the state newborn screening laboratory reporting that the newborn has a high phenylalanine level suspicious for phenylketonuria (PKU). You immediately call a metabolic specialist in your region and arrange for the newborn to be evaluated at the metabolic clinic the next day.

Metabolic disorders affect 1 in 3500 newborns. They typically are the result of a cell’s inability to produce a particular enzyme or metabolize a particular substance. These disorders are almost always inherited in an autosomal-recessive manner, so parents of an affected child are typically carriers (heterozygotes, who have only one copy of the mutant gene) who have no clinical manifestations of the disease. In some cases, the affected offspring does not immediately manifest symptoms. However, unless these disorders are detected and treated early, they can result in mental retardation, physical abnormalities, and, in some individuals, death. For some of these disorders, such as Tay-Sachs disease, there is no specific therapy, and mortality is unavoidable.

Newborn screening programs are an effective public health strategy for the detection and prevention of complications of many genetic diseases. All states in the United States screen newborns for PKU, galactosemia, sickle cell disease, and hypothyroidism. Tests are available for over 30 disorders in most states, including cystic fibrosis and the more common hemoglobinopathies. Testing varies by state and depends on the availability of funding for screening. Appropriate technology and follow-up, and the lack of treatment for some of these disorders, are important issues for newborn screening programs. Carrier testing is also available for many of these disorders. The ACT sheets produced by the American College of Medical Genetics provide a valuable resource for providers confronted with an abnormal newborn screening result.

Children with congenital abnormalities and developmental delays are also often evaluated initially by primary care physicians. Chromosomal imbalances are involved in approximately 25% of major congenital malformations, single gene in approximately 20%, and known teratogenic exposures in approximately 5%. A genetic cause for developmental delays is estimated to be present in approximately 5%-25% of affected individuals. Associated congenital malformations, hearing impairment, growth retardation, and family history increase the likelihood of a genetic etiology. A detailed history, including prenatal, birth, and family history, as well as a thorough physical examination with particular attention to growth parameters, neurologic status, and dysmorphic features or congenital malformations are important in assessing an individual with a congenital malformation or developmental delay.

American College of Medical Genetics Foundation: sponsored by the New York State Department of Health. Evaluation of the Newborn With Single or Multiple Congenital Anomalies: A Clinical Guide. Available at: http://www.health.state.ny.us/nys-doh/dpprd/.


Web Sites

American College of Medical Genetics ACT Sheets: http://www.acmg.net/resources/policies/ACT/condition-analyte-links.htm

Genetics and Rare Disease Information Center (GARD): http://rarediseases.info.nih.gov/GARD/

National Newborn Screening and Genetics Resource Center: http://genes-r-us.uthscsa.edu/

FUTURE DIRECTIONS & CURRENT CHALLENGES

Knowledge of human genetics has improved considerably over the past decade, and many new mutations causal of single-gene disorders have been identified. Completion of the International Hap Map Project, an extension of the Human Genome Project, has facilitated a large number of “genome-wide association studies” that have yielded a wealth of new data on the genetic underpinnings of many common disorders. Current studies are explaining an ever-increasing amount of the inherited component of disease risk for these conditions. This information will lead to the development of new diagnostic and screening tests, novel therapies, and strategies for the prevention of diseases. Pharmacogenetics...
and the use of genetic tests to guide screening, prevention, and treatment of cancers are already changing day-to-day clinical practice. The next wave of genomic discovery will be driven by the advent of extremely low-cost whole genome sequencing—very likely the “$1000 genome” will be achieved within the coming decade. The consequences of this will be myriad for clinical medicine.

Genomics is a rapidly moving field. This presents a challenge to efficiently conducting clinical trials that inform clinical guideline development for genomic applications. Therefore, it is incumbent on health care providers to increase their individual knowledge base regarding genomics. Primary care physicians face major challenges in the realm of clinical applications of genomics: (1) they must decide which portion of this new, complex health care delivery process they feel comfortable managing, and identify specialty resources to assist them with patient-care questions or patient referral; (2) they must become familiar with the standard components of the genetic testing process, including pretest counseling, informed consent, proper interpretation of test results, posttest discussion of the implications of test results for their patient and family members, and implementation of appropriate risk reduction and surveillance recommendations; (3) they must keep pace with the new genomic discoveries that are made every year and the most current versions of rapidly evolving disorder-specific evaluation and management recommendations.

Given the complexity and fast pace of genomic advances, a collaborative, multidisciplinary approach to patient care in the primary care setting will likely afford maximum benefits for the individual and their family.

Online Resources

Centers for Disease Control and Prevention: http://www.cdc.gov/node.do/id/0900f3ec8000e2b5
National Cancer Institute/National Institutes of Health: http://www.nci.nih.gov/cancertopics/pdq/genetics
National Coalition of Health Professional Education in Genetics: http://www.nchpeg.org

Acknowledgement

The author would like to acknowledge the work of Christine M. Mueller, DO, as a co-author of earlier editions of this chapter.
The study of pharmacogenomics addresses the interactions of multiple genes and gene products and their impact on drug therapy, with the goal of developing rational means to optimize drug therapy and ensure maximal efficacy with minimal side effects. In a gross way physicians already use pharmacogenomics when choosing cardiac drugs for patients. For example, hypertensive patients of African background and black race tend to respond better to diuretics and worse to angiotensin-converting enzyme inhibitors and β-blockers. A study investigating congestive heart failure in blacks was terminated prematurely because of an absolute risk reduction in the death rate of 4%. The Food and Drug Administration (FDA) then approved the combination of two well-known drugs, isosorbide and hydralazine, as an adjunct to standard treatment of heart failure in African Americans.

In practice, however, humans and their genome are much more complicated than a simple classification based on race. For example, hypertension in African Americans is higher than that in Caucasian Americans, but the same among African Cubans and Caucasian Cubans. Furthermore, studies of human genetic diversity often sample small numbers of members of a racial or ethnic group, and importantly, membership in a particular ethnic group or race is often defined more by the subject’s ethnic identification than by objective criteria. In addition, genetic studies are not usually designed to assess other important influences on medical phenomena such as environment, social class, poverty, and lifestyle. Using race to guide prescription of medication is a proxy for understanding the underlying genetic, environmental, social, economic, and lifestyle causes of illness.

**GENETIC VARIABILITY & ITS EFFECTS ON PHARMACOKINETICS & PHARMACODYNAMICS**

The effect of drugs is traditionally divided into pharmacokinetics (how drugs are absorbed, distributed, metabolized, and eliminated) and pharmacodynamics (target or targets underlying the therapeutic effect). In principle, genetic variation can influence either pharmacokinetics or pharmacodynamics, or both. Currently, most clinical application of pharmacogenetics involves pharmacokinetics, but over time more attention will shift to pharmacodynamics. The sequencing of the human genome and intensive research into how genetic variation affects drug response holds the promise of altering the paradigms for medication therapy. However, as will be discussed later, current clinical applications utilizing pharmacogenetics are still rather limited. The coming years should see steady growth in this field that will allow primary care providers and other health professionals to better manage drug therapy.


partial or total gene deletion, alteration of mRNA splicing (i.e., the process of removing introns from genomic DNA sequences that contain exons and introns), variation in gene promoters, and gene duplication or multiplication.

Introduction to some terms and nomenclature used in pharmacogenetics is helpful. In dealing with pharmacogenetic variation of drug-metabolizing enzymes, particularly the cytochrome P450 (CYP) enzymes, poor metabolizers represent individuals with little or no enzyme activity, either due to lack of expression of the enzyme or mutations that reduce enzymatic activity (e.g., a mutation that alters the active catalytic site). Extensive metabolizers are considered the “normal” situation and generally represent individuals with two normal copies of the enzyme gene on each chromosome. Intermediate metabolizers have enzyme activity roughly half that of extensive metabolizers. The most common genetic reason underlying intermediate activity is one copy of the normal gene and one variant copy associated with low activity. Ultrarapid metabolizers have enzyme activity significantly greater than the average population. This is often due to the individual having duplicated or multiplicated copies of a gene (i.e., more than the normal two copies of a gene, one on each chromosome). Gene duplication or multiplication is not seen with many genes but can occur with CYP 2D6. For example, an individual may have three or more functional copies of the CYP 2D6 gene instead of the normal two copies.

Genetic variants involving drug-metabolizing enzymes are named in a historical but often confusing system to those new to the field. By definition, the normal allele (individual copy of a gene on a chromosome) is defined as *1 (e.g., CYP 2D6*1). In order of historical discovery, variant alleles were designated *2, *3, *4, and so on, in some cases with subtypes (e.g., *3A, *3B) added later on. Unfortunately, this nomenclature does not give any clue to the nature of the genetic variation. For instance, *4 and *6 could represent fairly benign genetic variants whereas *5 could signify a variant that results in complete absence of enzyme activity.

Several organs can metabolize (biotransform) drug molecules, with the liver being the dominant organ for this purpose in humans and other mammals. The proteins that have been studied in greatest depth are the CYP enzymes, a complicated group of enzymes expressed in liver, intestines, kidneys, lungs, and some other organs. Several CYP enzymes account for the majority of drug metabolism in humans: CYP 3A4/5, CYP 2D6, CYP 2C9, and CYP 2C19. CYP 3A4, in particular, has been shown to play a role in the metabolism of over 50% of the prescribed drugs in the United States.

Genetic variation of CYP 2D6 was one of the first classic examples of pharmacogenetics. In the 1970s, the experimental (and now obsolete) antihypertensive drug debrisoquine was being tested. For the majority of individuals, this drug provided safe control of hypertension. However, some individuals developed prolonged hypotension after receiving the drug, with the hypotension lasting for days in some people. Debrisoquine was later found to be mainly metabolized by CYP 2D6, an enzyme found in the liver that is now known to metabolize about 25% of all drugs currently prescribed in the United States. Of the CYP enzymes, CYP 2D6 is the most highly genetically polymorphic (i.e., it shows the greatest range of genetic variation), with reasonably common genetic variants that include total gene deletion (CYP 2D6*5) and gene duplication, with rare individuals documented that have over 10 functional copies of the CYP 2D6 gene. Genetic variation of CYP 2D6, as will be discussed below, has clinical importance for psychiatric, cardiac, and opiate medications. CYP 2D6 poor metabolizers may experience severe adverse effects to standard doses of certain drugs whereas ultrarapid metabolizers may degrade a drug so quickly that therapeutic concentrations are not achieved with standard doses.

The CYP enzymes also underlie a number of clinically important drug-drug or drug-food interactions. For example, ketoconazole is a powerful inhibitor of multiple CYP enzymes, including CYP 3A4. Ketoconazole thus has potentially dangerous interactions with drugs metabolized by CYP 3A4 such as the immunosuppressive drug cyclosporine, if appropriate dose reductions are not made. On the contrary, several compounds markedly increase (induce) the expression of CYP enzymes, including rifampin, phenytoin, carbamazepine, phenobarbital, and the herbal antidepressant St. John’s wort. By increasing the expression of CYP enzymes and other proteins involved in drug metabolism and elimination, inducers such as rifampin can cause increased metabolism not only of other drugs but also of endogenous compounds such as steroid hormones and vitamin D. This is the mechanism underlying unintended pregnancy that can result in women using estrogen-containing oral contraceptives who also receive a CYP inducer such as rifampin. CYP inducers greatly increase the metabolism of the estrogen component of combined oral contraceptives, resulting in therapeutic failure. CYP inducers are also known to cause osteomalacia by accelerating the metabolism and clearance of the active form of vitamin D (1α,25-dihydroxyvitamin D₃).

 Genetic Variation Involving Pharmacokinetics

Although a number of nongenetic factors influence the effects of medications—including disease, organ function, concomitant medications, herbal therapy, age, and gender—there are now many examples in which interindividual differences in medication response are due to variants in genes encoding drug targets, drug-metabolizing enzymes, and drug transporters. Currently, most well-established applications of pharmacogenetics involve pharmacokinetics.


Genetic Variation Involving Pharmacodynamics

Understanding of genetic variation involving pharmacodynamics has developed more slowly than that of pharmacokinetics. In part, this is because the molecular targets of certain drugs are incompletely understood. A good example of pharmacodynamic genetic variation is for the β₂-adrenergic receptor, the target of β-agonists used in asthma therapy such as albuterol and salmeterol. The other example is the molecular target of warfarin, the vitamin K epoxide reductase (VKOR) protein, which will be discussed under Anticoagulation, later. The importance of understanding pharmacodynamic genetic variation is that it holds the potential of predicting therapeutic efficacy (or lack thereof). This could be especially valuable for disorders such as depression where weeks or even months may be required to determine effectiveness of a drug.


SELECTED CLINICAL APPLICATIONS

Although pharmacogenomics is far from fulfilling its promise of developing a patient-specific pharmacologic profile, there are several areas in which genetic testing is routinely used or is being evaluated for clinical use.

Oncology

Pharmacogenetics began to develop as a distinct discipline beginning in the 1950s, mainly when researchers tried to understand serious adverse effects that occurred in a small number of patients exposed to certain medications. These included prolonged muscle paralysis and apnea in response to the neuromuscular blocker succinylcholine, severe bone marrow toxicity following cancer treatment with azathioprine or 6-mercaptopurine (6-MP) chemotherapy, and the excessive hypotension following administration of the experimental antihypertensive agent debrisoquine, as described under Genetic Variation Involving Pharmacokinetics, earlier. These early “classic” cases of pharmacogenetics turned out to be due to genetic variation (polymorphisms) of enzymes that metabolized the particular drugs.

Azathioprine and 6-MP are agents used in the treatment of cancers (eg, acute lymphoblastic leukemia) and, more recently, in disorders with an autoimmune basis such as rheumatoid arthritis and inflammatory bowel disease. Azathioprine is converted to 6-MP in vivo (ie, it is a prodrug of 6-MP). Although azathioprine and 6-MP both have the potential for bone marrow suppression if used in high doses, about 1 in 300 Caucasians (less in a number of other populations) experiences very profound bone marrow toxicity following standard doses of azathioprine and 6-MP, in some cases resulting in death or severe morbidity due to anemia, thrombocytopenia, or leukopenia. Over several years, researchers determined that the enzyme thiopurine methyltransferase (TPMT) converted 6-MP to therapeutically inactive compounds. Certain individuals, however, had very low TPMT enzyme activity (ie, they are TPMT “poor metabolizers”); these individuals are the ones who develop severe toxicity to standard doses of 6-MP and azathioprine. Several clinical laboratory tests can predict upfront whether individuals will have difficulty metabolizing 6-MP and azathioprine.

Because of the significant impact of TPMT polymorphisms on 6-MP and azathioprine, the FDA urged the manufacturers of these drugs to revise the drug label to describe the impact of genetic variation on drug metabolism and of the possible use of genetic testing. Although there is still debate on how to alter dosing in patient with TPMT variants, the package inserts for both 6-MP and azathioprine now include information on pharmacogenetics of TPMT. TPMT poor metabolizers can still receive 6-MP or azathioprine but need markedly reduced dose.

Although genetic variation of TPMT can have a dramatic impact on medication therapy, even individuals completely lacking these enzymes may show no other clinical symptoms. This finding is also seen with absence of other drug-metabolizing enzymes such as butyrylcholinesterase (enzyme which hydrolyzes succinylcholine) or CYP 2D6. Consequently, without laboratory testing or suggestive previous clinical history of unusual medication response, genetic variation of these enzymes cannot be predicted.

TPMT is probably the best-studied pharmacogenetic application; however, newer pharmacogenetics applications in oncology are emerging. A second application involves the drug irinotecan (CPT-11), a chemotherapeutic agent used in the treatment of colorectal cancer. Irinotecan has complications due to genetic variation (polymorphisms) of enzymes that metabolize the particular drugs.

Anticoagulation, later. The importance of understanding pharmacodynamic genetic variation is that it holds the potential of predicting therapeutic efficacy (or lack thereof). This could be especially valuable for disorders such as depression where weeks or even months may be required to determine effectiveness of a drug.

PHARMACOGENOMICS
most common cause of a mostly benign condition called Gilbert syndrome, a condition often diagnosed incidently by a primary care physician following detection of unconjugated hyperbilirubinemia without associated hepatobiliary pathology. The UGT1A1*28 mutation only causes a partial decrease in enzyme activity, even in individuals possessing two copies of this variant allele. These individuals are, however, at high risk for severe toxicity following irinotecan therapy. With standard doses, such individuals may develop life-threatening neutropenia or diarrhea poorly responsive to therapy. A genetic test for UGT1A1*28 became FDA-approved and, similar to 6-MP and azathioprine, the package insert for irinotecan now includes specific information on UGT1A1 genetic variation. However, perhaps because of the ease of clinical detection of Gilbert syndrome, genetic screening for UGT1A1 has not been adopted universally.

Although the oncology applications for pharmacogenetics do not yet have widespread importance for primary care, they do illustrate the potential of understanding genetic variation. In addition, the FDA has emphasized the importance of including pharmacogenetic information in package inserts for drugs, establishing that physicians at the minimum need to consider pharmacogenetics where applicable in drug therapy.


### Psychiatry

As previously mentioned, about 25% of medications are metabolized by CYP 2D6 or CYP 2C19, but up to 60% of most commonly prescribed psychiatric medications are metabolized by these enzymes. Variation in metabolic rate and drug-drug interactions can reduce the therapeutic effect of a medication or cause significant side effects. For example, fluoxetine can inhibit CYP 2D6 and, when given with tricyclic antidepressants, may result in markedly elevated tricyclic levels, which in turn place a patient at risk for a variety of side effects, among them hypoten sion, cardiac arrhythmias, and heart block. Ideally, the role of pharmacogenomics in psychiatry is to guide the choice of medications and doses in each unique clinical setting. Choice of psychiatric drugs is often somewhat arbitrary, and drugs may be started at low doses and increased slowly. However, a cautious dosing approach may not be counterproductive in the setting of psychiatric crisis and may be frustrating for outpatients who must wait weeks to see if a drug is having the desired effect.

A clinical approach to the problem of predicting drug effectiveness and safety is to simply look up drugs in one of the many databases available such as ePocrates (http://www.epocrates.com) or The Medical Letter (http://www.medicalletter.com). But, is clinical psychiatry ready to avail itself of genetic testing? Pharmacogenetic testing available, or under study, falls into the categories of pharmacokinetics and pharmacodynamics, as mentioned earlier.

**Pharmacokinetics** testing (AmpliChip) is available for the CYP450 enzymes 2D6 and 2C19. This testing has the potential to help screen for potentially reduced or increased rate of drug metabolism and drug-drug interactions.

Among the most troublesome side effects of newer antipsychotic medications is weight gain. Since obesity increases cardiovascular risk in a number of ways, avoiding this harm would be an ideal use of genetic testing. And, studies are under way to test the hypothesis that screening for multiple factors which contribute to obesity, such as insulin resistance, glucose metabolism, and so on, may guide the choice of medication and prevent the metabolic syndrome in such patients. Likewise, studies to screen patients for the genes which increase the risk of clozapine-associated agranulocytosis have to potentially help reduce the risk of this dreaded side effect of an otherwise extremely effective medication.

**Pharmacodynamic** testing for clozapine efficacy is being investigated as well. Future applications may include screening for genetic variation in the neuroendocrine receptors for dopamine and serotonin, as well as transporter 5-HTT.

Studies involving these tests do not conclude that either of these tests, in their current state of development, has a major impact on clinical outcome.

### Anticoagulation

Anticoagulant-related bleeding complications occur in about 3% of patients in the first 3 months of therapy, with the highest risk in the first three months of therapy. During maintenance therapy there is a risk of bleeding complications of 7.6-16.5 per 100 patient-years. Thus, there is a need to accurately predict both the initial and maintenance doses of warfarin. Polymorphisms in CYP 2C9, which metabolizes 80% of the pharmacologically active S-enantiomer of warfarin, account for about 20% of the dose variability of chronic warfarin dosing. Adding another variable, VKOR, the enzyme that is the final step of the vitamin K recycling cycle and also the target of warfarin—as well as age, height, weight, cigarette smoking, and alcohol use—to a pharmacogenomics-based algorithm accounts for 50%-55% of the long-term variability in warfarin dosing, depending on the study. At this point, however, this is no better than the standard algorithm in routine use currently.

Focusing on initiation of therapy, in a small study (N = 48), Voora and colleagues showed that a pharmacogenomics-based model led to a stable international normalized ratio (INR) at
the same rate as the standard algorithm. However, there was no drop in the risk of overanticoagulation in the patients at highest risk because of CYP 2C9 polymorphisms.

There has been progress in both areas, but neither is ready for routine clinical use. There may be a role for pharmacogenetic testing in patients who exhibit extreme sensitivity or resistance to warfarin.

Opiates

Therapeutic and adverse effects of analgesic medications are also influenced by genetic variation. Perhaps the most classic effect is that seen in CYP 2D6 poor metabolizers. Codeine (methylmorphine) is demethylated by CYP 2D6 to morphine. Codeine is a weak agonist of the μ-opioid receptor responsible for analgesia; consequently, codeine is essentially a prodrug of morphine. CYP 2D6 poor metabolizers are unable to convert codeine to morphine and will consequently be “nonresponders” to codeine therapy. CYP 2D6 poor metabolizers are also much less likely to abuse codeine (because the active metabolite morphine is not generated), demonstrating that drug metabolism can influence abuse liability. CYP 2D6 ultrarapid metabolizers on the other hand are at risk for developing life-threatening opiate overdose when small doses of codeine are administered. Gasche and colleagues demonstrated that suppression of CYP 3A4 by clarithromycin, which eliminated a secondary pathway for codeine metabolism in the setting of transient renal insufficiency, potentiated the effect of this ultrarapid metabolism of codeine to morphine. CYP 2D6 also plays a role in the metabolism of other analgesics, including methadone, tramadol, hydrocodone, and oxycodone, although CYP 2D6 pharmacogenetics have not been systematically studied for these other drugs. The pharmacogenetics of analgesic targets such as the various opioid receptors is an area of active inquiry.

There are no studies that address the overall clinical efficacy and cost-effectiveness of genetic testing to guide pharmacotherapy. In the absence of such an approach, Flowers and Veenstra, echoing the standard analysis for screening tests, proposed a framework to address this question. At present, the most reasonable approach seems to be heightened awareness of the pitfalls in medication prescription, selected genetic testing in those who have had or seem to be at high risk for preventable side effects, and support of studies designed to ascertain the effectiveness of this technology.


THE FUTURE: CARDIOVASCULAR DISEASE

There has been significant progress in understanding the pharmacogenomics of some medication classes, as previously discussed. The situation in cardiovascular disease is much more complex, perhaps reflecting the multifactorial etiology of hypertension and cardiovascular disease in general. Polymorphisms in the renin-angiotensin, sodium, signal transduction pathways (G-proteins, α- and β-adrenoceptors), and endothelin systems as they pertain to hypertension have been identified. And, as previously noted, patients who have the CYP 2D6 poor-metabolizer genotype would seem to be at risk for adverse reactions to β-blockers, but these results were not reproduced in subsequent studies. There have been no studies that consistently link genotype to consistent results from specific medications choices. Thus, at this time genomics cannot be widely used to guide medication choices.

In addition to the preceding considerations, methodologic weaknesses mar many pharmacogenomics studies. These weaknesses include

1. Failure to control for all causes of treatment response such as compliance with therapy and drug-drug interactions.
2. Treatment response: often a single SNP is the variable measured with respect to outcome, whereas the actual gene polymorphism that results in different outcomes may be due to the interaction of several or many SNPs in several loci.
3. Noncoding portions of genes (introns) may regulate the timing or location of gene expression, yet studies often report only the gene product (eg, the receptor) but not the genome.
4. Characterization of the complex metabolic pathway of a drug is often not done. Thus, drug response may be measured with respect to one SNP but differences in responses to a medication may be related to variations in the metabolic pathway (absorption, transport, etc), and not the single SNP being tested.
5. Use of different clinical outcome measures from one study to another.
6. Genetic, social, and environmental differences in populations studied.
7. Lack of placebo control.
8. Different drugs used in studies; in particular, in studies of lipid-lowering agents.
9. Failure to account for linkage disequilibrium.

Despite the preceding reservations, our understanding of the scope of genomics as it pertains to cardiovascular disease is evolving. An intriguing example of this is the observation that genes related to hypertension, hyperlipidemia, diabetes mellitus, and thrombophilia may interact to lead to the metabolic syndrome. Furthermore, some of the characteristics associated with the metabolic syndrome, such as obesity, hypertension, and diabetes, predispose women to preeclampsia. Indeed, one study demonstrated a more than eightfold higher risk of cardiovascular death in women with preeclampsia and a preterm delivery.

As the field of pharmacogenomics develops, we suspect there will be increasing numbers of clinical applications of pharmacogenomic testing. As always it is the obligation of the practice physicians to order tests and treatments that are based on sound evidence.


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Background

According to the World Health Organization, between 65% and 80% of the world’s health care services are classified as traditional medicine. These practices become relabeled as complementary, alternative, or unconventional medicine when they are used in Western countries. In April 1995, a panel of experts, convened at the National Institutes of Health (NIH), defined complementary and alternative medicine (CAM) as "a broad domain of healing resources that encompasses all health systems, modalities, practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in a given historical period.”

Subsequent surveys of CAM use by the public and health care providers have defined it as those practices used for the prevention and treatment of disease that are not an integral part of conventional care, and are neither taught widely in medical schools nor generally available in hospitals. Table 49-1 lists the major types/domains of complementary and alternative medicine, while recognizing there can be some overlap, adapted from the National Center for Complementary and Alternative Medicine (NCCAM) at NIH.

A. Use of Complementary and Alternative Medicine

Practices that lie outside the mainstream of “official” or current conventional medicine have always been an important part of the public’s management of their personal health care. Complementary, alternative, and unconventional medicine has become increasingly popular in the United States. Two identical surveys of unconventional medicine use in the United States, done in 1990 and 1996, showed a 45% increase in use of CAM by the public. Visits to CAM practitioners increased from 400 million to over 600 million per year. The amount spent on these practices rose from $14 billion to $27 billion—most of it not reimbursed. Recent data from the National Health Interview Survey (NHIS) has increased this estimate to $33.9 billion. Professional organizations are now beginning the “integration” of these practices into mainstream medicine. In 2002, the number of CAM use was similar between 1997 and 2002 (36.5% vs 35.0%, respectively $P = 0.21$). The greatest relative increase in CAM use between 1997 and 2002 was seen for herbal medicine (12.1% vs 18.6%, respectively) and yoga (3.7 vs 5.1%, respectively), while the largest relative decrease occurred for chiropractic (9.9%-7.4%, respectively).

The public uses these practices for both minor and major problems. Multiple surveys have now been conducted on populations with cancer, human immunodeficiency virus (HIV), children, minorities, and women on CAM use. Rates of use are significant in all these populations. For example, more than 50% of women surveyed have been found to explore and use CAM both for themselves and as health care decision makers for their family. A recent national survey showed that 12% of children use CAM regularly. More than 68% of patients with cancer and HIV will use unconventional practices at some point during the course of their illness. Immigrant populations often use traditional medicines they experienced in their country of origin and not commonly used in the West.

The public’s interest and activity in CAM has increasingly resonated with the concurrent recognition that allopathic medicine cannot treat and solve many of the symptoms associated with acute and chronic illness. As a result, increasing scientific, educational, and clinical attention and resources have been committed to this area. Biomedical research organizations are investing more into the investigation of these practices. For example, the budget of the Office of Alternative Medicine at the US National Institutes of Health rose from $5 million to the present $123.1 million in 10 years and changed from a coordination office to an NCCAM. The
fiscal year 2009 appropriation for NCCAM is $125,471,000, which represents a +2.7% increase over the fiscal year 2008 appropriation of $122,224,000. During fiscal year 2008, 210 new and ongoing research project grants, 10 small business research grants, 6 centers, 52 career development awards, 16 other research grants, 27 individual training grants, 10 institutional training grants, and 2 research contracts were funded by the NCCAM. NCCAM-supported studies, now carried out at more than 260 institutions, encompass the wide range of CAM practices and have resulted in more than 1500 scientific papers published in peer-reviewed journals.

More than 95 of the nation’s 125 medical schools require their medical students to take either formal or informal elective CAM coursework. However, the extent to which CAM coursework has become part of both medically and surgically based residencies is not clear. An increasing percentage of hospital systems and individual hospitals have developed complementary and integrated medicine programs that are offered to inpatients on written orders from the attending physician and/or in their outpatient areas. Some health management organizations are offering “expanded” benefits packages that include specific alternative practitioners and services with a reimbursement option. A recent survey of CAM use in the US hospitals showed that 37% of hospitals offer CAM services. The majority of all services are offered on an outpatient basis, with massage therapy (54%), acupuncture (35%), and relaxation training (27%) among the most popular. On an inpatient basis, the top modalities offered are pet therapy (46%), massage therapy (40%), and music/art therapy (30%).

One result of these activities has been the translation of the terms CAM and allopathic medicine into the term integrative medicine. The Consortium of Academic Health Centers for Integrative Medicine has defined integrative medicine as the practice of medicine that reaffirms the importance of the relationship between practitioner and patient; focuses on the whole person; is informed by evidence; and makes use of all appropriate approaches, health care professionals, and disciplines to achieve optimal health and healing. The application of integrative medicine can be defined as the purposeful, coordinative application of appropriate preventive and treatment modalities that support and stimulate the patient’s inherent healing preferences and self-recovery capacities. As such, these are treatments that are derived from the variety of practices and health care systems from around the world. Thus, the term integrative medicine has adopted concepts from various movements such as CAM person-centered care, humanistic medicine, holistic health care, and the medical home.

CAM, and more specifically integrated medicine, is finding a growing place in American medical practice. Undoubtedly, various facets of it will continue to be debated informally among medical staff and individual physicians and formally in peer-reviewed essays and clinical research, as well as medical societies, academies, and organizations. And importantly, the individual Western-trained medical doctor will continue to be the primary arbitrator and counselor for the patient through the time-honored fundamentals of the therapeutic alliance; that is, compassion coupled with trust, integrity, and empathy; concern coupled with caring and active listening; competence coupled with skill, intellect, and common sense; and communication coupled with availability, continuity, and follow-through.

### B. Conventional Physician Use of CAM

Conventional physicians are not only frequently faced with questions about CAM, but also refer patients for CAM treatment and, to a lesser extent, provide CAM services. A review of 25 surveys of conventional physician referral and use of

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<th>Major Domains of CAM</th>
<th>Examples Under Each Domain</th>
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<td>Homeopathic medicine</td>
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<td>Native American medicine (eg, sweat lodge, medicine wheel)</td>
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<td>Naturopathic medicine</td>
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<td>Traditional Chinese medicine (eg, acupuncture, Chinese</td>
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<td>Tibetan medicine</td>
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<td>Mind-body medicine</td>
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<td>Therapeutic touch</td>
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<td>Bioelectromagnetic-based</td>
<td>Magnet therapy</td>
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<td>therapies</td>
<td>Electromagnetic devices</td>
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This table was adapted from the major domains of CAM and examples of each developed by the National Center for Complementary and Alternative Medicine, National Institutes of Health.
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COMPLEMENTARY & ALTERNATIVE MEDICINE

C. Risks of CAM

The amount of research on CAM systems and practices is relatively small compared with that on conventional medicine. There are over 1000 times more citations on conventional cancer treatments in the National Library of Medicine’s bibliographic database, MEDLINE, than on alternative cancer treatments. With increasing public use of CAM, and too often inadequate communication between patients and physicians about it, and few studies on the safety and efficacy of most CAM treatments, a situation exists for misuse and harm from these treatments. Many practices, such as acupuncture, homeopathy, and meditation, are low risk but require practitioner competence to avoid inappropriate use. Botanical preparations can be toxic and produce herb-drug interactions. Contamination and poor quality control also exist with these products, especially those harvested, produced, and shipped from Asia and India.

D. Potential Benefits of CAM

CAM practices have value for the way we manage health and disease. In botanical medicine, for example, there is research showing the benefit of herbal products such as *ginkgo biloba* for improving conditions due to circulation problems (though not Alzheimer disease) benign prostatic hypertrophy with saw palmetto and other herbal preparations, and the prevention of heart disease with garlic. A number of placebo-controlled trials have been done showing that *Hypericum* (St. John’s wort) is effective in the treatment of depression, although recent studies in the United States have cast doubt on the general validity of those studies. Additional studies report that *Hypericum* is as effective as some conventional antidepressants but produces fewer side effects and costs less. However, the quality of too many of these trials does not reach the standards set for drug research in this country. Thus, physicians need to have and apply basic skills in the evaluation of clinical literature.


Role of the Family Physician

What is the role of the family physician in the management of CAM? The goal is to help patients make informed choices about CAM as they do in conventional medicine. Specifically, physicians must continue to apply the ethical principle of beneficence, and play the role of patient advocate—a provider who protects, permits, promotes, and partners with patients about CAM practices as appropriate.

A. Protecting Patients From Risks of CAM

Many practices, such as acupuncture, biofeedback, homeopathy, and meditation are low risk if used by competent practitioners. But importantly, when used in place of more effective treatments, they can result in harm. The practitioners who apply these modalities should be qualified to help patients avoid inappropriate use. Many herbal preparations contain powerful pharmacologic substances with direct toxicity and herb-drug interactions. Contamination and poor quality control occur more often than with conventional
drugs, especially if preparations are obtained from overseas. The family physician can help distinguish between CAM practices with little or no risk of direct toxicity (eg, homeopathy, acupuncture) and those with greater risk of toxicity (eg, megavitamins and herbal supplements). Physicians should be especially cautious about those products that can produce toxicity, work with patients so they do not abandon proven care, and alert patients to signs of possible fraud or abuse. “Secret” formulas, cures for multiple conditions, slick advertising for mail order products, pyramid marketing schemes, and any recommendation to abandon conventional medicine are “red flags” and should be suspect.

**B. Permitting Use of Nonspecific Therapies**

Spontaneous healing and placebo effects account for the improvement seen in many illnesses. The medical literature does contain essays and polemics that attempt to separate and often denigrate these factors from those that are considered identifiable, tangible, specific aspects of a therapy. The practicing physician, however, is interested in how to combine both specific and nonspecific factors for maximum benefit. Many medical systems emphasize high-touch, personalized approaches for the management of chronic disease and the crises associated with acute disease. The physician can permit the integration of selected CAM approaches that are not harmful or expensive, but that may enhance these nonspecific factors.

**C. Promoting CAM Use**

Proven therapies that are safe and effective should be available to the public. As research continues, expanded options for managing clinical conditions will arise. Gradually, physicians and patients will have more options for management of disease. In arthritis, for example, there are studies suggesting improvements with homeopathy, acupuncture, vitamin and nutritional supplements, botanical products, diet therapies, mind-body approaches, and manipulation. A similar collection of studies exists for other conditions such as heart disease, depression, asthma, and addictions. The Cochrane Collaboration conducts systematic reviews (SRs) of randomized controlled trials (RCTs) on both conventional and complementary medicine and is an excellent source for evidence-based evaluation of such studies. As research accumulates, rational therapeutic options can be developed in these areas.

As the information is presented in peer-reviewed professional journals, the challenge will be to implement the coordinated application of integrative medicine by the clinical team into holistic care models in the hospital, office, clinic, and other care venues. The availability of pluralistic care delivery with onsite, certified, and licensed CAM practitioners will require the training of physicians in the appropriate selection of modalities for the required indication and evaluation methods related to safety, effectiveness, and interactions with other concurrent treatment interventions. In fact, more and more team-based care will be required to accomplish this. The physician may be the cornerstone of this team, but the effectiveness of the team in providing optimal care to the patient will require honest communication and listening, a shared commitment to treatment of the whole person, integrated plans of patient care, and appropriate referral.

**D. Partnering With Patients About CAM Use**

Over 60% of patients who use CAM practices do not reveal this information to their conventional physicians. Thus, there is a major communication gap between physicians and the public about CAM. Patients use alternative practices for a variety of reasons. These include because it is part of their culture or social network, because they are not satisfied with the results of their conventional care, or because they have an attraction to CAM philosophies and health beliefs. The overwhelming majority of patients use CAM practices as an adjunct to conventional medicine. Fewer than 5% use CAM exclusively. Patients who use alternative medicine do not foster antiscience or anticonventional medicine sentiments or represent a disproportionate number of the uneducated, poor, seriously ill, or neurotic. Often, patients do not understand the role of science in medicine and will accept anecdotal evidence or slick marketing as sufficient justification for use. The conventional practitioner can play a role in examining the research base of these medical claims and work with patients to incorporate more evidence into their health care decisions. Quality research on these practices can help to provide this evidence, and the physician can help interpret that evidence with patients.

Other social factors have also influenced the rise in prominence of CAM. These include the prevalence of chronic disease, increasing access to health information, the “computerization” of medical decision making, a declining faith that scientific breakthroughs will have relevant benefits for personal health, and an increased interest in spirituality. In addition, the public and professionals are increasingly concerned over side effects and escalating costs of conventional health care. Ignorance about CAM practices by physicians and scientists can broaden the communication gap between the public and the profession that serves them. Thus, in being patient advocates, all physicians should learn about these practices and discuss them with patients.

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Evidence Hierarchy or Evidence House?

We all need good evidence to make medical decisions. Evidence comes in a variety of forms and what may be good for one purpose may not be good for another. The term “evidence-based medicine” (EBM) has become a synonym for “good” medicine recently, and is often used to support and deny the value of complementary medicine. EBM uses the “hierarchy of evidence” (Figure 49-1). In this hierarchy, SR are seen as the “best” evidence, then individual RCTs, then nonrandomized trials, then observational studies, and finally case series. All efforts are focused on approximating evidence at the top of the pyramid, and lower levels are considered inferior. Clinical experiments on causal links between an intervention and outcomes become the “gold standard” when this model is used.

All family physicians have seen patients who recover from disease because of complex factors, many of which are not additive and cannot be isolated in controlled experiments. Under these circumstances, observational data from clinical practice may provide the best evidence rather than controlled trials. Patients’ illnesses are the human experience of the disease—the manifestation of the patient’s beliefs, fears, and expectations. As such they are complex, and holistic phenomena cannot be reduced to single, objective measures. Often highly subjective judgments about life quality may be the best information with which to make a decision. Such experiences may be captured only with qualitative research, not with scans or blood tests. In that case the meaning patients have of their illness and recovery is the “best” evidence for medical decisions.

Sometimes the “best” evidence does come from laboratory tests. For example, the most crucial evidence for management of St. John’s wort in patients on immunosuppressive medications comes from a laboratory finding that it accelerates drug metabolism via cytochrome P-450. Arranging evidence in a “hierarchy” obscures the fact that the “best” evidence may not be about cause and effect, may not be objective, and may not be clinical.

We suggest that family physicians not use an evidence hierarchy. Rather they build an evidence “house” (Figure 49-2). On the left side of this house is evidence for causal attributions, for mechanisms of action, and for “proof.” However, if physicians confine themselves to the left side of the house, they will never know about the relevance of a treatment for patients or what happens in the real world of clinical practice. They will also not know if proven treatments can be generalized to populations such as the ones they see or the health care delivery system in which they practice. The “rooms” on the right side of the house provide evidence about patient relevance and usefulness, in practices both proven and unproven.

How evidence is approached has ethical implications. Different groups prefer different types of evidence. Regulatory authorities are most interested in RCTs or SRs (left side), which may never be done because of the logistics of time, cost, and access. Health care practitioners usually want to know the likelihood of benefit or harm from a treatment (right side). Patients are intensely interested in stories and descriptions of cures (right side). Rationalists want to know how things work and so need
laboratory evidence (left side). If one type of evidence is selected to the exclusion of others, science will not allow for full public input into clinical decisions. A livable house needs both a kitchen and a bathroom and places to sleep and play. Each type of evidence has different functions and all need to be of high quality.


An Evidence-Based Approach

Fortunately, most treatment decisions only need information on whether a practice has a specific effect and on the magnitude of that effect in practice. This is evidence from randomized controlled trials and outcomes research, respectively. An evidence-based practice would then involve clinical expertise, informed patient communication, and quality research.

This presumes that the physician has good clinical and communication skills. Medical training and experience address these, but evaluation of the research evidence may not be something physicians feel fully prepared for in reading and understanding the CAM literature. Obtaining research, selecting appropriate research for clinical situations, and then evaluating the quality of that research in CAM are essential for a fully evidence-based practice that addresses these topics.

A. Finding and Selecting Good Information

Where can the family physician obtain research on CAM? A number of groups have collated and produced CAM-specific databases (Cochrane Collaboration, Evidence Based Medicine Reviews, and Natural Standard). Table 49-2 lists some good sources of clinical information on CAM and what they provide. When searching these databases, look for the following key terms: (1) meta-analyses, (2) RCTs, and (3) observational or prospective outcomes data. Although there are many other types of studies, it is necessary to be cautious about using these for problem-oriented decision making in practice. If no research information is found from the databases listed, it is likely that there is little relevant evidence for the practice on that clinical condition. A search for this information need not take up a lot of time.
A trained office assistant can often do the search, streamlining time spent on this process. After a literature search, the physician can have confidence knowing the quantity of evidence on the therapy. Patients are usually grateful for this effort as they will come to their physician in the hopes of obtaining science-based information they can trust.

### B. Risks and Types of Evidence for Practice

If there are studies on a specific type of CAM practice, then the risk of toxicity and the cost of the therapy indicate which types of data are needed. Low-risk practices include over-the-counter homeopathic medications, acupuncture and gentle massage or manipulation, meditation, relaxation and

<table>
<thead>
<tr>
<th>Source of CAM Information</th>
<th>Description</th>
<th>Where to Go</th>
</tr>
</thead>
</table>
| Cochrane Library          | Database of Systematic Reviews: systematic reviews of RCTs of CAM and conventional therapies | http://www.cochrane.org  
http://gateway.ovid.com |
| Natural Medicines Comprehensive Database | Comprehensive listing and cross-listing of natural and herbal therapies, separate “all known uses” and “effectiveness” sections, safety ratings, mechanisms of action, side effects, herb-drug interactions, and review of available evidence | http://www.naturaldatabase.com |
Individual guidelines at:  
http://www.guideline.gov  
http://www.cdc.gov/publications |
| Focus on Alternative and Complementary Therapies (FACT) | Quarterly review journal of CAM therapies Contains evidence-based reviews, focus articles, short reports, news of recent developments, and book reviews on complementary medicine | http://www.exeter.ac.uk/FACT |
| PubMed Clinical Queries Search Engine | The old standby has a clinical queries filter to limit your search results Click on “Clinical Queries” on the left blue banner to access the filter For the most comprehensive search, use the key words “complementary medicine” | http://www.pubmed.org |
| Agency for Healthcare Research and Quality (AHRQ) | For information on the quality, safety, efficiency, and effectiveness of health care for all Americans | http://www.ahrq.gov |
| Clinical Evidence | Promotes informed decision making by summarizing what is known, and not known, about > 200 medical conditions and > 2000 treatments | http://www.clinicalevidence.com/ceweb/condition/index.jsp |
| TRIP | Allows health professionals to easily find the highest-quality material available on the Internet | http://www.tripdatabase.com |
| Family Physicians Inquiry Network | Provides clinicians with answers to 80% of their clinical questions in 60 seconds | http://www.fpin.org/ |

CAM, complementary and alternative medicine; RCT, randomized controlled trial.
biofeedback, other mind-body methods, and vitamin and mineral supplementation below toxic doses. Low-cost therapies involving self-care are also often low risk. High-risk practices include herbal therapies, high dosage vitamins and minerals, vaccine products, colonics, and intravenous administration of substances. Some otherwise harmless therapies can produce considerable cost if they require major lifestyle changes. Herbal therapies can produce serious adverse effects secondary to their impact on cell function, including enzymatic reactions or contamination with toxic materials. Because patients frequently take herbal products along with calculated dose prescription medications, physicians should specifically inquire about their use. High-risk or high-cost practices and products require RCT data.

Under some circumstances, observational (outcomes) data are more important, and in other circumstances RCT data are more important. Outcomes research provides the probability of an effect and the absolute magnitude of effects in the context of normal clinical care. It is more similar to clinical practice and usually involves a wide variety of patients and variations of care to fit the patient's circumstances. It does not provide information on whether a treatment is specific or better than another treatment.

With low-risk practices, the physician wants to know the probability of benefit from the therapy. Quality outcomes data from practices are preferable to RCT data if the data are collected from actual practice populations similar to the practitioner's patient. This may be sufficient evidence for making clinical decisions. Often, it will be the only useful information available for chronic conditions. For example, if quality outcomes studies report a 75% probability of improving allergic rhinitis using a nontoxic, low-cost, homeopathic remedy, this information can assist in deciding on its use.

For high-risk, high-cost interventions, the physician should use randomized controlled trials (or meta-analyses of those trials). RCTs address the relative benefit of one therapy over another (or no therapy). RCTs can determine if the treatment is the cause of improvement and how much the treatment adds to either no treatment or placebo treatment. RCTs provide relative (not absolute) information effects between a CAM and control practice. They are difficult to do properly for more than short periods and difficult if the therapy being tested is complex and individualized or if there are marked patient preferences. In addition, RCTs remove any choice about therapy and, if blinded, blunt expectations—both of which have effects in clinical practice. Placebo controlled TCTS differences are largely dependent on the control group, which requires careful selection and management. Strong patient preferences for CAM, differing cultural groups, and informed consent may also alter RCT results. RCTs are more important if we need to know more about specific benefit-harm comparisons, such as with high-risk, high-cost interventions.

The more a CAM practice addresses chronic disease and depends on self-care (eg, meditation, yoga, biofeedback), or involves a complex system (eg, classical homeopathy, traditional Chinese medicine, Unani-Tibb), the more outcomes data are important. The more a CAM practice involves high-risk or high-cost interventions, the more essential RCT data become.

### C. Evaluating Study Quality

Once data are found and the preferred type of study is selected, the practitioner should apply some minimum quality criteria to these studies (Table 49-3). Three items can be

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trials</td>
<td>Were there concealed random allocation to comparison groups?</td>
</tr>
<tr>
<td></td>
<td>Were outcome measures of known or probable clinical importance?</td>
</tr>
<tr>
<td></td>
<td>Were there few lost to follow-up compared with the number of bad outcomes (&lt; 20%)?</td>
</tr>
<tr>
<td>Observational and outcomes studies</td>
<td>Were outcome measures assessed blind to patient treatment?</td>
</tr>
<tr>
<td></td>
<td>Were outcome measures of known or probable clinical importance?</td>
</tr>
<tr>
<td></td>
<td>Were there few lost to follow-up compared with the number of bad outcomes (&lt; 20%)?</td>
</tr>
<tr>
<td></td>
<td>Were confidence intervals reported and were they narrow or broad?</td>
</tr>
<tr>
<td>Reviews</td>
<td>Were explicit criteria for selecting articles and rating their quality used?</td>
</tr>
<tr>
<td></td>
<td>Was there a comprehensive search for all relevant articles?</td>
</tr>
<tr>
<td></td>
<td>Were negative and unpublished articles found?</td>
</tr>
</tbody>
</table>

Adapted, with permission, from Haynes RB et al: Transferring evidence from research into practice: 2. getting the evidence straight. ACP J Club 1997;126:A14.
quickly checked: (1) blind and random allocation of subjects to comparison groups (in RCTs) or blind outcome assessments (in outcomes research), (2) the clinical relevance and reliability of the outcome measures, and (3) the number of subjects that could be fully analyzed at the end of the study compared to the number entered. These same minimum quality criteria apply to RCTs or observational studies, except that blinded, random allocation to treatment and comparison groups does not apply in the latter. However, evaluation of effects before and after treatment can be blinded to the treatment given in any study. Detailed descriptions of patients, interventions, and dropouts are hallmarks of a quality outcomes trial.

Finally, one can ask if the probability of benefits reported in the outcomes study is worth the inconvenience, risk of side effects, and costs of the treatment and, in addition, whether confidence intervals were reported. Confidence intervals are the range of minimum to maximum effects expected in 95% of similar studies. If confidence intervals are narrow, the physician can be confident that similar results will occur with other patients. If confidence intervals are broad, the chance of obtaining those effects from treatment in other patients will be unpredictable.

If the quality screening questions show that there are marked quality flaws in the studies retrieved, the evidence in the study is insufficient and so should not be used as a basis for clinical decisions.

D. The Population Studied

Even if good evidence is found for a practice, physicians should determine whether the population in the studies is similar to the patient being seen. Although this matching is largely subjective, the physician can compare five areas. Specifically, determine if the study was done (1) in a primary, secondary, or tertiary referral center, (2) in a Western, Eastern, developing, or industrialized country, and (3) with diagnostic criteria similar to the patient (eg, the same criteria were used to diagnose osteoarthritis or congestive heart failure); finally, determine if (4) the age and (5) the gender of the study population were similar. If the study population is not similar to the patient being seen, then the data, even though valid, cannot be applied to the situation. The study country may be especially important for some CAM practices. For example, data on use of acupuncture to treat chronic pain may come from China. Pain perception may be different in China than in the United States. Results from a study done in one country may not be applicable in another. If the study and clinic population match, an appropriate body of evidence for moving forward with a therapeutic trial exists.

E. Balancing Beliefs

Belief in the treatment by the physician and the patient needs to be explicitly considered in CAM. In conventional medicine, both patient and physician accept the plausibility of treatment. Belief has long been known to affect outcome. Strong belief enhances positive outcomes and weak belief interferes with them. A physician may feel that a CAM practice has incredibly low plausibility although the patient may have a strong belief in the therapy. This so-called “prior probability” (or belief) by the physician and patient should be considered in the decision to allow or not allow the patient to use a treatment. If physician and patient have similar beliefs, then a decision is easily made. Sometimes, however, the patient has a strong belief in the therapy, but the physician finds it unbelievable. In such situations, the physician should work with the patient to decide the best action—including referral elsewhere as an option.

F. Alternative Diagnoses

Some diagnoses are not very useful for management of a patient’s illness. If the family physician’s conventional diagnosis is not helping a patient, the clinician may want to consider an evaluation by an alternative system. Chinese medicine uses energy diagnosis, for example, and homeopathy has a remedy classification system. Sometimes, obtaining an assessment from a CAM system may prove useful. For example, a 51-year-old woman with several years of idiopathic urticaria had obtained no relief from several conventional physicians. A homeopathic assessment showed that she might benefit from the remedy Mercurius 2006 (mercurius virax). She was given several small doses and the urticaria cleared.

The physician should also be alert to practitioners who pursue CAM diagnoses that are not useful. A complicated CAM evaluation and treatment with little effect might be managed simply and effectively by conventional medicine. For example, a 57-year-old man with cardiovascular disease and recurrent bouts of angina was treated by a CAM practitioner for 3 years with special diets and nutritional supplements without help. Consultation with a conventional practitioner shows that he had myxedema. A thyroid supplement cleared his angina rapidly. In cases in which the diagnostic approach of the medical system fails, a professional consultation may be needed. In situations in which the alternative system’s diagnostic and treatment approach is clear, a limited therapeutic trial with specific treatment goals and follow-up can be attempted. Of course, quality products and qualified practitioners must be located. In situations of serious disease, such as cancer, anxiety-ridden patients may seek out CAM treatments. Under these circumstances, good training and clinical experience and protection of patients from harm (even from themselves) should prevail.

Evidence-based medicine can be applied to complementary and alternative medicine. Figure 49-3 summarizes the steps involved and Table 49-4 summarizes questions for CAM management. Although evidence-based CAM may initially seem like a large task, appropriate data-driven clinical decisions can be made with CAM as with all medical care.
CHAPTER 49

American medicine continues to evolve in its focus, capabilities, technology, and demands. Our population is aging as the baby boomers reach the age of 65 years. Age is associated with chronic disease. By definition, chronic disease cannot be cured, but the patient is left with potential disability, diminished function, emotional challenges, economic burden, and overall challenges to quality of life. Conventional medicine is not always up to the task of providing the necessary and required care these patients deserve. But, cure need not always be the physician’s primary goal. Rather, the provision of individualized care suffused with empathy and compassion remains the basic foundation of medical practice. The knowledgeable use of integrated medicine in the treatment regimen will empower the person seeking care to participate in a process of healing with the physician focusing on the person’s inherent healing capacities, expectation, hope, understanding, and belief that well-being can be obtained and that it will occur.

Table 49-4. Questions for evidence-based CAMT management.

A patient is using a complementary and alternative medicine therapy (CAMT) or an alternative treatment is sought. The following questions should be answered.
1. Has the patient received proper conventional medical care?
2. Is the CAMT likely to produce direct toxic or adverse effects or is it high cost?
3. Are there clinical data from randomized trials or outcomes research on the CAMT?
4. Do the studies meet minimum quality criteria? (Table 49-3)
5. Is the study population similar to the patient using or seeking the CAMT?
6. Is the plausibility of the therapy acceptable to both patient and physician?
7. Can a quality product or a qualified practitioner be accessed?
8. Can the patient be monitored while undergoing the CAMT?
9. Is a full diagnostic assessment by a conventional or CAM system in order?

Figure 49-3. Decision tree for evidence-based complementary and alternative medicine.


Web Sites


National Center for Complementary and Alternative Medicine (NCCAM) www.altmed.od.nih.gov/NCCAM

Acknowledgment

Special thanks to Cindy Crawford in helping collecting background information and preparing the manuscript.
General Considerations

Pain is defined by the International Association for the Study of Pain as “an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage.” This definition emphasizes that the pain experience is multidimensional and may include sensory, cognitive, and emotional components. Additionally, the latter part of the definition allows for the possibility, as in chronic pain states, that the overt tissue damage may no longer be present. Pain persisting longer than 3-6 months is defined as chronic pain. Pain persisting for 3 months, however, is unlikely to resolve spontaneously and may continue to be reported by patients after 12 months. In addition, many of the secondary problems associated with chronic pain, such as deconditioning, depression, sleep disturbance, and disability, begin within the first few months of the onset of symptoms of pain. Studies indicate that early patient identification and treatment are essential to reduce pain chronicity and prevent further disability.

Chronic pain is one of the most common complaints seen in primary care. A survey of 89 general practices in Italy showed pain as a complaint for 3 of every 10 patients seen. Among these patients, pain was chronic for over half (53%). Women were more likely than men to report both acute (1.2:1) and chronic pain (1.8:1). The most common type of pain was musculoskeletal (63%). Similarly, a survey of over 10,000 women attending general practices identified a chronic pain complaint in 38% of women, with over 80% consulting their physician for their chronic pain complaint. The most common site for chronic pain was the back (54%).

Costs related to chronic pain are high. A survey of an employer claims’ database showed annual direct plus indirect costs for employees with painful conditions were 1.5-3.5 times greater than those for the average employee ($7088-16,874 vs $4849; P <0.01). Of the costs, about 60% were attributed to direct health care expenses. Among patients with low back pain, there is an estimated direct cost for medical expenses of $357 per month.

Pathogenesis

Acute pain occurs following some form of tissue injury (eg, ankle sprain) and is treated with RICE (rest, immobilization, compression, and elevation) and pain-soothing treatments, such as heat, ice, and massage. During the acute period of tissue injury and healing, patients appropriately limit activity to reduce risks of further injury (eg, development of a Charcot joint in a patient with neuropathy who risks aggravation of the injury because of impaired sensation). Studies show that patients improve best after acute injury when they reduce activities to what can be tolerated and allow healing to occur, in contrast to patients treated with either bed rest or acute physical therapy.

Chronic pain occurs after the acute healing period has been completed or in the context of chronic conditions (eg, neuropathy or arthritis). Restriction of activity in patients with chronic pain leads to deconditioning, with muscle and bone loss that increases pain and the risk for reinjury, and also promotes psychological sluggishness, if not depression. Consequently, the RICE approach will actually aggravate the symptoms of chronic pain. The natural response of restricting activities when experiencing pain is appropriate for acute injury pain but aggravates chronic pain. Patients with chronic pain require an active, progressive exercise program.
They must learn appropriate strategies for treating pain, must avoid a tendency to restrict activity excessively, and must resume more normal activity levels through a stepwise, progressive activity program.

Clinical Findings

The most common chronic pain conditions in young and middle adulthood are low back pain, neck pain, and headaches. Musculoskeletal diseases rank fifth in generating hospital expenses and first in generating expenses related to work absenteeism and disability. The most common cause of chronic pain in older adults is degenerative joint and disc diseases, with arthritis causing chronic pain in over 80% of elderly patients with pain. Other causes of chronic pain that occur more frequently with increasing age are pain related to cancer, vascular disease, and neuropathy (eg, postherpetic neuralgia). Throughout the life cycle, pain can be associated with a variety of general medical conditions, such as Crohn’s disease or sickle cell anemia.

The overall pain experience includes primary pain–generating signals, along with common secondary problems that develop regardless of pain etiology and that complicate pain management (Figure 50-1). Both physical (eg, joint restrictions and deconditioning) and psychological (eg, depression and anxiety) changes frequently accompany chronic pain. Psychological distress is common. In a survey of 500 patients with chronic low back, hip, or knee pain, depression or anxiety accompanied pain complaints for 46% of patients. Both depression and anxiety were identified in 23%, with depression alone in 20% and anxiety alone in 3%.

Patients with pain plus the combination of depression and anxiety experienced significantly greater pain severity and disability ($P < 0.0001$ for each). Psychosocial stress may result from difficulties related to school or work, family relationships, social isolation, and legal and financial areas. Although the possibility of secondary gain (eg, litigation) may increase pain complaints, true malingering and factitious disorders are uncommon, occurring in only 1%-10% of patients. The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*), appropriately recognizes the ability of psychological variables to influence complaints of pain and offers the designation of a pain disorder, reflecting the coexistence of both physical dysfunction and psychological factors, both of which affect patients’ overall presentation and function. The family physician is in a unique position to identify and treat the physical and psychosocial factors influencing complaints of pain.


Treatment

Chronic pain management focuses on reduction in symptoms and improvement of function rather than on disease cure. Both medication and nonmedication treatment modalities effectively decrease primary and secondary symptoms of chronic pain, with a range of treatments often being provided through a treatment team (Table 50-1). However, physicians and patients must accept that complete resolution
of complaints of pain may not be possible. Thus they need to work toward rehabilitative goals of reducing symptoms and minimizing disability. Although modern medicine and rehabilitation techniques can be beneficial, the patient’s mindset must shift from searching for a medical cure to engaging in collaborative rehabilitation, geared toward decreasing pain and optimizing function. Goals of chronic pain rehabilitation are improvement in both pain and secondary symptoms, including deconditioning, depression, and disability (Table 50-2). Early identification and treatment should reduce the severity of secondary symptoms.

### A. Psychological Approaches

Cognitive-behavioral therapy (CBT) is an effective psychological treatment technique that challenges dysfunctional precepts or perception of pain (“My pain must be cured. I can’t do anything if I have pain.”) and replaces it with one that is more conducive to change (“Pain limits me from lifting 25 pounds, but I can still carry a bag of groceries.”). CBT helps change patients’ perceptions or locus of control from external control (believing pain is not controllable by the patient) to internal control (believing the patient can positively influence symptoms). When patients endorse an external locus of control, they see themselves as victims of the pain and as powerless to improve their situation. This results in the expectation that only fate or the physician can help when pain becomes severe. When expectations are not met, these patients seek alternative evaluations and treatments (eg, another physician, a different diagnostic test, or surgical procedures) that may not be in their best interest. The clinician must help patients to move into a pain self-management, internal locus of control belief system, in which patients see themselves as the agent for change. Greater perceived self-control of pain decreases both pain and secondary symptoms. Although CBT is typically the purview of psychologists, the family physician can reinforce these concepts through interactions with the patient. Mind-body approaches can be very helpful and are often integrated with CBT in a self-management program (see section “Complementary and Alternative Therapies”).

Additionally, counseling should be directed toward issues concerning mood, sleep, and other psychosocial factors. Severe symptoms of depression or anxiety or significant psychosocial stressors may necessitate a psychiatric referral.

### B. Physical and Occupational Therapy

Identification and treatment of musculoskeletal dysfunctions and decisions concerning limitations on activity often require consultation with physical or occupational therapists. Reconditioning, active stretching and strengthening exercises, and graded activity programs are effective for managing chronic pain. Physical therapists should instruct patients in a daily exercise routine as well as flare management techniques (eg, trigger point massage, oscillatory movements, and use of heat and ice). Exercise therapy is most effective when initiated through a supervised physical therapy program rather than through self-exercise. Furthermore, exercise therapy effectively reduces pain in elderly patients with osteoarthritis.

Occupational therapists will address work simplification, body mechanics, and pacing skills. Occupational therapists can facilitate returning to a more normal activity schedule (eg, returning to work or school), even on a modified basis. Prolonged absence from normal activities increases the difficulty of reducing disability. Return to normal activity as soon as possible, however, should be the primary goal of pain management and the physician should work to expedite that return, with modifications if needed. Conflicts with an employer, fear of losing a job and benefits, or other intervening factors need to be identified and addressed to facilitate a successful return to work.

### Table 50-1. Comprehensive treatment of chronic pain.

<table>
<thead>
<tr>
<th>Specialist</th>
<th>Treatment Modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician</td>
<td>Analgesics, adjunctive medications, nerve blocks, medical counseling to foster self-management</td>
</tr>
<tr>
<td>Physical/occupational therapist</td>
<td>Musculoskeletal dysfunction, deconditioning, work simplification</td>
</tr>
<tr>
<td>Psychology/psychiatry</td>
<td>Address locus of control, depression therapy, anxiety therapy</td>
</tr>
<tr>
<td>Complementary/alternative therapist</td>
<td>Acupuncture, yoga/ta chi, meditation, chiropractic therapy</td>
</tr>
</tbody>
</table>

### Table 50-2. Appropriate treatment goals.

<table>
<thead>
<tr>
<th>General Goal</th>
<th>Specific Treatment Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased pain</td>
<td>Pain reduction to moderate levels; reduced frequency and duration of flares</td>
</tr>
<tr>
<td>Improved function</td>
<td>Return to school/work; increased number of household chores; increased participation in leisure activities</td>
</tr>
<tr>
<td>Improved sleep</td>
<td>Reduced number of wake-ups; improved overall sleep to 5 h per night</td>
</tr>
<tr>
<td>Improved mood</td>
<td>Increased participation in social activities; reduced time in bed/inactive; improved nutrition intake</td>
</tr>
<tr>
<td>Reduced use of medical resources</td>
<td>Reduced emergency department visits; reduced use of excessive analgesics; decreased repeat consultations or studies</td>
</tr>
</tbody>
</table>
C. Pharmacotherapy

Medications are prescribed to treat an underlying medical condition (eg, disease-modifying medications in rheumatoid arthritis), relieve symptoms of pain, and relieve secondary symptoms (eg, depression, anxiety, or sleep disturbance). Most medications used to treat chronic pain address the latter two factors (Table 50-3).

1. Pain relievers—Analgesics rarely eliminate pain entirely and may result in either significant adverse effects or habituation. Treatment should begin with simple analgesics, such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs). Daily doses of acetaminophen should not exceed 4 g, and patients need to consider the cumulative dosage from both over-the-counter and prescription pain relievers. Acetaminophen should be restricted in patients with significant alcohol intake or liver disease. A variety of available NSAIDs share similar efficacy and tolerability. Patients with gastrointestinal disease may tolerate cyclooxygenase-2 (COX-2) inhibitors better than standard NSAIDs; however, as noted below, these agents have been associated with increased risk of heart disease and stroke.

Tramadol is a novel analgesic that has weak serotonergic and noradrenergic properties as well as weak μ-opioid activation. Despite the opioid agonist effect, in the absence of a history of opioid dependence, tramadol does not pose the same level of concern regarding abuse potential, physical tolerance, and psychological dependence as the true opioids. It thus offers an option falling between first-tier of agents (ie, acetaminophen and NSAIDs) and the stronger opioid medications. Common side effects include sedation, dizziness, and nausea. Although the full dosage is 100 mg four times daily, a lower dosage (eg, 50 mg three times daily) is commonly prescribed, with extra dosing on an as-needed basis. The 400-mg maximum dose should be strictly adhered to given the potential for seizures at higher doses. For older adults or those taking other centrally acting agents, a maximum of 200-300 mg/d is a more reasonable maximum. As noted below, there is great concern regarding risk for falls and impaired cognition with these medications in older adults. Finally, the potential exists for inducing a serotonin syndrome when tramadol is used in combination with antidepressants or other serotonergic agents (eg, selective serotonin reuptake inhibitors [SSRIs] such as paroxetine or escitalopram, tricyclic antidepressants [TCAs] such as amitriptyline or nortriptyline, or novel agents such as trazodone or mirtazapine). This syndrome can be seen as a paradoxic excitation associated with excessive activation of central nervous system serotonin, with psychological effects that include hyperarousal, irritability, and agitation; neuromotor effects.

<table>
<thead>
<tr>
<th>Symptom Treated</th>
<th>Medication Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Analgesics</td>
<td>Acetaminophen, NSAIDs, tramadol, sustained-release morphine, oxycodone, or transdermal fentanyl</td>
</tr>
<tr>
<td></td>
<td>Long-acting opioids</td>
<td></td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>Antidepressants, Anticonvulsants</td>
<td>Duloxetine, 30-60 mg twice daily, Gabapentin, 300-1200 mg three times daily, Pregabalin, 75-200 mg three times daily</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>Muscle relaxants</td>
<td>Tizanidine, 2-8 mg at bedtime to three times daily</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>Antidepressants</td>
<td>Nortriptyline, 25-75 mg at bedtime, Trazodone 50-150 mg at bedtime</td>
</tr>
<tr>
<td>Depression</td>
<td>Antidepressants</td>
<td>Bupropion, extended release, 150-300 mg daily, Citalopram 20-40 mg daily</td>
</tr>
</tbody>
</table>

NSAIDs, nonsteroidal anti-inflammatory drugs.
that include tremor, jitteriness, rigidity, and (at an extreme) seizures; and cardiac effects that include tachycardia and hypertension.

Including opioids in the management of chronic pain is controversial. Although isolated treatment with opioids is not effective for managing chronic pain, opioids can provide a safe, cost-effective adjunctive pain therapy because of reduced morbidity and cost associated with organ toxicity from analgesics. Chronic opioid use has been shown to reduce both pain and disability. Opioids may be considered in patients with severe, disabling chronic pain that is unrelied with simple analgesics and is associated with significant impairment in daily functioning and quality of life. Opioids are most appropriately used when they are included as part of a more comprehensive rehabilitation program rather than as monotherapy. Relative contraindications include a history of substance abuse, serious psychopathology, and lack of motivation to engage in an appropriate therapy program or to improve functioning. Patients with no history of substance abuse are at low risk for abuse with prescribed medications. Patients with current addiction problems should be referred to a drug rehabilitation facility before pain management is initiated. Patients with recent substance abuse or addiction problems should be managed by a pain specialist, ideally in conjunction with a counselor specializing in treating patients with these types of problems.

Patients who have severe chronic pain that is constantly present are best managed with long-acting medication rather than frequent dosing with immediate-release agents. Short-acting medications are best used infrequently for intermittent, short-lived pain flares. Long-acting opioids include sustained-release morphine sulfate, sustained-release oxycodone, oxymorphone, transdermal fentanyl, and methadone. Methadone is least expensive (about one-tenth the cost of brand-name opioids); however, titration is difficult because of individual variability in metabolism. Opioid equivalence charts may be helpful when converting patients from one medication to another (Table 50-4). For example, the amount of opioid administered from a 100-μg/h fentanyl patch is roughly equivalent to an oral dose of 240 mg morphine sulfate daily. In general, musculoskeletal pain is more responsive to opioids than neuropathic pain, chronic headache, or fibromyalgia. Opioids may be a useful adjunctive treatment to other neuropathic medications in patients with neuropathic pain and, due to the high cost of gastrointestinal and renal effects of chronic analgesic therapy, can provide a cost-effective alternative for patients with chronic pain when properly monitored. Meperidine should be avoided given the potential for adverse effects related to accumulation of metabolite normeperidine and a somewhat greater addictive potential. A potential problem, particularly in geriatrics, is the preference of some physicians to use propoxyphene, a weak opioids, to avoid addiction in their patients. Unfortunately, this provides all of the risks of opioids with none of the benefits, given its limited analgesia and potential for inducing delirium due to the accumulation of the metabolite norpropoxyphene.


<table>
<thead>
<tr>
<th>Table 50-4. Opioid conversion chart.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine sulfate</strong></td>
</tr>
<tr>
<td><strong>Hydromorphone</strong></td>
</tr>
<tr>
<td><strong>Oxycodone</strong></td>
</tr>
<tr>
<td><strong>Hydrocodone</strong></td>
</tr>
<tr>
<td><strong>Oxymorphone</strong></td>
</tr>
<tr>
<td><strong>Meperidine</strong></td>
</tr>
<tr>
<td><strong>Fentanyl</strong></td>
</tr>
</tbody>
</table>

*Dose conversions are approximate, with variation based on both individual patients and drug preparations.
*Should be avoided (see text).
2. Adjunctive medications—Adjunctive medications supplement the benefits from analgesics, treat neuropathic or central pain, and treat secondary complaints. In addition, effective use of adjunctive agents often reduces the need for analgesic medications. Adjunctive agents interact with the mechanism of neuropathic or central pain and chronic headache by reducing nervous system wind-up, the process by which the nervous system amplifies and eventually perpetuates pain signals in the absence of ongoing nociceptive input from the periphery.

The two primary categories of adjunctive analgesics are antidepressants and anticonvulsants. Among the antidepressants, the greatest analgesia is achieved by dual serotonin- and norepinephrine-activating agents. Traditionally, this has meant prescribing TCAs. Agents such as nortriptyline have shown efficacy for neuropathic pain, fibromyalgia, and migraines, and their advantages include once-daily dosing, help for sleep, and modest cost. However, TCAs are associated with anticholinergic effects, orthostasis, and the potential for cardiac arrhythmia, the latter being a concern particularly in prepubertal children.

Three newer agents have dual norepinephrine and serotonin reuptake inhibition and have been used for chronic pain states. Venlafaxine is an energizing antidepressant with some utility for chronic pain states; the greatest concern as far as adverse effects is the potential to increase blood pressure at higher doses. Duloxetine, a newer dual-action agent, is the first antidepressant to come onto the market with an indication for pain associated with diabetic peripheral neuropathy and fibromyalgia, in contrast to the preceding agents, which are used off label. The newest of the dual-agents is milnacipran that carries an indication for fibromyalgia and should have a favorable side-effect profile as compared with the TCAs.

Comorbid depression, anxiety symptoms, sleep disturbance, and loss of energy are commonly seen in individuals with chronic pain. Many patients do not tolerate antidepressant medications or experience adverse effects (eg, sexual dysfunction with SSRIs). For such individuals, it may be preferable to find a tolerated agent that will help with mood and associated symptoms. For example, an anergic overweight woman with fibromyalgia may benefit from treatment with bupropion; alternatives to TCAs for a patient with depression and a sleep disturbance would include mirtazapine or trazodone.

Anticonvulsants, particularly gabapentin, have become a mainstay in the treatment of neuropathic pain. They are also beneficial for treating chronic headaches and may be beneficial for treating fibromyalgia. Newer anticonvulsant drugs that show promise in the treatment of neuropathic pain include topiramate, oxcarbazepine, lamotrigine, and zonisamide. Some have multiple mechanisms of action, including membrane stabilization involving sodium and calcium channels, N-methyl-D-aspartate blockade, and GABAergic (gamma-aminobutyric) effects. Pregabalin and gabapentin are related anticonvulsants with indications for pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. Pregabalin is approved for fibromyalgia as well.

Most muscle relaxants (eg, carisoprodol and cyclobenzaprine) used to treat acute musculoskeletal pain are associated with significant sedation, reducing their usefulness as a treatment for chronic pain, for which the primary focus is on reducing disability and time spent in bed. Tizanidine, a unique muscle relaxant with both antispasticity and α-adrenergic effects, results in reduced spasticity and reduced pain perception with both acute and chronic use. In addition to reducing spasticity related to neurologic conditions (eg, multiple sclerosis, stroke, or spinal cord injury), tizanidine can also reduce symptoms associated with myofascial pain, fibromyalgia, and headaches, with some evidence of benefit for neuropathic pain. Tizanidine is often used in low doses (2–8 mg daily) given at bedtime or divided into three daily doses. Tizanidine is mildly sedating, which can assist with associated sleep disturbance.

Regarding dosing, medical mythology suggested that low doses of adjunctive agents were analgesic. The older agent, gabapentin, has nonlinear pharmacokinetics, making optimal dosage selection difficult. Dose-response studies with both duloxetine and pregabalin have demonstrated a fairly linear response, indicating that efficacy may be found at higher doses among patients with a limited initial response to a low dose. The clinical applicability of this linear response with duloxetine and pregabalin has been confirmed in controlled clinical trials.


3. Adverse events with chronic pain medications—The annual costs associated with toxicity from nonopioid analgesics approach $1.9 billion, with $1.35 billion caused by NSAID toxicity. Gastric ulcers occur in 15%-30% of chronic NSAID users. In addition, renal impairment occurs in 24% and renal papillary necrosis in 12% of arthritic patients using...
chronic NSAIDs. Fortunately, renal insufficiency is often improved when the drugs are discontinued. NSAIDs must be used with particular caution in the elderly, as their use reduces the effectiveness of diuretics and doubles the risk for hospitalization from congestive heart failure.

COX-2 inhibitors were initially widely used in patients with chronic pain to minimize costs from gastric toxicity. COX-2 inhibitor analgesics now have limited use, especially in elderly patients, due to postmarketing identification of increased risk for myocardial infarction and stroke. Some of this increased risk may have resulted from inappropriate use of these medications. For example, a review of community-dwelling Medicaid recipients aged 50-84 years in Tennessee showed no increased occurrence of serious coronary heart disease in rofecoxib users prescribed daily dosages of 25 mg or less. Those prescribed more than 25 mg daily, however, had a 1.7 times greater risk of serious heart disease occurrence. Interestingly, a survey of chronic users of rofecoxib in 2001 showed that nearly one-fifth were prescribed more than 25 mg daily, with most using this high dosage chronically. A recent, large, observational study of Medicaid enrollees found no difference in cardiovascular event occurrence between patients using a COX-2 selective inhibitor versus a non-naproxen NSAID. Conversely, a Canadian retrospective analysis showed a higher risk of death and recurrent congestive heart failure in elderly patients with preexisting congestive heart failure prescribed rofecoxib or NSAIDs compared with celecoxib. These data suggest that significant toxicity may occur with both NSAIDs and selective COX-2 inhibitors.

Opioids are not associated with organ toxicity. Practitioners must monitor for evidence of the development of tolerance (reduced effectiveness of the medication over time) or abuse (failure to identify prescribed opioids on random urine testing or repeated lost or overused medications). In either circumstance, patients will likely need a change in treatment.

Newer anticonvulsants used to treat neuropathic pain do not require the frequent laboratory monitoring that is common with older anticonvulsants (eg, carbamazepine and sodium valproate). Gabapentin is cleared by the kidneys, requiring dose adjustment or reduced frequency of administration in patients with renal insufficiency. Dialysis patients receive gabapentin dosing after each treatment with hemodialysis.

TCAs, typically prescribed in low to moderate doses to treat neuropathic pain, are still associated with a small risk for cardiac arrhythmia. All prepubertal children treated with TCAs should receive a baseline electrocardiogram (ECG), followed by regular assessments of heart rate and blood pressure, periodic testing of antidepressant drug levels, and repeat ECGs. Similarly, older adults or individuals with a history of cardiac disease should also be monitored with blood tests and ECGs when TCA doses approach the low therapeutic range. SSRIs and bupropion have been associated with seizures in higher doses and should be used with caution in individuals with tendencies to seizure. Venlafaxine and milnacipran can have a cardiac stimulatory effect at higher doses and blood pressure should be watched. Antidepressants, particularly those with a prominent serotoninergic effect, have been associated with the potential for suicidality and should be monitored closely in patients at risk and in children or adolescents.

Tizanidine, duloxetine, and milnacipran have been associated with hepatotoxicity and should be avoided in individuals with a history of liver problems. Periodic liver enzyme screening should be obtained in patients taking these agents chronically.


4. Medication management in pediatric patients and in older patients—Chronically administered opioids are generally avoided in pediatric patients, although there are certainly exceptions with chronic disease states such as hemophilia and sickle cell disease. Acetaminophen and NSAIDs should be considered first-line therapy for pediatric patients with pain. TCAs and gabapentin have been extensively utilized for neuropathic pain in pediatric patients, and pediatric dosing guidelines are available. As noted, caution must be taken regarding the potential for cardiac conduction disturbance with the use of TCAs in prepubertal children.

When selecting medication for older adults, physicians need to strongly consider the side-effect profile, particularly for agents that have central nervous system effects—including opioids, antidepressants, and anticonvulsants. As opposed to the mild sedation or dizziness experienced by younger individuals, geriatric patients may experience more profound drowsiness, confusion, delirium, and increased risk for falls. Medical comorbidities and medications for these conditions increase the risk for adverse events in geriatric patients. The potential for activation or inhibition of cytochrome P450 pathways is problematic in patients taking multiple medications, particularly with a narrow therapeutic index, such as digoxin and warfarin. With the exception of gabapentin, the dosing of adjunctive analgesics typically is lower for older adults.

Low to modest doses of opioids may be a very useful part of the treatment regimen for geriatric patients with pain, particularly because of good tolerability at low doses. It is common to see older patients with arthritis who are unable to tolerate even the COX-2 agents. Additionally, as the degree of degenerative disease progresses, benefits from NSAIDs may be limited, necessitating stronger analgesia. When used judiciously, opioids typically are well tolerated and can allow individuals to retain a level of functioning sufficient to maintain their independence.
D. Intervenotional Pain Management

Intervenotional techniques are considered for patients failing conservative therapy or when specific nervous system pathology has been identified. Lumbar epidural steroid injections are effective for treating herniated discs or spinal stenosis. Sympathetic blocks reduce the burning pain of complex regional pain syndrome or reflex sympathetic dystrophy that may develop after acute extremity injury or surgery. Trigger point injections are useful for localized muscle pain. The benefit from injections is often transient, so these techniques are generally used in conjunction with physical therapy and medication management. Radiofrequency ablation (RFA) may be considered for recalcitrant symptoms of facet, disc, sympathetic, or neural pain; pulsed RFA appears to have the same beneficial effect with reduced risk of from unwanted damage to sensory nerves or deafferentation pain.

Implantable devices, including intrathecal pumps and dorsal column stimulators, can be used to treat individuals with cancer-related pain or severe incapacitating pain resulting from nonmalignant conditions. Intrathecal medications are considered for patients requiring high medication doses when side effects from oral medications become intolerable. Dorsal column stimulators are considered when pain is limited to a single extremity. For the treatment of pain resulting from nonmalignant conditions, it is essential to obtain psychological consultation prior to the surgery.

Nerve blocks may be particularly beneficial for postherpetic neuralgia, which can be quite difficult to treat. The early use of antiviral agents (eg, valacyclovir) for zoster is important in attenuating the initial infection and decreasing the acute pain as well as chronic symptoms. In addition, early treatment of zoster with TCAs (25 mg of amitriptyline daily for 90 days) reduces chronicity of symptoms of postherpetic neuralgia. Nerve blocks, particularly thoracic epidural local anesthetics or intercostal blocks, can be used in the acute or chronic stage. Early use of nerve blocks, especially within the first 2 months of onset of symptoms, greatly decreases the incidence and severity of postherpetic neuralgia.

E. Complementary and Alternative Therapies

Complementary and alternative treatments are used by 40% of chronic pain sufferers. Acupuncture reduces pain for a variety of painful musculoskeletal conditions, including fibromyalgia; and recent studies have shown efficacy in osteoarthritis. Chiropractic treatment is recommended for acute spinal pain, but there is no clear consensus on the effectiveness of chiropractic manipulation for chronic pain, and controlled studies are needed to provide efficacy data. Mind-body approaches (eg, meditation, guided imagery, biofeedback, and yoga) are effective in reducing pain. Additionally, as previously noted with CBT, mind-body therapies can engage the patient actively in treatment, changing the locus of control and encouraging use of health-promoting behaviors. Among biologically based treatments, glucosamine sulfate and chondroitin sulfate have had mixed success in studies, but they may provide an alternative to chronic non-steroidal treatment for some patients, particularly with knee osteoarthritis. Another agent which merits further study for possible analgesic and anti-inflammatory effects is fish oil, in a dose of 1-2 g/d.

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**References**


Hameline MT: Symptomatic outcomes and perceived satisfaction levels of chiropractic patients with a primary diagnosis involving acute neck pain. J Manipulative Physiol Ther 2006;29:288-296. [PMID: 16690383]


In 2005 the World Tourism Organization reported 783 million international arrivals across international boundaries. This represents over a 71% increase in 15 years. In the same year there were 29 million international departures from the United States. A figure less than pre-September 11, 2001 levels, but still an increase of 23% in just 3 years. Travelers may be business travelers to large cities where there are special dangers related to urban travel, but increasingly travelers are seeking out exotic locations as tourist destinations. Pretravel advice is often an afterthought for these travelers.

It is estimated that fewer than half of travelers seek any kind of pretravel advice. Many people ask their family physicians for recommendations, and at times the advice they receive is either uninformed or out of date. Individuals returning to their country of origin are even less likely to consult a physician before travel and preventable systemic illness is seen more commonly in this group than other tourists. It is important for all primary care physicians to be prepared to give accurate advice to travelers about both pretravel preparation and how to deal with illnesses contracted abroad. Sometimes there is not enough time to obtain the required immunizations, and priorities must be established. The goal of this chapter is to enable the family physician to provide guidance to patients wishing to be prepared for illnesses and emergencies related to travel.


Case Illustration

A 28-year-old man in good health is planning a 2-month trip to Kenya. He will be working in Nairobi but also plans to visit game parks and participate in outdoor activities.

• What history must be obtained?
• What specific advice should the patient be given, especially regarding hygiene, safety, and food preparation?
• What immunizations are needed?
• What malaria prophylaxis is recommended?
• Where can the physician find the answers to these questions?

The first step is to obtain a thorough history—including any preexisting medical conditions and use of medications that may have side effects or may interact with other drugs that will be prescribed—and to perform a thorough physical examination. What is the patient's exact itinerary, what countries will he visit en route, in what order? What accommodations will he have? Will he remain in urban areas or visit some rural regions? What is his immunization history? This information will help determine necessary immunizations and prophylaxis. The physician can also help the traveler ensure he has items, such as insect repellent, that may be essential. If the patient has a chronic illness, he should be given pertinent portions of his medical record and a list of allergies to take along in case he must seek medical care abroad.

Several web sites provide helpful information about travel and health requirements. (See listing at the end of this chapter.) After reviewing these requirements, the physician would find that this patient faces several risks that should be discussed. These include:

• Malaria, especially at lower elevations such as in game parks.
• Diarrhea, caused by parasites or bacteria such as Escherichia coli or Shigella.
• Typhoid fever and other salmonelloses.
• Hepatitis A, B, C, or E.
• Schistosomiasis, especially if swimming or wading in local bodies of water.
• Violence and petty thievery, especially in urban areas such as Nairobi.
• HIV/AIDS and other sexually transmitted diseases.
• Poor infrastructure for dealing with serious emergencies, such as motor vehicle accidents, especially outside of urban areas.

Travelers who monitor the most common risks found at their destination can better prepare in advance and equip themselves with resources to ensure a safe, smooth trip.

➤ Travelers’ Medical Kit

Every traveler should carry a medical kit that addresses basic care for common illnesses and injuries. The essential components of such a kit are listed in Table 51-1, but they must be adjusted, depending on individual needs. If a patient uses a medication that is taken regularly, he or she should be advised to carry along enough to last for the entire trip and probably 1 or 2 weeks extra. This will allow for unexpected changes in travel plans. A small supply should be kept in the carry-on bags, in case luggage is lost or delayed. All applicable airline regulations regarding carry-on baggage must be observed so that the medication is not confiscated. The traveler should carry a letter from a physician if he or she plans to take along any controlled substance. This letter will help answer questions from immigration officials and other authorities in case questions are raised. Travelers should not forget to bring spare eyeglasses or contact lenses, contact lens solution, and their ophthalmologic prescription, in case of loss or breakage.

If the traveler is planning a long stay, the physician may be asked to supply prescribed medications on a regular basis from the United States, particularly if the drug in question is not available at the international destination. Increasingly, however, medications prescribed in the United States are available abroad (often much more cheaply) and can be obtained without difficulty by a knowledgeable traveler. Travelers should be cautioned to carefully examine any medications bought overseas, because ingredients may differ from those used in the US products, and some ingredients may not be considered safe by the US standards.

Table 51-1. Medical kit for travelers.

<table>
<thead>
<tr>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insect repellent with up to 30% DEET, picaridin, or oil of lemon</td>
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<tr>
<td>eucalyptus</td>
</tr>
<tr>
<td>Permethrin spray for clothing and mosquito nets, if traveling to the</td>
</tr>
<tr>
<td>tropics</td>
</tr>
<tr>
<td>Sunscreen (minimum SPF 15)</td>
</tr>
<tr>
<td>Dressings, gauze pads, adhesive tape, adhesive bandages, small bottle</td>
</tr>
<tr>
<td>of disinfectant, elastic bandage (eg, ACE), scissors, tweezers</td>
</tr>
<tr>
<td>Thermometer</td>
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<tr>
<td>Moleskin, if extensive hiking is planned</td>
</tr>
<tr>
<td>Hand wipes, liquid soap, hand sanitizer, facial tissues</td>
</tr>
<tr>
<td>Aspirin, acetaminophen, or other analgesic drug</td>
</tr>
<tr>
<td>Antidiarrheal (eg, diphenoxylate, loperamide, bismuth subsalicylate)</td>
</tr>
<tr>
<td>Antacid (eg, calcium carbonate), H₂ blocker (eg, cimetidine)</td>
</tr>
<tr>
<td>Eye drops (for allergy and infection)</td>
</tr>
<tr>
<td>Ear drops (if risk of external otitis)</td>
</tr>
<tr>
<td>Dimenhydrinate or scopolamine, if motion sickness is a problem with</td>
</tr>
<tr>
<td>air or water travel</td>
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<tr>
<td>Throat lozenges and cough drops</td>
</tr>
<tr>
<td>Sleep aid</td>
</tr>
<tr>
<td>Laxative</td>
</tr>
<tr>
<td>Condoms and contraceptives</td>
</tr>
<tr>
<td>Antihistamines (preferably a nonsedating agent such as loratadine,</td>
</tr>
<tr>
<td>but diphenhydramine is often useful as a sleep aid in addition to its</td>
</tr>
<tr>
<td>antihistamine activity)</td>
</tr>
<tr>
<td>Cold and cough medications</td>
</tr>
<tr>
<td>Asthma medications and inhalers if needed</td>
</tr>
<tr>
<td>Prednisone or other steroid</td>
</tr>
<tr>
<td>Topical antibiotics, antifungals, steroids, and vaginal antifungal</td>
</tr>
<tr>
<td>drugs</td>
</tr>
<tr>
<td>Antibiotics (eg, ciprofloxacin, sulfamethoxazole-trimethoprim, amoxi-</td>
</tr>
<tr>
<td>cilin, amoxicillin-clavulanate, azithromycin, doxycycline)*</td>
</tr>
<tr>
<td>Malaria prophylaxis (see text)</td>
</tr>
<tr>
<td>Water purification kit or filter (see text)</td>
</tr>
<tr>
<td>Acetazolamide, if travel is contemplated to elevations &gt;8000 ft (2500</td>
</tr>
<tr>
<td>m) above sea level</td>
</tr>
<tr>
<td>Syringes and needles (3-5 mL syringes, 21-25 gauge needles), if travel-</td>
</tr>
<tr>
<td>ing in underdeveloped countries where instrument sterilization may be</td>
</tr>
<tr>
<td>uncertain</td>
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<tr>
<td>Injectable epinephrine if traveler has a history of anaphylactic reac-</td>
</tr>
<tr>
<td>tions to foods or insect bites</td>
</tr>
</tbody>
</table>

DEET, n,n-diethyl-meta-toluamide; SPF, sun protection factor.
*Inclusion of antibiotics depends on familiarity of the traveler with these medications and the likelihood they will be needed, based on the itinerary.

➤ Insurance

Travelers should check their health insurance policies to determine whether they include coverage for medical expenses incurred abroad. If coverage is provided, they should bring a blank insurance form in case it is needed or it

becomes necessary to contact the insurance company. Term
travel health insurance policies are also available. Evacuation
insurance is essential in the event of a serious accident or
medical problem. Some policies will return travelers to their
home cities; others will evacuate them to the nearest location
where they can receive medical care comparable to that avail-
able in their home country. Among the more well-known
companies offering evacuation insurance and emergency travel
insurance are CSA Travel Protection (http://www.csatravelpro-
tection.com), International SOS (http://www.internationalsos.com), MEDEX Insurance (http://www.medexassist.com),
MedjetAssist (http://www.medjetassistance.com), and Multi-
National—HCC Medical Insurance Services, LLC (http://
www.hccmis.com/legal/). Policies can also be obtained through
tavel agencies. Finally, the traveler may wish to purchase trip
insurance. This type of insurance ensures reimbursement in
case a trip must be canceled for medical or other reasons
beyond the traveler’s control. (It should be noted that most
trip insurance policies do not cover cancellation for personal
reasons, such as a change in plans.) This insurance is espe-
cially attractive for older travelers, who are more likely to have
a medical emergency that prevents them from traveling.

Air Travel Concerns

Some medical conditions require special attention during air
travel. These conditions include any severe, common illness;
anemia; clotting disorders; disfiguring dermatoses; dyspnea
at rest; incontinence; otitis media; pulmonary or acute upper
respiratory infections; and sickle cell hemoglobinopathies.
Medical contraindications to air travel are listed in Table 51-2.
Any traveler with an acute infectious disease should be cleared
by a physician before traveling. If there is any question about
the diagnosis, the individual should not travel until the risk is
known. Exposure to tuberculosis and other serious infections
can occur in flight and an individual with a serious infec-
tious disease should not travel on a commercial flight. Ill or
handicapped travelers must notify the airline 72 hours before
departure to be sure the plane is properly equipped. Services
such as a wheelchair, oxygen, stretcher, and other necessary
equipment can usually be provided with advance notice.

Food & Water Sanitation

Many infectious diseases can be prevented by attention to
food and water sanitation and good hygiene. These diseases
include intestinal viral, bacterial, and parasitic infections.
The guidelines that follow can help travelers prevent many
food- and water-borne illnesses.

Travelers should be advised to avoid eating food that has
not been cooked adequately or peeled by them. Cooking
must be thorough, not just warming, and a clean knife must
be used for peeling. If fish are eaten, they should be fresh,
not dried or old looking. Cans should be inspected for
bulging or gas formation. Only dairy products that have
been pasteurized should be consumed, and products that
have been ultrapasteurized by the ultraheat treatment
(UHT) method are preferred. Raw vegetables and fruits
should be cleaned with a brush, soap, and water, and then
ideally sterilized with boiling water or by soaking in a bleach
solution (approximately 2 teaspoons or 10 mL of chlorine
bleach in 1 L of clean water). Hands must be kept clean and
fingernails trimmed. Clean silverware and plates should be
used; these can be rinsed in boiling water or bleach rinse to
sterilize them.

Travelers should be advised that bottled or canned drinks
are safe as long as the seal is intact. Iced and lukewarm drinks
should not be trusted, but hot drinks such as coffee or tea are
generally safe if prepared recently and still hot when served.
Tap water can be purified by either boiling it, treating it with
iodine or chlorine, or by filtering it with a reliable ultrafilter
water purification system, as described below:

• Bring water to a rolling boil for 1 minute. Although the
  actual temperature reached will be slightly lower at higher
elevation, this does not seem to have clinical relevance.

• Treat the water with iodine (10 drops of tincture per liter)
  and let stand for 30 minutes, or treat it with chlorine
  (1–2 drops of 5% chlorine bleach per liter of water) and let
  stand for 30 minutes. Although chlorine may not kill all

<table>
<thead>
<tr>
<th>Table 51-2. Contraindications to air travel.</th>
</tr>
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<tbody>
<tr>
<td>Unstable angina</td>
</tr>
<tr>
<td>Myocardial infarction in past 2 wk (or 6 wk if complicated)</td>
</tr>
<tr>
<td>Active bronchospasm</td>
</tr>
<tr>
<td>Neurosurgery or skull fracture in the past 2 wk</td>
</tr>
<tr>
<td>Uncontrolled cardiac disease (congestive heart failure or arrhythmia)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention in past 5 d (or 2 wk if complicated)</td>
</tr>
<tr>
<td>Cerebral infarction in the past 2 wk</td>
</tr>
<tr>
<td>Pneumothorax in the past 2-3 wk</td>
</tr>
<tr>
<td>Colonoscopy with polypectomy in the past 24 h</td>
</tr>
<tr>
<td>Late pregnancy (long flights)</td>
</tr>
<tr>
<td>Highly contagious diseases, including active tuberculosis</td>
</tr>
<tr>
<td>Major uncontrolled psychiatric disorders</td>
</tr>
<tr>
<td>Cyanosis</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Recent middle ear surgery</td>
</tr>
<tr>
<td>Scuba diving in the past 24 h</td>
</tr>
<tr>
<td>Hemoglobin &lt;7.5 g/dL</td>
</tr>
<tr>
<td>Heart, lung, or gastrointestinal surgery in the past 3 wk</td>
</tr>
<tr>
<td>Noncommunicating lung cysts</td>
</tr>
</tbody>
</table>
parasitic cysts or viruses, water treated with chlorine has a better taste than iodized water; furthermore, chlorine does not affect thyroid function over long periods of use.

- Reliable water filtration systems are available through various sources. (eg. Campmor [http://www.campmor.com] includes information on several systems.) A pore size of 0.2 μm is needed to filter out all enteric bacteria and parasites. If the water is cloudy or especially dirty-looking, some gross filtration or sedimentation must be done first before using a small-pore filter. Adding iodine resins to the filter will kill viruses if contact is sufficient.

**Injury Prevention & Personal Security**

The leading cause of mortality and morbidity in travelers is motor vehicle accidents. Drivers should be aware of local motor vehicle laws and never mix alcohol with driving or any activity that requires mental alertness. Other common accidents that occur during travel include drowning, carbon monoxide poisoning, electric shock, and drug reactions. Travelers should be aware that jet lag and other causes of drowsiness while traveling (eg, medications to alleviate motion sickness) may heighten the risk of injury. If a traumatic injury occurs, travelers should be cautioned not to agree to blood transfusions unless absolutely necessary.

Although the risks to personal security in many parts of the world may be similar to those encountered in many urban areas of the United States, a traveler may be at greater risk in areas where he or she is obviously a foreigner or tourist. Most commonly, the risks to personal security are related to theft of personal belongings and the occasional violent methods used, especially in the urban areas of Africa and Latin America. Women, especially those traveling alone, are at greatest risk of personal assault, often because the sexualized image of Western women portrayed by American media has given the men of many cultures a mistaken impression of their willingness and availability.

Another rarely discussed but important area of personal security is that of sexual activity while traveling. The freedom from a daily schedule and uniqueness of the situation may cause travelers to let down their normal guard. The incidence of sexually transmitted diseases, especially HIV, is quite high in many popular tourist destinations, including much of Africa, the Caribbean, Thailand, and some parts of Latin America. Travelers should be cautioned to use good judgment (especially in situations involving alcohol use), barrier protection such as condoms, and caution with oral-genital contact.

**Immunizations**

Up-to-date immunization information can be obtained from the Centers for Disease Control and Prevention (CDC) web site, www.cdc.gov/travel, which contains a wealth of information.

No vaccines are currently required for travel, with the exception of yellow fever vaccine if travel is planned through an endemic area. However, travelers from the United States should be up-to-date on all routine immunizations, including diphtheria, pertussis, tetanus, measles, mumps, varicella, rubella, influenza, pneumonia, and for children Haemophilus influenzae type b (see Chapter 7). For previously immunized adults, a single dose of polio vaccine is recommended if traveling to an area with a risk of polio. Europe, Australia and the Western Pacific, and the Western Hemisphere have been certified polio free.

Typhoid and hepatitis A vaccines are recommended for travelers to most areas of the world. Two typhoid vaccines are currently available in the United States: Ty21a and Vi. Efficacy of both vaccines is 50%-80%. Ty21a is a live oral vaccine that conveys protection for 5 years. It is taken as a series of four tablets, one every other day. The tablets must be kept refrigerated until taken. Vi is a parenteral vaccine that provides protection for 2 years. Persons receiving this vaccine have a higher incidence of systemic reactions such as fever or malaise for the first 2-3 days after administration than those who receive the oral vaccine, and they may also develop injection site soreness.

Meningococcal vaccine is indicated for travelers to areas of sub-Saharan Africa and any area where meningococcal disease is endemic or epidemic. Saudi Arabia now requires that Hajj and Umrah visitors be vaccinated with a tetravalent vaccine before entering the country. Meningococcal conjugate vaccine group 4 (MCV4) is preferred among persons aged 11-55 years, and meningococcal polysaccharide vaccine group 4 (MPSV4) is the recommended vaccine among persons aged 2-10 years and for those over 55 years. Duration of immunity lasts at least 5 years and adverse reactions are generally mild. Japanese encephalitis (JE) vaccine is recommended for travelers to endemic areas of rural Asia, especially if the traveler plans to live there or stay longer than

**Obtaining Medical Care Abroad**

Obtaining reliable medical care abroad can be difficult. Frequent travelers may wish to become members of the International Association for Medical Assistance to Travelers (IAMAT), which provides up-to-date advice on where to seek competent medical care for virtually any area of the world. (Contact information: 1623 Military Rd., No. 279, Niagara Falls, NY 14304-1745; (716) 754-4883; www.iamat.org.) The International Society of Travel Medicine (www.istm.org) and the American Society of Tropical Medicine and Hygiene (www.astmh.org) are also excellent resources for those seeking to find travel clinics anywhere in the world.

30 days. Cholera vaccine is no longer available in the United States; however, an oral vaccine, *Vibrio cholerae* whole cell/B subunit vaccine (Dukoral) is available abroad and may be useful in certain situations. No country now requires cholera vaccination; however, some local authorities may ask for this documentation. A single dose of the oral vaccine is sufficient or a medical waiver written on physician letterhead will satisfy this request. Rabies vaccine is recommended for travelers to high-risk developing countries and countries where rabies immune globulin is not available. Long-term travelers or those who may have extensive outdoor or nighttime exposure and those whose occupations place them at risk should consider this vaccine. Postexposure vaccination is still required.

Hepatitis B vaccine is recommended for travelers to high-risk areas, especially long-term travelers, and those engaging in high-risk sexual behaviors. Medical workers must be vaccinated, as should the future adoptive parents of children from a developing country.

Table 51-3 summarizes information for these and other vaccines. For additional information, refer to the CDC web site listed at the end of the chapter.


### Table 51-3. Vaccines that may be administered to travelers.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Efficacy (%)</th>
<th>Partial Protection Begins</th>
<th>Duration of Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live Vaccines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td>&gt;95</td>
<td>28 d after first dose</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Tuberculosis (BCG)</td>
<td>Variable</td>
<td>6-8 wk</td>
<td>Variable</td>
</tr>
<tr>
<td>Typhoid Ty21a (oral)</td>
<td>50-80</td>
<td>After 3rd dose</td>
<td>5 y</td>
</tr>
<tr>
<td>Varicella</td>
<td>&gt;99</td>
<td>After 4-6 wk</td>
<td>At least 10 y</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>&gt;99</td>
<td>After 10-14 d</td>
<td>At least 10 y</td>
</tr>
<tr>
<td><strong>Inactive Vaccines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholera (oral)</td>
<td>80-85</td>
<td>After 7 d</td>
<td>At least 6 mo</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>95-97</td>
<td>After 2nd dose</td>
<td>5-10 y</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>95-100</td>
<td>2 wk after 1st dose</td>
<td>&gt;6 y</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>90-95</td>
<td>4 wk after 2nd dose</td>
<td>At least 15 y</td>
</tr>
<tr>
<td>Influenza (inj)</td>
<td>86-87</td>
<td>1-2 wk</td>
<td>6 mo-1 y</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>80-91</td>
<td>10 d after 2nd dose</td>
<td>2-4 y</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>75-100</td>
<td>After 14 d</td>
<td>5 y or more depending on vaccine</td>
</tr>
<tr>
<td>Pertussis</td>
<td>80-86</td>
<td>After 2nd dose</td>
<td>At least 2 y</td>
</tr>
<tr>
<td>Pneumococcal PCV7</td>
<td>&gt;90</td>
<td>After 2nd dose for invasive disease</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pneumococcal 23</td>
<td>56-81</td>
<td>Variable</td>
<td>5-10 y</td>
</tr>
<tr>
<td>Polio (inj)</td>
<td>&gt;95</td>
<td>After 3rd dose</td>
<td>Probably life-long</td>
</tr>
<tr>
<td>Rabies</td>
<td>&gt;99</td>
<td>7 d after 2nd dose</td>
<td>2 y</td>
</tr>
<tr>
<td>Tetanus</td>
<td>&gt;99</td>
<td>After 2nd dose</td>
<td>10 y</td>
</tr>
<tr>
<td>Tick borne</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalitis</td>
<td>95-100</td>
<td>2 wk after 2nd dose</td>
<td>3 y</td>
</tr>
<tr>
<td>Typhoid Vi (inj)</td>
<td>50-80</td>
<td>After 10 d</td>
<td>2 y</td>
</tr>
</tbody>
</table>

BCG, bacillus Calmette-Guérin; inj, injectable; MMR, measles, mumps, rubella.
TRAVELERS’ DIARRHEA

ESSENTIALS OF DIAGNOSIS

- Twofold increase in the frequency of unformed bowel movements, usually more than 4-5 stools per day.
- Abrupt onset while traveling or soon after returning home.
- Usually associated with abdominal cramps, rectal urgency, bloating, and malaise.
- Generally is self-limiting after 3-4 days.

General Considerations

Travelers’ diarrhea occurs in a significant number of people who travel to foreign countries, and about 30%-50% of travelers to high-risk areas (Mexico, Latin America, Africa, Asia, and the Middle East) will develop diarrhea during a 1- to 2-week stay. It is caused by fecal-oral contamination of food or water by bacteria, parasites, and viruses. The condition is more common in young adults and the best chance for prevention involves strict attention to hygiene, sanitation, and food preparation, as outlined earlier. Food from restaurants and street vendors are common sites for exposure, and thus eating in a private home may be safer. It is extremely difficult to avoid all dangers in food and drink, and multiple studies have shown no correlation between personal hygiene measures and travelers’ diarrhea. Nevertheless, it is prudent to follow basic hygiene measures while abroad.

In contrast to the developed world, where viruses are the most common cause of diarrhea, enterotoxigenic E coli and other bacteria such as Shigella, Salmonella, Vibrio, and Campylobacter species, are the most common causes of diarrhea in most parts of the developing world. There are significant regional differences.

Clinical Findings

Travelers’ diarrhea is characterized by the abrupt onset of at least a twofold increase in loose stools, usually four to five stools per day. It usually does not begin immediately on arrival in a foreign country but starts 2-3 days into the stay or soon after returning home. Common signs and symptoms include loose or watery stool, abdominal cramping, bloating, urgency, malaise, and nausea. Vomiting occurs in up to 15% of those affected. Symptoms usually resolve in 3-4 days if not treated but can last longer. Depending on the cause, fever, bloody stool, and painful defecation may occur, but these symptoms are not common. Physical findings include a benign abdomen with diffuse tenderness but no rigidity and increased bowel sounds. Patients may appear dehydrated depending on the severity of the diarrhea. Although travelers’ diarrhea rarely is life threatening, it can result in significant morbidity; one in five travelers with diarrhea is bedridden for a day and more than one-third have to alter their activities. Stool examination and culture may yield a causative agent, but in 40%-70% of cases no pathogen is identified.

Treatment

Treatment for travelers’ diarrhea includes fluid replacement and usually includes fluoroquinolone antibiotics (or in children, azithromycin). (See Table 51-4 for doses.) Trimethoprim-sulfamethoxazole and doxycycline are no longer generally recommended due to the development of widespread resistance. Rifaximin can also be used to treat noninvasive E coli–induced travelers’ diarrhea. It is very useful in Latin America and Mexico, but is less useful when Campylobacter is the causative pathogen. In some countries, particularly Thailand and Nepal, Campylobacter infections may be resistant to fluoroquinolones; thus azithromycin or other antibiotics may be needed. Although a 3- to 5-day course on antibiotics is usually recommended, there is evidence that 1-2 days of treatment may be sufficient.

Bismuth subsalicylate can be used by chewing two tablets (or taking 1 oz of liquid) every 30 minutes up to eight doses. Loperamide or diphenoxylate may be used for adults but never in the presence of high fever or bloody stool. Generally, it is best to combine these agents with antibiotics especially if diarrhea is moderate or severe.

Table 51-4. Antibiotics used for the treatment of travelers’ diarrhea.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin (Cipro)</td>
<td>500 mg twice daily for 1-2 d</td>
<td>Other quinolones (eg, ofloxacin, norfloxacin, and levofloxacin are presumed to be effective as well)</td>
</tr>
<tr>
<td>Rifaximin (Xifaxan)</td>
<td>200 mg three times daily for 3 d</td>
<td>Not effective in persons with dysentery</td>
</tr>
<tr>
<td>Azithromycin (Zithromax)</td>
<td>In adults: 500 mg daily for 3 d or 1000 mg in a single dose In children: 10 mg/kg daily for 3 d</td>
<td>Antibiotic of choice in children and pregnant women, and for quinolone-resistant Campylobacter</td>
</tr>
</tbody>
</table>
Fluid replacement using World Health Organization ORS salts are available in most countries. In the United States the salts can be obtained through Cera Products website, www.ceraproductsinc.com. A simple rehydration solution can be made at home using: 1/2 teaspoon of table salt, 1/2 teaspoon of baking soda, and 4 tablespoons of sugar in 1 L of water; orange juice can be added to provide potassium. Adults should drink 8 oz after every diarrheal stool. Children younger than 2 years should be given 2-4 oz and those between 2 and 10 years, 4-7 oz. Acetorphan (Racecadotril), available in Europe but not in the United States, may be an effective adjunct to oral rehydration solutions. Women who are breast-feeding an infant with diarrhea should continue to do so. Patients can also be instructed to eat boiled rice, which often leads to faster resolution of the diarrhea.

Prevention

Although, as mentioned earlier, the effectiveness of dietary precautions have not been conclusively proven to prevent travelers’ diarrhea, it is important for travelers to observe good hygiene and sanitation and pay strict attention to food preparation and avoid high-risk food and adventurous eating behavior.

The CDC does not recommend antibiotic prophylaxis for most travelers; however, it may be indicated in patients with active inflammatory bowel disease, brittle diabetes mellitus type 1, AIDS and other immunosuppressive disorders, unstable heart disease, and those on proton pump inhibitors. Travelers planning an exceptionally critical short trip, where even 1 day of illness could impact the purpose of the trip, may wish to use a prophylactic medication.

Fluoroquinolones have been found to give about 90% protection. Ciprofloxacin 500 mg daily, levofloxacin 500 mg daily, norfloxacin 400 mg daily, or ofloxacin 300 mg daily, have all been used. Rifaximin has also been found to be safe and effective. In a double-blind trial, 210 US adults arriving in Mexico were randomized to receive rifaximin (200 mg 1-3 times a day) or placebo for 2 weeks. Travelers’ diarrhea developed in 14.7% of the rifaximin group and in 53.7% of the placebo group. Rifaximin provided 72% protection against travelers’ diarrhea. Bismuth subsalicylate (Pepto-Bismol two tablets four times a day) provides about 60% protection against travelers’ diarrhea.

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A. Symptoms and Signs

Classical symptoms of malaria in a nonimmune person are fever, chills and sweats, headache, and muscle and joint pains. Nausea, vomiting, abdominal pain, and diarrhea can also occur. Symptoms usually begin 10 days to 4 weeks after infection; however, malaria symptoms might start as
early as 7 days or as late as 1 year, depending on the species, after you return from a malaria area. Physical findings include fever, tachycardia, and flushed skin; mental confusion and jaundice may be present. The spleen and liver are often palpable, especially in persons who have had repeated infections.

Severe malarial infection, usually due to *P. falciparum*, causes a multitude of complications, including cerebral malaria (with seizures, coma, or death), renal failure, hemoglobinuria, hemolytic anemia, acute respiratory failure, shock, and hypoglycemia. Long-term complications include hypersplenism, nephrotic syndrome, and a seizure disorder.

**B. Laboratory Findings**

The gold standard for diagnosis remains thick and thin blood smears stained with Giemsa stain. Thick films are more sensitive to pick up infections, and the thin film is more accurate for identification of species. The films must be fixed and stained properly, and experience is required to interpret the findings. Reputable laboratories can be difficult to identify by a traveler abroad. Also, where malaria is no longer endemic (ie, the United States), health care providers may not be familiar with the disease. Clinicians seeing a febrile patient may not consider malaria among the potential diagnoses and not order the needed diagnostic tests. Laboratory workers may lack experience with malaria and fail to detect parasites when examining blood smears.

Rapid diagnostic “dipstick” tests are available and, in select cases, travelers may be given instruction in their use. These tests are not generally recommended for travelers but could be considered for travelers to isolated malaria-endemic areas without adequate medical facilities. Various tests are available for either *P. falciparum* alone or with other species. Some representative web sites with information on rapid diagnostic tests for malaria available in the United States are http://www.binax.com, http://www.rapidtest.com, and http://www.premiermedcorp.com. Complete information about these diagnostic tests is also available from the WHO web site at http://www.wpro.who.int/sites/rdt/home.htm.

### Table 51-5. *Plasmodium* species causing human malaria.

<table>
<thead>
<tr>
<th>Species</th>
<th>Average Incubation Period</th>
<th>Duration of Untreated Infection (max)</th>
<th>Duration of Attack</th>
<th>Periodicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. falciparum</em></td>
<td>7-14 d</td>
<td>2 y</td>
<td>&gt;16 h</td>
<td>Daily or none</td>
</tr>
<tr>
<td><em>P. vivax</em></td>
<td>13 d</td>
<td>4 y</td>
<td>8-12 h</td>
<td>48 h</td>
</tr>
<tr>
<td><em>P. malariae</em></td>
<td>13-28 d</td>
<td>≥ 40 y</td>
<td>8-10 h</td>
<td>72 h</td>
</tr>
<tr>
<td><em>P. ovale</em></td>
<td>14-17 d</td>
<td>4 y</td>
<td>8-12 h</td>
<td>48 h</td>
</tr>
</tbody>
</table>

**C. Differential Diagnosis**

The differential diagnosis of malaria includes most febrile tropical illnesses prevalent in the area the traveler has visited (see the section Fever in a Returning Traveler, later). The illnesses most often confused with malaria include influenza and viral infections, dengue fever, babesiosis, relapsing fever, yellow fever, hepatitis, typhoid fever, kala-azar, urinary tract infections, tuberculosis, endocarditis, and meningitis (especially in patients with cerebral symptoms).

#### Treatment

The medications used for the treatment of malaria vary and are frequently used in combinations. Ideally, determination of the correct treatment involves the identification of the species of malaria, knowledge of where the traveler has been, and the medical history of the patient. No one drug acts on all stages of the disease, and different species of parasites show different responses. However, if a traveler plans to visit a remote area without adequate medical facilities, he or she may wish to take along medication for presumptive treatment if symptoms of malaria develop. Presumptive self-treatment should never take the place of being evaluated at a medical facility; however, it could be lifesaving if help is not nearby.

The medication currently recommended for self-treatment of malaria is atovaquone-proguanil. Mefloquine is the second-line treatment, but only if these agents are not being used as prophylaxis (see Table 51-6). Artemisinin-based combination therapies (ACT) are available abroad but not in the United States. Artemisinin is derived from the plant *Artemisia annua* (sweet wormwood), which has been used for centuries in China for medical purposes. Artemisinin derivatives such as artemether and artemunate are well tolerated and are given in combination with another drug such as amodiaquine, sulfadoxine-pyrimethamine, mefloquine, or lumefantrine. There have been very rare reports of any resistance. Combination therapy has the advantages of slowing the development of resistance, reducing the length of the required treatment course, and more effectiveness. Sulfadoxine-pyrimethamine (Fansidar) is still a popular choice for treatment, especially in Africa; however, there is widespread resistance to this agent in...
many areas of the world. Allergic reactions are a problem, and sulfadoxine-pyrimethamine can cause Stephens-Johnson syndrome, toxic epidermal necrolysis, anemia, thrombocytopenia, seizures, gastrointestinal upset, headaches, tremor, and kernicterus in newborns. For more information about malaria in general, visit the Roll Back Malaria web site at http://www.rbm.who.int.

### Prevention

**A. General Measures**

Travelers to endemic areas should be advised about basic measures to prevent mosquito bites, including wearing long sleeves, long pants, and light-colored clothing at dusk; avoiding perfumes that might attract mosquitoes; and treating bed nets with permethrin. A mosquito repellent containing 30%-50% DEET (n,n-diethyl-meta-toluamide) is recommended. Picaridin or oil of lemon eucalyptus have both shown good activity as repellents, but there is still not enough evidence on the optimal concentrations needed.

### B. Malaria Prophylaxis

Chloroquine and sulfadoxine-pyrimethamine can cause Stephens-Johnson syndrome, toxic epidermal necrolysis, anemia, thrombocytopenia, seizures, gastrointestinal upset, headaches, tremor, and kernicterus in newborns. For more information about malaria in general, visit the Roll Back Malaria web site at http://www.rbm.who.int.

**Table 51-6. Prophylaxis and treatment dosages for malaria.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult Dosage</th>
<th>Dosage in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malaria Prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine</td>
<td>300 mg base (500 mg salt) per week</td>
<td>5 mg base/kg/wk to max of adult dose</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>250 mg salt/wk</td>
<td>5 mg salt/kg/wk or the equivalent in divided adult tablets, based on child’s weight: 10-19 kg: 1/4 tab/wk 20-30 kg: 1/2 tab/wk 31-45 kg: 3/4 tab/wk &gt;45 kg: use adult dose</td>
</tr>
<tr>
<td>Atovaquone-proguanil</td>
<td>1 adult tab (250 mg atovaquone/100 mg proguanil) per day</td>
<td>Pediatric tabs contain 62.5 mg atovaquone/25 mg proguanil; dosages are based on child’s weight: 5-8 kg: 1/4 pediatric tab daily 8-10 kg: 1/2 pediatric tab daily 11-20 kg: 1 pediatric tab/d 21-30 kg: 2 pediatric tabs/d 31-40 kg: 3 pediatric tabs/d &gt;40 kg: 1 adult tab/d</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg/d</td>
<td>Children ≥8 y: 2 mg/kg/d up to max of the adult dose.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Malaria Treatment</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mefloquine</td>
<td>1250 mg once</td>
<td>25 mg/kg once, up to max of adult dose^d^</td>
</tr>
<tr>
<td>Atovaquone-proguanil</td>
<td>4 tabs once daily for 3 d</td>
<td>Using adult tabs, based on child’s weight: 11-20 kg: 1 tab/d for 3 d 21-30 kg: 2 tabs/d for 3 d 31-40 kg: 3 tabs/d for 3 d &gt;40 kg: use adult dose</td>
</tr>
<tr>
<td>Sulfadoxine-pyrimethamine</td>
<td>3 tabs once</td>
<td>Children &gt;1 y: 1/4 tab 1-3 y: 1/2 tab 4-8 y: 1 tab 9-14 y: 2 tabs given all at once</td>
</tr>
</tbody>
</table>

Tab, tablet.

^a Cautious use in pregnancy.

^b Not for use in pregnant or lactating women.

^c Contraindicated in pregnant or lactating women and in children younger than 8 years.

^d This regimen tends to cause considerable gastrointestinal upset.
prevent relapses or delayed-onset clinical presentations of malaria caused by dormant liver stages of \( P \) \textit{vivax} or \( P \) \textit{ovale}.

In choosing an appropriate chemoprophylactic regimen, the traveler and the health care provider should consider several factors. The travel itinerary should be reviewed in detail to determine whether the traveler is actually at risk for acquiring malaria. The next step is to determine whether significant antimalarial drug resistance has been reported in that location. Resistance to antimalarial drugs has developed in many regions of the world. Health care providers should consult the latest information on resistance patterns before prescribing prophylaxis for their patients.

Four medications are currently available and approved in the United States for malaria prophylaxis: chloroquine, mefloquine, doxycycline, and atovaquone/proguanil.

1. **Chloroquine** is still effective for prophylaxis in Central America above the Panama Canal and in some areas of the Middle East. It should not be used for prophylaxis in other areas. Most strains of \( P \) \textit{falciparum} and some strains of \( P \) \textit{vivax} have developed resistance to chloroquine. Some of its side effects include pruritus, headache, myalgia, alopecia, and spotty depigmentation. It can cause exacerbations of psoriasis,eczema, and dermatitis, and caution should be used if it is prescribed to people with these disorders. Retinal injury may occur with lifetime doses over 100 g. Chloroquine is safe in pregnancy and breast-feeding. Prophylaxis should begin 1-2 weeks before the traveler's planned arrival in a malaria-endemic area and should continue for 4 weeks after return. See Table 51-6 for prophylactic dosages in adults and children.

2. **Mefloquine** is effective for prophylaxis in most of the world except the border area between Thailand and Myanmar. \( P \) \textit{falciparum} shows a patchy resistance to the drug in some areas. It is considered safe to use in pregnancy and breast feeding although small amounts of drug are passed in breast milk. The most serious side effects are neuropsychiatric, such as bad dreams, paresthesias, hallucinations and even psychotic reactions. Other side effects include vertigo, seizures, hepatotoxicity, headache, confusion, gastrointestinal upset, pruritus and depression. It is contraindicated with serious psychiatric disorders or seizures. Caution is advised in patients with cardiac conduction abnormalities. As with chloroquine, prophylaxis should begin 1-2 weeks before arrival in a malaria-endemic area and continue for 4 weeks after return. See Table 51-6 for prophylactic dosages.

3. **Atovaquone/proguanil** is effective and safe for children but is not recommended for use in pregnant women or women breast-feeding infants lighter than 5 kg. Side effects include abdominal pain, vomiting, and headache. The drug is contraindicated in patients with severe renal insufficiency. Prophylaxis should begin 1-2 days before arrival in a malaria-endemic area and continue for 7 days after return (see Table 51-6).

4. **Doxycycline** is efficacious, safe, and the most inexpensive choice for prophylaxis. Its use is contraindicated in pregnancy, breast-feeding, and in children younger than 8 years. Side effects include gastrointestinal upset, vaginal yeast infection, phototoxicity, hepatic toxicity, pseudomembranous colitis, and increased intracranial pressure. Prophylaxis should begin 1 day before arrival in a malaria-endemic area and continue for 4 weeks after return (see Table 51-6).

**Primaquine** is the agent used if terminal prophylaxis is desired. It has also been used for prophylaxis of the primary infection in special circumstances. It should be used only after consultation with a malaria expert and only in those with documented evidence of a normal glucose-6-phosphate dehydrogenase (G6PD) level.

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**TREATMENT OF THE RETURNING TRAVELER**

Despite the best preparations, many travelers become sick while abroad or are ill upon their return home. Of the 50 million travelers to the developing world each year, over 50% will have a travel-related health impairment and 10-20% will consult a physician, either while abroad or after returning home, due to a travel related illness. This section describes three common problems faced by the family physician—fever, diarrhea and eosinophilia—with the goal of assisting the physician make a final diagnosis and provide appropriate treatment to the returning traveler. The differential diagnosis depends on the traveler’s itinerary and other factors, and all possibilities cannot be covered here. Fever and eosinophilia, in particular, may occur as symptoms in a wide range of infectious and inflammatory conditions.

**Fever in a Returning Traveler**

Fever in a returning traveler requires a thorough history (including immunizations and any use of prophylactic medications, illness in companions, sexual activities, and any nonprescribed drug use) and physical examination. Often localized symptoms or signs (eg, respiratory symptoms, jaundice) help narrow the diagnosis. See Table 51-7 for the physical findings in various disorders. If the diagnosis is not immediately obvious, consideration must be given to diseases that are endemic in the area(s) visited. Stable patients may be safely observed for a few days, and most fevers will resolve spontaneously. No definite cause is found in at least 25% of returning travelers with a fever; however, in a recent
Table 51-7. Possible diagnoses with certain physical findings in febrile travelers.

<table>
<thead>
<tr>
<th>Finding</th>
<th>Possible Associated Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>Dengue, typhoid, rickettsial infections, syphilis, gonorrhea, brucellosis, hemorrhagic fever viruses, other viral illnesses including arboviruses</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Hepatitis, malaria, yellow fever, leptospirosis, relapsing fever</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Rickettsial infections, brucellosis, dengue, acute HIV, visceral leishmaniasis, Lassa fever</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Amebiasis, malaria, hepatitis, leptospirosis</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Malaria, relapsing fever, trypanosomiasis, typhoid, brucellosis, visceral leishmaniasis, typhus, and dengue</td>
</tr>
<tr>
<td>Eschar</td>
<td>Rickettsial infections (especially Tsutsugamushi disease), <em>Borrelia</em>, Crimean-Congo hemorrhagic fever</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Dengue, meningococcemia, Lassa fever, Marburg and Ebola fever, Crimean-Congo fever, Rift Valley fever, yellow fever, rickettsial infections (Rocky Mountain spotted fever, louse-borne typhus).</td>
</tr>
</tbody>
</table>


Table 51-8. Selected causes of fever in a traveler returning from the tropics (not in order of frequency).

<table>
<thead>
<tr>
<th>Short Incubation (≥28 d)</th>
<th>Long Incubation (≥28 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arboviruses such as Chikungunya Babesiosis</td>
<td>Brucellosis (some cases) Filariasis</td>
</tr>
<tr>
<td>Bacterial diarrhea</td>
<td></td>
</tr>
<tr>
<td>Bartonellosis</td>
<td></td>
</tr>
<tr>
<td>Borrellosis</td>
<td></td>
</tr>
<tr>
<td>Brucellosis (some cases)</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus and other viruses</td>
<td></td>
</tr>
<tr>
<td>Dengue fever, yellow fever, and hemorrhagic fever viruses</td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A (some cases)</td>
<td></td>
</tr>
<tr>
<td>Histoplasmosis and other fungal diseases</td>
<td></td>
</tr>
<tr>
<td>Influenza and other acute respiratory infections</td>
<td></td>
</tr>
<tr>
<td>Leptospirosis</td>
<td></td>
</tr>
<tr>
<td>Listeriosis</td>
<td></td>
</tr>
<tr>
<td>Malaria (some cases)</td>
<td></td>
</tr>
<tr>
<td>Meningococcemia</td>
<td></td>
</tr>
<tr>
<td>Plague</td>
<td></td>
</tr>
<tr>
<td>Rickettsial diseases</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td></td>
</tr>
<tr>
<td>Typhoid or paratyphoid fever and enteric fever</td>
<td></td>
</tr>
</tbody>
</table>

Report from the GeoSentinel Network, 21% of patients were found to have malaria, 6% to have dengue fever, and 17% to have a disease preventable by a vaccine or chemoprophylaxis. Fever usually has an infectious cause, but occult malignancies and rheumatologic conditions should be considered in the differential diagnosis.

If illness persists or the patient is unstable or seriously ill, laboratory investigation becomes the key to the diagnosis. Laboratory studies that may be appropriate include a complete blood count; malaria smear, and smears for *Borrelia, Babesia, and Filaria*; typhoid culture or antigen test, including urine for *Salmonella* and *Legionella* antigens; urinalysis; liver function tests; cultures of blood, urine, and possibly cerebrospinal fluid; stool examination; biopsy of skin lesions, lymph nodes or other masses, bone marrow aspirate; hepatitis serology; and other serologies depending on the patient’s possible exposures. Acute and convalescent sera can be helpful in making a final diagnosis.

A chest radiograph should generally be done in febrile patients, especially if tuberculosis is suspected, and purified protein derivative (PPD) testing for tuberculosis should be performed. Seriously ill patients must be hospitalized, and any patient suspected of having a highly contagious condition must be isolated. This is especially true of travelers returning from Africa with hemorrhagic fever. Any case of suspected viral hemorrhagic fever must be reported to the local health department and to the CDC.

Differential diagnoses to consider in a traveler returning with fever are listed in Table 51-8. It is important to remember that “the common is still common,” and, in fact, the most common causes of fever in returned travelers are routine illnesses such as upper and lower respiratory tract infections, sinusitis, urinary tract infections, and influenza. Thus, the conditions in Table 51-8 should be considered only if a more common cause is not readily apparent.

Malaria is one of the more common and worrisome causes of fever in a returning traveler. Most cases of serious fever requiring hospitalization in travelers are due to malaria. Infections, particularly with *P falciparum*, frequently occur within 2 weeks of the mosquito bite, but may occur up to 5 years after exposure, especially if caused by *P vivax* or *P ovale*. In a seriously ill febrile traveler to a malarial area, for whom no cause can be found, it may be wise to include empiric treatment for malaria, even if the results of the blood smear are negative. (Refer to the earlier discussion of malaria.)


Diarrhea in a Returning Traveler

As discussed earlier, travelers’ diarrhea is an acute condition that usually resolves within 2 weeks. Most acute bacterial infections can be treated successfully with ciprofloxacin or other antibiotics. Some travelers, however, develop persistent diarrhea or other gastrointestinal (GI) symptoms that can be difficult to diagnose and treat. In fact, a recent study showed that 63% of a group of 97 healthy student travelers to Mexico, who returned a questionnaire, developed diarrhea compatible with travelers’ diarrhea. Six months later, 18% still reported loose stools, 18% reported abdominal pain, and 9% had fecal urgency. Of the 60 patients who had acquired diarrhea in Mexico, 7 (11.7%) met the criteria for IBS 6 months later. Finally, sometimes underlying GI pathology, such as celiac sprue and other malabsorption disorders and even gastrointestinal malignancy, can be unmasked after a bout of diarrhea in a traveler.

Some causes of persistent diarrhea in a returning traveler are listed in Table 51-9. If a patient’s response to antibiotic treatment is inadequate or the diarrhea persists for more than 7 days, a stool examination should be performed. Preferably three stools should be examined. In addition to checking for ova and parasites, an evaluation for Giardia antigen and bacterial cultures should also be performed. If symptoms of rectal disease are present, anoscopic and sigmoidoscopic examination should be done with biopsies as needed. If the results of these tests are negative, the physician should consider an empiric trial of metronidazole for the treatment of a possible Giardia or other protozoan infection. Irritable bowel syndrome (IBS) and, less commonly, inflammatory bowel disease may develop after travel in those who experience a bout of bacterial or viral diarrhea. In fact one study showed that 63% of a group of 97 healthy student travelers to Mexico, who returned a questionnaire, developed diarrhea compatible with travelers’ diarrhea. Six months later, 18% still reported loose stools, 18% reported abdominal pain, and 9% had fecal urgency. Of the 60 patients who had acquired diarrhea in Mexico, 7 (11.7%) met the criteria for IBS 6 months later. Finally, sometimes underlying GI pathology, such as celiac sprue and other malabsorption disorders and even gastrointestinal malignancy, can be unmasked after a bout of diarrhea in a traveler.

Table 51-9. Selected causes of persistent diarrhea in a returning traveler.

| Parasites, especially Giardia, Entamoeba histolytica, Cyclospora, Cryptosporidium, microsporidia (especially if immunocompromised) |
| Bacteria, such as Campylobacter, E coli spp (enteropathogenic or toxin-producing stains), Shigella, Salmonella, Aeromonas, Vibrio cholerae and noncholera vibrios, Yersinia, Clostridium difficile |
| Lactase deficiency and other disaccharidase deficiencies |
| Bacterial overgrowth and tropical sprue |
| Irritable bowel syndrome |
| Inflammatory bowel disease |
| Idiopathic (Brainerd diarrhea) |

Eosinophilia in a Returned Traveler

A high level of eosinophilia (>450 eosinophils/µL) almost always indicates a parasitic infection. High levels of eosinophilia are characteristically found in helminthic infections, especially for those helminthes that have an extraintestinal migration phase and produce tissue infection. Strongyloides and lymphatic and tissue filariasis cause some of the highest levels, and infection in humans can persist for many years if not treated. Protozoans, such as Giardia and Plasmodium species, do not generally cause eosinophilia, with the exceptions noted in Table 51–10. Schistosomiasis has become a serious problem for people swimming or rafting in freshwater in Africa. Allergic disorders, such as allergic rhinitis or asthma, can also cause eosinophilia. In one study from Israel, 82 of 995 travelers (8.2%) were found to have significant eosinophilia. Of these, 44 (53.7%) were found to have schistosomiasis mostly acquired in sub-Saharan Africa. Of the remaining 38 cases a definitive parasitological diagnosis could only be made in 9 (23.7%) travelers. This is compatible with other studies. A therapeutic trial of albendazole was given to most of the cases without a specific diagnosis and about 90% reported a favorable response with resolution of symptoms and a significant decrease in the eosinophil count after 2 months.

The workup for a traveler with eosinophilia must include multiple stool examinations, including stool concentration if schistosomiasis is suspected. Biopsy specimens of skin lesions (onchocerciasis) or swollen lymph nodes (filariasis) can be examined for definitive diagnosis. Several serologic tests are available from the CDC and other specialized laboratories. These include tests for toxocariasis, strongyloidiasis,
Table 51-10. Selected causes of eosinophilia in a returned traveler.

<table>
<thead>
<tr>
<th>Infectious Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helminthic: Angiostrongyliasis, ascariasis, capillariasis, clonorchiasis, cutaneous larva migrans, echinococcosis, enterobiasis, fasciolopsiasis, filariasis, gnathostomiasis, hookworm, loiasis, onchocerciasis, paragonimiasis, schistosomiasis, strongylidiasis, toxocariasis, trichinosis</td>
</tr>
<tr>
<td>Protozoal: Blastocystis hominis, Dientamoeba fragilis, Isospora belli</td>
</tr>
<tr>
<td>Fungal: Bronchopulmonary aspergillosis</td>
</tr>
<tr>
<td>Viral: Hepatitis B, HIV</td>
</tr>
<tr>
<td>Ectoparasitic: Scabies</td>
</tr>
<tr>
<td>Other: Tropical pulmonary eosinophilia (related to tissue filarial infections)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Noninfectious Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic disorders: Atopic eczema, urticaria, asthma, allergic rhinitis, drug reaction</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>Vasculitis</td>
</tr>
</tbody>
</table>

HIV, human immunodeficiency virus.

Filariasis, trichinosis, schistosomiasis, cysticercosis, and paragonimiasis. A therapeutic trial of albendazole is probably warranted as above if no diagnosis is found.


Web Sites

http://www.cdc.gov/travel (includes advice regarding special needs, children, and pets. There is information about vaccines, and the site also has safety information about cruise ships. Finally, there is also information about recent disease outbreaks.)
http://www.paho.org (The Pan-American Health Organization web site has information on countries in the western hemisphere.)
http://www.promedmail.org (ProMED is a listserv that monitors for emerging diseases worldwide.)
https://www.travmed.com (This web site has general information on travel medicine with links to many other sites.)
http://www.who.int (The World Health Organization web site has much useful information, including worldwide disease surveillance.)
General Considerations

The Surgeon General’s Report on Mental Health, issued by former Surgeon General David Satcher, MD, called the nation’s attention to the importance of mental health in overall health. The report cited the commonality of mental illness and the fact that undertreatment of mental illness is an enormous problem fueled by stigma and barriers to access. Several demographic groups were identified as being at particularly high risk for having unmet mental health needs: children and youth, older adults, and members of medically underserved ethnic and racial groups. Because these groups rely largely on the primary care setting for their mental health needs, the report strongly recommended an expanded role for primary care physicians and allied health practitioners in providing mental health services.

Depression is the leading cause of disability (lost years of healthy life) in Western countries at ages 15-44 years old. The estimated annual cost of depression in the US economy is $83 billion, including expenses related to care, absenteeism, reduced productivity on the job, and premature death and suicide. In the United States, the point prevalence and lifetime prevalence of depression are 6.6% and 16.6%, respectively. While depression may occur at any age, the typical age of onset of major depression is 27-35 years and the highest rate of depression exists in adults ages 40-59. Depression is twice as common among women as men. Recent data continue to support the Surgeon General’s Report that blacks and Hispanics with a diagnosis of depression in the previous 12 months are less likely to receive mental health care than their white counterparts (58.9% vs 51.8% vs 71.1%).

Depression often coexists with other chronic medical illnesses, particularly in later life. Medical illness and disability—more common in the elderly—are risk factors for depression. Depression diminishes quality of life, leads to nonadherence with self-care (diet, exercise, taking medication as prescribed), increases use of other medical services, is a risk factor for suicide, and is associated with cognitive impairment in older adults. Additionally, major psychosocial risk factors for depression include bereavement, caregiver strain, social isolation, disability, role transitions, and severe medical problems.

Depression is associated with abnormal functioning of the brain and often has a genetic basis. It often goes unrecognized and untreated and can therefore increase morbidity and mortality in populations such as the elderly and ethnically and racially diverse groups with high prevalence of chronic illness. However, depression is treatable and some interventions can significantly reduce its symptomatology and incidence. Depression is often a chronic illness, following a relapsing course. In order to prolong recovery and prevent recurrence, maintenance treatment beyond the acute treatment of the episode is usually medically appropriate, thus making the primary care setting an appropriate medical home for depression care. In addition, many people prefer to be treated in the general medical sector rather than being referred to specialty mental health care.


Prevention

There is increasing interest in early preventive interventions with patients who are at high risk for developing depression in the wake of medical events such as stroke, myocardial infarction, macular degeneration, interferon therapy, and arthritis. Preventive interventions may include psychoeducation about the particular challenges being confronted, stress-coping techniques, the use of problem-solving therapies to help patients cope more effectively with increasing limitations, supporting general health and wellness (good nutrition/exercise/relaxation), facilitating support of family/friends/support groups, and protecting sleep quality through better sleep hygiene. Prevention strategies for addressing depression in the elderly have also been shown to be effective in the primary care setting. Over the past decade, it has become clear that antidepressant treatments can have a very favorable impact on the long-term course of depressive illness, particularly in preventing recurrences of disease.

A. Depression and Other Chronic Illnesses

Depression commonly co-occurs with chronic diseases, complicating treatment and worsening chronic disease outcome. Depression is an independent risk factor in the development of cardiovascular diseases (heart disease, stroke). Stroke is also independently associated with depression. Other chronic conditions that frequently co-occur with depression include HIV/AIDS, arthritis, chronic pain syndromes, sickle cell disease, and cancer. (Tables 52-1 and 52-2.) Depression can negatively affect the outcome of the co-occurring condition because it impacts a person’s ability to follow a treatment plan, including adherence to medication or other therapies, diet, and exercise. Screening, diagnosis, and treatment of depression could have an impact on the course and management of chronic diseases.

Although approximately one-third of individuals with chronic medical conditions may experience symptoms of depression, individuals with chronic illnesses often overlook symptoms and signs of depression, assuming that feeling “down” or depressed is normal while living with a serious, chronic illness. In addition, because symptoms and signs of depression are frequently masked by other medical conditions, health care providers treating individuals with chronic diseases may not recognize that the underlying cause of depressed mood, decreased energy, sleep changes, or appetite changes is depression. Therefore, a high index of suspicion of depression should be maintained when treating patients who present with symptoms and signs of chronic physical conditions, multiple somatic complaints, or chronic pain complaints. Screening should be utilized in these instances populations with consistent systems in place for diagnosis, treatment, and follow-up. The American Heart Association and the American Psychiatric Association specifically recommend screening for depression in patients with coronary heart disease.

Table 52-1. Depression in elderly patients with co-occurring illnesses.

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>% With Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>40</td>
</tr>
<tr>
<td>Chronic heart disease</td>
<td>20</td>
</tr>
<tr>
<td>Diabetes</td>
<td>24</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>40</td>
</tr>
<tr>
<td>Stroke</td>
<td>20-50</td>
</tr>
</tbody>
</table>


Table 52-2. Prevalence of depression in patients with cancer.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Prevalence of Depression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>1.5-46</td>
</tr>
<tr>
<td>Colon</td>
<td>13-25</td>
</tr>
<tr>
<td>Gynecological</td>
<td>12-23</td>
</tr>
<tr>
<td>Lung</td>
<td>11-44</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>8-19</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>22-57</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>33-50</td>
</tr>
</tbody>
</table>

B. Impact of Health Disparities

Overall, studies show that disparities exist between whites and racially and ethnically diverse groups in mental health status, in utilization of mental health services, in quality of care and outcome regardless of socioeconomic status in the four major underserved ethnic and racial groups: African Americans, American Indians, Asian Americans, and Hispanics. Risk of mental illness and poor mental health outcomes in diverse and underserved populations is increased due to nonfamilial factors associated with depression (eg, socioeconomic status, environmental factors, access to health care, and higher rates of health disorders). Despite increases in the rate of antidepressant medication use over the past 12 years among all racial and ethnic groups, this increase has been disproportionately higher in whites compared with non-Hispanic blacks.

The increased risk of living in poverty with inadequate access to health care and inadequate treatment, more prevalent in populations of color, may multiply stress and contribute to persistent and recurring episodes of depression. For nonwhite populations, the chronic stress of discrimination and subsequent effects on immune regulation of living as a member of a marginalized racial and ethnic group can also contribute to depression. Because of the independent increased risk of chronic diseases and mental illness in diverse racial and ethnic populations, the impact of mental illness on chronic diseases is increased substantially.

The increased risk of living in poverty with inadequate access to health care and inadequate treatment, more prevalent in populations of color, may multiply stress and contribute to persistent and recurring episodes of depression. For nonwhite populations, the chronic stress of discrimination and subsequent effects on immune regulation of living as a member of a marginalized racial and ethnic group can also contribute to depression. Because of the independent increased risk of chronic diseases and mental illness in diverse racial and ethnic populations, the impact of mental illness on chronic diseases is increased substantially.

The type and level of severity of depression runs along a spectrum, ranging from subclinical varieties to major depression. Major depression typically occurs in episodes, each with a clear beginning and end. After an initial episode, more than 50% will have additional episodes in their lifetime. Among older adults with depression, about half had experienced depression earlier in their life, the other half experience it for the first time after the age of 60.

A. Initial Assessment

The American Academy of Family Physicians states that mental health care is an integral component of the continuum of care in the primary care setting. However, the reluctance of individuals to seek care for mental health problems along with a likelihood of somatization of emotional issues pose giant obstacles for mental health care in these settings. Studies report that approximately 40% of patients with major depression do not want or perceive the need for treatment. Only 20%-30% of patients with emotional or psychological issues report these to their primary care physicians, and the most common somatic symptom reported by more than half of patients with major depression was “feeling fatigued, weak, or tired all over.” Recent data suggest a discordance between patients presenting with symptoms of depression and physicians’ appraisal of depression symptoms during primary care visits.

Initial assessment should include a focused psychiatric history and examination and, for older adults, a brief clinical cognitive examination. In addition, a medical history, physical examination, focused neurologic examination, and laboratory studies to rule out physical conditions with similar symptoms are preferred as part of the assessment. It is also important to assess other domains, particularly for older adults, including level of functioning or disability, loss or grief concerns, physical environment, and psychosocial situation.

B. Symptoms and Signs

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) classifies depressive disorders into three categories: major depressive disorder, dysthymic disorder, and depressive disorder not otherwise specified. Specific features associated with these disorders are described as follows:

1. Major depressive disorder—The nine typical symptoms that may appear during a major depressive episode:

   - Depressed mood: Feeling sad, low, empty, hopeless, gloomy, or down in the dumps; different from a normal sense of sadness or grief.
   - Anhedonia: Inability to enjoy usually pleasurable activities (eg, sex, hobbies, daily routines).
   - Change in appetite or weight: A decrease in appetite (most patients) or an increase in appetite associated with craving specific foods.
   - Change in sleep pattern: Insomnia (difficulty falling asleep, staying asleep, or waking early) in most patients; hypersomnia in some.
   - Change in activity: Retardation of psychomotor activities (speech, thinking, movement) or increased or agitated psychomotor activities (cannot sit still, pacing, hand wringing).
   - Loss of energy: Decreased energy, tiredness, fatigue.
   - Cognitive changes: Inability to think, concentrate, or make decisions.
   - Sense of worthlessness or guilt: Excessive feelings of low self-esteem, self-blame, and lack of self-worth.
   - Thoughts of death or suicide (including suicidal ideation, suicidal attempts).

In more than 90% of patients diagnosed with a major depressive disorder (characterized by several major depressive episodes), two of these nine features are present: depressed mood or anhedonia (the loss of interest or pleasure)
that predominates for at least 2 weeks and causes significant distress or impairment in the individual’s social, occupational, or other important areas of functioning. A total of five of the nine features, including one of the first two, must be present during this same 2-week period for the patient to be diagnosed with the disorder.

Because depression in older patients often occurs in the context of medical and neurologic illnesses, more emphasis should be placed on sad, downcast mood and diminished interest in pleasurable activities instead of somatic complaints.

2. **Dysthymic disorder**—Dysthymic disorder is distinguished by a chronically depressed mood that occurs for most of the day more days than not for at least 2 years. Periods of depressed moods often include at least two of the following: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, poor concentration or difficulty making decisions, and feelings of hopelessness.

3. **Depressive disorders not otherwise specified**—This DSM-IV-TR category encompasses four distinct presentations: premenstrual dysphoric disorder (markedly depressed mood, marked anxiety, decreased interest in activities), regularly occurring during the last week of the luteal phase; depression due to a medical condition; seasonal affective disorder (SAD); and substance-induced mood disorder, prominent and persistent depressed mood that is due to the direct physiologic effects of substance use.

**C. Screening Measures**

1. **Depression**—The US Preventive Services Task Force (USPSTF) guidelines and the American Academy of Family Physicians recommend screening for depression in the primary care setting using a two-question initial screening test to detect the presence of depressed mood and anhedonia (“Over the past 2 weeks, have you felt down, depressed or hopeless?” and “Over the past 2 weeks, have you felt little interest or pleasure in doing things?”). These are the first two questions of the nine-item Patient Health Questionnaire (PHQ-9), a screening tool for depression developed and validated in mental health and primary care settings and based on the DSM-IV-TR criteria for depression. A positive response to either question requires a more detailed clinical interview or a more specific tool that uses standard diagnostic criteria (ie, DSM-IV-TR) to determine the presence or absence of specific depressive disorders and the severity of depression. The presence of co-occurring psychological problems (eg, anxiety, panic attacks, or substance abuse) should also be identified.

Table 52-3 lists several screening instruments for depression. The PHQ-9 appears to perform as well as longer instruments. Studies have found the PHQ-9 to be effective in diverse populations including African Americans, Chinese Americans, Latinos, and others. Several instruments are useful for screening for depressive symptoms in older adults in primary care practices, including the Geriatric Depression Scale. Positive findings from an instrument and clinical interview, resulting in a diagnosis of major depression, must be followed up with appropriate treatment and monitoring.

2. **Suicide**—Assessing risk factors for suicide is an essential part of the diagnostic process. Risk factors for attempted suicide include mood disorders or other mental disorders, comorbid substance use disorders, history of deliberate self-harm, development of disability, and history of suicide attempts. Some instruments for detecting risk of depression (eg, PHQ-9) identify the presence of suicidal ideation. Up to three-quarters of suicide victims will have seen a primary care physician in the month before death, signaling an opportunity for lifesaving interventions. Once a risk of suicide is established, referral to specialty mental health services is indicated.

**Table 52-3. Depression and suicide screening instruments.**

<table>
<thead>
<tr>
<th>Instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck Depression Inventory</td>
</tr>
<tr>
<td>Center for Epidemiologic Studies Depression Screen (CES-D)</td>
</tr>
<tr>
<td>Geriatric Depression Scale</td>
</tr>
<tr>
<td>Patient Health Questionnaire (PHQ-9)</td>
</tr>
<tr>
<td>Scale for Suicide Ideation</td>
</tr>
</tbody>
</table>


Kroenke K et al: The patient health questionnaire-2: Validity of a two-item depression screener. Med Care 2003;41:1284. [PMID: 14583691]


**D. Differential Diagnosis**

The most critical comorbid conditions to assess for in a person with depression include alcohol- and substance-use disorders and medications that can cause mood disturbances (eg, prednisone). Depression in later life often coexists with cognitive impairments and other central nervous system illnesses, and the co-occurrence increases the risk of developing symptoms of Alzheimer’s disease compared with those with cognitive impairments without depression. Depending on the clinical presentation, physicians should also assess the patient for a variety of general medical problems that could be contributing to mood symptoms. Accidental misuse of medications and physical, verbal, or emotional abuse by caregivers or relatives should also be evaluated.


**Treatment**

Treatment of mental disorders has increased substantially over the past decades, yet the majority of adults with mental disorders do not receive treatment or do not receive treatment in accordance with accepted standards of care. Predictors of receiving guideline-concordant care include being white, female, severely ill, and having mental health insurance coverage.

Effective treatments for depressed patients include pharmacologic, psychotherapeutic (behavioral or counseling), and complementary and alternative therapies—and combinations of these. Selection of an initial treatment modality should be influenced by both clinical (eg, severity of symptoms) and other factors (eg, patient preference). In general, evidence-based recommendation for treatment of moderate to severe depression in the primary care setting involves a combination of pharmacotherapy and psychotherapy, and for the treatment of mild to moderate depression, psychotherapy alone.

Although the majority of depressed patients are treated in primary care settings, some cases are especially difficult to manage in general medical clinics without specialized services. Specialized psychiatric care is strongly indicated if clinical findings support a diagnosis of psychotic depression, bipolar disorder, active suicidal ideation, depression with comorbid substance abuse, depression with comorbid dementia, or other needs for more specialized assessment.

**A. Psychotherapeutic Interventions**

For patients with mild to moderate major depressive disorder psychotherapy alone may be appropriate. Cognitive-behavioral therapy (CBT) and interpersonal therapy are psychotherapeutic approaches used in the treatment of patients with major depressive disorder, with documented beneficial outcomes. Factors to consider when determining how often to see an individual patient include the goals of the psychotherapy, the frequency necessary to create and maintain a therapeutic relationship, the frequency required to ensure treatment adherence, and the frequency necessary to monitor and address suicidality. If the regimen needed to address these parameters cannot be met in the primary care setting, referral for specialty mental health services may be indicated (to psychiatric nurses, counselors, psychologists, or psychiatrists). However the service is provided, physicians should ensure that patients are made aware of psychotherapy as an option and are assisted in accessing it.

**B. Pharmacotherapy**

Antidepressant medications may be provided as an initial primary treatment for patients with mild symptoms of major depressive disorder, and these medications should be provided for all patients with moderate to severe symptoms. Improvement should be noted within 6-8 weeks of initiating therapy. Studies have shown that maintenance antidepressant therapy is effective in preserving improvements and preventing recurrent depression.

The most commonly used antidepressant medications are listed in Table 52-4. Selective serotonin reuptake inhibitors (SSRIs) are usually the first-line of therapy due to their generally less problematic side effects. Other medications likely to be optimal for most patients include desipramine, nortriptyline, bupropion, and venlafaxine. Because of their potential to cause serious side effects and the need for dietary restrictions, monoamine oxidase inhibitors (MAOIs) are typically reserved for patients who do not respond to other treatments. Patients prescribed antidepressant medication should be monitored to assess their response to pharmacotherapy as well as the emergence of side effects, clinical condition, and safety. If no response is seen within the initial 6- to 8-week period of pharmacologic therapy, referral for specialty mental health care may be considered.

Numerous factors can influence how an individual responds to a particular antidepressant medication, including a person’s ethnic/racial origins and age. For example, African Americans and Asians are more likely than others to metabolize antidepressants more slowly, resulting in an increased likelihood of experiencing side effects. Antidepressants best avoided in the elderly, because of cardiotoxic side effects and other safety concerns, include amitriptyline, imipramine, and doxepin.

**C. Complementary and Alternative Therapies**

Some studies show a beneficial effect of exercise programs in treatment of depression in comparison to antidepressant medication alone. Meditation-based cognitive therapy has been shown to be effective for treatment of and decreasing recurrence
of major depressive disorder. A variety of coping and self-management strategies can also be helpful such as peer support, exercise, good nutrition, practiced relaxation, setting aside time for pleasurable activities, and setting small achievable goals. Increasing evidence in the medical literature supports the beneficial role of spirituality in the health and mental health of patients. (See additional discussion in Section F.)

D. Combination Therapy

The combination of psychotherapy and medication is recommended for patients with moderate to severe depression. Patients who have a history of only partial response to adequate trials of either treatment alone may benefit from combined treatment. Sequential treatment of psychotherapy and pharmacotherapy may also be beneficial. Patients with poor adherence to individual treatments may also benefit from combined treatment of any form. Most studies of CBT support its use either alone or in addition to pharmacotherapy in decreasing depressive recurrence.

E. Improving outcomes

Several primary care intervention programs, which have been shown to improve outcomes for patients with depression for up to 5 years, include provider training (in counseling, psychotherapy, medication management), patient education, resources to support medication management or evidence-based psychotherapy, and consistent follow-up at set intervals. Primary care settings instituting variations of these basic criteria or interventions show consistent improvement in outcomes across different cultural groups (race and ethnicity, gender, age, urban vs rural) compared with regular

---

Table 52-4. Medications used in treatment of depression.

<table>
<thead>
<tr>
<th>Drug Type: Brand (Generic)</th>
<th>Typical Daily Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective Serotonin Reuptake Inhibitors (SSRIs)</strong></td>
<td></td>
</tr>
<tr>
<td>Celexa (citalopram)</td>
<td>20-60 mg</td>
</tr>
<tr>
<td>Lexapro (escitalopram)</td>
<td>10-20 mg</td>
</tr>
<tr>
<td>Luvox (fluvoxamine)</td>
<td>50-300 mg</td>
</tr>
<tr>
<td>Luvox CR (fluvoxamine, controlled-release)</td>
<td>100-300 mg</td>
</tr>
<tr>
<td>Paxil (paroxetine)</td>
<td>20-50 mg</td>
</tr>
<tr>
<td>Paxil CR (paroxetine, controlled-release)</td>
<td>12.5-62.5 mg</td>
</tr>
<tr>
<td>Prozac (fluoxetine)</td>
<td>20-80 mg</td>
</tr>
<tr>
<td>Prozac Weekly (fluoxetine)</td>
<td>90 mg</td>
</tr>
<tr>
<td>Zoloft (sertraline)</td>
<td>50-200 mg</td>
</tr>
<tr>
<td><strong>Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)</strong></td>
<td></td>
</tr>
<tr>
<td>Cymbalta (duloxetine)</td>
<td>40-60 mg</td>
</tr>
<tr>
<td>Effexor (venlafaxine)</td>
<td>75-375 mg</td>
</tr>
<tr>
<td>Effexor XR (venlafaxine, extended-release)</td>
<td>37.5-225 mg</td>
</tr>
<tr>
<td>Pristiq (desvenlafaxine)</td>
<td>50 mg</td>
</tr>
<tr>
<td>(trazodone)</td>
<td>150-400 mg</td>
</tr>
<tr>
<td><strong>Dopamine Reuptake Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Wellbutrin (buproprion)</td>
<td>200-450 mg</td>
</tr>
<tr>
<td>Wellbutrin SR (buproprion, sustained-release)</td>
<td>150-400 mg</td>
</tr>
<tr>
<td>Wellbutrin XL (buproprion, extended-release)</td>
<td>150-450 mg</td>
</tr>
<tr>
<td><strong>Tricyclics</strong></td>
<td></td>
</tr>
<tr>
<td>(amitriptyline)</td>
<td>50-200 mg</td>
</tr>
<tr>
<td>Aventyl (nortriptyline)</td>
<td>75-150 mg</td>
</tr>
<tr>
<td>Norpramin (desipramine)</td>
<td>100-300 mg</td>
</tr>
<tr>
<td>Pamelor (nortriptyline)</td>
<td>75-150 mg</td>
</tr>
<tr>
<td>Sinequan (doxepin)</td>
<td>25-300 mg</td>
</tr>
<tr>
<td>Surmontil (trimipramine)</td>
<td>50-200 mg</td>
</tr>
<tr>
<td>Tofranil (imipramine)</td>
<td>75-200 mg</td>
</tr>
<tr>
<td>Vivactil (protriptyline)</td>
<td>15-60 mg</td>
</tr>
<tr>
<td><strong>Tetracyclics</strong></td>
<td></td>
</tr>
<tr>
<td>(maprotiline)</td>
<td>75-200 mg</td>
</tr>
<tr>
<td>Remeron (mirtazapine)</td>
<td>15-45 mg</td>
</tr>
<tr>
<td>Remeron SolTab (mirtazapine)</td>
<td>15-45 mg</td>
</tr>
</tbody>
</table>

*This list represents the most commonly prescribed antidepressants.

aThese dosages represent an average range for the treatment of depression. The precise effective dosage varies from patient to patient and depends on many factors. Starting dosages tend to be lower for older adults.

bGeneric version is available at lower cost.

cOnly Generic is available.

F. Addressing Disparities and Cultural Differences

The United States is becoming increasingly diverse—by 2042 less than 50% of the US population is projected to be non-Hispanic, single-race white. Hispanics will constitute the largest numerical minority group. This population shift compels health care providers to increase their cross-cultural competency to meet patients’ needs. Lack of cultural understanding may result in underdiagnosis and misdiagnosis of depression, which can relate to language differences, health literacy barriers, somatic presentations, use of culturally based idioms of distress, misinterpretation of illness presentation, or miscommunication between physicians and patients. (See Table 52-5.)

Studies have shown that different racial and ethnic groups, as well as age and gender groups, experience and communicate symptoms of depression differently and prefer different forms of treatment. For example, among Latinos, depression is often expressed largely in somatic terms (e.g., “nerves” or headaches). Asian patients may present similarly with somatic complaints during a depressive episode.

<table>
<thead>
<tr>
<th>Table 52-5. Factors affecting cultural competence in assessment, diagnosis, and treatment of depression.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recognition of:</strong></td>
</tr>
<tr>
<td>• Language differences</td>
</tr>
<tr>
<td>• Health literacy barriers</td>
</tr>
<tr>
<td>• Somatic presentations</td>
</tr>
<tr>
<td>• Use of cultural idioms of distress</td>
</tr>
<tr>
<td>• Treatment preference</td>
</tr>
<tr>
<td>• Nonwestern context of mental illness and care (e.g., spirituality and balance, herbs, nature, relational, circular, mind/body/spirit, present oriented)</td>
</tr>
</tbody>
</table>

Patient-provider communication is critical to diagnosis and treatment. The physician should elicit patients’ explanatory models (what patients believe is causing their illness) and agendas (what patients seek from treatment), the role of family members in their lives, and how those family members will react to the patient being treated for a mental illness, and how patients perceive treatment (e.g., taking medicine for depression and discussing personal issues and feelings with someone outside their usual group of confidants). For some people, real-world experiences of racism and prejudice may leave people suspicious of diagnoses that do not require radiologic or laboratory examinations. The communication skills of the provider to convey humility, empathy, respect, and compassion are important factors in the accurate diagnosis and effective treatment of depression in ethnically, racially, and culturally diverse populations.

A potentially important social determinant is a patient’s spirituality. The mere presence of a religious affiliation and, even more so, the saliency of a person’s religion, has been shown to be a protective factor for depression, particularly in older adults with medical illnesses or disability. This is important for providers not only because it may largely influence how patients cope with their illnesses, but also because studies have shown that validating this aspect of a patient’s life and incorporating it into treatment plans can positively affect the patient’s adherence to treatment and even speed up rates of remission.

Overall, nonwhite patients are less likely to adhere to treatment recommendations than whites. Studies have shown that providers tend to dominate discussions and have shorter visits with nonwhite patients, which limits patients’ ability to actively participate in their care. Patients should have enough time to speak, ask questions, and discuss different treatment options.
Primary care practitioners are the sole contacts for more than 50% of patients with mental illness and therefore are important in ensuring recognition and treatment of depression. The good news is that most patients can be treated to remission, especially if medication and psychotherapy are combined. Depression is generally a chronic, relapsing illness; however, treatment works not only to make patients well, but also to keep them well. Treatment provides symptomatic relief, facilitates functional improvements, and prevents relapse and recurrence.

Resources & Web Sites

- Wells K et al: Five-year impact of quality improvement for depression: results of a group-level randomized controlled trial. Arch Gen Psychiatry 2004;61:378. [PMID: 15066896]
- Alzheimer’s Association: http://www.alz.org
- American Association for Geriatric Psychiatry: http://www.aagppa.org
- Depression and Bipolar Support Alliance: http://www.dbsalliance.org
- Intervention Research Center for Late Life Mood Disorders, University of Pittsburgh: www.latelifedepression.org
- National Alliance for the Mentally Illness: www.nami.org
- National Institute of Mental Health: www.nimh.nih.gov
General Considerations

Anxiety is a diffuse, unpleasant, and often vague subjective feeling of apprehension accompanied by objective symptoms of autonomic nervous system arousal. The experience of anxiety is associated with a sense of danger or a lack of control over events. The psychological component varies from individual to individual and is strongly influenced by personality and coping mechanisms.

Many factors contribute to the experience of anxiety by individuals in our society. We live in a rapidly changing culture characterized by continuous technologic advancements, proliferation of ever more refined information, and a mass media and entertainment industry saturated with violence and sexuality, all of which promote feelings of insecurity. In the workplace, downsizing, restructuring, mergers, and specialization are commonplace; transient work relationships and the elimination of benefits such as health insurance and retirement provisions increase the sense of insecurity.

Anxiety is pathologic when it occurs in situations that do not call for fear or when the degree of anxiety is excessive for the situation. Anxiety may occur as a result of life events, as a symptom of a primary anxiety disorder, as a secondary response to another psychiatric disorder or medical illness, or as a side effect of a medication.

The majority of individuals with mental disorders receive psychiatric care from primary care settings, whereas fewer than 20% receive care in specialized mental health settings. Among mental disorders, anxiety disorders have the highest overall prevalence rate, yet only 23%-59% of anxious patients receive treatment. The estimated 1-year prevalence rate is 17% with a lifetime prevalence rate at 25%. Patients with anxiety disorders are at increased risk of other medical comorbidities, longer hospital stays, more procedures, higher overall health care costs, failure in school or at work, low-paying jobs, and financial dependence in the form of welfare or other government subsidies.

Pathogenesis

A. Biomedical Influences

Because the symptoms of anxiety are so varied and prevalent, several etiologies exist to explain them. A recent meta-analysis revealed a significant genetic component, especially for panic disorder, generalized anxiety, and phobias. Temperament, which has genetic roots, is a broad vulnerability factor for anxiety disorders.

The inhibitory transmitter g-aminobutyric acid (GABA) occupies about 40% of all synapses and is clearly implicated in the anxiety disorders, as is the endocrine system. Exposure to a stressor activates the release of an endogenous opioid, β-endorphin, which is co-released with adrenocorticotropic hormone.

B. Psychological and Social Influences

Family dysfunction and parental psychopathology are involved in the development and maintenance of anxiety. Families of anxious children are more involved, controlling, and rejecting, and less intimate than are families who do not manifest anxiety. Parents of anxious children promote cautious and avoidant child behavior.

Behavioral and cognitive explanations define anxiety as a learned response. Anxiety develops in response to neutral or positive stimuli that become associated with a noxious or aversive event. Fearful associations develop from the situational context and the physical sensations present at the time. The patient may generalize (ie, classify objects and events based on a common characteristic) and thereby establish new cues to trigger anxiety. Previously neutral situations become feared and avoided. By avoiding anxiety-arousing stimuli, anxiety is diminished.
As panic and avoidance become more chronic, the behaviors involved become more habitual and awareness of one’s thoughts in relation to these anxiety states diminishes. Information-processing prejudices such as selectively attending to threatening stimuli become involuntary and unconscious. A person’s appraisal of an event, rather than intrinsic characteristics of that event, defines stress, evokes anxiety, and influences the ability to cope. Failure to cope elicits fear and vulnerability.


### Prevention

Training in stress inoculation, relaxation training, and cognitive-behavioral therapy can be implemented through an integrated curriculum in public education during the early and middle years. School settings provide fertile environments for group modeling and an opportunity to reach large numbers of people. The work of Dr Martin Seligman (see Gillham et al) demonstrates the sizable advantages of such school-based programs.


### Clinical Findings

#### A. Symptoms and Signs

Examination of the patient usually yields few clues to assist in establishing the diagnosis of an anxiety disorder. Diagnosis is complicated by the amount of symptoms and their overlap with other disease states; thus anxiety often becomes a diagnosis of exclusion. Table 53-1 lists various symptoms of anxiety by organ system.

Despite the variety and diffuse nature of many of these symptoms, anxiety disorders can often be identified by exploration of the patient’s history, along with a few laboratory values. The symptoms of each anxiety disorder are sufficiently specific to arrive at the diagnosis by taking a thorough history from the patient, including pertinent past, social, and family information. Recognition of anxiety subtypes is often made on the basis of history alone.

### B. Diagnostic Criteria

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) differentiates several anxiety disorders. Diagnostic criteria for each disorder are presented below.

#### 1. Panic disorder—A panic attack involves a discrete period of intense fear or discomfort that has a sudden onset, rapidly builds to a peak, usually in 10 minutes or less, and is often accompanied by a sense of imminent danger or impending doom and an urge to escape. Many describe this disorder as “a fear of fear” developing from interoceptive conditioning. These patients tend to overestimate the probability of panic. About 33%-50% of panic-stricken people from community samples have agoraphobia, a fear of being in places or situations from which escape might be difficult or embarrassing or in which help may not be available. Individuals suffering from panic disorder without agoraphobia have higher success rates than those with agoraphobia.

#### 2. Simple phobias—Phobia refers to significant, provoked, and irrational anxiety that a person experiences when near a specific object or situation that is feared. Patients with simple phobias do not usually seek treatment. They avoid the particular object or situation that evokes anxiety.

#### 3. Social phobia—This involves clinically significant anxiety that occurs when an individual is exposed to certain types of social or performance situations. The lifetime prevalence of social phobia is estimated to be as high as 13%. Social phobia affects most areas of life, particularly education, career, and romantic relationships.

The Mini-SPIN is a brief three-item derivative of the Social Phobia Inventory (SPIN) that has been validated for the use of screening for social phobias.

#### 4. Obsessive-compulsive disorder (OCD)—This involves intrusive thoughts that cause marked anxiety or distress. Compulsions (compelling acts) neutralize anxiety. The disorder typically stages as Obsession → Anxiety → Compulsion → Relief. Onset is usually gradual and the course is typically chronic. Up to 80% of patients with OCD evidence depression, anxiety, substance abuse, work disability, or all of these findings.

<table>
<thead>
<tr>
<th>Table 53-1. Somatic symptoms of anxiety.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>System</strong></td>
</tr>
<tr>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Bladder</td>
</tr>
<tr>
<td>Central nervous</td>
</tr>
<tr>
<td>Respiratory</td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
</tbody>
</table>

5. Post-traumatic stress disorder (PTSD)—This involves the patient reexperiencing an extremely traumatic event accompanied by symptoms of increased arousal and avoidance of stimuli associated with the trauma. Rape, war-related stress, assault, and accidents commonly precipitate PTSD. The traumatizing effect is linked to the fact that these events are unexpected, uncontrollable, or inescapable. Optimally, new experiences are assimilated and expressed. Acute stress disorder entails the same PTSD-type symptoms, which occur immediately in the aftermath of a traumatic event but resolve within 4 weeks.

6. Generalized anxiety disorder (GAD)—This involves at least 6 months of persistent and excessive anxiety and worry with an inability to stop worrying. Uncontrollable and unpredictable aversive events may play an important role in the development of GAD. Further, patients with GAD have much less tolerance for uncertainty and are especially disturbed by not being able to predict the future. These chronic worriers commonly display insomnia; feel irritable, tense, and tired; and have difficulty concentrating. The degree of comorbidity between GAD and other psychiatric disorders is high. Patients with GAD show higher general medical utilization than patients with depression.

Several validated tools have been developed to screen for GAD including the two-item and seven-item Generalized Anxiety Disorder scales (GAD-2, GAD-7). These self-report questionnaires are easy to use and can assist primary care physicians in assessing the severity of GAD as well.

7. Substance-induced anxiety disorder—In this disorder, anxiety is a direct physiologic consequence of a drug of abuse, medication, or exposure to a toxin.

8. Adjustment disorder with anxious mood—In patients with this disorder, clinically significant symptoms of anxiety occur in response to an identifiable stressor within 3 months after the onset of the stressor and resolve within 6 months after the termination of the stressor. However, symptoms may persist longer if they occur in response to a chronic stressor (eg, a disabling chronic medical condition) or to a stressor that has enduring consequences (eg, financial effects of a divorce).

9. Anxiety disorder due to a general medical condition—In this disorder, prominent symptoms of anxiety are judged to be a direct physiologic consequence of a general medical condition. It is estimated that up to 20% of medical patients experience anxiety during the course of their medical illness.

When organic etiology is ruled out for a somatizing presentation, the patients involved usually are less educated, have psychiatric disorders, and belong to a culture that deemphasizes emotional displays while focusing on bodily concerns. Many of these patients lack social support and have suffered trauma.

C. Laboratory Findings

There are no gold standard laboratory studies to diagnose anxiety disorders. It is reasonable to perform a limited empiric evaluation to identify the etiology of the symptoms as well as evaluate for comorbid medical problems that may complicate the treatment. This evaluation may include a complete blood count, electrolyte, glucose, creatinine, calcium, liver panel, and thyroid function test. Further testing should be tailored on an individual basis, depending on the clinical circumstances. Urine drug screening should be considered, because illicit drug use and withdrawal may be a possible differential diagnosis and patients with anxiety may self-medicate with drugs of abuse.


D. Imaging Studies

Imaging studies are completed only to preclude any laboratory abnormalities or organic disease that may mimic anxiety or panic. Such studies include, but are not limited to, thyroid scan and cardiac diagnostics. Functional magnetic resonance imaging (MRI) is a technique that enables one to map cognitive, affective, and experiential processes onto brain substrates. It is a proxy measure about how complex processes are implemented in different neural systems. Magnetic resonance spectroscopy (MRS) is a noninvasive in vivo method used to quantify metabolites that are relevant to a wide range of brain processes. Recent studies have shown that there are significant metabolic differences between patients with anxiety disorders and healthy controls in various regions of the brain.


E. Special Tests

Psychological tests resort to self-report of symptoms and are major assessment tools for anxiety. This is unfortunate given that most other medical diagnoses (eg, diabetes mellitus) rely on both symptom self-report and systematic biomedical measurements (eg, the glucose tolerance test).

The State-Trait Anxiety Inventory measures the frequency and intensity of transient anxiety processes and anxiety proneness as a character trait. Other validated measures are the Anxiety Sensitivity Inventory, Agoraphobic Cognitions and Body Sensations Questionnaires, and the Panic Belief Questionnaire.

Comorbidity can comprehensively be assessed by the Minnesota Multiphasic Personality Inventory-II (MMPI-2), a test composed of 567 true-false test items that can be...
completed in about 2 hours. The Profile of Mood States (POMS) primarily measures mood states in psychiatric outpatients. Its advantage over the MMPI-2 is a completion time of about 10 minutes.


Differential Diagnosis

Because anxiety is a ubiquitous symptom of numerous conditions, family physicians must be alert to the possibility of alternative medical causes. A thorough evaluation and workup is essential to alleviate patients' concerns that their symptoms are due to other chronic or severe medical conditions.

The first step in planning a diagnostic evaluation is to perform a thorough history and physical examination. Table 53-2 presents the differential diagnosis of other medical conditions that may present with anxiety-like symptoms.

| Cardiovascular: | Acute coronary syndrome, congestive heart failure, mitral valve prolapse, dysrhythmia, syncope, hypertension |
| Drugs: | β-Agonists, caffeine, digoxin toxicity, levodopa, nicotinic acid, pseudoephedrine, selective serotonin reuptake inhibitors, steroids, stimulants (methylphenidate, dextroamphetamine), theophylline preparations, thyroid preparations |
| Endocrine disorders: | Hyper/hyperthyroidism, hyperadrenalism |
| Neoplastic: | Carcinoid syndrome, pheochromocytoma, insulinoma |
| Neurologic disorders: | Parkinsonism, encephalopathy, restless leg syndrome, seizure, vertigo, brain tumor |
| Pulmonary: | Asthma (acute), chronic obstructive pulmonary disease, hyperventilation, pneumonia, pneumothorax, pulmonary edema, pulmonary embolus |
| Psychiatric: | Affective disorders, drug abuse and dependence/withdrawal syndromes |
| Other conditions: | Anaphylaxis, anemia, electrolyte abnormalities, porphyria, menopause |

The clinician must rule out psychiatric disorders and ascertain if symptoms of anxiety are secondary to a medical illness or to a side effect of a medication. If anxiety did not predate a medical illness, subsequent anxiety may represent an adjustment disorder with anxious mood. The most likely organic cause of anxiety is alcohol and drug use (withdrawal or intoxication). Caffeine toxicity and increased sensitivity to caffeine also commonly mimic symptoms of anxiety.

Symptoms of cardiovascular abnormalities such as chest discomfort, shortness of breath, and palpitations are also cardinal symptoms of anxiety. Many anxious patients function poorly because they believe that they have heart disease. The electrocardiogram can be a useful tool to differentiate anxiety from a significant cardiac abnormality. Further evaluation should be considered based on the patient's symptoms and risk profile.

A careful auscultatory examination of the heart may reveal evidence of mitral valve prolapse, the most common valvular abnormality in adults. Long-term studies have shown that complications from mitral valve prolapse are rare, but often these patients present with palpitations and a generalized sense of being unwell that may mimic anxiety.

Musculoskeletal pain syndromes and esophageal disorders, including esophageal motility disorders and gastroesophageal reflux disease, are the most common noncardiac explanations of chest pain. Anxiety exacerbates gastrointestinal conditions such as colitis, ulcers, and irritable bowel syndrome. Treating anxiety often resolves or improves gastrointestinal symptoms and its associated chest pain.

Most patients with chronic unexplained chest pain have concomitant psychiatric diagnoses, especially anxiety. When further cardiac evaluation yields normal results, the anxious patient is more effectively reassured.

The primary care physician must be alert to acute medical conditions that can present with hyperventilation or dyspnea such as pulmonary conditions. The differentiation between these entities can be as simple as checking a pulse oxygen saturation but will often require more advanced diagnostic studies such as chest radiography, computed tomography (CT), or pulmonary angiography. Anxiety, hyperventilation, and dyspnea may accompany recurrent pulmonary emboli with few reliable physical signs. Anxiety has been shown to have a negative impact on quality of life in patients with asthma.

Hyperthyroidism and hypoglycemia may be mistaken for anxiety. Hypoparathyroidism, hyperkalemia, hyperthermia, hyponatremia, hypothyroidism, menopause, porphyria, and carcinoid tumors are less common causes of organic anxiety syndromes.

Depression is the most common psychiatric disorder associated with anxiety. Symptoms that discriminate clinical depression from anxiety include depressed mood, lack of energy, and loss of interest and pleasure.

Ingested substances such as medications or alcohol can elicit anxiety symptoms. Patients with anxiety disorders commonly drink to excess. Alcohol and drug problems involving dependence rather than abuse are most strongly
associated with problems involving anxiety. Anxiety disorder and alcohol disorder can each initiate the other, especially in cases of alcohol dependence. Although many alcoholic patients present with anxiety, these symptoms decrease rapidly when the patient stops drinking. Only a small percentage (perhaps 10%) has persistent symptoms of anxiety.

Lavoie KL et al: What is worse for asthma control and quality of life: depressive disorders, anxiety disorders, or both? Chest 2006;130:1039-1047. [PMID: 17035436]


ANXIETY DISORDERS

Treatment

The continuity of care and established physician-patient relationship characteristic of the primary care setting offer treatment advantages for patients with an anxiety disorder. However, physicians often miss signs of psychiatric problems in their patients because of a biomedical orientation. The result is excessive diagnostic testing, increased costs, frustrated patients, and cynical physicians.

Positive patient expectations and trust have a formidable impact on prognosis. By increasing their familiarity with standard cognitive-behavioral techniques and psychotropic medications, family physicians can enhance outcomes for patients with anxiety disorders. Several of the cognitive-behavioral techniques described later can easily be implemented by a busy family physician as supplemental treatment to psychopharmacology. Seeing patients more frequently while maintaining the time constraints of a 15-minute office visit can improve patient functioning without overwhelming the busy family physician. Other interventions can be offered through referral to mental health specialists. If after several 15-minute office visits the patient remains unimproved or nonadherent, referral or consultation is also appropriate.

Other characteristics have also been shown to facilitate the treatment of anxiety disorders. These include female gender, more years of practitioner experience, and social support. Positive characteristics of the organization such as level of expertise, time availability, financial resources, and administrative support are also helpful. A conducive reimbursement system has obvious positive consequences.

A. Pharmacotherapy

Medications provide symptomatic relief but do not cure the underlying anxiety disorder for which they are prescribed. The decision to prescribe medication should be based on the patient's degree of emotional distress, the level of functional disability, and the side effects of the medication. Table 53-3 provides a summary of the dosage range, indications, and financial costs associated with psychotherapeutic agents commonly used in the treatment of anxiety disorders.

Usage of family physicians as supplemental agents commonly used in the treatment of anxiety, these symptoms decrease rapidly when the patient stops drinking. Only a small percentage (perhaps 10%) has persistent symptoms of anxiety.

1. Selective serotonin reuptake inhibitors (SSRIs)—SSRIs are now considered the first line of medication treatment for most anxiety disorders, with the exception of situational anxiety. SSRIs are well tolerated, have low potential for overdose, and are not associated with psychological or physical dependence. Relative to benzodiazepines, SSRIs do not impair learning or memory.

Recommendations on dosing have been to start low and titrate slowly upward to therapeutic levels in order to minimize jitteriness and insomnia that may occur with higher initial doses. Exceptions would be the treatment of OCD and PD with or without agoraphobia, which often requires higher than usual dosing. When a patient exhibits both depression and anxiety, SSRIs are strongly recommended. Common side effects include nausea, diarrhea, headache, and sexual dysfunction.

2. Benzodiazepines—These agents remain the treatment of choice for panic attacks, anticipatory anxiety, phobic avoidance, and transient situational stress reactions. They may be used as short-term therapy of panic disorder until concurrent SSRIs become effective. Use of benzodiazepines should be limited to 2-4 months of continuous therapy to limit the potential for psychological or physical dependence. Common side effects include anterograde amnesia, difficulty in balance, impairment of driving ability, and additive effects with alcohol. Use in elderly patients has been associated with paradoxical excitement and an increased risk of falls and hip fractures especially with longer-acting agents.

Tolerance to the antianxiety effects is uncommon. The abrupt discontinuation of benzodiazepines, especially those with short half-lives, is associated with withdrawal syndromes of relatively rapid onset. A rebound syndrome, similar to but more transiently intense than the original disorder, may begin over a few days. Abrupt discontinuation of high doses of alprazolam may result in psychotic behaviors or seizures; a slow taper is essential.

Usual treatment initially combines an SSRI and a benzodiazepine. Studies have shown that patients who received combined treatment demonstrated more rapid improvement than those receiving either class of drug alone. There appears to be no additional benefit from taking a benzodiazepine after the first 5 or 6 weeks.

3. Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)—Venlafaxine (Effexor, Effexor XR) and duloxetine (Cymbalta) are both approved for treatment of GAD. Duloxetine is also approved for treatment of peripheral neuropathy and fibromyalgia. Side effects include headache, elevated blood pressure, and increased heart rate. Sexual dysfunction and GI intolerance occur less often than with SSRIs.

4. Buspirone (BuSpar)—Buspirone has an unknown mechanism of action but appears to affect neurotransmitters in a manner different than benzodiazepines. Because of delayed onset of action of at least 2 weeks, it is indicated only in the treatment of GAD. Although studies have found buspirone to be as effective as benzodiazepines for GAD, many patients...
### Table 53-3. Pharmacotherapy for anxiety disorders.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Usual Dosage Range</th>
<th>FDA Approved Indications</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Benzodiazepines**<sup>a</sup>  
Alprazolam<sup>b</sup> (Xanax, Xanax XR, Niravam) | 0.5–4 mg (3-6 mg, up to 10 mg daily for panic) divided into 3 doses | Short-term relief of anxiety  
Panic disorder | XR dosed once daily  
Reduce doses for elderly or patients with hepatic disease  
Physical dependence can occur with relatively short-term use  
Abrupt discontinuation can result in rebound anxiety or withdrawal symptoms  
Rapid-dissolve tablet available |
| Chlorazepate<sup>b</sup> (Tranxene) | 15–60 mg in divided doses | Short-term relief of anxiety | Reduce doses for elderly or patients with hepatic disease  
Physical dependence can occur with relatively short-term use |
| Clonazepam<sup>b</sup> (Klonopin) | 0.25–0.5 mg twice daily (max dose 4 mg/day) | Panic disorder | Long duration of effect results in smoother control  
Rapid-dissolve tablet available |
| Diazepam<sup>b</sup> (Valium) | 2–10 mg 2–4 times daily (max dose 40 mg/day) | Anxiety disorders  
Short term relief of anxiety | Reduce doses for elderly or patients with hepatic disease  
Physical and psychological dependence can occur with continuous use |
| Lorazepam<sup>b</sup> (Ativan) | 2–6 mg in divided doses | Short-term relief of anxiety  
Anxiety associated with depression | Effective when given orally or by IM/IV injection  
Preferred in patients with hepatic insufficiency because of no active metabolites |
| **Selective Serotonin Reuptake Inhibitors (SSRIs)**  
Escitalopram (Lexapro) | 10 mg once daily | Generalized anxiety disorder | No significant additional benefit if dose increased to 20 mg |
| Fluoxetine<sup>b</sup> (Prozac) | 10–60 mg once daily | GAD  
Panic disorder  
OCD  
PTSD  
PMDD | Doses should be taken in morning  
Start with low dose and titrate to effective dose |
| Paroxetine<sup>b</sup> (Paxil, Paxil CR) | 10–60 mg (12.5–62.5 mg CR) once daily | Panic disorder  
Social anxiety disorder  
GAD  
PTSD  
OCD  
PMDD | Start with low dose and titrate to effective dose  
Abrupt discontinuation can result in rebound anxiety or withdrawal symptoms  
CR formulation has lower gastric intolerance |
| Sertraline (Zoloft) | 25–200 mg once daily | Panic disorder  
Social anxiety disorder  
OCD  
PTSD  
Pediatric OCD | Start with low dose and titrate to effective dose  
Abrupt discontinuation can result in rebound anxiety or withdrawal symptoms |
| **Miscellaneous**  
Venlafaxine (Effexor, Effexor XR) | 75–225 mg in 2–3 divided doses | GAD  
Social anxiety disorder | Initiate with 37.5 mg daily and titrate up to effective dose  
XR formulation dosed once daily  
Taper dose upon discontinuation to avoid rebound or withdrawal symptoms |
| Buspirone<sup>b</sup> (BuSpar) | 10–60 mg in divided doses | GAD | Not for situational anxiety; therapeutic benefit may not be achieved for up to 1 mo  
No risk of physical or psychological dependence  
Avoid in patients with severe renal or hepatic impairment |

XR, extended release; IM, intramuscular; IV, intravenous; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PMDD, premenstrual dysphoric disorder; CR, controlled release; PTSD, post-traumatic stress disorder.

<sup>a</sup>All benzodiazepines are Schedule IV controlled substances.

<sup>b</sup>Generic formulations are available.
who previously received benzodiazepines do not perceive it to be as effective because they do not experience the “buzz” they had with benzodiazepines. Buspirone does not impair driving or cognition and is not addictive with alcohol. The most common side effects are restlessness, dizziness, and headache. Recent studies suggest that buspirone may be effective as an adjunctive therapy in treatment resistant depression.

5. Tricyclic antidepressants (TCAs)—These may be considered after failed trials of SSRIs, when other agents are not an option because of side effects or concerns of addiction or dependence. They are more commonly used as adjunctive therapy when the patient also has insomnia or chronic pain. Adherence is low secondary to the high incidence of intolerable side effects such as dry mouth, constipation, and urinary retention.

6. β-Blockers—These are primarily used to reduce the autonomic symptoms (rapid heart rate, flushing, sweating) associated with performance or social anxiety. The medication is usually taken only when needed about 30 minutes before an anxiety-inducing situation. Dizziness, drowsiness, and light-headedness are the most common side effects.

7. Atypical anticonvulsants—These agents are being used frequently as adjunctive therapy to augment the activity of SSRIs in patients with refractory symptoms of anxiety. Gabapentin (Neurontin) has been shown to augment SSRI activity in the treatment of panic disorder and OCD and to reduce anxiety associated with chronic pain syndrome. Pregabaline (Lyrica) has also been used for GAD but is only approved for fibromyalgia and peripheral neuropathy. Clinical studies have also demonstrated the effectiveness of other atypical anticonvulsants such as carbamazepine, valproic acid, and lamotrigine. Doses should start low and be titrated to effective dose to minimize side effects. Most common side effects are drowsiness, dizziness, and blurred vision.

B. Psychotherapeutic Interventions

1. Behavioral therapy—This focuses on overt behavior, with an emphasis on “how to” improve rather than “why” the problem exists. Several forms of behavioral therapy are available to assist patients in managing anxiety. The family physician’s role involves explaining a behavioral procedure and prescribing homework. Time management need not suffer; 15-minute office visits sequenced about 1-2 weeks apart are usually adequate to provide therapy.

During exposure therapy the patient is repeatedly brought into contact with what is feared until discomfort subsides. The longer the exposure interval and the more intensive the exposure experience (massed trials) are, the better. To enhance adherence initially, often a significant other is present, or a benzodiazepine is used; as therapy proceeds, both are gradually eliminated.

Although few people are formally educated in stress management, a large repertoire of coping skills is available.

Table 53-4 shows a partial list of such strategies that can be given as a patient handout.

Table 53-4. Effective coping strategies.

<table>
<thead>
<tr>
<th>Strategy</th>
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<tbody>
<tr>
<td>Talk or write about stressful problems</td>
</tr>
<tr>
<td>Do enjoyable activities</td>
</tr>
<tr>
<td>Get enough rest and relaxation</td>
</tr>
<tr>
<td>Exercise regularly</td>
</tr>
<tr>
<td>Eat properly (beware of caffeine, chocolate, and alcohol)</td>
</tr>
<tr>
<td>Plan your time and set priorities</td>
</tr>
<tr>
<td>Accept responsibility for your role in a problem</td>
</tr>
<tr>
<td>Make expectations realistic</td>
</tr>
<tr>
<td>Get involved with others</td>
</tr>
<tr>
<td>Build in self-rewards</td>
</tr>
<tr>
<td>Utilize a sense of humor</td>
</tr>
<tr>
<td>Learn assertiveness</td>
</tr>
<tr>
<td>Attend support groups</td>
</tr>
</tbody>
</table>

Numerous types of relaxation training are useful in the treatment of all anxiety disorders and also have been shown to assist in anger management. Learning to relax is an inexpensive and easily accessible strategy. Reduction in the body’s consumption of oxygen, blood lactate level (associated with muscle tension), metabolism, and heart and respiration rates occurs during practice. Home practice for 20 minutes or more twice each day in a quiet place produces significant effects. Commercialized relaxation tapes are available for eidetic imagery and progressive muscle relaxation.

Panic attacks can be mediated by a highly effective technique, breathing retraining, which involves slow, deep (diaphragmatic) breathing. Slow inhalation, holding the breath, and slow exhalation are repeated for 10 or more sequences. During slow, deep breathing the patient is told to substitute realistic thoughts (“I’m having a panic attack and I’m not in any danger”) for panic-inducing thoughts (“I’m having a heart attack and I’ll die soon”). This provides a sense of self-mastery and restores oxygen-carbon dioxide balance to the body. Interceptive exposure, in which patients go through the symptoms of a panic attack (elevated heart rate, hot flashes, sweating, etc) in a controlled setting, can also be beneficial, by reinforcing for patients that these symptoms need not develop into a full-blown attack.

In the worry exposure technique, the patient is asked to do the following:

1. Identify (perhaps write down) and distinguish worrisome thoughts from pleasant thoughts.
2. Establish a 30-minute worry period at the same place and time each day.
3. Use the 30-minute period to worry about concerns and to engage in problem solving.
4. Postpone worries outside the 30-minute worry period with reminders that they can be considered during the...
next worry period (the patient may choose to write down new worries to avoid worrying about forgetting them).

5. During intrusions replace worries with attention to present moment experiences, activities, or pleasant memories.

This strategy challenges dysfunctional beliefs about the uncontrollability of thoughts and the dangerous consequences of failing to worry. Delusional jealousy also can be mediated by this approach.

In mismatch strategy, the physician asks the patient to write a detailed account of the content of the worry (e.g., exposure to a particular situation normally avoided) and then asks the patient to worry about what could happen in that situation. Finally, the patient is instructed to enter the situation and observe what really happens to assess the validity of the worry thoughts.

Lastly, the family physician can ask the patient to practice alternative endings for worry sequences. Rather than rehearsing catastrophic outcomes, the patient contemplates positive scenarios in response to worry triggers.

2. Cognitive therapy—Cognitive therapy is behavioral therapy of the mind. Based on the theory that thoughts, images, and assumptions usually account for the onset and persistence of anxiety, cognitive therapy assumes that the way patients perceive and appraise events and interpret arousal-related bodily sensations as dangerous (anxiety sensitivity) provokes symptoms of anxiety. Cognitive changes are the best predictors of treatment outcome for the anxiety disorders.

Achieving thought control is of central importance to mental health. Patients with OCD and GAD are especially prone to poor thought control. These patients devalue their ability to adequately deal with threats. Homework involving “self-talk” must be believed by the patient to be useful.

Because alternative interpretations and explanations (cognitive restructuring) are always available for upsetting events, patients can assume more control of and accept more responsibility for their adaptation. Acceptance of these assumptions empowers the patient. Documented durable improvement results from cognitive restructuring (substituting rational assumptions and perspectives and transforming the meaning of events and physiologic arousal cues).

Although it is not possible to control all outside events, it is possible to control one’s reaction to any event. Patients are advised that as soon as they are aware of being upset, they should pause and reflect on

1. The event.
2. Thoughts about the event.
3. Associated feelings.
4. Another way to perceive the event (another meaning) that is also true and makes sense.

When time permits, patients may enter this information in a small notebook for review with the family physician at a subsequent office visit.

C. Complementary and Alternative Therapies

Use of alternative therapies is more common among people with psychiatric problems and especially people with self-defined anxiety than among the rest of the population. Most alternative therapies are used without supervision. Because there are so few data on the relative effectiveness of these therapies, most people tend to try a therapist who has been recommended and, by trial and error, find a preferred therapy.

Massage therapies can be classified as energy methods, manipulative therapies, and combinations of each. Swedish massage is the most common form of massage and is usually given with oil. Movements called effleurage (smooth stroking) and pétrissage (kneading-type movements) are done up and down the back and across many tissues of the body. The Trager method, similar to many other types of massage therapy, involves gentle holding and rocking of different body parts. Reflexology, an energy method, could be called a massage therapy because it involves kneading, stroking, rubbing, and other massage procedures. These procedures are centered on particular points of the feet, hands, or ears. Although few controlled studies exist utilizing massage therapy, most people report anxiety-reduction benefits. There are no empiric data on the efficacy of reflexology.

Acupuncture has been demonstrated to reduce anxiety across a variety of populations and presenting problems. However, additional double-blind, placebo-controlled studies are needed.

Research indicates the benefits of yoga to quality of life and improved health. Yoga, which involves body postures and asanas (body maneuvers), appears to exercise various tissues, organs, and organ systems and provides an avenue to address character armors, attitudes, and tensions. Specific application to stress management is widespread with generally significant positive results. As is the case with acupuncture, however, better controlled research is needed.

Herbal therapies for anxiety include kava-kava, inositol, and melatonin. Several clinical studies have demonstrated the effectiveness of short-term use of kava-kava which has a mechanism of action similar to that of the benzodiazepines. However, long-term use or high doses are associated with development of peripheral neuropathy. The Food and Drug Administration (FDA) has issued a warning regarding the potential for kava-kava to cause hepatotoxicity, and this product has been removed from the market in several European countries. Inositol has been shown to be effective in the treatment of panic disorder and OCD but should not be used in combination with SSRIs. Melatonin has been primarily promoted to reduce the symptoms of jet lag and sleep-cycle disturbances.
Because of the inconsistent effects shown in only small studies, valerian, St. John’s wort, and passionflower are not routinely recommended, although their side effect profiles are benign. Limited data support the role of valerian in relieving anxiety and insomnia, but it has additive effects with other central nervous system depressants and alcohol disturbances.


D. Consultation or Referral

Attempting the previously discussed treatment recommendations during multiple 15-minute continuity office visits often renders referral unnecessary. However, referral may be necessary when symptoms reoccur or when tapering a medication is difficult. Referral is appropriate when the family physician is uncomfortable with an indicated therapy, when patients are potentially suicidal or are actively abusing drugs, when noncompliance is suspected, or when psychopathology is severe. Referral of patients with OCD and PTSD is mandatory. Given the expected need to individualize treatment and provide novel treatment options, the busy family physician has neither the time nor the expertise to engage in the comprehensive interventions required.

If psychotherapy is the preferred method of managing symptoms, the specialized training of a clinical or a counseling psychologist is recommended. When psychopharmacology is warranted, the expertise of a psychiatrist is unmatched. Sound treatment is based on specific and accurate diagnosis and relies on empirically validated procedures that take into account the personality of the patient.

Table 53-5 provides several referral treatments and their indications for the effective nonpharmacologic management of anxiety disorders.

E. Management of Specific Anxiety Disorders

1. Panic disorder—Recommended treatment includes breathing retraining, cognitive restructuring, interoceptive exposure, and relaxation training. If anxiety is short term, benzodiazepines should be used; if anxiety is chronic, paroxetine, fluvoxamine, citalopram, fluoxetine, sertraline, nefazodone, or imipramine should be used.

Although current treatments allow control of panic disorder, full recovery is questionable. Psychological treatments involve lower relapse rates, higher levels of acceptability, lower attrition rates, and are better tolerated than many pharmacologic treatments. Exposure and deep breathing are especially effective for patients with panic attacks and agoraphobia.

The percentage of patients who become free of panic attacks from medication is generally 50%-80% in acute pharmacologic trials, and this percentage rises with longer treatment. SSRIs reduced panic attack frequency to zero in 36%-86% of patients and were well tolerated over long-term

<table>
<thead>
<tr>
<th>Type of Intervention</th>
<th>Description</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual</td>
<td>Insight, empowerment, support</td>
<td>Privacy, complicated patient</td>
</tr>
<tr>
<td>Group</td>
<td>Interactive, common interest</td>
<td>Social skills, support, vicarious learning</td>
</tr>
<tr>
<td>Family</td>
<td>Therapeutic environment and patient</td>
<td>Enabling, dysfunctional family</td>
</tr>
<tr>
<td>Eye movement desensitization and re-processing (EMDR)</td>
<td>Follow oscillation movement of object (pencil) thinking of trauma Mixed results</td>
<td>Post-traumatic stress disorder</td>
</tr>
<tr>
<td>Hypnosis</td>
<td>Relaxation induction; suggestions</td>
<td>Suggestible patient</td>
</tr>
<tr>
<td>Biofeedback</td>
<td>EMG, EKG, EEG monitoring of physiologic parameters to alter activity; cost is a limiting factor</td>
<td>Headaches, tension, blood flow, etc</td>
</tr>
<tr>
<td>Stress inoculation/anxiety management</td>
<td>Multifaceted, comprehensive cognitive-behavioral therapy</td>
<td>All anxiety disorders</td>
</tr>
<tr>
<td>Assertiveness training</td>
<td>Learn skills to be firm, not nasty</td>
<td>Dependent, unassertive, aggressive patients</td>
</tr>
<tr>
<td>Transcranial magnetic stimulation (TMS)</td>
<td>Noninvasive, painless method of brain stimulation via electrical current using changing magnetic fields</td>
<td>Applications are in their infancy</td>
</tr>
</tbody>
</table>

EMG, electromyogram; ECG, electrocardiogram; EEG, electroencephalogram.
administration. Additionally, because of the high rate of depression comorbidity associated with panic attacks, SSRIs are the pharmacologic treatment of choice.

Benzodiazepines are best used for acute management. In most studies relapse after discontinuation of medications has been relatively high, ranging from one-third to three-fourths of patients, suggesting the need to be on the medications for at least 6 months.

2. Simple phobias—Recommended treatment includes exposure therapy, deep breathing, relaxation training, and cognitive restructuring, as well as short-term use of benzodiazepines.

3. Social phobia—Recommended treatment includes exposure therapy, cognitive restructuring, relaxation training, social skills training, and group therapy; medications that may be helpful include paroxetine, sertraline, clonazepam, and β-blockers.

When fearing negative evaluation, patients narrow their attention to social threat cues. Cognitive therapy corrects these distortions whereas exposure therapy reduces anticipatory fear. In cognitive-behavioral group settings, 81% of patients had significant improvement that was maintained 5.5 years later.

The SSRIs sertraline and paroxetine are both approved by the FDA for treatment of social anxiety disorder. β-Blockers on an as-needed basis may be helpful in patients who experience performance anxiety, even though published data supporting their benefit are limited. These agents can reduce hand tremor and tachycardia symptoms without causing cognitive impairment.

4. Obsessive-compulsive disorder (OCD)—Recommended treatment includes referral as well as exposure therapy, response prevention, cognitive restructuring, and pharmacotherapy with fluoxetine, fluvoxamine, sertraline, or clomipramine. Behavior therapy and SSRIs are primarily recommended. Homework assignments expose patients to stimuli associated with their obsessions. During response prevention, patients refrain from rituals (fixed behaviors that reduce anxiety) for progressively longer intervals until discomfort diminishes.

Pharmacologic options can at best reduce OCD symptoms by 50%, which may improve the patient’s quality of life. Effective dosages are usually significantly higher than those required for depression or other anxiety disorders (e.g., fluoxetine, up to 80 mg/d). TCAs other than clomipramine do not appear to be effective in patients with OCD.

5. Post-traumatic stress disorder (PTSD)—Recommended treatment involves referral for individual or group psychotherapy, stress management, relaxation training, cognitive restructuring, and/or eye movement desensitization and reprocessing, which includes brief exposure to trauma-related images while patients track the therapist’s rapid finger movements with their eyes or receive other bilateral stimulation and cognitive interventions. Psychological treatments lead, on average, to large improvements in PTSD symptoms. Trauma-focused cognitive behavioral therapy including focus on exposure and cognitive restructuring has been shown to be superior to other therapies. Some form of exposure or desensitization is essential. Patients put frightening memories into words while receiving new and incompatible information. Systematic exposure to the traumatic memory in a safe environment allows a reevaluation of and habituation to threat cues.

Although there is no established pharmacotherapy for PTSD, about 70% of patients seem to benefit from pharmacotherapy with moderate to marked effects. SSRIs appear to have the greatest efficacy of any single class of medications. Sertraline, paroxetine, and fluoxetine have been shown to produce acute improvement and decreased relapse rates in patients with PTSD. Clonazepam and buspirone may be helpful in suppressing hyperarousal symptoms. The anticonvulsant carbamazepine has been shown to decrease flashbacks, hyperarousal, and impulsivity. Carbamazepine, lithium, and β-blockers may be helpful in patients with poor impulse control.

Like OCD, PTSD is especially hard to treat. Early intervention reduces tendencies for substance abuse, secondary gain, litigation, and malingering. Referral is mandatory.

6. Generalized anxiety disorder (GAD)—Recommended treatment includes worry exposure, thought control techniques (mismatch, cognitive restructuring), and relaxation training. Pharmacotherapy may include venlafaxine, sertraline, escitalopram, paroxetine, buspirone, and benzodiazepines.

No treatment is convincingly effective for GAD. Although cognitive-behavioral therapy appears to produce superior results, effects remain variable. Cognitive psychotherapy decreases probability overestimation (i.e., overestimating the likelihood of negative events) and catastrophic thinking, and has been shown to improve sleep.

Nonvalidated coping strategies such as physical action, thought replacement, analysis, counterpropaganda, and talking to a friend have been used, with varying success. No one strategy is more efficient and none is rated “very efficient” by patients. Talking to a friend may be more efficient when thoughts are intense, whereas thought replacement may work well when intensity is low.

Antidepressants are often considered first-line therapy for GAD, in part because of the frequent association of GAD with depression. Although the TCAs are effective for GAD, the SSRIs are more frequently prescribed because of a more favorable side-effect profile. The SSRIs are well-demonstrated medications of choice for most anxiety disorders, notably escitalopram (Lexapro), sertraline (Zoloft), and paroxetine (Paxil). The SNRIs, venlafaxine (Effexor), and duloxetine (Cymbalta) also have demonstrated effectiveness in the treatment of GAD. The atypical anticonvulsants gabapentin (Neurontin) and pregabalin (Lyrica) also have shown benefit.
in GAD, especially in patients with neuropathy or chronic pain syndromes. Benzodiazepines should be reserved for initial short-term overlap with the SSRIs since SSRIs have a delayed onset of effectiveness. When conspicuous worry, apprehension, irritability, and depression exist, buspirone has been especially effective and has been shown to be comparable to benzodiazepines in multiple studies of GAD.

7. Other anxiety disorders—Treatment of patients with substance-induced anxiety disorder consists of eliminating the drug of abuse, medication, or toxin exposure that is the cause of the disorder. In patients with persistent symptoms of adjustment disorder with anxious mood, referral for psychotherapy is recommended.

F. Special Populations

1. Children and youth—Transient fears are common in children of all ages and represent part of the normal developmental process. Normal fears need to be distinguished from the anxiety disorders of adulthood, which are more prevalent among children and adolescents than any other mental problem. Children with anxiety disorders exhibit a high rate of comorbidity, especially with other, secondary anxiety disorders.

Anxiety is often manifested among children by avoidance behavior, distorted thinking, or subjective distress. The DSM-IV-TR anxiety designations of childhood and adolescence include separation anxiety disorder (excessive anxiety concerning separation from home or from those to whom the child is attached) and overanxious disorder (at least 6 months of persistent and excessive anxiety and worry). Separation anxiety disorder is treated by exposure to the feared event (e.g., the child attends school despite discomfort). Psychotherapy is the treatment of choice for overanxious disorder.

Cognitive-behavioral treatment for children with anxiety disorders is the first-line treatment recommended. Similar approaches to those described for adults are utilized, with emphasis on exposure paradigms. Response rates for children have ranged from 70% to 80%.

Targeted use of medication to lower agitation, improve energy, decrease psychotic symptoms, or improve concentration might make certain patients more accessible to psychotherapy. Despite these advantages, caution remains in effect regarding the prominent prescribing of medication for the treatment of childhood anxiety disorders. Few data are available on the impact of age on absorption, metabolism, therapeutic levels, or possible drug interactions. It is expected that to achieve the same serum levels in children compared with adults the relative dose would be higher.

Despite this caution, FDA indications for adults with anxiety disorders are often used in children and adolescents. Approximately 50%-70% of children with these disorders respond to SSRIs. Combination therapy with cognitive behavioral treatment and sertraline has been shown to be effective and safe in children if monitored closely.


Stewart SH, Kushner MG: Introduction to the Special Issue on “Anxiety Sensitivity and Addictive Behaviors.” Addict Behav 2001;26:775. [PMID: 11768544]


2. The elderly—Although the most common form of psychiatric condition in the elderly, anxiety disorders are still underdiagnosed. Polypharmacy is often present. Altered pharmacokinetics and pharmacodynamics in the geriatric population lead to greater sensitivity to and prolonged half-life of the medication due to decreased clearance of the drugs. Because of these drug complications, psychotherapy is attractive.


G. Patients With Related Conditions

1. Personality disorders—Personality disorders are lifelong characterologic problems that significantly complicate treatment and outcome. Poor compliance, medication abuse, interpersonal agitation, and poor insight characterize patients with personality disorders. These patients suffer more from anxiety than patients without personality disorders. Prescribing of benzodiazepines is contraindicated. (For further discussion of personality disorders, see Chapter 54.)

2. Hyperventilation—During hyperventilation excessive rate and depth of breathing produce a marked drop in carbon dioxide and blood alkalinity. These changes can be subtle. A person may slightly overbreathe for a long time. Even a yawn may trigger symptoms, accounting for the sudden nature of panic attacks during sleep. Breathing retraining is recommended.

3. Insomnia—Patients with anxiety disorders commonly have sleep problems that worsen anxiety. Sympathomimetic amines may cause sleep-onset insomnia, whereas alcohol abuse produces sleep-termination insomnia. Benzodiazepines are
frequently prescribed as sedative-hypnotics. For sleep-onset insomnia, triazolam and zolpidem are rapidly acting compounds with short half-lives. For sleep maintenance, longer-acting drugs such as flurazepam and quazepam are more effective. Tolerance for the sedative effects, alteration of sleep topography, suppression of rapid eye movement (REM; dream sleep), impaired cognitive function, the occurrence of falls, and REM rebound following discontinuation are contraindications to the use of benzodiazepines in treatment of chronic insomnia.

Sleep hygiene suggestions provide an effective initial treatment option. Patients are asked to review and alter lifestyle patterns that interfere with sleep. Table 53-6 outlines these suggestions for patient use. Adherence with recommendations and shift work are limiting factors.


Prognosis

Just 30 years ago, most estimates were that 80% of patients with anxiety disorders would not significantly benefit from available treatment. Today the opposite is true. For the majority of patients with anxiety disorders—especially panic disorder, specific phobias, and social phobia—treatment with a combination of cognitive-behavioral therapy and an SSRI carries an excellent prognosis. Although these treatments show promise in the treatment of OCD, GAD, and PTSD, efficacy is more variable.

Web Sites

Anxiety Disorders of America: http://www.adaa.org/
Anxiety/Panic Internet Resource: http://www.algy.com/anxiety
Internet Mental Health: http://www.mentalhealth.com/
General Considerations

Personality disorders (PDs) are a heterogeneous group of deeply ingrained and enduring behavioral patterns characterized by inflexible and extreme responses to a broad range of situations, manifesting in cognition (ways of perceiving and interpreting self, others, and events), affectivity (range, intensity, lability, and appropriateness of response), interpersonal functioning, and impulse control. PDs impinge on medical practice in multiple ways, including self-destructive behaviors, interpersonal disturbances, and nonadherence. Appropriate physician responses and effective treatments exist for many PDs. Correct diagnosis and proper intervention will help to improve patient outcomes. Borderline personality disorder (BPD) is an extremely debilitating disorder which can significantly interfere with the doctor-patient relationship. BPD will receive extra focus in several sections of this chapter.

Ten PDs are currently distinguished clinically. They are often grouped into three clusters: odd or eccentric (cluster A); dramatic, emotional, or erratic (cluster B); and anxious or fearful (cluster C). These groupings are helpful in broadly categorizing PD difficulties but are limited in their usefulness because they do not signify similarities in etiologies and treatment response. Table 54-1 summarizes the 10 PDs.

PDs are relatively common, with a prevalence of 7.6% in the general US population. Patients with PDs may seek help from family physicians for physical complaints, rather than psychiatric help. Higher rates for all types of PDs are found in medical settings. Prevalence of BPD in the general community is 1.4%.

PDs have a pervasive impact because they are central to who the person is. They are major sources of long-term disability and are associated with greatly increased mortality. Patients with PDs have fewer coping skills and during stressful situations may have greater difficulties, which are worsened by poor social competency, impulse control, and social support. Patients with BPD are frequently maltreated in the forms of sexual, physical, and emotional abuse; physical neglect; and witnessing violence.

PDs are identified in 70%-85% of persons identified as criminal, 60%-70% of persons with alcohol dependence, and 70%-90% of persons who are drug dependent.

Borderline, schizoid, schizotypal, and dependent PDs are associated with high degrees of functional impairments and greater risk for depression and alcohol abuse. Obsessive-compulsive and narcissistic PDs may not result in appreciable degrees of impairment. Dependent PD is associated with a marked increase in health care utilization.

Pathogenesis

A. Personality Disorders

PDs are syndromes rather than diseases. Avoidant, dependent, and schizoid PDs appear to be heritable. Similarly, schizotypal disorder is considered to be heritable, as one end of a schizotypal-schizophrenia spectrum. Twin and adoption studies suggest a genetic predisposition for antisocial PD, as well as environmental influences, via poor parenting and role modeling. Histrionic PD may be related to indulged tendencies toward emotional expressiveness.

B. Borderline Personality Disorder

BPD may result from both constitutional and environmental factors. Genetically, BPD is five times more common among first-degree relatives of those with the disorder, but to say to what degree BPD is heritable is difficult given the reciprocity between family and child that occurs during development. BPD symptoms have been attributed to highly pathologic and conflicted interactions between parent and child. The conflict brings great ambivalence about relationships and interferes with the child’s ability to regulate affect. (Additional discussion of this process appears later, under Termination of Care, later.) Child sexual abuse has been thought causal in BPD, but a recent meta-analysis did not support this hypothesis. It is certainly the case that traumatic childhood experiences are common in patients with BPD. As
a group, patients with antisocial and borderline PDs report higher frequencies of perinatal brain injury, head trauma, and encephalitis.

C. Common Comorbid Conditions

Substance abuse disorders frequently co-occur in community and clinical populations, particularly with antisocial, borderline, avoidant, and paranoid PDs. Anorexia nervosa, bulimia nervosa, and binge eating may be seen in patients who are obsessional, borderline, and avoidant, respectively. Self-injurious skin picking can be conceptualized as an impulse control disorder and has been found with significant frequency in patients with obsessive-compulsive PD and BPD. Up to 50% of patients with BPD have major depressive disorders or bipolar disorders.

Prevention

Except for efforts to address the roots of criminal behaviors that are common in antisocial PD, there is no literature on prevention of PDs. Primary prevention could consist of better treatment of parental mental illnesses that have a negative impact on parent-child interactions and public health interventions to reduce prenatal brain insults. Both primary and secondary prevention could occur with increased interventions in family functioning and parenting skills.

Clinical Findings

PDs were once referred to as character disorders. Various descriptive labels have appeared in the literature, such as the oral fixated character, the impulsive personality, and the introverted personality type. Each of these represents a theory of personality (psychoanalytic, developmental, and analytical, respectively).

Currently, there are few points of correspondence between personality theory and diagnosis of PDs. A relatively atheoretical, categorical perspective dominates clinical practice in the United States. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) exemplifies the categorical perspective. PDs appear as “Axis II disorders,” which should not imply that PDs are conditions that are less severe than clinical disorders such as depression, which appear on Axis I. Instead, the additional axis provides a place where pervasive, persisting disorders may be differentially recorded. Mental retardation, similarly pervasive and persistent, is also an Axis II disorder.

A. Symptoms and Signs

1. PD—Clinical lore about appearance and presentations of PDs exists. Anything extreme in appearance that is not ethnically appropriate or currently fashionable may suggest a PD. Examples include flamboyant jewelry, particularly in men, tattoos and piercing in older men and women, steel-toed boots in men, and excessive cosmetics and large hair ribbons in women.

The patient’s style of interacting with the physician can be revealing about personality difficulties. For example, the dependent patient will seek much advice and be unable to make an independent decision. The patient with antisocial PD may be “smooth talking” or threatening. Interactions with patients with BPD can be very difficult. The patient may switch from extreme idealization to devaluation of the physician. The patient may cause “splitting” among staff, with some people siding with the patient and others extremely angry with the patient. Table 54-2 describes problem behaviors associated with various PDs, as well as helpful responses and management strategies.

Physician countertransference may be a sign of a PD. Reactions such as anger, guilt, desire to punish, desire to

| Table 54-1. Clinical features and clusters of 10 DSM-IV-TR personality disorders. |
|---------------------------------|---------------------------------|---------------------------------|
| Cluster A: odd, eccentric       | Personality Disorder            | Clinical Features               |
| Cluster B: dramatic, emotional, erratic | Antisocial                | Manipulative; selfish, lacks empathy; explosive anger; legal problems since adolescence |
|                                  | Borderline                 | Dependent and demanding; unstable interpersonal relationships, self-image, and affects; impulsivity; micropsychotic symptoms |
|                                  | Histrionic                | Dramatic; attention seeking and emotionality; superficial, ie, vague and focused on appearances |
|                                  | Narcissistic              | Self-important; arrogance and grandiosity; need for admiration; lacks empathy; rages |
| Cluster C: anxious, fearful     | Avoidant                  | Anxiously detached; feels inadequate; hypersensitive to negative evaluation |
|                                  | Dependent                | Clinging, submissive, and self-sacrificing; needs to be taken care of; hypersensitive to negative evaluation |
|                                  | Obsessive-compulsive      | Preoccupied with orderliness, perfectionism, and control |
Table 54-2. Problem behaviors associated with personality disorders.

<table>
<thead>
<tr>
<th>Personality Disorder</th>
<th>Paranoid</th>
<th>Schizotypal</th>
<th>Schizoid</th>
<th>Antisocial</th>
<th>Borderline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s perspective</td>
<td>People are malevolent. Situation is dangerous.</td>
<td>Understanding of care may be odd or near delusional.</td>
<td>Illness will bring too much attention and invade privacy.</td>
<td>Threatened if unable to feel “on top.” Illness presents opportunity for crime.</td>
<td>Fears abandonment. Overreacts to symptoms and situation.</td>
</tr>
</tbody>
</table>

2. BPD—Physicians may over- or underattribute patient difficulties to BPD; therefore, it is important to be sensitive to BPD phenomena and to ascertain whether patient difficulties and symptoms represent BPD. BPD diagnostic criteria call for a pervasive pattern of instability in interpersonal relationships, self-image, and affect, and marked impulsivity.
beginning by early adulthood and present in a variety of contexts as indicated by at least five of the following:

1. Frantic efforts to avoid real or imagined abandonment (not including suicidal behaviors).
2. A pattern of unstable and intense interpersonal relationships characterized by alternating extremes of idealization and devaluation.
3. Identity disturbance: a markedly and persistently unstable self-image or sense of self.
4. Impulsivity in at least two areas that are potentially self-damaging (not including suicidal behaviors).
5. Recurrent suicidal behavior, gestures, threats, or self-mutilating behavior.
6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
7. Chronic feelings of emptiness.
8. Inappropriate intense anger or difficulty controlling anger.
9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

BPDs make up a heterogeneous group with subgroups consisting of patients differing in affective, impulsive, and micropsychotic symptom clusters. These differences can suggest different treatments, discussed later. Patients with BPD have significantly higher rates of suicidal ideation and 70%-80% exhibit self-harming behavior at least once. Suicide attempts are often regarded as manipulative gestures, but suicide rates are very high in this population: 3%-9.5% of patients with BPD receiving inpatient care eventually kill themselves. Self-harming behaviors in the form of self-mutilation, such as wrist scratching, are symptomatic of BPD. Nausea and vomiting may be a primary care analogue of self-mutilation in some patients with BPD, and a common chief complaint. Obtaining a history suggesting BPD may mitigate the need for extensive and invasive gastrointestinal symptom evaluations and may suggest more effective treatment strategies directed to personality functioning.

**B. Special Tests**

No laboratory tests exist for PDs. Structured clinical interviews and personality inventories may be helpful in differentiating PDs and tracking treatment response. Interpretation by a psychologist enhances the value of the results. A consult should be considered in cases of diagnostic uncertainty. Two frequently used tools for assessment are the Structured Clinical Interview for DSM-IV-TR Axis-II Personality Disorders (SCID-II) and the Personality Assessment Inventory (PAI). The SCID-II is a semistructured interview used to differentiate the Axis-II diagnostic categories. The PAI includes sub-scales for the following PDs; the BPD subscale consists of items evaluating affective instability, identity problems, negative relationships, and self-harm, whereas the Antisocial PD subscale assesses antisocial behaviors, egocentricity, and stimulus seeking. Administration of the full-scale instrument yields additional information of interest, such as a broad assessment of psychological disorders (e.g., anxiety-related disorders, depression), and constructs relevant to treatment outcome.

**American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text revision. APA, 2000.**


**Differential Diagnosis**

**A. Personality Disorders**

Accurate diagnosis is essential for proper response to and treatment of PDs. The following comparisons may help avoid misattribution of BPD to other PDs.

- Histrionic PD patients are dramatic and manipulative but lack the affective instability of BPD. Impulsivity, when seen, is related to attention seeking and sexual acting out.
- Dependent PD patients fear abandonment, but patients with BPD have more affective instability and impulsivity.
- Schizotypal PD patients have the micropsychotic symptoms of BPD, but are odder and lack the affective instability of BPD.
- Paranoid PD patients have volatile anger, but lack self-destructive and abandonment issues of the BPD patient.
- Narcissistic PD patients have rages and reactive mood, but have a stable, idealized self-image in contrast to the patient with BPD, who has an unstable identity.
- Antisocial PD patients are often less impulsive than intentionally aggressive for materialistic gains. Patients with BPD act out when needy to gain support.

**B. Other Mental Disorders**

A PD is not diagnosed if symptoms are explained by an Axis I condition or substance use. Although PDs may share impulsivity, raging, and grandiosity with bipolar disorder, they seldom have the same intensity and rate of speech or irrationality of thought that a manic episode brings. Substance use disorders differ from antisocial PD when illegal behaviors are restricted to substance use and procurement. Dissociative
identity disorder, formerly known as multiple personality disorder, may have a more traumatic etiology similar to BPD. Patients with obsessive-compulsive disorder recognize that their behavior and thoughts are irrational while patients with obsessive-compulsive PD are comfortable with their behavior. A diagnosis of PD does not apply when changes in behavior result from changes in brain function. For example, although personality changes are expected in dementia, a diagnosis of PD is not indicated. An Axis I diagnosis "personality change due to a . . . [general medical condition]" is available when a change in personality characteristics is the direct physiologic consequence of a general medical condition. Because transient changes in personality are common in children and adolescents, diagnosis of a PD is not appropriate for a patient younger than 18 years unless the behavioral pattern has been present for at least 1 year.

C. Cultural Considerations

Culturally related characteristics may erroneously suggest PDs. Promiscuity, suspiciousness, and recklessness have different norms in different cultures. The degree of physical or emotional closeness sought and the intensity of emotional expression also differ. Manner of dress and health beliefs may seem strange to the conventional western physician. Evaluate the patient’s degree of acculturation. Passivity, especially with one’s elders, is not a sign of dependency in most recently immigrated individuals. Constricted affect is a normal response when entering a new environment. Asking someone from the culture if the behavior is extreme can be helpful, as can checking for significant interpersonal difficulties.

Treatment

Miller has described how experienced family physicians differ-entially and efficiently respond to visits that can be categorized as routine, ceremony, or drama. In some cases, good application of family medicine’s care principles may be beneficial psychotherapeutically. (Compare the psychotherapy of PDs described below with the patient-centered method of family practice.) Suggestions for helping patients with PDs in a nonpsychiatric medical setting appear in Table 54-2. Table 54-3 offers suggestions for helping patients who present with BPD.

Common wisdom has held that personality cannot be changed. However, increasingly specific psychopharmacologic and psychotherapeutic interventions have brought improved outcomes and some cures. The most effective treatments are multidisciplinary, combining medications, individual and group psychotherapies, and a high level of coordination among providers. Comorbid substance dependence, violent acting out toward others, or severely self-harming behaviors must be addressed first, via inpatient care.


Table 54-3. Working with patients with BPD in medical settings.

| 1. Recognize the characteristics. The patient fears abandonment and increases demands on the physician. May be noncompliant, manipulative, somatize, or “split” the health care team. |
| 2. Behavior is need driven. Demands may be overt or covert. Identify needs and motivations. Patient has little insight into problems. Externalization is symptomatic. |
| 3. Tolerate patient’s behaviors. Speaking “harshly or strictly” will activate abandonment fears and worsen the situation. Use a nonfrontational and an educational approach. |
| 4. A long-term plan provides stability for the patient. Follow continuity of care principles. This may be curative for the patient. |
| 5. Titrate closeness and visit frequency. Avoid extremes of constant availability. |
| 6. Set limits. Make clear agreements about call and office visits. Point out to patients that you are almost always involved in solving some type of problem and are unable to give full attention to their problems without an appointment. Suggest that patients schedule fairly frequent visits so that a regular time is available to discuss the problems they are experiencing. |
| 7. Foresee problems related to abandonment fears such as when the social situation is disturbed, when the patient is referred, or when there are changes in physician or staff. |
| 8. Use a multidisciplinary approach. Involve a highly skilled clinical psychologist or clinical social worker in the care. Encourage communication and cooperation among the care team. |
| 9. Monitor your and the staff’s reactions. Frustration and anger may be expected. Discuss the situation. Help the staff to recognize the etiology of the frustration might originate in the patient’s personality not in the crisis of the moment. Coordinate responses to patients. |
| 10. Set personal limits for the number of these challenging patients that you accept into your practice. |

A. Risk Management

Physicians should acknowledge the threats and challenges associated with PDs. General risk management considerations include:

- Having good collaboration and communication with a qualified mental health professional.
- Attention to documentation of communications and risk assessments.
- Attention to transference and countertransference issues described earlier.
- Consultation with a colleague regarding high-risk situations.
- Careful management of termination of care, even when it is the patient’s decision.
- Informed consent from the patient and, if appropriate, family members, regarding the risks inherent in the disorder and uncertainties in the treatment outcome.

B. Consultation or Referral

Consultation or referral should be considered when the following exist:
• The patient has several psychiatric diagnoses.
• The patient is experiencing depressive or anhedonic symptoms even if subthreshold (risk for suicide).
• The patient has significant problems with self-regulation.
• The patient has moderate to severe substance use disorder(s).
• The diagnosis is uncertain or the presentation is puzzling.
• Initial treatment by the family physician is ineffective.
• The physician or staff are unable to compensate for and are overwhelmed by the patient’s personality problems.

Patient acceptance of treatment can be difficult. The patient may disagree about what is wrong. Symptomatically, patients with PD may externalize blame for their problems. PD behavioral patterns also tend to be egosyntonic. That is, even patients who agree that their behavior is excessive may believe that the excess is reasonable, given their perception of the circumstances. Treatment may also be difficult if it is perceived as an attempt to control the patient; referral may be experienced as devaluing or as abandonment. Thus treatment and referral suggestions should be offered with an understanding of how patients with various PDs may perceive them. Table 54-2 describes patient perspectives on care common to different PDs.

C. Pharmacotherapy

In many cases, medications are effective only as a means to manage stress-exacerbated symptoms. For example, under stress, paranoid, schizoid, or schizotypal patients may experience delusions, distress, and hallucinations, which can be helped with antipsychotic medications. When not stressed, the odd behavior and beliefs of these patients remain unresponsive to treatment. Patients with narcissistic, antisocial, or histrionic PDs are not helped with current medications, including antidepressants, unless a mood disorder coexists.

Some PDs may be successfully treated with medications. Avoidant PD appears to be an alternative conceptualization of social phobia. It can be treated with selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs). Patients with obsessive-compulsive PD may become less irritable and compulsive with SSRIs. Rejection sensitivity seen in patients with dependent PD may be helped by SSRIs.

Not based on diagnosis per se, Soloff has proposed three symptom-specific pharmacotherapy algorithms for PDs. They are based on differential medication effects on cognitive disturbances, behavioral dyscontrol, and affective dysregulation. Soloff’s first algorithm is for treatment of PDs in which cognitive-perceptual symptoms are most significant (ie, patients with suspiciousness, paranoid ideation, and micropsychotic symptoms). The second algorithm is for treatment of affective dysregulation (ie, patients with a depressed, angry, anxious, labile mood). The third algorithm is for treatment of impulsive-behavioral symptoms (ie, patients with impulsive aggression, binging, or self-injuring behaviors). Practice guidelines largely in accord with Soloff’s symptom-based approach were published for treatment of BPD by the American Psychiatric Association (APA) in October 2001 and re-recommended in 2005. Recent systematic reviews continue to support a symptom-based approach and incorporate new studies of mood-stabilizing medications. It should be noted that current recommendations are based on a small database that lacks sufficient randomized controlled trials. Therefore, each treatment should be approached as an empirical trial, with the patient as a coinvestigator. Side effects, risk–benefit ratios, conjoint medications, and patient preferences should be considered carefully. Pharmacotherapy is an adjuvant to psychotherapy; medications do not cure character and will never be a substitute for the work of a therapist. Furthermore, some medications may worsen symptoms.

SSRIs and SNRIs are effective with affective dysregulation seen in cluster BPDs. Tricyclic antidepressants are no more effective than SSRIs and should not be used, given their cardiotoxic effects with overdose and a possibility of paradoxical worsening of symptoms. Monoamine oxidase inhibitors (MAOIs) were proven useful in treating BPD prior to the advent of SSRIs and offer a second treatment option for affective dysregulation, including rejection sensitivity. Mood stabilizers offer an additional level of treatment, especially for anger. Valproate and carbamazepine may be offered alone while lithium should be used in conjunction with an antidepressant, although lithium is the second choice, given its serious side effects. Although patients with BPD often complain of anxiety, benzodiazepines are contraindicated, having been shown to cause increased impulsivity. Clonazepam, a benzodiazepine with anticonvulsant and antimanic properties, is associated with increased serotonin levels and may be useful adjunctively for anxiety, anger, and dysphoric mood.

Antipsychotics are the most researched medications for the treatment of PDs and should be the first-line treatment when cognitive-perceptual symptoms are significant. Low doses should be tried first. There is no evidence that antipsychotics are helpful for PD cognitive-perceptual symptoms in the long term. Antipsychotics may also be used adjuvantly with antidepressants for affective dysregulation, particularly with anger. Antipsychotics such as risperidone may exacerbate or induce manic symptoms, although they produce symptom improvement in bipolar disorder when used in conjunction with mood-stabilizing medications. When the recent guidelines were written, there was insufficient evidence that third-generation antipsychotics (eg, risperidone or olanzapine) would be effective with cognitive-perceptual symptoms in BPD, but given the side-effect profiles of conventional versus third-generation antipsychotics, the newer drugs are being used increasingly, empirically. The atypical antipsychotic clozapine is effective in personality disturbances that are cognitive-perceptual and impulsive but, given its risk for agranulocytosis, should be reserved until several trials of other medications have failed.

Risperidone appears superior to conventional antipsychotics in treatment of impulsivity and aggression, especially in BPD. However, SSRIs at low to moderately high doses
should be tried first. If needed, low-dose antipsychotics may then be added to SSRIs, or used more aggressively as a last line of treatment. Mood-stabilizing medications are indicated as midlevel treatment for impulsivity. Lithium is effective, perhaps because of its impact on serotonin levels. The anticonvulsant divalproex sodium has been used to treat irritability and impulsivity in patients with BPD who have not responded to SSRI therapy, apparently independent of the presence of abnormal electroencephalographic findings. Carbamazepine is also effective as a mood stabilizer. Use of mood stabilizers requires various laboratory tests to monitor metabolic functioning. Various antipsychotic medications carry risks for extrapyramidal symptoms, tardive dyskinesia, weight gain, diabetes mellitus, extended QT intervals, and other problems.


D. Psychotherapeutic Interventions

Some PDs are amenable to some forms of psychotherapy, but there is currently limited empirical support for the treatment of most PDs. Specific treatments described below may result in significant improvements over time, when compared to wait-list control or treatment as usual conditions. The largest changes are observed in measures of self-reported distress or symptoms (eg, target complaints, level of depression). Measures assessing interpersonal problems and social role functioning also show improvement, although to a much smaller degree.

Treatments of less than 1-year duration probably represent crisis interventions or treatments of concurrent Axis I disorders rather than attempts to address core PD psychopathology. Psychotherapy for borderline and narcissistic personalities tends to take significantly longer. Even with extended duration, treatment goals tend to be for functional improvement such as decreased symptom severity and decreased acting out, rather than complete remission of symptoms. Anxiety-related PDs, such as avoidant and dependent PDs, are most amenable to psychotherapy, followed by BPD, followed by schizotypal PD. Cognitive-behavioral psychotherapy, which challenges irrational beliefs, may be effective with avoidant, dependent, obsessive-compulsive, narcissistic, and paranoid PDs. Because individuals with antisocial PD are manipulative and seldom take responsibility for their behavior, psychotherapy is difficult and relatively rare, unless court-ordered interventions are counted as psychotherapy, which is questionable. Furthermore, persons showing characteristic psychopathy traits (eg, lack of remorse, aggressiveness) are the least amenable to treatment.

Successful treatment of borderline and narcissistic PDs requires high levels of therapist experience. Skills in managing the therapeutic alliance and creating a stable, trusting relationship are crucial. Psychotherapy for narcissistic PDs may be highly specialized wherein the patient’s hypersensitivity to slights is confronted only after much trust building and attainment of positive transference.

Group therapy and partial hospitalization are effective for patients with schizotypal and borderline PDs. Dialectical behavior therapy is a unique form of psychotherapy that is efficacious for the treatment of BPD. During individual and group therapies the patient’s beliefs, contradictions, and acting out are empathically accepted. That is, the patient’s personality is responded to positively, and dysfunctional behaviors are responded to matter-of-factly, neither sympathizing with, nor punishing, the patient. Sessions focus on learning to solve problems, control emotions, manage anxiety, and improve interpersonal relationships. After many months of this consistent and intensive treatment, limits are set on the patient’s behavior.

Besides establishing a strong therapeutic alliance, several recommendations may be useful in the treatment of all personality disorders: maintain a consistent and validating treatment process; build motivation and reinforce commitment to change; increase self-knowledge and foster new learning experiences; target cognitive structures of personality/pathology; and adopt a structured approach to treatment (eg, setting appropriate interpersonal boundaries, use of therapy contract).


E. Transfer and End-of-Care Separation Strategies

Patients with certain PDs may have great difficulty separating from their family physician. Separation is also difficult for patients with chronic illnesses and other psychiatric disorders or those who are socially isolated. Responses to termination can be understood in the context of attachment and loss. According to attachment theory, humans form strong bonds that serve basic biological functions by ensuring that the very young are protected. Separation of the young from their object of attachment results in crying, clinging, increased anxiety, and a possibility of depression or anger upon rapprochement. Even for patients without mental disorders, attachment-related behaviors can resurface during times of stress as panic and anxiety, particularly with the helplessness and dependence that accompany illness and hospitalization or loss of the powerful figure that the physician may represent.
Developmentally oriented theorists have suggested that BPD pathology originates in a disturbed attachment process. Abandonment is extremely traumatic for children. Depression and difficulty forming new relationships result. The notion in BPD is that during the critical period of ages 2-3 when the child typically practices separation from the mother, the parent of the borderline progeny is unable to accept the child’s distancing from the parent and is inconsistent upon the child’s return, alternatively rejecting or indulging the child. This pattern repeats through childhood and is replicated in adulthood, where there is great ambivalence about relationships. BPD relational patterns seem to approximate the practicing phase of childhood where there is highly emotional approaching and distancing from the pseudoparental object. Tenuous relationships may be formed and abandonment fears are strong. This interpersonal pattern applies to the physician-patient relationship, as well. The patient, fearing abandonment, alternates between extremes of overvaluing and devaluing the physician. During times away from the physician, the patient may be preoccupied with thoughts of the physician and may experience physical distress.

The following suggestions may help to avoid serious problems for patients undergoing separation:

- Inform patients in advance of upcoming separations.
- Review with patients their responses to previous losses. This will give some prediction about how the patient will react to the termination as well as help the physician-patient team identify strengths on which to capitalize and weaknesses to address.
- Take the pending separation as an opportunity to review the patient’s health care and the role of the physician-patient relationship in the process of care.
- Have patients express how the relationship has been beneficial, what they may have learned about themselves in that relationship, and how that could be helpful in future relationships.
- Resist a desire to not say goodbye to patients. This may happen for a number of reasons, including fear of hurting patients, reluctance to cause “clingy” behaviors, or anger at noncompliant yet demanding patients.
- Understand the patient’s reaction to the news. Some patients may be cool or otherwise noncommittal to the physician’s leaving. A patient who does not want to speak about an upcoming separation can be offered the opportunity to speak about it at a future visit. The patient should know that any and all emotional responses are acceptable. Issues of trust and feelings of abandonment warrant explicit discussion.
- Initiate the discussion with a brief statement that the physician is leaving. Follow this with a brief silence that allows patients to understand and respond. If the silence persists, ask patients what they are thinking or feeling. Body language may provide clues. They can be asked to elaborate on their feelings or, if not responding, gently confronted with a question like, “I am wondering what this news is like for you.”
- When possible, introduce patients to their new care provider. This meeting facilitates information transfer and symbolizes a turning over of the relationship with the patient.
- Ask new patients how they feel about their previous physician.

F. Termination of Care

Despite the physician’s best efforts, it is sometimes necessary to terminate care against the patient’s wishes. The following steps and policies should be considered:

- Have a clear policy about what circumstances will produce care termination, such as repeated drug abuse, violent acting out including threatening, repeatedly missed appointments, physician’s opinion that care has reached maximal therapeutic benefit, and so on.
- Try contracting with the patient to stop these behaviors first.
- Give patients written, advanced warning that care is being terminated. Thirty days warning is typical. The physician may need to provide care in the interim unless circumstances argue otherwise. If not, patients should be given directions on where they may receive care.
- Ethical practice includes physician freedom to choose whom they will serve. However, termination of a patient with a mental disorder requires consideration of patient competency and emotional status, or else abandonment is possible. Consulting with a colleague is an appropriate means to ensure that consideration is given to patient needs.
- Be aware of any specific policies or actions required by state laws and regulations.

Prognosis

Perhaps half of all patients with PDs never receive treatment. Several of the PDs, although pervasive in their negative effects, are perhaps not sufficiently impairing or distressing to warrant treatment. Treatment outcomes are improving for the PDs that are extremely debilitating, such as BPD. PDs with anxiety components have good potential for improvement. Debate remains as to whether any treatment other than incarceration can be effective for individuals with antisocial PD, and with this, whether effect seen comes with age (ie, the person becomes less disruptive as age 40 is approached). Patients with BPD appear to improve by age 40, as well. Patients with BPD who are in treatment improve at a rate seven times their natural course.
General Considerations

Somatoform disorders involve unexplained physical symptoms that bring significant distress and functional impairment. They present one of the more common and most difficult problems in primary care. They are seldom “cured” and should be approached as a chronic disease. Recognition, a patient-centered approach, and specific treatments may help alleviate symptoms and distress. Factitious disorder and malingering, although not true somatoform disorders, are addressed separately in this chapter because of their similarity in the form of medically unexplained symptoms.

Features that characterize the spectrum of somatoform disorders include the following:

- Physical symptoms or irrational anxiety about illness or appearance, for which biomedical findings are not consistent with a general medical condition. Somatoform disorders have specific courses, symptoms, and complaints (Table 55-1).
- Symptoms develop with or are worsened by psychological stress, and are not intentional.
- Extensive utilization of medical care. Paradoxically, treatment and attempts to reassure patients can be counterproductive.
- Feelings of frustration on the part of the physician. Patients are often seen as “difficult patients.”

Somatic expression of psychological distress can be normal, and degree of dysfunction determines whether the symptoms constitute a disorder. Furthermore, symptoms may be sufficient to suggest that the patient’s condition is better described by a primary or comorbid mental disorder that may respond to specific therapies.

Presentations of illness without complete physical explanation have a significant impact on primary care practice. Ten percent of all medical services are provided to patients with no organic disease. Twenty-six percent of primary care patients meet criteria for somatic “preoccupation”: 19% of patients have medically unexplainable symptoms and 25%-50% of visits involve symptoms that have no serious cause. Where true somatoform disorders are present, symptoms persist much longer and the cost of ambulatory care is 9-14 times greater than in controls. Individuals with somatoform disorders undergo numerous medical examinations, diagnostic procedures, surgeries, and hospitalizations. They risk increased morbidity from these procedures. Eighty-two percent stop working at some point because of their difficulties. With appropriate recognition and treatment, costs of care may be reduced by 50%.


Pathogenesis

To some degree, somatic symptoms related to psychological and emotional states are common and should be considered normal. Examples include the experience of anger through jaw tightening, tension through shoulder stiffening, loss or grief through chest discomfort, loss or grief through chest discomfort, disappointment or fear through a sinking feeling in the gut, and shame through a reddening of the face, and so on. Children often feel ill when they learn that a friend is sick or when family stress is high. An example of nonpathologic fear of having a disease is “student’s syndrome,” perception of medical students in pathology class that every symptom they experience could represent a serious diagnosis.

Genetic factors, demonstrated in adoption studies, appear to play a role in the development of somatic sensitivities and obsessive tendencies. Traumatic experiences in the form of sexual, physical, and emotional abuse and witnessing violence are predictive of somatoform disorders. Operant reinforcements and classically conditioned associations will also play a role, both in changes in perception of physical sensations and in pain-related behaviors. In particular, some individuals are susceptible to overexperiencing sensations. This phenomenon may occur through a difference in neuron
## Table 55-1. Somatoform disorders, factitious disorder, and malingering.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Volitional?</th>
<th>Symptom Presentation</th>
<th>Type of Symptoms</th>
<th>Symptom Duration</th>
<th>Treatment Modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatization disorder</td>
<td>no</td>
<td>Sees self as sickly; frequent medical care. Begins before age 30.</td>
<td>Multiple systems or functions. Four sites/functions producing pain. Two GI symptoms other than pain. One sexual symptom other than pain. One pseudoneurologic symptom.</td>
<td>Chronic, recurring, and/or stable</td>
<td>Frequent visits, therapeutic relationship with provider, active listening, avoidance of excessive or invasive treatments, focus on management vs cure, consider CAM modalities.</td>
</tr>
<tr>
<td>Undifferentiated somatoform disorder</td>
<td>no</td>
<td>Same as somatization disorder except symptom number insufficient to meet criteria.</td>
<td>Some of above symptoms and/or vague somatoform complaints such as fatigue for at least 6 mo</td>
<td>&gt;6 mo</td>
<td>Same as above.</td>
</tr>
<tr>
<td>Conversion disorder</td>
<td>no</td>
<td>Onset after acute stress.</td>
<td>Pseudoneurologic symptom or symptom complex such as stroke-like weakness, sensory loss, or pseudoseizure</td>
<td>Sudden onset; short duration</td>
<td>Reassurance that symptom will resolve over days. Avoid labeling as mental illness.</td>
</tr>
<tr>
<td>Pain disorder</td>
<td>no</td>
<td>Preoccupation with pain; examination out-of-proportion with disease or injury.</td>
<td>Pain insufficiently explained by any organic cause. Frequently associated with disability, relationship disruptions, depression, anxiety.</td>
<td>Sudden onset; worsens with time</td>
<td>Focus on functionality, symptom management, and non-narcotic therapy.</td>
</tr>
<tr>
<td>Hypochondriasis</td>
<td>no</td>
<td>Fearful of disease; preoccupied with symptoms; not reassured.</td>
<td>Multiple symptoms over time; misinterpretation of normal sensations, may have unusual health and prevention behaviors.</td>
<td>Long history, worsens after actual illness</td>
<td>SSRI may be beneficial, otherwise similar to somatization.</td>
</tr>
<tr>
<td>Body dysmorphic disorder</td>
<td>no</td>
<td>Excessive concern about imagined defect in appearance.</td>
<td>Specific complaints of defect (other than obesity); behaviors to hide or avoid public exposure of “defect”.</td>
<td>Usually several years</td>
<td>SSRI may be beneficial, otherwise similar to somatization.</td>
</tr>
<tr>
<td>Factitious disorder with physical symptoms</td>
<td>Yes—motivation primary gain: sick role, attention</td>
<td>Unexplained fever, bleeding, injuries.</td>
<td>Nonhealing and unremitting; tend to receive multiple procedure/operations over time; falsify records</td>
<td>Chronic; multiple admissions; remits with confrontation</td>
<td>Accurate diagnosis, may remit with confrontation.</td>
</tr>
<tr>
<td>Malingering</td>
<td>Yes—motivation secondary gain: money, disability, drugs, etc.</td>
<td>Similar to above.</td>
<td>Vague pain and/or paralysis common; belligerent with providers if need not met</td>
<td>Multiple episodes of same problem</td>
<td>Confrontation.</td>
</tr>
</tbody>
</table>

All of these disorders are more common in the young, some beginning in the teens but most commonly in the 20s-30s. Similar symptoms presenting for the first time in the elderly should prompt more extensive investigations for organic cause. True factitious disorder is rare, while the prevalence of malingering is unknown.

Supportive counseling may be considered in cases of factitious disorder and malingering if the patient does not have a personality disorder that would impede care.
gating, in which the threshold of firing is reduced by anxiety or psychological stress. Patients with hypochondriasis can experience a cycle of symptom amplification whereby obsession about the body focuses attention on sensations, which causes anxiety, increasing sensations and further worsening obsessiveness. Other disorders, such as body dysmorphic disorder, may be related to obsessive-compulsive disorders or even a mild thought disorder.

Because families differ in how they respond to symptoms and illnesses, individual differences in health beliefs and illness-related behaviors are to be expected. Families also shape the tendency to experience, display, and magnify somatic symptoms; thus, somatoform disorders or malingering in children may be modeled or reinforced by adults. Social risk factors include single parenthood, living alone, unemployment, and marital and job difficulties.

Gender ratios and prevalence of somatoform disorders differ across cultures. In North America, somatization, conversion, and pain disorders are more frequent in women whereas hypochondriasis and body dysmorphic disorder involve men and women equally. Somatoform symptoms are more prevalent among Chinese American, Asian, and South American patients. These differences are most likely due to Western/empirical explanatory models contrasted with culturally based understandings in which ancient people’s associations of phenomena and symptoms still affect the beliefs and expectations of modern populations.

Disorders with somatoform characteristics specific to certain cultures include the dhat syndrome in India, which is a concern about semen loss, and koro in Southeast Asia, a preoccupation that the penis will disappear into the abdomen. A sense of having worms in the head or burning hands is sometimes reported by people in Africa and Southeast Asia. Cultures influence how emotions should be expressed and sanction religious and healing rituals that may appear conversion-like. Thus, somatoform-like symptoms should be evaluated for appropriateness to the patient’s social context. Behaviors sanctioned by the culture are typically not considered pathologic.

• Multiple symptoms. Fainting, menstrual problems, headache, chest pain, dizziness, and palpitations are the symptoms most likely to be somatoform.
• Vague or highly personalized, idiosyncratic complaints.
• Inability of more than three physicians to make a diagnosis.
• Presence of another mental disorder, especially depressive, anxiety, or substance use disorders.
• Distrust toward the physician.
• Physician experience of frustration.
• Paradoxic worsening of symptoms with treatment.
• High utilization, including repeated visits, frequent telephone calls, multiple medications, and repeated subspecialty referrals.
• Disproportionate disability and role impairment.

B. Diagnostic Criteria

Somatoform disorders are mental disorders that involve physical symptoms or irrational anxiety about illness or appearance, and for which biomedical findings are not consistent with a general medical condition. Specific diagnosis requires that the symptoms have brought unneeded medical treatment or significant impairment in social, occupational, or other important areas of functioning. Somatoform disorders cannot be caused by a general medical condition or by direct effects of substances. If the disorder occurs in the presence of a general medical condition, complaints or impairment must be in excess of what would be expected from the physical findings and history. Although somatoform disorders may occur concurrently with other mental disorders, other diagnoses such as depression or anxiety may be sufficient to supersede the somatoform diagnosis.

1. Somatization disorder—This persistent pattern of recurring, multiple somatic complaints begins before age 30. Patients view themselves as “sickly.” Current diagnostic criteria require a history of pain related to at least four different sites or functions: two gastrointestinal symptoms other than pain, one sexual symptom other than pain, and one pseudoneurologic symptom other than pain. Multiple sites of pain are common, while functional pain is most often expressed as dysmenorrhea, dyspareunia, or dysuria. Common gastrointestinal symptoms include nausea, bloating, diarrhea, and multiple food intolerances. Sexual symptoms include sexual indifference, sexual dysfunction, and menstrual problems. Pseudoneurologic symptoms can be motor related (eg, impaired coordination or balance, paralysis/weakness, difficulty swallowing, urinary retention) or sensory-perceptual (eg, minor hallucinations, loss of sensation, double vision, blindness). Seizures, amnesia, and loss of consciousness are also possible.

2. Undifferentiated somatoform disorder—This is a residual diagnosis for clinically significant, somatoform complaints persisting for more than 6 months, when insufficient in
number to meet diagnostic criteria for somatization disorder. Examples include chronic fatigue, weakness, and anorexia as well as the symptoms described with regard to somatization disorder. Unlike somatization disorder, symptoms need not begin before the age of 30.

3. Conversion disorder—This diagnosis consists solely of pseudoneurologic symptoms (ie, deficits affecting the central nervous system, voluntary motor, or sensory functions). Psychological factors in the form of stressors or emotional conflicts are expected and precede the symptoms. Depending on the medical naiveté of the patient, symptoms are often quite implausible, not conforming to anatomic pathways or physiologic mechanisms. The symptoms, however, are not thought to be volitional. Symptoms may symbolically represent emotional conflicts, such as arm immobility as an expression of anger and impotence. Other clues indicating that the symptoms are pseudoneurologic include worsening in the presence of others; noninjuries despite dramatic falls; normal reflexes, muscle tone, and pupillary reactions; and striking inconsistencies on repeated examinations. Groups of symptoms also tend to not fit together physiologically. Symptoms may be experienced with a relative lack of concern (so-called la belle indifférence), but dramatic or histrionic presentations are more common. Course is an important consideration. Conversion disorder is rare before age 10 or after age 35 years. Symptoms are transient, rarely lasting beyond 2 weeks, and respond to reassurance, suggestion, and psychological support. Although primary and secondary gains may result from conversion disorder, these gains are not the motivating factor as they would be with factitious disorder or malingering.

4. Pain disorder associated with psychological factors—This disorder is the psychiatric equivalent of chronic nonmalignant pain syndrome, except that no minimum duration of symptoms is required. Psychological factors play a significant role in the pain picture, including its onset, severity, exacerbation, and maintenance. Physical pathologies are possible and frequent but organic findings are insufficient to explain the severity of the pain. Functional deficits are common, including disability, increased use of the health care system, abuse of medications, and relational and vocational disruptions. Depression or anxiety may be secondary or may also be primary or comorbid predisposing the patient to an increased experience of pain as well as a deficient ability to cope. Insomnia is also frequently associated with pain complaints.

5. Hypochondriasis—The individual with hypochondriasis is preoccupied with fears of having a serious disease. The preoccupation may originate in an overfocus on and misinterpretation of normal physiologic sensations (eg, orthostatic dizziness), erroneous attributions about the body (eg, “aching veins”), or obsession about minor physical abnormalities. Patients are easily alarmed by contact with ill persons or media coverage of disease. Fears persist despite medical reassurance. More global symptoms may suggest a primary diagnosis of panic disorder, while more specific bodily concerns may be better explained by a diagnosis of body dysmorphic disorder. The key to diagnosing hypochondriasis is primary fear of disease rather than generalized worry or fear of a specific defect.

6. Body dysmorphic disorder—This disorder involves excessive preoccupation with a minor or imagined defect of one or more body parts, excluding the diagnosis of a primary eating disorder. Although many people are concerned about their appearance, the concerns and behaviors associated with this disorder are extreme, distressing, time consuming, and debilitating. Self-consciousness is significant, and avoidance of public exposure, hiding of defects, and nondisclosure to the physician are common. Medical, dental, and surgical treatments are sought but may only worsen preoccupations. Concern may not focus exclusively on a false belief one is obese, which would indicate an eating disorder. Similarly, a belief that sexual characteristics are incorrect may be better represented in a diagnosis of gender identity disorder. Transient or more generalized concerns about appearance may indicate major depressive episodes. Patients who insist that an imagined defect is real and hideous will meet the criteria for delusional disorder, somatic type.

7. Malingering, factitious disorder, and factitious disorder by proxy—These are not somatoform disorders; symptoms are voluntary and deceptive. Deception is obtained by feigning or self-inducing symptoms or by falsifying histories or laboratory findings. Common symptoms include fever, self-mutilation, hemorrhage, and seizures. Persons connected to health professions are common perpetrators. Malingering and factitious disorder differ by whether symptom gain is primary or secondary. In malingering, symptoms are produced to gain rewards or avoid punishments (secondary gains). Factitious disorder involves production of symptoms in order to assume the sick role (primary gain). Unlike malingering, factitious disorder is considered a mental disorder principally because the need to be in the sick role is abnormal. Factitious disorder by proxy occurs when illness is caused by a caregiver, typically to meet a need for drama and to be a rescuer of the patient. Signs of factitious disorder include direct evidence, such as inconsistent laboratory or physical findings or observations (eg, injection of bacteria), as well as vague clues, such as patients who are migratory or have no visitors, are comfortable with more aggressive treatments including extended hospitalization, or whose presentation is exaggerated and quite dramatic (Munchausen syndrome).


C. Screening and Diagnostic Measures

Keeping somatoform disorders in the differential is the key to making the correct diagnosis over time. Valid diagnostic and
A therapeutic alliance should be built by a
Adapted, with permission, from Phillips KA: Body dysmor-
Questions to evaluate body dysmorphic
duration of symptoms, and age of the patient, may be able to
distinguish somatoform from other disorders. It is
to determine the primary disorder in order to
choose effective treatment. Clinical factors, such as context,
duration of symptoms, and age of the patient, may be able to
distinguish somatoform from other disorders.

<table>
<thead>
<tr>
<th>Table 55-2. Questions to evaluate body dysmorphic disorder.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you worry about the appearance of your face or body? If so, what is your concern?</td>
</tr>
<tr>
<td>2. How bad do you think your (face or body part) appears?</td>
</tr>
<tr>
<td>3. How much time do you spend worrying about your (face or body part)?</td>
</tr>
<tr>
<td>4. Have you done anything to hide or rid yourself of the problem?</td>
</tr>
<tr>
<td>5. How does this concern with your appearance affect your life?</td>
</tr>
</tbody>
</table>


 screening questionnaires exist, but often lack clinical utility due to length and training required for interpretation. A directed interview with specific questions based on patient complaints is most effective for primary care providers. When doubts remain, referral to a specialist skilled in use of diagnostic questionnaires is indicated. Patients under consideration for somatoform disorder should be screened for depression. Questions should also evaluate patients suspected of having body dysmorphic disorder as needed. (Table 55-2).

### Differential Diagnosis

Diagnosis should be considered provisional until there is considerable external support. General medical conditions characterized by multiple and confusing somatic symptoms (eg, hyperparathyroidism, porphyria, multiple sclerosis, and systemic lupus erythematosus) should be considered. Conversion disorder, in particular, is often misdiagnosed. Shaibani and Sabbagh have described several clinical tests that may reveal whether conversion symptoms are pseudoneurologic. Onset of multiple physical symptoms in early adulthood suggests somatization disorder but in the elderly suggests a general medical condition. Primary or secondary depression should be considered in any patient suspected of having somatoform disorder. Other mental disorders, including anxiety disorders and substance-related disorders, are frequently seen with somatoform disorders and in some cases may better explain symptoms and thus constitute the better diagnosis. Personality disorders (eg, histrionic, borderline, or antisocial personality disorder) are also frequently associated with somatoform disorders. It is important to determine the primary disorder in order to choose effective treatment. Clinical factors, such as context, duration of symptoms, and age of the patient, may be able to distinguish somatoform from other disorders.

### Complications

Failure to recognize and properly treat somatoform complaints can lead to excessive diagnostic procedures and treatments, which perpetuate patient preoccupations and place the patient at risk for iatrogenic harm. Use of unidentified, unconventional, or alternative treatments by patients with somatoform disorders may interact negatively with prescribed medications. Dependencies on sedative, analgesic, or narcotic agents are common iatrogenic complications.

### Treatment

Characterizing medically unexplained symptoms as pathology may lead physicians to misconstrue patients as suffering solely from a psychiatric disorder. In reality, primary care patients are usually quite different from those seen in specialty psychiatric care. Primary care patients present with undifferentiated symptoms that are best addressed with a comprehensive approach that includes continuity of care and attention to the physician-patient relationship. “Pathologizing” makes patients feel illegitimate, in itself a major source of distress, and produces stereotypes of patients as “crock, whiners, or difficult.” Patient characteristics considered as difficult include extensive or exaggerated complaints, nonadherence with treatment recommendations, and behaviors that raise suspicion of seeking drugs. When patients are so labeled, the relevance of the patient’s experience and the potential of partnership between patient and physician are both obviated. A patient-centered method, so important to family practice, becomes impossible. Even without attributions of a mental disorder, somatoform symptoms present one of the most difficult challenges in primary care. Uncertainties associated with the diagnosis, the sense that the focus is not medical and therefore the interaction is inappropriate, patient symptom amplification, and the sense that services are being overused inappropriately contribute to the perception that the patient is difficult.

### A. General Recommendations

Somatoform symptoms exist on a continuum and rarely indicate that the patient’s difficulties reflect solely a mental disorder. Comprehensive, continuous, patient-centered care appropriately addresses most primary care patient presentations. The following general recommendations apply to such an approach.

1. **First visits**—A therapeutic alliance should be built by a thorough history and physical examination and by a review of the patient’s records. The physician should show curiosity and interest in the patient’s complaints and validate the patient’s suffering. Psychogenic attributions should be avoided. To appear puzzled initially is a good strategy. Delivery of a diagnosis is a key treatment step with somatoform disorders. Different disorders require different types of information. Suggestions for statements to be made to the patient appear in Table 55-3.
2. Management—The disorder should be treated as a chronic illness, with the focus on functioning rather than cure. Gradual change should be expected, with periods of improvement and relapse. Physicians should try to avoid excessive and/or invasive diagnostics and treatment in order to minimize iatrogenic harm. When procedures or treatments are undertaken, they should be chosen only on the basis of objective evidence, not subjective complaints. When new symptoms arise, at least a limited physical examination should be performed to avoid misdiagnosis and assure the patient that his or her concerns are taken seriously. The need for unnecessary tests and procedures can be avoided by having the patient feel “known” by the physician.

3. Patient-centered care—Feelings of illegitimacy by patients and common physician attitudes toward patients contribute to power differentials and struggles. Physicians should speak with patients as equals, listen well, ask lots of questions, answer lots of questions, explain things understandably, and allow patients to make decisions about their care. A collaborative relationship should be developed in which the physician works together with the patient to

| Table 55-3. Delivering the diagnosis in somatoform and related disorders. |
|-----------------------------|-----------------------------|
| Disorder                     | Statements |
| Somatization disorder        | 1. I know that you are experiencing much discomfort and feeling very ill. |
|                              | 2. You have a medical disorder called somatization disorder. |
|                              | 3. This disorder runs in families and has a unique pattern of symptoms. It does not cause physical deterioration or shorten life. |
|                              | 4. It is not curable, but manageable. A specific treatment plan is required. |
| Conversion disorder          | 1. Avoid terms “conversion disorder” and “psychogenic.” |
|                              | 2. After thorough evaluation, the (symptom name, eg, blindness) will resolve very quickly. |
|                              | 3. It is, in fact, starting to improve at this time. |
| Pain disorder                | 1. I have reviewed your records and thoroughly evaluated you. |
|                              | 2. All appropriate interventions have been tried. |
|                              | 3. You have a medical condition called somatoform pain disorder. |
|                              | 4. Your disorder is not life-threatening but I know that you are experiencing much discomfort and (specific function, eg, moving) quite poorly. |
|                              | 5. Our goal must be rehabilitation, not necessarily being pain free. |
|                              | 6. A specific treatment plan is required. |
| Hypochondriasis              | 1. Reassurance of nonpathology is unlikely to be helpful. A diagnostic label will be helpful. |
|                              | 2. You have a syndrome of neurologic amplification of body sensations. |
|                              | 3. The syndrome is not life-threatening but requires careful monitoring. |
|                              | 4. We need to schedule regular appointments. I want you to discuss your concerns at these appointments and I’ll examine you thoroughly. |
| Body dysmorphic disorder     | 1. I can see that you are very concerned about this sense that your (body part, eg, nose) is ugly. |
|                              | 2. You get very anxious when you think about people seeing it and want to hide it. You even want to stay away from others because you are so anxious. |
|                              | 3. What I suggest we do for now is try these measures to treat your anxiety so that your suffering is less and you function better, not missing out on things that you would otherwise like to do. |
| Factitious disorder          | 1. The physician may decide to directly confront a patient. However, if family or other social situation is available to promote the patient’s need to save face, a therapeutic double bind is suggested. A thorough physical examination and attempt to build a therapeutic alliance must be performed before delivering the diagnosis. |
|                              | 2. Sometimes people do things to make themselves ill. We call this problem factitious disorder. |
|                              | 3. You have an unusual problem. I believe it will respond to one more attempt to treat it. If, however, the problem does not respond to this attempt, a diagnosis of factitious disorder will be established. |
| Malingering                   | 1. Informing the patient that his or her deception has been detected can be dangerous and should be handled carefully. In some cases it may be better to deprive the patient of any benefits of the sick role, which will extinguish the behavior. |
|                              | 2. I guess I am wondering if there might be some reason for you to be sick right now. |
|                              | 3. Have you thought about what might happen if you continue to do this? |

understand and manage patient problems. The “common ground” shared by the physician and the patient should be monitored and differences discussed.

4. Office visits—Regular, brief appointments should be scheduled, thus avoiding “as-needed” medications and office visits that make medical attention contingent on symptoms. Practical time-related strategies include negotiating and setting the agenda early in the visit, paying attention to the emotional agenda, practicing active listening through appropriate reactions and follow-up questions, soliciting the patient’s attributions for the problems, and communicating empathetically.

5. Psychosocial issues—Reassurance should be provided to the patient, but not before a thorough exploration of symptoms. Psychosocial questions should be interspersed with biomedical ones to explore all issues: physiologic, anatomic, social, family, and psychological. The physician should inquire about trauma and abuse. As trust builds, the patient should be encouraged to explore psychological issues that may be related to symptoms. In this way, symptoms can be linked to the patient’s life and feelings. Physicians should avoid using the term stress too liberally, as it may be misconstrued as the cause of the patient’s symptoms or an excuse for an incomplete evaluation. Eventually and subtly, patients are likely to reveal their personal issues and concerns.

6. Family involvement—With the patient’s permission, family members should be invited to participate in patients’ visits. An occasional family conference can be valuable. Each person’s opinion about the illness and treatment can be solicited, and family members can be asked how family life would be different if the patient were without symptoms. Physicians should solicit and constantly return to the patient’s and family’s strengths and areas of competence.

Those with extreme but transitory dysmorphic concerns may benefit from temporary treatment with an atypical antipsychotic medication.

C. Consultation or Referral

Involvement of a mental health clinician may be helpful to diagnose comorbid mental conditions, offer suggestions for psychotropic medications, and engage some patients in psychotherapy. Patients, however, are unlikely to see the value of consultation or may experience referral as an accusation that their symptoms are not authentic. Pressuring the patient to accept a consultation is unlikely to be effective and may render the consultant encounter unproductive. Trust must first be established and psychological issues must be made a legitimate subject for discussion. The idea of referral can be introduced later. When possible, it can be more effective to see the patient along with the mental health clinician so that a comprehensive approach continues to be emphasized, the patient does not feel abandoned, and worry that the patient’s concerns are not taken seriously are alleviated. Extreme distress or preoccupations worsening to delusional levels may require inpatient hospitalization.

D. Psychotherapeutic Interventions

Standardized group or individual cognitive-behavioral therapies can be an effective treatment for chronic somatoform disorders, reducing somatic symptoms, distress, impairment, and medical care utilization and costs. Cognitive interventions train the patient to identify and restructure dysfunctional beliefs and assumptions about health. Behaviorally, the patient is encouraged to experiment with activities that are counter to usual habits such as avoidance, “doctor shopping,” or excess seeking of reassurance. In addition, patients can learn relaxation and meditation techniques to manage symptoms of anxiety. Jon Kabat-Zinn and colleagues have shown significant and long-term improvements in health behaviors and anxiety scores using mindfulness meditation in a model that may have application to somatoform disorders. Patients with high emotional distress respond more rapidly to psychotherapy and patients able to at least partially attribute symptoms to psychological factors show better therapeutic outcomes than patients who firmly believe that their physical symptoms have a physical cause.
E. Complementary and Alternative Therapies

It is to be expected that patients with somatoform symptoms often try alternative treatments such as herbal remedies, mind-body interventions, and other non-Western medical approaches. In these patients, conventional treatments appear to have failed, distrust of physicians may be high, and distress is great. Federal regulations require that label claims and instructions on herbal products and supplements address symptoms only; therefore, there are no specific herbal agents for somatoform disorders, per se. Given the plethora of symptoms that can exist in patients with somatoform disorders, it is not surprising that there are numerous alternative medications that patients may try.

Patients with pain disorder or primary or comorbid anxiety may benefit from body and mind-body interventions such as massage, movement therapies, manipulations, relaxation, guided imagery, and hypnosis. The placebo effect of various remedies may be helpful, particularly if the agents are largely inert, as bothersome side effects seen in conventional medicines may be avoided. Alternative therapies often include “nonspecific therapeutic effects” that go beyond the placebo effect and can be beneficial. Nonspecific effects include warmth and listening skills of the practitioner, empowerment that comes from legitimization of the patient’s problem, and an egalitarian approach to care. Physicians may wish to recommend alternative treatments and collaborate with alternative practitioners but should also be prepared to protect the patient by cautioning against treatments that are potentially harmful, excessively expensive, or that circumvent conventional treatments that are needed for demonstrated medical conditions.

F. Patient Education

The American Academy of Family Physicians has developed a patient education handout for somatoform disorders. Information is similar to and expands on the key statements for somatization disorder appearing in Table 55-3. The web address for the handout is http://www.familydoctor.org/handouts/162.html.
General Considerations

The prevalence of alcohol and drug disorders in primary care outpatients is between 23% and 37%. The cost to society of these disorders is staggering. Each year in the United States substance use disorders are associated with 100,000 deaths and costs of approximately $100 billion. The high prevalence of these disorders in primary care outpatients suggests that family physicians are confronted with these problems daily. However, these disorders rarely present overtly. Patients in denial about the connection between their substance use and the consequences caused by it frequently minimize the amount of their use and often do not seek assistance for their substance use problem.

The epidemiology of alcohol and drug disorders has been well studied and is most often reported from data of the National Institute of Mental Health Epidemiologic Catchment Area Program (ECA). Lifetime prevalence rates for alcohol disorders from the ECA survey data were 13.5%. For men, the lifetime prevalence was found to be 23.8%, and for women, 4.7%. The National Comorbidity Survey revealed lifetime prevalence of alcohol abuse without dependence to be 12.5% for men and 6.4% for women. For alcohol dependence, the lifetime prevalence was 20.1% in men and 8.2% in women. The ECA data yield an overall prevalence of drug use disorders of 6.2%. As with alcohol use disorders, drug use disorders occur more frequently in men (lifetime prevalence 7.7%) than in women (4.8%). Characteristics known to influence the epidemiology of substance use disorders include gender, age, race, family history, marital status, employment status, and educational status.

Pathogenesis

The difference between abuse and dependence is an important one. With substance abuse, patients retain control of their use. This control may be affected by poor judgment and social and environmental factors, and mitigated by the consequences of the patient’s use. Patients who become dependent (addicted) no longer have full control of their drug use. The brain has been “hijacked” by a substance that affects the mechanism of control over the use of that substance. This addiction is far more than physical dependence. The need to use the drug becomes as powerful as the drives of thirst and hunger. Evidence that the brains of addicted individuals are different from those of nonaddicted persons is enormous. Many of these abnormalities predate the use of the substance and are thought to be inherited. In genetically predisposed individuals, substances of abuse cause changes in the dopaminergic mesolimbic system that result in a loss of control over substance use. These changes are mediated by several neurotransmitters: dopamine, γ-aminobutyric acid (GABA), glutamate, serotonin, and endorphins. The different classes of substances of abuse act through one or more of these neurotransmitters, ultimately affecting the level of dopamine in the mesolimbic system (otherwise known as the reward pathway). These changes in the brain are permanent and are the primary reason for relapse in the addicted patient trying to maintain abstinence or control of use.

Prevention

Although neurobiology plays a large role in addiction, the precursors of substance abuse are also environmental and include family, school, community, and peer factors (Table 56-1). These multiple factors make the design of effective prevention very difficult. Primary prevention is designed to prevent the use of substances, thereby making abuse impossible. These programs are designed primarily for the young. Secondary prevention consists of screening programs to identify abuse early and to redirect the patient’s behavior before addiction.
becomes overt. In tertiary prevention, the focus is on the treatment of addictive behavior in an effort to prevent the consequences of compulsive use. Prevention programs can be divided into those that address the four environmental areas of risk: family, school, peers, and community. Family physicians can support these efforts by including the following behaviors in their practice:

- Supporting efforts to strengthen parenting skills, family support, and communication.
- Providing patient and community education about drug and alcohol use, abuse, and treatment.
- Screening and assessing patients of all ages for substance use disorders in the office and hospital.
- Supporting community efforts in substance abuse prevention.
- Endorsing and promoting public policy that supports prevention, early detection, and treatment of substance use disorders.

**Clinical Findings**

**A. Symptoms and Signs**

The signs and symptoms of substance abuse are varied and often subtle. This is complicated by the fact that most patients do not recognize their substance use as the cause of their problems and are often quite resistant to that interpretation. Consequently, the family physician must have a high index of suspicion, recognizing that the prevalence of substance use disorders in outpatient primary care is high. A perspective that recognizes the prevalence of these disorders will enable physicians to interpret potential clues to substance use (Table 56-2).

The diagnosis of substance abuse or dependence is made primarily on the basis of a careful history. However, substance-disordered patients may be deliberately less than truthful in their history, and often the patient’s denial prevents the physician from seeing the connection between substance use and its consequences. Signs of sedative hypnotic or alcohol withdrawal may be misinterpreted as an anxiety disorder. Chronic use of stimulants may present as a psychotic disorder. In fact, in the face of active substance

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**Table 56-1.** Environmental risk factors for substance abuse.

<table>
<thead>
<tr>
<th>Family factors</th>
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</thead>
<tbody>
<tr>
<td>Sexual or physical abuse</td>
</tr>
<tr>
<td>Parental or sibling substance abuse</td>
</tr>
<tr>
<td>Parental approval or tacit approval of child’s substance use</td>
</tr>
<tr>
<td>Disruptive family conflict</td>
</tr>
<tr>
<td>Poor communication</td>
</tr>
<tr>
<td>Poor discipline</td>
</tr>
<tr>
<td>Poor supervision</td>
</tr>
<tr>
<td>Parental rejection</td>
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<tr>
<td>School factors</td>
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<tr>
<td>Lack of involvement in school activities</td>
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<tr>
<td>Poor school climate</td>
</tr>
<tr>
<td>Norms that condone substance use</td>
</tr>
<tr>
<td>Unfair rules</td>
</tr>
<tr>
<td>School failure</td>
</tr>
<tr>
<td>Community factors</td>
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<tr>
<td>Poor community bonding</td>
</tr>
<tr>
<td>Disorganized neighborhoods</td>
</tr>
<tr>
<td>Crime</td>
</tr>
<tr>
<td>Drug use</td>
</tr>
<tr>
<td>Poverty</td>
</tr>
<tr>
<td>Low employment</td>
</tr>
<tr>
<td>Community norms that condone substance use</td>
</tr>
<tr>
<td>Peer factors</td>
</tr>
<tr>
<td>Bonding to peer group that engages in substance use or other antisocial behaviors</td>
</tr>
</tbody>
</table>

**Table 56-2.** Clinical clues of alcohol and drug problems.

<table>
<thead>
<tr>
<th>Social history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrest for driving under the influence of alcohol once (75% association with alcoholism) or twice (95% association)</td>
</tr>
<tr>
<td>Loss of job or sent home from work for alcohol or drug reasons</td>
</tr>
<tr>
<td>Domestic violence</td>
</tr>
<tr>
<td>Child abuse/neglect</td>
</tr>
<tr>
<td>Family instability (divorce, separation)</td>
</tr>
<tr>
<td>Frequent, unplanned absences</td>
</tr>
<tr>
<td>Personal isolation</td>
</tr>
<tr>
<td>Problems at work/school</td>
</tr>
<tr>
<td>Mood swings and psychological problems</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of addiction to any drug</td>
</tr>
<tr>
<td>Withdrawal syndrome</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Anxiety disorder</td>
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<tr>
<td>Recurrent pancreatitis</td>
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<tr>
<td>Recurrent hepatitis</td>
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<tr>
<td>Hepatomegaly</td>
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<tr>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Myocardial infarction &lt; age 30 (cocaine)</td>
</tr>
<tr>
<td>Blood alcohol level &gt; 300 or &gt; 100 without impairment</td>
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<tr>
<td>Alcohol on breath or intoxicated at office visit</td>
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<tr>
<td>Tremor</td>
</tr>
<tr>
<td>Mild hypertension</td>
</tr>
<tr>
<td>Estrogen-mediated signs (telangectasias, spider angiomas, palmer erythema, muscle atrophy)</td>
</tr>
<tr>
<td>Gastrointestinal complaints</td>
</tr>
<tr>
<td>Sleep disturbances</td>
</tr>
<tr>
<td>Eating disorders</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
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</tbody>
</table>
Modified, with permission, from American Psychiatric
DSM-IV-TR criteria for substance abuse.

### Table 56-3. CAGE questions adapted to include drugs.\(^a\)

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have you felt you ought to <strong>Cut</strong> down on your drinking or drug use?</td>
</tr>
<tr>
<td>2. Have people <strong>Annoyed</strong> you by criticizing your drinking or drug use?</td>
</tr>
<tr>
<td>3. Have you felt <strong>Guilt</strong>y about your drinking or drug use?</td>
</tr>
<tr>
<td>4. Have you ever had a drink or used drugs first thing in the morning to</td>
</tr>
<tr>
<td>steady your nerves or to get rid of a hangover or to get the day</td>
</tr>
<tr>
<td>started? (Eye-opener)</td>
</tr>
</tbody>
</table>

\(^a\)Two or more yes answers indicates a need for a more in-depth assessment. Even one positive response should raise a red flag about problem drinking or drug use.


### B. Screening Measures

The diagnosis of substance use disorders is most typically begun with a screening test that identifies a user at risk. The CAGE (Cut down, Annoyed, Guilty, and Eye opener) questionnaire (Table 56-3) is perhaps the most widely used screening tool for the identification of patients at risk for substance use disorders. When a patient answers yes to two or more questions of the CAGE, the sensitivity is 60%-90% and the specificity 40%-60% for substance use disorders. Because a screening test is more predictive when applied to a population more likely to have a disease, clinical clues to substance use disorders may be useful indicators to determine who to screen (see Table 56-2).

### C. Methods to Differentiate Abuse From Dependence

#### 1. Diagnostic criteria—Once a patient with a substance use problem is identified, it becomes necessary to determine whether the disorder involves abuse or dependence. Substance abuse is a pattern of misuse during which the patient maintains control, whereas in substance dependence, control over use is lost. Physiologic dependence, evidenced by a withdrawal syndrome, may exist in either state. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* diagnostic criteria for substance abuse and dependence are listed in Tables 56-4 and 56-5.

#### 2. Withdrawal syndromes—Although not always seen with substance abuse, physiologic dependence suggests abuse unless the patient is on long-term prescribed addictive medicines. Table 56-6 contrasts signs and symptoms of withdrawal from alcohol and other sedative-hypnotic drugs, opiates, and cocaine and other stimulant drugs. Alcohol withdrawal may

### Table 56-4. DSM-IV-TR criteria for substance abuse.

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A maladaptive pattern of substance use, leading to clinically significant</td>
</tr>
<tr>
<td>impairment or distress, as manifested by two (or more) of the following</td>
</tr>
<tr>
<td>occurring at any time within a 12-month period:</td>
</tr>
<tr>
<td>1. Recurrent substance use resulting in failure to fulfill major role obli-</td>
</tr>
<tr>
<td>gations at work, school, or home (eg, repeated absences or poor</td>
</tr>
<tr>
<td>work performance related to substance use; substance-related</td>
</tr>
<tr>
<td>absences, suspensions, or expulsions from school; neglect of children or</td>
</tr>
<tr>
<td>household).</td>
</tr>
<tr>
<td>2. Recurrent substance use in situations in which it is physically</td>
</tr>
<tr>
<td>hazardous (eg, driving an automobile or operating a machine when</td>
</tr>
<tr>
<td>impaired by substance use).</td>
</tr>
<tr>
<td>3. Recurrent substance-related legal problems (eg, arrests for</td>
</tr>
<tr>
<td>substance-related disorderly conduct).</td>
</tr>
<tr>
<td>4. Continued substance use despite having persistent social or inter-</td>
</tr>
<tr>
<td>personal problems caused or exacerbated by the effects of the substance</td>
</tr>
<tr>
<td>(eg, arguments with spouse about consequences of intoxication, physical</td>
</tr>
<tr>
<td>fights).</td>
</tr>
</tbody>
</table>

The symptoms have never met the criteria for Substance Dependence for this class of substance.


### Table 56-5. DSM-IV-TR criteria for substance dependence.

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A maladaptive pattern of substance use, leading to clinically significant</td>
</tr>
<tr>
<td>impairment or distress, as manifested by three (or more) of the following</td>
</tr>
<tr>
<td>occurring at any time in the same 12-month period:</td>
</tr>
<tr>
<td>1. Tolerance as defined by either of the following:</td>
</tr>
<tr>
<td>a. A need for markedly increased amounts of the substance to achieve</td>
</tr>
<tr>
<td>intoxication or the desired effect.</td>
</tr>
<tr>
<td>b. Markedly diminished effect with continued use of the same amount of</td>
</tr>
<tr>
<td>the substance.</td>
</tr>
<tr>
<td>2. Withdrawal, as manifested by either of the following:</td>
</tr>
<tr>
<td>a. The characteristic withdrawal syndrome for the substance.</td>
</tr>
<tr>
<td>b. The same (or closely related) substance is taken to relieve or</td>
</tr>
<tr>
<td>avoid withdrawal symptoms.</td>
</tr>
<tr>
<td>3. The substance is often taken in larger amounts or over a longer</td>
</tr>
<tr>
<td>period than was intended.</td>
</tr>
<tr>
<td>4. There is a persistent desire or unsuccessful efforts to cut down or</td>
</tr>
<tr>
<td>control substance use.</td>
</tr>
<tr>
<td>5. A great deal of time is spent in activities necessary to obtain the</td>
</tr>
<tr>
<td>substance, use the substance, or recover from its effects.</td>
</tr>
<tr>
<td>6. Important social, occupational, or recreational activities are given</td>
</tr>
<tr>
<td>up or reduced because of substance use.</td>
</tr>
<tr>
<td>7. The substance use is continued despite knowledge of having a persis-</td>
</tr>
<tr>
<td>tent or recurrent physical or psychological problem that is likely</td>
</tr>
<tr>
<td>to have been caused or exacerbated by the substance.</td>
</tr>
</tbody>
</table>

be life threatening, if not properly treated. Opiate withdrawal is not life threatening and neither is withdrawal from cocaine or other stimulants, although they both may be associated with morbidity and relapse to substance abuse.

In dealing with sedative-hypnotic, alcohol, or opiate withdrawal, assessment of the degree of withdrawal is important to determine appropriate use and dose of medication to reduce symptoms and, in the case of sedative hypnotic drugs or alcohol, prevent seizures and mortality. The Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-AR) allows quantification of the signs and symptoms of withdrawal in a predictable fashion that allows clinicians to discuss the severity of withdrawal for a given patient and thus choose intervention strategies that are effective and safe.

This tool is available online and can be downloaded from the American Society of Addiction Medicine (ASAM) web site (http://asam.org).

### D. Laboratory Findings

Biochemical markers may help support the diagnostic criteria gathered in the history, or can be used as a screening mechanism to consider patients for further evaluation (Table 56-7).

<table>
<thead>
<tr>
<th>Marker</th>
<th>Substance</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean corpuscular volume (MCV)</td>
<td>Alcohol</td>
<td>24</td>
<td>96</td>
<td>63</td>
</tr>
<tr>
<td>γ-Glutamyltransferase (GGT)</td>
<td>Alcohol</td>
<td>42</td>
<td>76</td>
<td>61</td>
</tr>
<tr>
<td>Carbohydrate-deficient transferrin (CDT)</td>
<td>Alcohol</td>
<td>67</td>
<td>97</td>
<td>84</td>
</tr>
</tbody>
</table>

### Differential Diagnosis

Because substance abuse is a behavioral disorder, when considering a differential diagnosis, psychiatric disorders often come to mind. Indeed, there is a high comorbidity between substance use disorders and psychiatric disorders. Approximately 50% of psychiatric patients have a substance use disorder. For patients with addictions, however, the rates of psychiatric disorders are similar to the general population. Problems such as substance-induced mood disorders (frequently noted in alcohol, opiate, and stimulant abuse) and substance-induced psychotic disorders (most frequently associated with stimulant abuse) complicate differentiation of primary psychiatric disorders from those that are primarily substance use disorders. Most clinicians agree that psychiatric disorders cannot be reliably assessed in patients who are currently or recently intoxicated. Thus detoxification and a period of abstinence are necessary before evaluation for other psychiatric disorders may effectively be done.

Other than the dilemma of determining whether a substance-induced or comorbid psychiatric disorder is present, differential diagnosis in substance abuse revolves around the issues of abuse versus dependence (see earlier discussion). The essential difference is a loss of control over use in dependence that is not present in abuse. This distinction is complicated, however, by the chronic and waxing and waning...
nature of substance use disorders. As a result, it is necessary to examine a patient’s behavior over an extended period of time, looking for evidence of past loss of control of use that may not currently be present. Usually in addiction a pattern of progressively increasing loss of control becomes evident as the consequences of chronic substance abuse unfold.

Complications

The medical complications of substance abuse are legion and profoundly affect the health of our population (Table 56-8). The number of deaths attributed to the abuse of substances exceeds 500,000 yearly, with tobacco use accounting for 380,000 of these deaths. (For discussion of tobacco use, see Chapter 57.) Cardiovascular disease and cancer lead this list. Alcohol causes approximately 100,000 deaths yearly and is associated with motor vehicle accidents, other accidents, homicides, cirrhosis of the liver, and suicide. Injection drug use is responsible for the fastest growing population of HIV infection. In addition to medical complications, substance abuse causes considerable neuropsychiatric morbidity, both as a primary cause (Table 56-9) and by exacerbating existing psychiatric disorders.

Acute substance-induced psychosis is often indistinguishable from a primary psychotic disorder such as schizophrenia in the setting of substance abuse. Neurocognitive states such as dementia may be substance induced and result in permanent brain damage. Depression, commonly diagnosed and treated in the primary care setting, may often be complicated by a substance-induced mood disorder. Often what appears to be treatment-resistant depression is actually the result of persistent substance abuse. Withdrawal syndromes often present as episodes of anxiety, sleep disorders, mood disorders, or seizure disorders.

Table 56-8. Medical complications of substance abuse.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Trauma, Hypertension, Cardiomyopathy, Dyshynergias, Ischemic heart disease, Hemorrhagic stroke, Esophageal reflux, Barret esophagus, Mallory-Weiss tears, Esophageal cancer, Acute gastritis, Pancreatitis, Chronic diarrhea, malabsorption, Alcoholic hepatitis, Cirrhosis, Hepatic failure, Hepatic carcinoma, Nasopharyngeal cancer, Headache, Sleep disorders, Memory impairment, Dementia, Peripheral neuropathy, Fetal alcohol syndrome, Sexual dysfunction, Substance-induced mood disorders, Substance-induced psychotic disorders, Immune dysfunction</td>
</tr>
<tr>
<td>Cocaine (other stimulants)</td>
<td>Chest pain, Congestive heart failure, Cardiac dysrhymias, Cardiovascular collapse, Seizures, Cerebrovascular accidents, Headache, Spontaneous pneumothorax, Noncardiogenic pulmonary edema, Nasal septal perforations</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>Hepatitis C, B, HIV infection, Subacute endocarditis, Soft tissue abscesses</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Substance-induced mood disorder, depressed/elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance-induced anxiety disorder</td>
</tr>
<tr>
<td>Substance-induced psychotic disorder</td>
</tr>
<tr>
<td>Substance-induced personality change</td>
</tr>
<tr>
<td>Substance intoxication</td>
</tr>
<tr>
<td>Substance withdrawal</td>
</tr>
<tr>
<td>Delirium</td>
</tr>
<tr>
<td>Wernicke disease</td>
</tr>
<tr>
<td>Korsakoff syndrome (alcohol-induced persisting amnestic disorder)</td>
</tr>
<tr>
<td>Transient amnestic states (blackouts)</td>
</tr>
<tr>
<td>Substance-induced persisting dementia</td>
</tr>
</tbody>
</table>


Treatment

Many substance use disorders resolve spontaneously or with brief interventions on the part of physicians or other authority figures in the workplace, legal system, family, or society. This occurs because patients with substance abuse disorders continue to maintain control over their use, and when the consequences of that use outweigh the benefits of the drug, they choose to quit. Patients with substance dependence disorders, on the other hand, have impaired control by definition. They rarely improve without assistance.

Substance use disorders can be treated successfully. Brief interventions and outpatient, inpatient, and residential...
treatment programs reduce morbidity and mortality associated with substance abuse and dependence. Determining the type and intensity of treatment that is best for a given patient may be difficult. ASAM has developed guidelines for clinicians to help determine the level and intensity of treatment for patients (Table 56-10). Once patients have been adequately assessed, treatment can begin. Detoxification, patient education, identification of defenses, overcoming denial, relapse prevention, orientation to 12-step recovery programs, and family services are the goals of substance abuse treatment.

A. Intervention

Once screening and diagnosis are complete, it is time for the physician to share the assessment with the patient. Because of the nature of substance abuse, patients rarely choose to seek help for their alcohol or drug problem until the consequences far outweigh the positive aspects of treatment. Intervention may be seen as a means of bringing these consequences to the attention of the patient. It can be accomplished by a wide range of approaches, some quite informal, others carefully orchestrated and executed. Physicians or family members can often intervene simply by giving the patient feedback about his or her behavior, describing the feelings that behavior generates, avoiding enabling behavior, and offering help.

The traditional intervention for alcohol or drug addiction is a formal process, best accomplished by an addictions specialist trained in this process. This approach is often effective, resulting in positive results in about 80% of cases. Although effective, the traditional, formal model of intervention is often less than ideal for the family physician. Specialist involvement and orchestration of significant relationships of the patient are sometimes difficult to achieve. In addition, if the intervention fails, it may be difficult if not impossible for the physician to continue a relationship with the patient. Another approach to consider is that of the brief intervention. This highly effective approach to intervention is based on motivational interviewing and the stages of change model (also known as the transtheoretical model).

1. Stages of change—Underlying the strategy of the brief intervention is the stages of change model, developed by Prochaska and DiClemente. In this model, behavioral change is viewed as a process that evolves over time through a series of stages: precontemplation, contemplation, preparation, action, maintenance, and termination. The individual must progress through each of these stages to reach the next and cannot leap past one to get to another.

Individuals in the precontemplation stage are not planning to take any action in the foreseeable future. This is the stage most often described as denial. Patients in this stage do not perceive their behavior as problematic. In the contemplation stage, people perceive they have a problem and believe they should do something about it. Many addicted patients who do not appear to be ready for traditional treatment programs are in this stage. They recognize that they have a substance problem, believe they should stop using the addictive substances, but seem unable to do so. In the preparation stage, patients have made a decision to change and plan to do so soon, usually within the next month. These patients are ready to enter action-oriented treatment programs. Action refers to the stage of change during which patients make specific changes in their behavior. In the case of addiction, abstinence is the generally agreed upon behavior that signifies action. Maintenance is the period after action during which the changed behavior persists and patients work toward preventing relapse. Maintenance often requires a longer sustained effort than patients anticipate, and failure to continue with maintenance behavior is a common cause of relapse. Termination describes the stage in which there is no temptation, and there is no risk of returning to old habits. In the case of addiction, most patients must work toward a lifetime of maintenance rather than termination. The risk of relapse is such that few truly reach this final stage for the disease of addiction.

2. Brief interventions—Presenting the diagnosis of a substance use disorder by itself may be viewed as a brief intervention. Most physicians who have worked with these patients will not be surprised to hear that as many as 70% of patients are in the precontemplation or contemplation stage when presented with the diagnosis. The resistance associated with these stages tends to force clinicians into one of two modalities—either avoiding the diagnosis or confronting and arguing with the patient. Both of these approaches are futile. One approach in presenting the diagnosis is to use the DEATH glossary (Table 56-11), a list of pitfalls to avoid when presenting the diagnosis of addiction. On a more positive note, the SOAPE glossary (Table 56-12) describes suggestions to use when talking to patients about their addiction.

Table 56-10. American Society of Addiction Medicine placement criteria.

<table>
<thead>
<tr>
<th>Levels of service</th>
<th>Assessment dimensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 0.5: Early intervention</td>
<td>1. Acute intoxication and/or withdrawal potential</td>
</tr>
<tr>
<td>Level I: Outpatient services</td>
<td>2. Biomedical conditions and complications</td>
</tr>
<tr>
<td>Level II: Intensive outpatient/partial hospitalization services</td>
<td>3. Emotional/behavioral conditions and complications (eg, psychiatric conditions, psychological or emotional/behavioral complications of known or unknown origin, poor impulse control, changes in mental status, transient neuropsychiatric complications)</td>
</tr>
<tr>
<td>Level III: Resident/inpatient services</td>
<td>4. Treatment acceptance/resistance</td>
</tr>
<tr>
<td>Level IV: Medically managed intensive inpatient services</td>
<td>5. Relapse/continued use potential</td>
</tr>
<tr>
<td></td>
<td>6. Recovery/living environment</td>
</tr>
</tbody>
</table>

Table 56-11. DEATH glossary: pitfalls to avoid when presenting the diagnosis.

<table>
<thead>
<tr>
<th>Drinking or drug use details are not relevant; talking with a drunk is not useful. Patients will often give long and complex explanations for their drug or alcohol use and why they do not have a problem with it. It may be necessary to interrupt these explanations and move on. In addition, patients who are intoxicated cannot process the information given to them and it is appropriate to reschedule them and ask them not to drink prior to that visit.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology:</strong> Patients may try to elicit or provide an explanation for their addiction. It is unlikely that this will be useful. Just as when treating other chronic illnesses without clear etiologies, it is important to focus on the evidence for the diagnosis and the plan for treatment, and not be distracted by theoretical discussions of etiology.</td>
</tr>
<tr>
<td><strong>Arguments:</strong> Arguments can seriously damage the patient physician relationship and should be avoided at all costs. Respect, sympathy, and support are your best defenses against arguments.</td>
</tr>
<tr>
<td><strong>Threats:</strong> Threats are a serious cause of damage to the therapeutic relationship; threats, guilt, and shame do not promote recovery.</td>
</tr>
<tr>
<td><strong>Hedging:</strong> Although arguments are detrimental, there should be no hedging on the diagnosis. If the patient appears unable to accept the diagnosis, an agreement to disagree should be made as well as another appointment to continue the discussion.</td>
</tr>
</tbody>
</table>


Even for patients in the precontemplative stage at presentation of the diagnosis, continued use of the brief intervention strategy will ultimately reduce the amount of drug use if not result in abstinence.

Brief interventions should include some of the elements of motivational interviewing. These elements include offering empathetic, objective feedback of data; meeting patient expectations; working with ambivalence; assessing barriers and strengths; reinterpreting past experience in light of current medical consequences; negotiating a follow-up plan; and providing hope.

B. Detoxification

Detoxification and treatment of withdrawal, and any medical complications, must have first priority. Alcohol and other sedative-hypnotic drugs share the same neurobiological withdrawal process. Chronic use of this class of drugs results in downregulation of the GABA receptors throughout the central nervous system. GABA is an inhibitory neurotransmitter and is uniformly depressed during sedative-hypnotic use. Abrupt cessation of sedative-hypnotic drug use results in upregulation of GABA receptors and a relative paucity of GABA for inhibition. The result is stimulation of the autonomic nervous system and the appearance of the signs and symptoms listed in Table 56-6. Withdrawal seizures are a common manifestation of sedative-hypnotic withdrawal, occurring in 11%-33% of patients withdrawing from alcohol.

Table 56-12. SOAPE glossary for presenting the diagnosis.

| Support: Use phrases such as “we need to work together on this,” “I am concerned about you and will follow up closely with you,” and “As with all medical illnesses the more people you work with, the better you will feel.” These words reinforce the physician-patient relationship, strengthen the collaborative model of chronic illness management, and help convince the patient that the physician will not just present the diagnosis and leave. |
| **Optimism:** Most patients have controlled their alcohol or drug use at times and may have quit for periods of time. They may expect failure. By giving a strong optimistic message such as “You can get well,” “Treatment works,” and “You can expect to see improvements in many areas of your life,” the physician can motivate the patient. |
| **Absolution:** By describing addiction as a disease and telling patients that they are not responsible for having an illness, but that now only they can take responsibility for their recovery, the physician can lessen the burden of guilt and shame that is often a barrier to recovery. |
| **Plan:** Having a plan is important to the acceptance of the illness. Using readiness to change categories can help in designing a plan that uses the patient’s willingness to move ahead. Indicating that abstinence is desirable, but recognizing that all patients will not be able to commit to that goal immediately can help prevent a sense of failure early in the process. Ask “What do you think you will be able to do at this point?” |

Explanatory model: Understanding the patient’s beliefs about addiction may be important. Many patients believe this is a moral weakness and that they lack willpower. An explanation that willpower cannot resolve illnesses such as diabetes or alcoholism may go a long way to reassure the patient that recovery is possible.


Alcohol withdrawal seizures are best treated with benzodiazepines and by addressing the withdrawal process itself. Long-term treatment of alcohol withdrawal seizures is not recommended, and phenytoin should not be used to treat seizures associated with alcohol withdrawal. The cornerstones of treatment for alcohol withdrawal syndrome are the benzodiazepines. All drugs that provide cross-tolerance with alcohol are effective in reducing the symptoms and sequelae of alcohol withdrawal, but none has the safety profile and evidence of efficacy of the benzodiazepines. Table 56-13 summarizes recommendations in the treatment of alcohol withdrawal. Opiate withdrawal may not be life threatening, but the symptoms are significant enough that without supportive treatment, most patients will not remain in treatment. Table 56-14 outlines recommendations for the treatment of opiate withdrawal. The symptoms of cocaine and other stimulant withdrawal are somewhat less predictable and much harder to improve. Despite multiple studies with many different drug classes, no medications have been shown to reliably reduce the symptoms and craving associated with cocaine withdrawal.
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Table 56-13. Treatment regimens for alcohol withdrawal.

| Use the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) for monitoring: |
| Assess the patient using the CIWA-Ar scale every 4 h until the score is below 8 for 24 h |
| For CIWA-Ar >10 |
| Give chlordiazepoxide, 50–100 mg, or diazepam, 10–20 mg, or oxazepam, 30–60 mg, or lorazepam, 2–4 mg |
| Repeat the CIWA-Ar 1 h after the dose to assess the need for further medication |
| Non-symptom-driven regimens: |
| For patients likely to experience withdrawal use chlordiazepoxide, 50 mg, every 6 h for four doses followed by 50 mg every 8 h for three doses, followed by 50 mg every 12 h for two doses, and finally by 50 mg at bedtime for one dose |
| Other benzodiazepines may be substituted at equivalent doses |
| Patients on a predetermined dosing schedule should be monitored frequently both for breakthrough withdrawal symptoms as well as for excessive sedation |

C. Patient Education

Patients’ knowledge and understanding of the nature of substance use disorders are the key to their recovery. For patients still in control of their use, education about appropriate substance use will help them to choose responsibly if they continue to use. For patients who meet the criteria for substance dependence (addiction), abstinence is the only safe recommendation. Once having made the transition to addiction, patients can never use addictive substances reliably again. The neurobiological changes in the brain are permanent, and loss of control may occur at any time when the brain is presented with an addictive substance. The occurrence of loss of control can be unpredictable; consequently, addicted patients may find that they can use for a variable period of time with control, which gives them the false impression that they were never addicted in the first place or perhaps that they have been cured. Invariably if they continue to use addictive substances, they will lose control of their use and begin to experience consequences at or above the level they did before. Understanding that the problem of addiction is a chronic disorder for which there is remission but not cure becomes essential. The question then becomes not whether to remain abstinent but rather how to remain abstinent.

D. Identification of Defenses and Overcoming Denial

During this phase of treatment patients typically work in a group therapy setting and are encouraged to look at the defenses that have prevented them from seeking help sooner. Denial can best be defined as the inability to see the causal relationship between drug use and its consequences. For example, a patient who believes he drank because he lost his job may be encouraged to consider that he lost his job because he drank.

E. Relapse Prevention

Once patients are educated to the nature of their disease and have identified destructive defense mechanisms, relapse prevention becomes the primary goal. Identification of triggers for alcohol and drug use, plans to prevent opportunities to relapse, and new ways to deal with problems help patients to maintain their abstinence. In most treatment programs a relapse prevention plan is developed and individualized for each patient.

F. Twelve-Step Recovery Programs

It would be difficult to overstate the contribution 12-step programs make to recovery. Despite millions of dollars in research and the efforts of a large segment of the scientific community, no treatment, medication, or psychotherapy has taken the place of the 12 steps.

Twelve-step recovery has its roots in Alcoholics Anonymous (AA), founded in 1935. Today over 200 recovery organizations use the 12 steps with some modifications for patients with substance use disorders. These programs include Al-Anon, for friends and family of alcoholics; Narcotics Anonymous (NA), for those with drug problems other than alcohol; and Cocaine Anonymous, for those with cocaine addiction. At the heart of each of these fellowships is the program of recovery outlined in the 12 steps (Table 56-15). AA and related 12-step programs are spiritual,
The 12 Steps of Alcoholics Anonymous lists some of the self-described limitations of AA. Alcoholics Anonymous World Service.

1. Admitted we were powerless over alcohol—that our lives had become unmanageable;
2. Came to believe that a Power greater than ourselves could restore us to sanity;
3. Made a decision to turn our will and our lives over to the care of God as we understood Him;
4. Made a searching and fearless moral inventory of ourselves;
5. Admitted to ourselves, and to another human being the exact nature of our wrongs;
6. Were entirely ready to have God remove all these defects of character;
7. Humbly asked Him to remove our shortcomings;
8. Made a list of all persons we had harmed, and became willing to make amends to them all;
9. Made direct amends to such people wherever possible, except when to do so would injure them or others;
10. Continued to take personal inventory and when we were wrong promptly admitted it;
11. Sought through prayer and meditation to improve our conscious contact with God as we understand Him, praying only for knowledge of His will for us and the power to carry that out;
12. Having had a spiritual awakening as the result of these steps, we tried to carry this message to alcoholics, and to practice these principles in all our affairs.

Source: Alcoholics Anonymous World Service.

Not religious in nature. No one is told they must believe in anything, including God. Agnostics and atheists are welcome in AA, and are not asked to convert to any religious belief. Newcomers in AA are encouraged to go to meetings regularly (daily is wise initially), get a sponsor, and begin work on the 12 steps. A sponsor is usually someone of the same sex, who is in stable recovery and has successfully negotiated the steps. The sponsor helps guide the newcomer through the steps and provides a source of information and encouragement. At meetings members share their experiences, relaying information about strategies for recovery. AA meetings vary in their composition and structure; consequently, if a patient feels uncomfortable at one meeting, another may be more acceptable. There are meetings for women or men only; those for young people, physicians, lawyers, and for virtually any special interest group in most large cities. There is often a great deal of confusion about what AA does and does not do. AA is not treatment. Despite the close connection many treatment programs have with 12-step recovery fellowships, these fellowships are not affiliated with treatment centers by design. Table 56-16 lists some of the self-described limitations of AA and other 12-step groups.

From multiple sources, it appears clear that AA and other 12-step recovery programs are among the most effective tools to combat substance disorders. About 6%-10% of the population have been to an AA meeting during their lives. This number doubles for those with alcohol problems. Although 50% of those who come to AA leave, of those who stay for a year, 67% stay sober; of those who stay for 2 years, 85% stay sober; and of those who stay sober for 5 years, 90% remain sober indefinitely. Outcome studies of 8087 patients treated in 57 different inpatient and outpatient treatment programs showed that those attending AA at 1-year follow-up were 50% more likely to be abstinent than those not attending. Adolescents studied were found to be four times more likely to be abstinent if they attended AA/NA when compared with those who did not. Finally, in an effort to identify which groups in AA did better than others, studies of involvement in AA (defined as service work, having a sponsor, leading meetings, etc.) found that those who were involved maintained abstinence better than those who just attended meetings.

Having a list of AA members willing to escort potential new members to meetings is a powerful tool for physicians to help patients into recovery. Generally in every AA district, there is a person identified as the chair of the Cooperation with Professional Community Committee who can help physicians identify people willing to perform this service. Al-Anon and NA have similar contacts. These contacts can often supply physicians with relevant literature to help dispel some of the myths patients may hold regarding 12-step recovery. Patients often use these myths as excuses for why AA will not work for them, and understanding this as resistance and ambivalence about entering a life of recovery is important for the physician. Family physicians are in a unique position to encourage patients to invest in 12-step recovery. Recovering persons are keenly aware of this fact and physicians are encouraged and welcomed at open AA and other 12-step meetings to become more familiar with the way they work.

Table 56-16. Limitations of 12-step groups.

<table>
<thead>
<tr>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA does not solicit members; it will only reach out to people who ask for help.</td>
</tr>
<tr>
<td>AA does not keep records of membership (although some AA groups will provide phone lists for group members).</td>
</tr>
<tr>
<td>AA does not engage in research. There is no formal control or follow-up on members by AA.</td>
</tr>
<tr>
<td>AA does not make medical or psychiatric diagnoses. Each member needs to decide if he or she is an addict.</td>
</tr>
<tr>
<td>AA as a whole does not provide housing, food, clothing, jobs, or money to newcomers (although individual members may do this).</td>
</tr>
<tr>
<td>AA is self-supporting through its own members’ contributions; it does not accept money from outside sources.</td>
</tr>
</tbody>
</table>

G. Pharmacotherapeutic Treatment of Addiction

Agents useful in the treatment of withdrawal were discussed earlier (see Detoxification). The agents discussed here are used to help prevent relapse into alcohol or other drug use. These drugs attempt to influence drug use by one of several mechanisms:

1. Sensitizing the body’s response to result in a negative reaction to ingesting the drug, causing an aversion reaction such as with disulfiram and alcohol.
2. Reducing the reinforcing effects of a drug, such as the use of naltrexone in alcoholism.
3. Blocking the effects of a drug by binding to the receptor site, such as naltrexone for opiates.
4. Saturating the receptor sites by agonists, such as the use of methadone in opioid maintenance therapy.
5. Unique approaches, such as the creation of an immunization to cocaine.

Drug therapy for addiction holds promise. As our understanding of the neurobiology of addiction improves, so does the chance that we can intervene at a molecular level to prevent relapse. At the current level, however, pharmacotherapy to prevent relapse must be relegated to an adjunctive position. No drug alone has provided sufficient power to prevent relapse to addictive behavior. Still in some patients the use of appropriate medication may give them the edge necessary to move closer to recovery.

1. Pharmacotherapy for alcoholism—Disulfiram, naltrexone, possibly other opioid antagonists, selective serotonin reuptake inhibitors (SSRIs), and acamprosate are currently used in the prevention of relapse in alcoholism. Acamprosate appears to be the most promising of these medications. Although the goal of abstinence for patients addicted to alcohol cannot be met by medication alone at this time, in selected patients it may improve their chances for stable recovery.

A. Disulfiram—Disulfiram inhibits aldehyde dehydrogenase, the enzyme that catalyzes the oxidation of acetaldehyde to acetic acid. Thus, if a patient taking disulfiram ingests alcohol, the acetaldehyde levels rise. The result is referred to as the disulfiram-ethanol reaction. This manifests as flushing of the skin, palpitations, decreased blood pressure, nausea, vomiting, shortness of breath, blurred vision, and confusion. The reactions are usually related to the dose of both disulfiram and alcohol. This reaction can be severe and with doses of disulfiram over 500 mg and 2 oz of alcohol death has been reported. Common side effects of disulfiram include drowsiness, lethargy, peripheral neuropathy, hepatotoxicity, and hypertension.

In the United States, doses of 250-500 mg are most commonly used. Because of individual variability in the disulfiram-ethanol reaction, often these doses do not produce a sufficient reaction to deter the patient from drinking. In the United Kingdom, it is common to perform an ethanol challenge test to determine the appropriate dose to produce an aversion effect. Whether disulfiram is actually effective in preventing relapse is the subject of some debate. Most studies have failed to show a statistically significant result. On closer examination, it appears that compliance with the medication appears to be the most important factor. In a large Veterans Administration multicenter study, a direct relationship was found between compliance with drug therapy and abstinence. In addition, the involvement of a patient’s spouse in observing the patient’s consumption of disulfiram results in considerable improvement on outcome. It appears that disulfiram can be a useful adjunct for patients who have a history of sudden relapse and who have a social situation in which compliance may be adequately monitored.

B. Naltrexone—Naltrexone, an opioid antagonist, has been shown to reduce drinking in animal studies and in human alcoholics. Initial optimism over the potential of this discovery was tempered by several studies indicating that the effects of reducing drinking and preventing relapse diminished over time and overall failed to reduce relapse to heavy drinking. Still, the effect of naltrexone on alcohol craving is promising in that it suggests that the opioid system is involved in the craving for alcohol in alcoholism; this may open the door to the development of other opioid-active drugs that will have an impact on drinking.

C. Serotonergic drugs—Animal studies have consistently shown that SSRIs reduce alcohol intake in animal models. The data with respect to humans are less clear or consistent. It appears that the SSRIs reduce drinking in heavily drinking, nondepressed alcoholics, but probably only about 15%-20% from pretreatment levels. When abstinence is the outcome studied, the results are not promising. However, the SSRIs may eventually find a place in concert with other anticraving medication. SSRIs appear to reduce drinking in a more robust fashion in alcoholics with comorbid depression.

D. Acamprosate (calcium acetyltomaurinate)—Acamprosate has been shown to reduce craving for alcohol in alcoholics. It appears to affect both GABA and glutamine neurotransmission, both important in alcohol’s effect in the brain. Unlike naltrexone, the effects of acamprosate on relapse appear to be greater and longer lasting. Twice as many alcoholics remained abstinent in a 12-month period while taking acamprosate compared with those who took placebo. The addition of disulfiram to the regimen appears to increase the effectiveness of acamprosate. Acamprosate has a very benign side-effect profile and appears to be free of any effects on mood, concentration, attention, or psychomotor performance. Acamprosate has been studied extensively in Europe with good results, although a recent randomized controlled trial (RCT) in the United States found it not to be as effective as naltrexone.
2. Pharmacotherapy for cocaine addiction—The state of the art in the pharmacologic treatment of cocaine addiction makes it difficult to recommend any medication-based treatment with any confidence. Despite great interest and much activity devoted to finding an effective pharmacologic intervention for cocaine and other stimulant addiction, none has withstood the test of rigorous study. Heterocyclic antidepressants such as desipramine, SSRIs, monoamine oxidase inhibitors, dopamine agonists such as bromocriptine, neuroleptics, anticonvulsants, and calcium channel blockers have all been tried in cocaine addiction. Variable results, often positive in animal studies, have led to attempts to treat cocaine addicts with these drugs. As each potentially effective drug is studied more rigorously; however, little in the way of positive results is found. These drugs are used to try to ameliorate the craving for cocaine or to mediate the withdrawal symptoms of anhedonia and fatigue. An attempt to use stimulants such as methylphenidate or amphetamine for cocaine dependence in a way analogous to that of methadone maintenance for opiate addiction has produced disappointing results. One of the more interesting approaches to a pharmacologic answer to cocaine addiction has been the development of a “vaccine” for cocaine. In this approach, a cocaine-like hapten linked to a foreign protein produces antibodies that attach to cocaine molecules, preventing them from crossing the blood-brain barrier. This approach has had some success in animal models but has yet to be tested on humans.

3. Pharmacotherapy for opiate addiction—Agonist maintenance treatment with methadone is the primary pharmacologic treatment for opioid treatment. The rationale for the use of methadone and its longer-acting relative, levo-α-acetylmethadol (LAAM), is to saturate the opiate receptors, thus blocking euphoria and preventing the abstinence syndrome. Methadone and LAAM treatment programs are highly regulated by the federal government; therefore, the average family physician would not be prescribing this drug, although certainly he or she might see patients who are on a maintenance program. Methadone programs are frequently referred to as “harm reduction programs” because the primary beneficiary of these programs is society. Reductions in crime and in the costs of active intravenous heroin abuse are clearly demonstrated as a result of these programs. The addict also benefits with a dramatic decrease in the risk of death due to addiction or contraction of HIV disease. There is social stabilization in the addict’s life as well, especially when appropriate social services are provided by the maintenance program.

Antagonist maintenance with naltrexone was initially thought to be ideal given its essentially complete blockade of opioid-reinforcing properties. Unfortunately, only 10%-20% of patients remained in treatment when this approach is used. The most important use of naltrexone at this time appears to be in the management of health care professionals with opioid dependence. Compliance with a naltrexone regimen ensures abstinence and allows health care professionals to work in an environment where opioids may be accessible. Doses of 350 mg weekly divided into 3 days will provide complete protection from the effects of opioids.

Buprenorphine, a partial opioid agonist with K antagonist effects, is now being used as an alternative to methadone maintenance treatment. Dosing of this medication is problematic, with 65% of patients remaining abstinent at 16 mg/d compared with 28% abstinence at 4 mg/d. Suboxone, a combination of buprenorphine and naloxone, is another alternative that is effective for patients who do not require higher doses of methadone. Buprenorphine may decrease the use of cocaine in opioid-dependent patients. It also has less potential for diversion, making it an attractive alternative to methadone. The Drug Addiction Treatment Act of 2000 allows office-based maintenance treatment of opioid dependence by primary care physicians who have met necessary requirements. This criterion usually includes licensure under state law, registration by the Drug Enforcement Agency, reasonable access and ability to refer patients to ancillary services if needed, and at least 8 hours of training in the management and treatment of opioid addiction from an approved association. The FDA approved the use of suboxone for treatment of opioid addiction in 2002. Treatment with suboxone has three phases termed induction, stabilization, and maintenance. Therapy should start 12-24 hours after cessation of short-acting opioids or 24-48 hours after discontinuing use of long-acting opioids. Induction typically lasts 3-7 days. Day 1 consists of starting with a 4/1 mg dose of suboxone, followed by a second dose 2 hours later if withdrawal symptoms persist. Over the next 6 days, this dose is titrated up to a maximum of 32/8 mg/d. Stabilization then begins and usually lasts 1-2 months. The goal of this stage of therapy is to find the minimal effective dose to decrease cravings, eliminate withdrawal, and minimize side effects of suboxone. Most patients require a daily dose between 12/3 mg and 24/6 mg to achieve these goals. Maintenance therapy is indefinite and focuses on monitoring for illicit drug use, minimizing cravings, and avoiding triggers to use.


**Web Sites**

- National Institute on Alcohol Abuse and Alcoholism: niaaa.nih.gov
- National Institute on Drug Abuse (NIDA): nida.nih.gov
- American Society of Addiction Medicine (ASAM): asam.org
- Alcoholics Anonymous (AA): aa.org
A. Smoking Behavior and Disease Risk

Cigarette smoking, which is responsible for over 400,000 deaths annually, represents the single most avoidable cause of premature death in the United States today. While the prevalence of smoking in the United States has declined over the past half century, about 40 million adults are current smokers ensuring that this behavior will continue to influence rates of premature morbidity and mortality rates for years to come. Most people begin smoking during their teenage years and struggle to quit as adults; smoking prevalence among adults is about 20%. Clinician needs to view nicotine dependence as a chronic health condition with exacerbations and remissions.

The best evidence on the benefits of smoking cessation comes from a 2007 systematic review by the International Agency for Research on Cancer which found that some of the benefits of smoking cessation occur shortly after quitting while other smoking-related risks are not moderated for months or years. An individual’s disease risk depends on previous duration and intensity of smoking, the presence of preexisting illnesses, and individual susceptibility. On a population-wide basis, it is now clear that progress achieved in extending life expectancy has been due in part to successful tobacco control, especially efforts to persuade and assist smokers to quit. There are benefits to quitting even among those who have already experienced health problems caused by smoking.

B. Tobacco Dependence and Implications for Treatment

Most smokers report that they want to quit and approximately 40% attempt to stop smoking annually. Difficulty quitting is best predicted by how much one smokes on a daily basis and within 30 minutes of waking up each day, both of which are measures of nicotine dependence. However, most quit attempts are unplanned and usually only last a few days or weeks and are unsupported by the provision of pharmacotherapy and counseling support. Also, many smokers turn to methods with no proven efficacy (e.g., selective serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants [other than nortriptyline], anxiolytics, benzodiazepines, β-blockers, silver acetate, mecamylamine, appetite suppressants, caffeine, ephedrine, St. John’s wort, dextrose tablets, lobeline, moclobemide [a monoamine oxidase inhibitor], acupuncture, hypnotherapy, or use of low tar cigarettes) further lowering quit success and contributing to a cycle of failed quit efforts that make the prospect of stopping smoking appear hopeless to many smokers. The reality is smoking should be thought of as a chronic relapsing problem with exacerbations and remissions.

In the United States, approximately 70% of smokers seek health care in any given year. Thus, health care professionals are in a unique position to treat tobacco dependence with counseling, provision of evidence-based drug treatments, and follow-up care.

Smoking cessation treatment often begins with a brief intervention, in which a physician or any other health care provider advises smokers to quit and may recommend methods for quitting. For many smokers, the only contact with the health care system may be through their family physician, and office visits often provide the impetus for smokers to attempt to stop smoking.

Meta-analyses report that brief counseling interventions have significant potential to reduce smoking rates, with even minimal brief interventions conferring an estimated 30% increased likelihood of cessation. A recent Cochrane...
review of brief smoking cessation advice from a physician compared with no advice (or usual care) identified a significant increase in the odds of quitting. Although previous studies have examined the effect of brief interventions in controlled settings, little research has been conducted to examine their effects in nonexperimental settings over an extended period of time.

C. Use of Brief Interventions to Promote Smoking Cessation

A recent Cochrane review evaluating the effectiveness of brief smoking cessation advice from a physician found that advice from a physician compared with no advice (or usual care) significantly increased the odds of being smoke-free after 6 months and yielded an absolute difference of 2.5% in the rate of smoking cessation.

The Public Health Service (PHS) guidelines for treating tobacco use and dependence, last updated in 2008, continue to recommend that health care workers screen all patients for tobacco use and provide advice and follow-up behavioral treatments to all tobacco users. Current users are advised to quit; those who are willing to make a quit attempt are given appropriate assistance, along with arrangements for a follow-up visit. In addition, those who are identified as former smokers are given advice to prevent relapse, and persons who have never used tobacco are encouraged to remain tobacco free. The aim of these guidelines is to increase smoking cessation through improved understanding of the health consequences of smoking, better information about the availability and proper use of treatments, and the provision of encouragement and support.

Controlled studies have found that physician involvement, especially more extensive interventions, increases quit rates. This approach has also been found to be cost-effective since tobacco cessation interventions cost about $2500 per year of life saved, whereas mammography screening costs about $50,000 per year of life saved.

Based on a recent comprehensive review of the efficacy of different smoking cessation treatments, the PHS has recommended that all smokers receive counseling and support to quit preferably in combination with approved pharmacotherapy. Despite this treatment guideline, population-based surveys reveal that most tobacco users today are still not routinely receiving treatment assistance from their health care provider during visits. For example, a recent survey reported that tobacco counseling occurred in fewer than one-fourth of doctor visits by tobacco users, and cessation medications were prescribed on fewer than 3% of occasions. Studies have documented that utilization of evidence-based stop smoking treatments are lowest among those who are uninsured and have the greatest need for assistance in quitting tobacco (ie, those with mental health and other substance abuse problems). Encouraging smoking cessation is now recognized as an important part of medical care.

The guideline continues to emphasize use of the 5 A’s in clinical settings: Ask about tobacco use, Advise to stop smoking, Assess willingness to quit, Assist in quitting, and Arrange for follow-up. The American Academy of Family Physicians has attempted to simplify this to 2 A’s: Ask about tobacco use and Act to advise smoker to quit, assess interest in a quitting, assisting in organizing pharmacotherapy and arranging for follow-up. These systematic approaches to tobacco dependence require less than 3 minutes to deliver with the potential to result in behavior change. Other key points from the 2008 PHS clinical guideline include:

1. The chronicity of tobacco dependence, requiring repeated assessment and multiple interventions to achieve cessation.
2. The need for all health care delivery systems to systematically identify and document tobacco use status and to offer treatment to every tobacco user.
3. To provide both pharmacotherapy and counseling support to all patients making a quit attempt.
4. To offer every patient who uses tobacco at least a brief intervention.
5. Counseling support is effective in a variety of settings (eg, individual, group, or via telephone) and effectiveness increases with treatment intensity. Counseling should address both practical issues (problem solving/skills training) and social support.
6. The use of effective first-line medications (all forms of nicotine replacement therapy, bupropion, or varenicline) should be encouraged for all quit attempts and individualized as appropriate.
7. While counseling and pharmacotherapy are each effective when used by themselves, the combination is more effective than either alone for treating tobacco dependence.
8. Use of telephone quitlines should be promoted since counseling is effective with diverse populations and offers broad geographic reach.
9. Motivational messages can be delivered to tobacco users who are not currently interested in making a quit attempt.
10. Tobacco dependence treatments are efficacious and cost-effective; health plans and employers should ensure that all insurance plans include smoking cessation counseling and pharmacotherapy as covered benefits.

A standardized tobacco use assessment tool can help identify those individuals who are highly nicotine-dependent and/or lack the motivation and confidence to quit so that treatments options can be customized to each individual. Physician advice to stop smoking increases the likelihood that patients will try to quit and enhances the odds of those who do quit remaining off cigarettes. Long-term cessation rates approach 20% with counseling and increase to 30% when counseling is combined with pharmacotherapy.
D. Pharmacotherapy

Tobacco users have a physical dependence on nicotine, in addition to a variety of reinforced psychological and social behaviors. The Fagerstrom nicotine dependence scale is useful in quantifying the magnitude of addiction and to aid in selecting pharmacotherapy; however, consumption of the first daily cigarette within 30 minutes of awakening serves as an excellent proxy measure of nicotine dependence.

The use of pharmacotherapy doubles the effect of any tobacco cessation intervention. Patients who are willing and able to participate in counseling programs in addition to receiving pharmacotherapy should be encouraged to do so. Use of adjunctive pharmacotherapy should be strongly considered for all persons, including hospitalized patients, given the distinct health benefits associated with cessation. Counseling can be provided individually, as part of group visits or via telephone.

The US PHS guideline on management of tobacco dependence recommends varenicline, sustained-release bupropion, and all forms of nicotine replacement (eg, resin or gum, inhaler, nasal spray, lozenges, and patch) as first-line agents. A medical chart form to facilitate both patient discussion and documentation relating to use of first-line adjunctive pharmacotherapy for the treatment of tobacco dependence is given in Table 57-1. Patients should be queried about experiences with prior use of cessation medications and asked if they are interested in a particular agent. Clinicians are encouraged to apply appropriate clinical judgment when assessing contraindications to the use of a particular agent. This chart can be used to document the prescription, any discussion of possible side effects, and other instructions given to the patient.

1. Nicotine replacement therapy (NRT)—Patients should be counseled to stop smoking completely prior to initiating NRT to avoid the potential risk of nicotine overdose, although this rarely occurs in clinical practice. Nicotine patches, lozenges, and resin are available over the counter, whereas nicotine nasal sprays and the nicotine inhaler systems both require prescriptions. Reduced dose regimens of nicotine replacement might be considered for patients consuming fewer than 10 cigarettes daily or those weighing less than 100 lb (~45 kg). Using two forms of nicotine replacement (eg, patch plus resin) results in higher quit rates and should be recommended if other forms of nicotine replacement are not effective alone. Quit rates with use of NRT range between 20% and 24%; use of NRT is recommended for a minimum of 6-8 weeks; however, some patients elect to continue nicotine-containing therapy for the long term.

Nicotine medications appear to be safe for most people. Side effects of NRT mainly include local irritation (ie, mouth sores, skin rash, nasal and throat irritation) associated with the route of administration of the medication (ie, mouth, skin, nares). Side effects are typically mild and transient. Studies show that only about 1 in 12 person reports discontinuing use of NRT because of side effects.

Nicotine-containing products are not associated with the occurrence of acute cardiac events. This finding is consistent with the observation that NRT is rarely able to achieve blood levels of nicotine associated with smoking. Nonetheless, NRT should be approached cautiously among patients who are within 2 weeks of an acute myocardial infarction, are known to have significant arrhythmias, and have significant or worsening symptoms of angina.

2. Bupropion (Zyban)—Sustained-release bupropion is started at a dose of 150 mg daily for 3 days before increasing to 150 mg twice daily on day 4. Treatment with bupropion is begun 1-2 weeks before the anticipated quit date; its use is contraindicated among patients with a history of seizure disorders, current substance abuse, or other conditions that may lower the seizure threshold. The standard treatment course of bupropion (Zyban) in 8 weeks yields quit rates of about 30%.

Bupropion is contraindicated among patients with a history of seizure disorder, current substance abuse, or other conditions that may lower the seizure threshold.
3. **Varenicline (Chantix)**—This agent binds to $\alpha_4\beta_2$ nicotinic receptors in the central nervous system to moderate symptoms of nicotine withdrawal, leading to reduced craving, decreased smoking satisfaction, and diminished psychological reward. Varenicline (Chantix) is started 1 week prior to the identified quit date, titrating up from a dose of 0.5 mg daily for 3 days, to 0.5 mg twice daily for days 4-7, then to 1 mg twice day beginning on day 8. Rates of continuous abstinence are 44%. A full treatment course of 12 weeks is recommended and those who are abstinent at 12 weeks may continue with another 12 weeks of treatment. The most commonly encountered side effects are nausea, insomnia, and abnormal dreams; these are generally rated as mild and often resolve within several days or may be managed with a dose reduction as needed. Varenicline is minimally metabolized and is essentially excreted in the urine. There are no known drug interactions. Dose modification is necessary with severe renal disease.

The Food and Drug Administration (FDA) has initiated an investigation of cases of suicidal thoughts as well as aggressive and erratic behavior in some patients who have taken varenicline. There are also reports of drowsiness that affected patients’ ability to drive or operate machinery. Preliminary review by the FDA suggests that many of the cases may be newly identified mental illness in persons who experienced depressed mood, suicidal thoughts, and/or changes in emotion and behavior within days to weeks of starting on varenicline.

Varenicline’s role in these cases has not been established. Trying to stop smoking, with or without treatment, is associated with nicotine withdrawal symptoms, including irritability and drowsiness; symptoms of existing mental illness may worsen with cessation. Not all of the cases reported to the FDA were known to involve patients with prior mental illness, and not all patients concerned had stopped smoking.

Clinicians should remember to support patient quit attempts by placing a follow-up call within 1-2 weeks of the quit date. Instruct patients to contact your office if they experience unusual mood swings while using this medication. Remind patients that irritability, mood swings, and drowsiness occur due to nicotine withdrawal. These symptoms are most common right after a person stops smoking and typically lessen with time. In addition, patients should be counseled to use caution when driving or operating machinery until they know how quitting smoking with varenicline may affect them.

Based on information currently available, the potential benefits of varenicline greatly outweigh its risk. Clinicians are encouraged to screen for mental health issues prior to prescribing and to monitor patients for behavioral symptoms.

Clonidine and nortriptyline both represent second-line pharmacotherapy for use among patients in whom first-line agents have been judged to be inappropriate or ineffective. (Therefore, neither of these products is included in Table 57-1.) Although neither clonidine nor nortriptyline is approved by the FDA as adjunctive therapy for smoking cessation, several studies have demonstrated an approximate doubling in abstinence rates. Studies of clonidine have reported a variety of dosing levels. Common side effects with use of clonidine include dry mouth and sedation. It should be noted that the abrupt discontinuation of clonidine can result in rebound hypertension and other symptoms. Only a limited number of studies have examined the use of nortriptyline as a cessation aid and its use is tempered by concerns about potential side effects.

Only a limited number of studies have examined the use of nortriptyline as a cessation aid. Although results suggest that nortriptyline nearly doubles the odds of quitting and remaining abstinent at 1 year, its use is tempered by concerns about potential side effects. Use of either clonidine or nortriptyline for smoking cessation requires a clear discussion of risks and benefits with the patient and close monitoring by the treating physician.

Clinical experience with use of the pharmacotherapies for cessation in pregnant women and adolescents is generally limited. Smokers with concurrent or prior depression may benefit from use of bupropion. Clinical judgment is advised regarding a comprehensive assessment of the risks and benefits associated with use of adjunctive pharmacotherapy in each of these settings.

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**E. Payments for Cessation Services**

Since 2005, the Centers for Medicare and Medicaid Services has provided reimbursement for smoking cessation services by clinicians provided that the patient is a Medicare beneficiary and has a disease or adverse health effect that is either

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Gonzales D et al: Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 2006;296:47-55. [PMID: 16820546]


Jorenby DE et al: Efficacy of Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation. JAMA 2006;296:56-63. [PMID: 16820547]


Tonstad S et al: Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA 2006;296:64-71. [PMID: 16820548]
caused by or affected by tobacco use. Payment is based on two Healthcare Common Procedural Coding System (HCPCS) codes:

- G0375: Smoking and tobacco use cessation counseling visit; intermediate, longer than 3 minutes up to 10 minutes.
- G0376: Smoking and tobacco use cessation counseling visit; intensive, longer than 10 minutes.

Payment varies by region but averages approximately $13 for G0375 and $25 for G0376. Additional payment may be received based on the evaluation and management service (99201-99215, including modifier -25) provided on that same day and separately identifiable from the smoking cessation counseling. Counseling which lasts less than 3 minutes is included in the standard physician visit and is not separately reported. Medicare beneficiaries are eligible for up to four counseling sessions for each quit attempt and up to two quit attempts are covered over a 12-month interval. A useful resource which provides a listing HCPCS, CPT (current procedural terminology), and ICD-9 (international classification of diseases) codes related to tobacco cessation counseling can be found at: http://www.aafp.org/online/etc/medialib/aafp_org/documents/clinical/pub_health/askact/coding. Par.0001.File.tmp/Coding-list.pdf. Accessed August 16 2010.

Private health insurance plans are variable in their policies regarding reimbursement for smoking cessation counseling services. In addition to the two G-codes, alternative HCPCS codes include S9075 for smoking cessation treatment and S9453 for smoking cessation classes. The patient’s health record should document all services provided. Medicare part D has covered cessation FDA-approved drug therapies for eligible beneficiaries since 2006 as part of the prescription drug benefit although over-the-counter formulations of nicotine replacement therapies are generally not reimbursed. A 2006 survey found that 39 states covered some form of tobacco-dependence treatment (ie, counseling and/or FDA-approved pharmacotherapy) for Medicaid recipients.

F. Patients at the Precontemplation Stage of Quitting

For patients who are currently unwilling to make a quit attempt, clinicians should present a brief motivation intervention structured around “the 5 R’s”:

1. **Relevance**—make tobacco cessation personally relevant (personal medical history, family composition).
2. **Risk**—review the negative effects of quitting (include both immediate- and long-term risks).
3. **Rewards**—identify the benefits of quitting (improved sense of taste and smell, personal sense of accomplishment, money saved, health benefits).
4. **Roadblocks**—identify perceived barriers to quitting and ways of overcoming these impediments (symptoms of withdrawal, weight gain, lack of social supports).
5. **Repetition**—repeat this intervention at all office visits.

G. Relapse

Although risk of relapse is greatest immediately following the quit attempt, it can occur months or even years following cessation. Because tobacco use status will be determined for all patients at each visit, physicians should encourage all former tobacco users to remain abstinent and encourage these patients to express specific concerns or difficulties. These topics can be addressed briefly during the scheduled office visit or explored more fully during a subsequent appointment. Approaches can include reassurance, motivational counseling, extended pharmacotherapy, recommendations for exercise, or referral to supportive or behavioral therapy.

H. Emerging Pharmacotherapies for Cessation

As a potent modulator of the central nervous system, nicotine stimulates a variety of physiologic and behavioral effects through the release of a variety of neurotransmitters. To date, therapeutic approaches to smoking cessation have tended to focus on nicotinic acetylcholine receptors, which modulate the release of dopamine and other signaling substances, via use of nicotine replacement therapy or varenicline. In contrast, the mechanism of action for bupropion is poorly understood.

While at the present time no new FDA-approved therapies are anticipated to become available for the next 3-5 years, candidate products for cessation therapy are focusing on other central nervous neurotransmitter systems involving the actions of glutamate and GABA (γ-aminobutyric acid), as well as antagonists for selective glycine receptors, cannabinoid receptors, and NMDA (N-methyl D-aspartate) receptors. Another area of research involves development of nicotine-based vaccines to block the effects of nicotine in smokers.

**Summary**

Nicotine dependence should be considered a chronic health condition with exacerbations and remissions. Clinicians have an important role to play in helping their patients to stop smoking. The systematic identification of all smokers is the
initial step in addressing smoking cessation. First-line pharmacotherapy to support a quit attempt includes nicotine replacement (gum, patch, lozenge, nasal spray, or inhaler), bupropion, or varenicline. Use of these agents can increase quit rates by 1.5 to 3-fold.

All offices should implement a systematic approach for the identification and assessment of smoking status among all patients. This must include asking about tobacco use and acting to provide office-based or off-site counseling, as well as arranging linkages to quitlines, print and Internet-based educational materials, community-based cessation classes, and access to pharmacotherapy.

Most health plans provide some coverage for pharmacotherapy and tobacco cessation counseling or classes. Medicare programs cover pharmacotherapies and tobacco cessation counseling for smokers who have a tobacco-related health condition or whose therapy is affected by tobacco use. Although the Medicaid program covers smoking cessation drugs, federal law allows for state exclusions and coverage for both pharmacotherapy and counseling is variable.

Smoking cessation treatments delivered by clinicians, whether physicians or nonphysicians (eg, psychologist, nurse, dentist, or counselor), can increase abstinence. Therefore, all members of the health care system should be empowered to provide smoking cessation interventions. Finally, it is important to emphasize that the combination of pharmacotherapy and behavioral counseling for each smoker will help to maximize the likelihood of achieving long-term abstinence.


General Considerations

Interpersonal violence is endemic in the United States. There has been growing public awareness through the media, community advocacy groups, and education in the schools to address this family-based problem. Inextricably tied to social, economic, cultural, and behavioral factors, interpersonal violence requires a multidisciplinary approach by the physician that addresses prevention, detection, intervention, and resolution.

Family physicians must maintain a high index of suspicion for interpersonal violence in their patient populations. Subtle presentations in patient behavior are often difficult to detect, and cultural and social factors may limit the manner and nature of presentation to the physician. Although challenges and opportunities for prevention and intervention are available on a societal level, the family physician is in a unique position to make a meaningful impact before violence escalates.

Interpersonal violence encompasses a wide variety of circumstances. These include:

- Emotional/psychological abuse.
- Financial abuse.
- Neglect (of dependent person).
- Physical violence.
- Sexual violence.
- Stalking, bullying, or internet aggression.
- Homicide.

These manifestations can be further characterized by the status of the individual vulnerable to such acts. Those at greatest risk include children, the elderly, pregnant women, persons who are physically or mentally challenged, immigrants, and members of racial or cultural minorities.

Definitions

Emotional/psychological abuse includes humiliation, controlling behavior, repeated verbal assaults (name-calling), isolation (rejection, withholding attention and affection), threats, and public harassment, all of which can produce psychological trauma that reduces a person’s self-worth, value, and sense of efficacy. Emotional/psychological violence often coexists with chronic physical or sexual violence, but can also stand alone.

Financial abuse is when a person withholds resources such as money or transportation, or limits freedom of movement or association (eg, domination, isolation) of another person—a tactic often found in abusive relationships. Financial abuse most often involves the inappropriate transfer or use of an elder’s funds for the caregiver’s purposes.

Neglect is the chronic failure of a person who is responsible for the physical and emotional needs of another person to provide for those needs. This form of abuse most often occurs in family relationships and is directed at children, elders, or disabled family members. However, caregivers in other social/community settings, including child and adult day care, schools, group homes, nursing facilities, and hospitals, may be involved in neglect of a dependent person.

Physical violence, as defined by the Centers for Disease Control and Prevention (CDC), is the “intentional use of physical force with the potential for causing death, disability, injury, or harm.” This includes, but is not limited to, the following acts: scratching, pushing, shoving, throwing, grabbing, biting, choking, shaking, slapping, punching, burning, use of a weapon, and use of restraints or one’s body, size, or strength against another person. In the most extreme cases, physical violence may involve homicide.

Sexual violence, according to the CDC, is defined as “any sexual act that is perpetrated against someone’s will. Sexual violence may include a completed nonconsensual sex act (ie, rape), an attempted nonconsensual sex act, abusive sexual contact (ie, unwanted touching), and noncontact sexual abuse (eg, threatened sexual violence, exhibitionism, verbal sexual harassment). It includes the following four types:

- “A completed sex act is defined as contact between the penis and the vulva or the penis and the anus involving penetration, however slight; contact between the mouth
and genital opening of another person by a hand, finger, or other object.”

- “An attempted (but not completed) sex act.”
- “Abusive sexual contact” is defined as intentional touching, either directly or through the clothing, of the genitalia, anus, groin, breast, inner thigh, or buttocks of any person without his or her consent, or of a person who is unable to consent or refuse.
- “Noncontact sexual abuse” does not include physical contact of a sexual nature between the perpetrator and the victim. It includes acts such as voyeurism; intentional exposure of an individual to exhibitionism; unwanted exposure to porrnography; verbal or behavioral sexual harassment; threats of sexual violence to accomplish some other end; or taking nude photographs of a sexual nature of another person without his or her consent or knowledge, or of a person who is unable to consent or refuse.

Stalking, bullying, or internet aggression may take the form of harassment, threats, or physical violence that can lead to emotional or physical injury, and in some cases death. In its definition for stalking, CDC includes acts such as repeatedly following a person, appearing at a person’s home or place of business, making harassing phone calls or leaving objects or written, text, or internet messages, or vandalizing a person’s property. In addition to these acts, bullying can include spreading rumors, teasing, social isolation, and influencing others to “gang up” on someone in person or through aggression on the internet.

Web Site
Centers for Disease Control and Prevention fact sheet on interpersonal violence: http://www.cdc.gov/ViolencePrevention/intimatepartnerviolence/definitions.html

Epidemiology
Numerous studies have revealed disturbing evidence about the magnitude of interpersonal violence in the US society as well as opportunities for intervention. An estimated 25% of women and 7.9% of men are victimized at some point in their lives by a former spouse, cohabiting partner, or date. In one survey, 7.7% of women and 0.3% of men reported having been raped, and 22.1% of women and 7.4% of men had been physically assaulted. A typical respondent male victim averaged 4.4 physical assaults while women averaged 6.9 physical assaults. Thus, repeat victimization offers an opportunity for physicians to identify and intervene with persons at risk.

The annual incidence of all interpersonal violence has been estimated at 47 assaults per 1000 women and 32 assaults per 1000 men. Other estimates suggest that as a result of the 1.3 million women and 800,000 men who are physically abused in the United States each year, there are over 2 million injuries and 1300 deaths. Of particular concern is the finding that persons living in homes in which violent acts occur are more than four times as likely to be involved in additional violent acts than are those living in homes that are violence free.

Children, pregnant women, and the elderly are particularly vulnerable groups. Each year approximately 800,000 children in the United States are identified as victims of family violence or neglect. Half of homeless women and children report fleeing domestic violence. Pregnant women are at a greater risk of suffering physical abuse. It is a sobering fact that homicide is the leading cause of maternal death in the United States, and each year between 1,500 and 1,800 children die from abuse or neglect. Additionally, more than 500,000 elders are abused or neglected in domestic settings each year.

In mixed-sex domestic violence, the female partner is 30% more likely to be killed than the male partner, and most of these murders are committed with firearms. Although 28% of female homicide victims were killed by their current or former male partners, only 3% of men were murdered by current or former female partners.

African American, American Indian, and Alaska Native women and men report higher rates of domestic violence than the population as a whole, but socioeconomic factors confound the interpretation of such data. African Americans have a spousal homicide rate 8.4 times that of whites, whereas partners in interracial marriages have similar rates.

Other studies indicate a higher number of unreported incidents of physical and sexual abuse. More difficult to measure is emotional/psychological abuse or neglect, which is often insidious and difficult to detect.

Natural History of Interpersonal Violence in Adults
Interpersonal violence among known partners occurs in cycles. Although there are clear steps to the cycle of violence,
this should not imply that there is no escalation. In fact, with each cycle the victim is exposed to additional risk. Similar cycles have been found with elder abuse, child abuse, and sexual predatory behavior. The steps in known partner abuse are outlined in Figure 58-1.

**Detection & Intervention**

Refer to Chapter 42 for more detailed information about abuse in the elderly.

**A. Adults**

1. **Identification and screening**—To identify cases of interpersonal violence, it is essential that family physicians maintain a high index of suspicion at all times. Victims of abuse often feel ashamed, have low self-esteem, or are unable to share their circumstances readily. Creating an atmosphere that promotes a welcoming, frank, and professional discussion will allow patients the opportunity to bring their concerns forward to the physician.

   Screening tools have been advocated; however, the value of these tools for domestic violence has not been clearly demonstrated. Because of a lack of specific studies, the US Preventive Services Task Force has issued an “I” recommendation on methodologies of screening for family and intimate partner violence, indicating that there is insufficient evidence for or against the use of such tools. http://www.cdc.gov/violenceprevention/pub/IPV_cost.html

   The American Medical Association and American College of Obstetricians and Gynecologists recommend specific direct questioning of patients, when appropriate, in a non-threatening manner. The policy of the American Academy of

   ![Figure 58-1](image)

   **Figure 58-1.** Steps in the cycle of interpersonal violence. With each new cycle the level of violence usually escalates.
Family Physicians regarding family violence can be found at the association’s website (http://www.aafp.org/x16506.xml). Several simple screening questions may be of value in the patient interview and should be incorporated by the physician when taking a relevant history, at the time of the well visit, or when screening for other diseases. Much like screening for alcohol abuse or depression, low-threat questions can be incorporated to ascertain the possibility of abuse in the home situation (Table 58-1). Often, these questions can be incorporated into a history or review of symptoms questionnaire with little difficulty. Periodic rescreening of patients is advised.

The use of prompts in electronic medical records is an interesting area of development. Certain complexes, complaints, and findings could trigger a reminder for the physician to ask a question about violence in the home or workplace. Much research remains to be done to ascertain the value of such prompting.

Additional questions have been proposed by various advocacy groups. Screening questions suggested for attorneys can be adapted by the family physician and obtained from the American Bar Association website at http://www.abanet.org/domviol/screeningtoolcdv.pdf. Valuable tools for identifying violence exposure and related symptoms can also be found on the Veterans Administration website at http://www ptsd.va.gov/public/index.asp. Family physicians should endeavor to become familiar with a wide range of potential questions in order to utilize an appropriate approach from a wide repertoire.

### Table 58-1. Screening questions for interpersonal violence in adults.

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you feel safe in your current relationship?</td>
</tr>
<tr>
<td>2. Do you perceive any threats to your safety on a regular basis?</td>
</tr>
<tr>
<td>3. Have you been hit or hurt by someone in the past?</td>
</tr>
<tr>
<td>4. Would you care to share any concerns you might have regarding</td>
</tr>
<tr>
<td>interpersonal violence in your home or among your friends?</td>
</tr>
<tr>
<td>5. Have you ever been or are you currently concerned about harming</td>
</tr>
<tr>
<td>your partner or someone close to you?</td>
</tr>
<tr>
<td>6. Would you like information about interpersonal violence or</td>
</tr>
<tr>
<td>substance abuse programs in our community?</td>
</tr>
</tbody>
</table>

**Interventions** — The abusive spouse/partner or family member often accompanies the patient to the office visit to monitor the information being delivered and the manner in which it is portrayed by the victim. Although it is not abnormal for a spouse or significant other to attend a physician visit, the physician should be alert to cues, including nonverbal behaviors that might signal an abusive situation. In particular, physicians should carefully evaluate situations in which someone else does all the talking for a competent and able patient.

Perpetrators of abuse often have a history of interpersonal violence in their family of origin or were victims of nonfamily interpersonal violence at some point in their lives. It is often difficult to identify the inciting event, because frank communication with those who perpetrate violence is usually difficult. Insecurity, anger, a need to control, and moral issues are often complicated by defensiveness, shame, embarrassment, low self-esteem, and fear on the part of the abuser. Often, abusive individuals have no viable model of behavior in which to contextualize the intervention of a physician; to avoid being the victims of a confrontation, they may revert to controlling behavior in the office or become aggressive. Physicians must consider the safety of their staff when confronting such individuals.

Intensive therapy is often required for both the abuser and the victim and resources should be readily available in health practices. A period of physical separation is often required initially for the safety of the victim. Referral to an appropriate safe house in the community and obtaining a personal protective order from a judge are important first steps, and the patient should be encouraged to take these steps, if appropriate. The use of an advocate, volunteer or paid, is of great value in assisting the victim to follow through with these initial steps. Legal advice is often necessary, and family physicians should have a list of resources available for patients to seek legal advice early in the process.

During this period, therapy for the victim is aimed at improving objective decision making, reestablishing self-esteem, reversing the cycle of self-blaming, and addressing the reality of the situation. Reality-oriented interventions complement insight-based approaches. Objective testing of victim hypotheses of what happened often results in greater fear, so a supportive, encouraging therapist and environment are required. Eventually, group therapy can be utilized when the victim has reorganized his or her thoughts and is able to share experiences in a productive way with others.

The abuser also requires therapy. Depending on the circumstance, this may occur in the penal system or be mandated by the courts to take place in a child welfare agency. Therapy is aimed at reordering the emotional responses of the abuser and improving self-esteem. Developing a new worldview and set of behaviors is very difficult and takes a great deal of effort on the part of the therapist and the abuser.

Family therapy may have a place in the early stages of the cycle of violence. If both the abuser and the victim recognize the maladaptive pattern of behavior in their arguments prior to the onset of physical or severe emotional abuse, couple’s counseling may be successful in ending the cycle of violence. However, communications skills training alone may not be enough to create a change in behaviors. A few evidence-based treatments for children and offending and/or nonoffending caregivers also exist and are well supported by

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Consideration needs to be given to the patient’s spiritual, ethnic, and cultural background in order to place any intervention into a context that will maximize its success. “One size fits all” therapies may not have lasting benefit. It is critical that the family physician be supportive of the therapist and encourage the victim to continue in therapy. “Relapse” rates (ie, returning to the abusive relationship) are high; physicians should not become judgmental about such reconciliations but rather should remain supportive of victims.

B. Children

Specific and direct questioning about childhood injuries is advocated by emergency physicians and pediatricians. Direct questioning of parents/caregivers should be done in private to maximize value, maintain confidence, and reassure family members of the physician’s intent to help, not hurt, the child or the family. This may require or be best facilitated by a multidisciplinary team trained to assess and report child abuse, neglect, or other forms of child victimization.

There are specific cues that should heighten the physician’s index of suspicion regarding domestic violence and child abuse. “Red flags” should be raised when

- One partner insists on accompanying the other parent and child, and speaks for them.
- A parent is reluctant to talk with the other partner present.
- The child’s history does not fit the injury or illness.
- A parent makes frequent appointments for vague, poorly defined complaints.
- A child has recurrent, medically unexplainable somatic problems (eg, failure to thrive, abdominal or genital pain or injuries, headaches, enuresis (wetting), encopresis (fecal soiling), problems eating or sleeping).
- Medical attention for injuries is sought later than would be expected.
- The family uses emergency department services more often than is usual.
- A parent attempts to hide the child’s injuries with clothing.
- A parent or child has several injuries, at various stages of healing.


Family physicians should be alert to the symptoms and signs of potential child abuse or neglect listed in Table 58-2.

It is also important to recognize that children may have interpersonal violence experiences other than child abuse or neglect by family members that can manifest in similar ways in terms of health, mental health, and functional impairments. These include sexual exploitation; witnessing violence in their communities (eg, shootings, stabbings); bullying at or after school by peers, older children, or adults; and electronic aggression (eg, harassment or bullying that occurs through e-mail, chat rooms, instant messaging, web sites [including blogs], or text messaging).

### Table 58-2. Symptoms and signs of potential abuse and neglect in children.

<table>
<thead>
<tr>
<th>Physical Abuse</th>
<th>Neglect</th>
<th>Emotional Abuse</th>
<th>Sexual Abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burns</td>
<td>Malnutrition</td>
<td>Self-injury</td>
<td>Self-injury</td>
</tr>
<tr>
<td>School problems</td>
<td>Lack of supervision</td>
<td>Anger</td>
<td>Inappropriate sexuality for age/seductiveness</td>
</tr>
<tr>
<td>Self-destructive or suicidal behavior</td>
<td>Poor dental hygiene</td>
<td>Depression</td>
<td>Genital swelling, bruises, bleeding, sexually transmitted infections, yeast or urinary tract infections, pregnancy</td>
</tr>
<tr>
<td>Unexplained cuts, bruises, or welts</td>
<td>Inappropriate clothing</td>
<td>Apathy</td>
<td>Poor hygiene</td>
</tr>
<tr>
<td>Inappropriate fear of adults</td>
<td>Poor hygiene</td>
<td>Eating disorders</td>
<td>Eating disorders</td>
</tr>
<tr>
<td>Early-onset depression, alcohol or drug use</td>
<td>Extreme hunger</td>
<td>Anxiety</td>
<td>Sleep disorders</td>
</tr>
<tr>
<td>Bruises in the shape of objects</td>
<td>Anger</td>
<td>Excessive aggression</td>
<td></td>
</tr>
<tr>
<td>Injuries in uncommon locations</td>
<td></td>
<td>Fear of a particular person</td>
<td></td>
</tr>
<tr>
<td>Bite marks</td>
<td></td>
<td>Withdrawal</td>
<td>Suicidal behavior</td>
</tr>
</tbody>
</table>
C. Special Populations

Several groups within the US population are especially vulnerable to interpersonal violence. These groups include recent immigrants, ethnic and racial minorities, the homeless, people with disabilities, and gays and lesbians. (For additional discussion on gays and lesbians, see Chapter 62.)

Vulnerable populations, including those with physical or mental challenges, may find it difficult to contextualize their experience or communicate it in a manner the physician can understand. Patience and time are warranted. Followers of some religious and cultural traditions may tolerate levels of behavior that are not accepted by the mainstream culture in the United States. This is not to say that some cultural paradigms are inherently more violent than others; rather, the norms of acceptable or expected behaviors, including the sharing of intimate family details, create additional challenges to discovery of aberrant and abusive relationships for the physician. These challenges may apply to a wide variety of behaviors, including child-rearing, depression and other mental health problems, and sexuality concerns.

The key to identification of abuse in these situations is an understanding of cultural influences. To this end, enlisting the collaboration of an advocate who has proper training and connection with the culture is essential. This person may also play an important role in supporting the patient’s decision making when seeking appropriate interventions.

Open-ended questions about a patient’s cultural norms may provide an appropriate avenue and manner for inquiry into the presence or absence of interpersonal violence in the patient’s life. An inherent lack of trust in law enforcement may be a specific challenge in poor minority communities and among the homeless. Misunderstanding of interpersonal violence and the stigma associated with it may inhibit reporting or seeking of assistance. Additional information can be obtained from specific resources such as the University of Michigan Program for Multicultural Health, available at http://www.med.umich.edu/multicultural/ccp/cdv.htm. A resource for the African American community is available at http://www.dvinstitute.org, and for the American Indian or Alaska Native community is http://www.tribal-institute.org/lists/domestic.htm.

The possibility that partners in same-sex relationships may be victims of interpersonal violence is sometimes overlooked. A wide range of social factors may contribute to underreporting of abuse in this population, and frequency of physical and sexual abuse may be higher than most physicians would expect. Gay and lesbian patients should be questioned, as all patients are, in a safe environment and in a nonthreatening manner. In a recent study of a random sample of 284 gay or bisexual men, almost all respondents indicated that they had experienced psychological abuse, more than one-third reported physical abuse, and 10% reported having engaged in unwanted sexual activity because of partner force or threats of force. More than half of recipients of partner violence reported sustaining injury.

### Prevention

Given the pervasiveness of interpersonal violence, and the inherent difficulties of detection and intervention, methods of primary prevention are of critical importance in addressing this problem. The effectiveness of prevention programs remains an ongoing topic of study.

Family physicians should consider a routine discussion of interpersonal violence as part of the normal health maintenance routine. This can be part of the usual discussion of safety issues, including seat belt use, gun safety, and smoke protectors. In a matter-of-fact manner, the physician can introduce the discussion of interpersonal violence in a wide variety of contexts, including well-woman care, well-child visits, routine “physicals,” and other health maintenance visits.

A routine discussion of parenting techniques, referral to appropriate parenting classes, and provision of printed information have all been shown to have a positive effect on families at risk for child abuse or neglect. A plan for abuse identification, prevention, and training can be part of the individual education plan and the transition plan for children with developmental and physical disabilities.

Living situations of elderly patients should be well documented and understood, especially if the caregivers are not well known or are not part of the physician’s personal practice. Information obtained and communication established during times of calm may be useful later should an incident occur.

### Safety Instructions for Patients

The American Bar Association provides a domestic violence safety plan on its web site at http://www.abanet.org/tips/dvsafety.html. Adult patients can be referred to this resource for updated recommendations on how to protect themselves in situations in which interpersonal violence is an imminent threat. Family physicians should also be aware of local resources and update contacts with them annually to ensure a readily available system of referral for safe houses, therapeutic care or social services, and legal intervention. Although these options vary from community to community, local resources can usually provide assistance to physicians when dealing with complicated cases.

### Reporting

Healthcare providers should familiarize themselves with the laws of their state regarding the required reporting of violent crimes. In general, acts of violence that involve lethal force or firearms and rape must be reported to the local police...
agency. Adequate and complete documentation of all encounter details—including quotations, details, and time requirements—is an important medicolegal requirement. Family physicians working in emergency departments should follow the policies and procedures of their institution in the management and reporting of such violent crimes.

The reporting of an individual’s confidentially expressed intent to harm another person places the physician in a far more difficult ethical and legal position that may require legal advice. In emergencies, particularly when a patient is believed to be in danger, the patient should be told to call 911.

The reporting of child abuse to Child Protective Services is a requirement in all 50 states. Some states require reporting to the local police agency as well. It is important for physicians to know the laws in their state (see Child Information Gateway: http://www.childwelfare.gov/systemwide/laws_policies/state/). Reporting requirements and processes vary and many non-accidental injuries and their consequences are under-addressed in medical settings.


To aid a physician’s understanding and ease any anxiety associated with reporting, physicians should learn the process for reporting in their county or state and what happens after child victimization is reported to Child Protective Services.

Elder abuse is also covered by state laws, and physicians should report in accordance with the local law at the time of the suspected abuse. In general, Adult Protective Services (APS) should be notified of suspected neglect or abuse. Other agencies that may require notification, depending on the state, include the Area Agency on Aging and the County Department of Social Services.


Web Sites

American Bar Association Commission on Domestic Violence: http://www.abanet.org/domviol/
http://www.childwelfare.gov/
PHYSICIAN-PATIENT COMMUNICATION

The Therapeutic Alliance

It is within the context of communication that the therapeutic alliance between physician and patient is formed. When communication with a patient is nonjudgmental, respectful, and genuine, the stage is set for a successful therapeutic alliance. Medical knowledge is vitally necessary, but alone it is insufficient to accomplish the tasks of caring for a patient. It is the ability of the physician to translate medical knowledge for the patient and to enlist the trust of the patient that will ultimately lead to good health care for the patient.

Good communication has several beneficial effects on the relationship between the physician and the patient. It improves patient satisfaction, adherence, and health. It also improves physicians’ satisfaction with their work and the accuracy of information they obtain from patients and decreases the likelihood that physicians will be sued for malpractice.

Patient Satisfaction

The impact of good communication on patient satisfaction is the best studied of these benefits. Ware and colleagues extensively reviewed the evidence for the validity of using patient satisfaction and other patient rating scales, concluding that patients’ ratings of interpersonal aspects of care provide not only useful and valid information for quality assessment but also the best source of data on the interpersonal aspects of care.

Patients generally want more information than their physicians give them. The amount of information given to the patient strongly correlates with patient satisfaction. Physicians spend a small fraction of their time giving information, 1 minute out of 20, and believe that they spend more time than they actually do. Thus the correlation between the amount of information patients receive and their satisfaction with the visit is a strong and consistent observation in the medical literature.

Many other physician behaviors also correlate with satisfaction. These include courtesy, attention, listening, empathy, and sympathy. Patients whose physicians communicate and interpret emotions well and are friendly, concerned, take time to answer questions, and give explanations are more satisfied. Patients rate their physicians positively if they are encouraging, open, and attentive and negatively if they dominate the encounter.

Physicians’ personal qualities are rated highly if the encounter centers on the patient rather than on the physician’s concerns. Physicians who ask many directive questions and keep tight control over the interaction tend to have patients who feel that their physicians do not listen to them.

Physician Satisfaction

Physician satisfaction, although not as well studied as patient satisfaction, is very important for physicians’ personal and professional lives. Physicians find reward and meaning in their interpersonal relationships with patients. The quality of those relationships is directly related to physician satisfaction with their work. Good communication with patients will improve the quality of the relationship and thus improve physician satisfaction.

Accuracy of Information Obtained

In 1988, George Engel said, “The interview is the most powerful, encompassing, sensitive, and versatile instrument available to the physician.” In a 1984 study, Beckman and Frankel...
discovered that physicians frequently interrupted patients before they completely expressed their concerns, and rarely returned to patients’ initial concerns. They found that physicians controlled the interview with directive questions and they postulated that these interviewing tactics resulted in a loss of relevant information. They also found that these behaviors resulted in an incomplete clinical picture and disorganized care, thus leading to the collection of inaccurate information. Accurate information is lost when physicians use medical jargon. In one study, 50% of physician-patient interactions were adversely affected by the physicians’ use of medical jargon. Patients frequently believed they understood the jargon, but actually did not.

Other behaviors by the physician interfere with accurate data collection. Excessive control of the interview by the physician limits patients’ ability to communicate all of their concerns; hence the patient database is flawed. The way a question is asked has an important impact on the information received. Patients who are asked “What concerns you about this problem?” give better information than patients who are asked “What worries you about this problem?” The use of closed-ended questions (questions that have yes/no answers) limits the ability of patients to describe symptoms in their own words. In summary, physicians can improve the accuracy of their medical interviews if they use open-ended questions, allow patients to fully answer a question before interrupting, and avoid the use of medical jargon.


Health Outcomes

The relationship between improved health and good communication is more difficult to study than the correlation between patient satisfaction and good communication. Outcomes are influenced by many more variables and are temporally more distant. However, evidence indicates that good communication between physicians and patients correlates with good health outcomes. Patients with peptic ulcer disease who are involved in their own care through shared decision making with their physicians have less functional impairment due to their illness. When there is agreement between physicians and patients about the nature and severity of the patient’s health problem, improvement in or resolution of the problem occurs more often. Physicians who are less controlling, give more information, and show more emotion have patients with fewer functional limitations, lower blood pressure, and lower blood glucose levels. Patients who can express their emotions, both positive and negative, have improved health outcomes; in addition, when the ratio of patient to physician talk is high, patients are healthier.

Open-ended questions are superior to directive questions. Patients who are allowed to tell their story in their own words have lower blood pressures. In a study in which anesthesiologists were trained to give patients more detailed information about what to expect during their hospitalization, the patients required less pain medicine and left the hospital earlier.

Malpractice Suits

Physicians who communicate well are less likely to be named in a lawsuit. Patients of frequently sued physicians are more likely to say they were rushed, never received explanations, felt ignored, and felt their physicians did not communicate with them. There was no correlation between quality of care and adverse outcomes and malpractice claims in one study. These studies and others suggest that physicians are sued because patients are unhappy with their care and not because of poor quality of care.

Adherence

There is ample evidence that good communication leads to better adherence to a physician’s advice. Francis and colleagues found a strong association between patient satisfaction and adherence: poor adherence results when parents of young patients have unmet expectations from the visit, when there is a lack of warmth on the part of the physician, and when parents fail to receive an explanation for their child’s illness. A number of communication techniques are associated with improved adherence. Patients are more likely to be adherent if they have the opportunity to explain their understanding of their problem and ask questions. When patients are coached to ask more questions they are more likely to keep future appointments. Physicians who recognize nonverbal cues have patients who keep appointments more often.

Communication Skills

All the communication techniques described so far can be easily learned and used in the standard medical interview. Several excellent textbooks are available for thorough review of these (see Coulehan and Block, and Cole and Bird). The following techniques are especially important.

1. A statement such as “How did you hope I might help you at this visit?” will elicit important concerns that patients might not otherwise express.

2. Expressing empathy is an important basic skill. Empathy has three components in the physician-patient relationship. The first component is knowing how the patient views a problem, the second is understanding that point of view, and the third is acknowledging to the patient that the physician understands his or her point of view. To be genuinely empathetic the physician needs to accomplish all three of these.
COMMUNICATION

3. Patients should be allowed to completely express their concerns and should be asked if they have any specific requests.

4. Patients’ explanation of their problem should be elicited and a mutual understanding of that problem negotiated. A question such as “What do you think is the cause of your problem?” is often helpful.

5. Patients should be encouraged to express feelings about their illness by asking “How are you feeling about this illness?” It is important for physicians to be aware that they do not need to resolve patients’ negative feelings. Simply expressing negative emotions is a relief for patients.

6. Patients should be given specific information about their health condition.

7. Physicians should involve patients in their treatment plan. Patients who are collaborators in their care will feel in control of their illness; this will lead to an improved ability to cope with the illness. Patients who are passive will feel that the illness controls them and may give up working to improve their health. Physicians can accomplish this by asking questions about how patients feel the proposed treatment plan might work and by giving them choices about the plan.

8. Reassurance is a powerful communication tool. At its best it can allay anxiety and enable patients to cope with difficult health problems. When offered prematurely, however, it can seem insincere and worsen anxiety. It is important for the physician to truly understand the patient’s concerns and perform a thorough medical evaluation of the problem before offering reassurance.

SPECIAL COMMUNICATION CHALLENGES

There are a number of situations that physicians find especially challenging. Many of these topics are reviewed in detail in other chapters of this book. The focus here is mainly on the communication issues that these special situations pose for clinicians and their patients.

➡️ The Angry Patient

Although other emotional responses of patients toward their illness are difficult for physicians to deal with, none poses a greater challenge than the patient who is angry. Anxiety and sadness can be difficult responses to address, but physicians usually find it easier to be sympathetic or empathetic. The natural reaction to anger is defensiveness, not empathy. It requires considerable communication skills to develop empathy with a patient who is angry.

The clinician must first recognize anger, then acknowledge it, understand it, and respond to it. Recognizing it is easy if patients state that they are angry, but often they do not. Recognizing anger in a patient often requires that the physician recognize defensiveness in him- or herself. If a physician is feeling defensive, it is likely that the patient is angry. There may be other cues such as patient voice tone or agitation. If a physician senses that the patient is angry, and the patient has not volunteered this, it is important for the physician to explore the anger. An observation such as “You seem upset” may be helpful in encouraging the patient to share his or her feelings. It is important that the physician’s language match what he or she sees in the patient. If the patient seems furious and the physician says “You seem a little upset,” the patient is likely to become angrier. Conversely, if the physician says “You seem furious” and the patient is a little piqued, the patient will deny it.

Once the patient has shared that he or she is angry, the physician is in a position to explore why. Patients may be angry for a myriad of reasons, most of which have little to do with the physician. Until a physician understands why the patient is angry, he or she will be unable to address the anger in a constructive way. Often patients state the reason for their anger in response to the initial reflection “you seem upset.” If they do not, the physician will need to acknowledge the anger and ask specifically about it. “I see that you are upset; are you willing to share with me what it is about?” The answer to this question will determine how the physician proceeds. The patient’s anger may be directed at the physician justifiably and may require an apology. It is more likely to be directed at someone or something else over which the physician has no control. The task is then to empathize with the patient. Once the patient feels understood, the physician will be able to move the conversation to other areas.

It is important to understand that anger is often displaced, especially when a patient is ill. The sadness and loss of control patients feel about their illness are directed in the form of anger at those caring for them. The anger is really directed at the illness, not the physician. If the patient seems angry with the physician or another member of the health care team and the physician genuinely feels that the team has provided good care, the patient may be manifesting displaced anger. This anger also needs to be explored and understood but may not be resolved as easily as other forms of anger. Awareness that the anger is displaced may, however, prevent an automatic defensive response on the part of the physician, which typically encourages the patient to feel justified in his or her anger. In such situations, it is important after exploring the anger to redirect the conversation to the difficulties and frustrations of the patient’s illness.

➡️ Adherence

Adherence is a complex problem for physicians and their patients. Negotiation is one of the key concepts when addressing problems with adherence. The physician and the patient need to agree about the nature of the problem at hand and agree about the evaluation and treatment of it.
Without this agreement, there is no reason for the patient to follow the advice of the physician. Patients come to their physicians with certain beliefs about their illness and expectations about its evaluation and treatment. They will follow their physician’s advice if the advice is consistent with these beliefs. Various communication strategies set the stage for successful negotiation.

Eliciting accurate information about patient adherence is the first step in dealing with nonadherence. If a physician does not know that the patient is not following medical advice, he or she cannot intervene to help. Several methods are suggested in the medical literature to elicit information about adherence. The physician can count medication, measure drug levels, look at outcomes, or ask the patient. The most effective method is to ask. With a well-framed question, patients will give accurate information about their adherence 80% of the time. Asking a patient “Are you taking your medication?” is unlikely to yield accurate information. The answer to this type of question is an automatic yes. Physicians who ask specific questions about medication names, dosages, and times elicit more accurate information about adherence. Giving patients permission to be nonadherent with a question such as “Some of my patients have difficulty remembering to take their blood pressure medicine every day; I wonder if you have found this also?” is often fruitful. Patients are relieved to hear that their problem is common and assume from the tone of the question that the physician is likely to be forgiving.

Once it has been established that the patient is not following medical advice, the next task is to determine the reason(s). Because these usually have to do with patients’ beliefs, goals, and expectations, questions to elucidate these will be important. Patients’ beliefs are varied and it is impossible to predict them without asking. A patient might have had a father who took the same medicine the physician is prescribing and who died of complications of the disease anyway. A patient might believe that she can tell when her blood pressure is high and therefore takes her medicine only on these days. A patient might believe that he has no control over his illness and therefore the treatment will not work. Useful questions to elicit patients’ beliefs, goals, and expectations include the following: “Do you know anyone with your condition?” and if so, “How was he or she treated?” “What happened to him or her?” “Have you read anything about your condition?” “What have you read?” “What do you think caused what you have?” “How do you think you should be treated?” “What kinds of tests do you think you should have?” “What might prevent you from following my advice?”

These types of questions will quickly demonstrate where the physician and patient disagree. The next step is to come to some common agreement with the patient about how to proceed. The nature of the disagreement will determine how the problem is resolved. It is important to realize that it needs to be resolved in such a way that the physician feels he or she is providing good medical care and the patient feels he or she is receiving good medical care. To accomplish this, the physician and patient will need to influence each other. There are some common useful strategies for negotiation. The physician can correct misperceptions, refer the patient to a trusted source (friend, family member, article, organization, etc), explore options with the patient, suggest alternatives that are consistent with the patient’s beliefs or goals, or compromise.

A word about the use of fear as a motivating tactic is important. It is commonly used by physicians and is usually unsuccessful for a variety of reasons. It greatly increases anxiety, which often encourages the behavior physicians are trying to stop. For example, the typical response to “If you don’t stop smoking you are going to get lung cancer!” is to smoke more in response to the increased anxiety. Fear can make an illness seem more overwhelming and a common response to reduce anxiety is to deny the problem exists; thus adherence is worsened, not improved. Fear tactics are not only ineffective, but are often counterproductive.

Patients are much more likely to adhere with treatment recommendations if physicians point out the positive results of following the advice rather than the negative results of not following it. “If you stop smoking you will reduce your chances of lung cancer” is a more powerful motivator than “If you don’t stop smoking you might get lung cancer.” Physicians should focus on patients’ successes, even if they are small, rather than on their failures; encourage patients’ strengths, attitudes, and actions; and offer hope. When patients are hopeful about their condition they are more likely to be able to make changes in their lives to accomplish the task at hand. When physicians are hopeful they are more effective clinicians.

Patients’ behavior is strongly influenced by their social context; thus it is important to explore this. What is their cultural background and do they share the same cultural beliefs about their condition as this group? They might subscribe to a belief that holds that illness is a punishment for bad behavior. They might come from a culture in which herbal remedies are used for their condition. Friends and family are also important: A patient might believe that a weight-loss diet will help his heart condition, but he has a wife who does the cooking and who believes that the main way to express her love is to feed her loved ones. Another patient may be unable to quit smoking because all of her friends smoke.

In summary, effective communication is the main tool a physician has to assess adherence to advice and to intervene for the good of the patient if the patient is not following that advice. The key principles of good communication concerning adherence include a nonjudgmental exploration of the problem, information giving, encouraging the patient to share beliefs and asking questions, asking about the social context of the problem, and focusing on the positive results of the advice being given to patients.

Communicating with Patients Who Have a Terminal Illness

Much of caring for patients at the end of life involves communicating with them and their families. Communication revolves around two main areas: giving bad or sad news and
discussing goals and wishes for medical care. Certainly all the general rules for communication are important in these circumstances. There are unique and predictable difficulties for patients and physicians when discussing end-of-life care. The discussion here focuses on “the bad-news consultation.”

The first communication problem a clinician typically encounters is how much to tell the patient about his or her illness. Physicians often assume that patients desire full information about their illness and this is usually a correct assumption. However, some patients do not want to know a bad prognosis; thus the physician needs to be skilled at assessing the patient’s desire for information. A question such as “If it is bad news, do you want to know?” might be helpful to begin this discussion. If the patient does not want to be given bad news, there are two further areas for discussion. The first is to determine if there is someone else that the patient wants to receive the news and the second is to explore the reasons that the patient does not want to know.

Once the physician has determined the patient does want to hear the bad news, it is important to set up the interview carefully. When patients are satisfied with this initial interview they are less likely to be depressed later in their illness. Does the patient want anyone else to be present? Is the setting private and free of interruptions? Does the physician have enough time? The physician’s attitude should be to convey understanding and reassurance. The main goal of the session is to give the news. Any further discussion of treatment goals and choices may overwhelm the patient and should be deferred to a future visit.

The next task is to give the news. A “warning” such as “I’m afraid I have some bad news” will help the patient prepare for the information. The news should then be delivered in a simple, direct, and straightforward manner. The physician should pause to give the patient time to react and assess the patient’s reaction before proceeding. Often the reaction is obvious: the patient may cry or become angry. The patient may, however, be silent, and the physician may need to ask “How are you feeling about this news?” At this point the patient’s reaction will direct the rest of the interview. Regardless of where the discussion goes from this point, the clinician should continuously monitor and respond to the patient’s emotions, understanding, and desire for information.

Attention to the end of this interview is important for future care. The physician should inquire about the patient’s understanding of his or her illness: “Can you tell me what you understand about your illness?” The physician should communicate continued support (“I’m going to do everything I can to help you through this”) and should offer hope, but he or she should be realistic (“Let’s hope for the best and prepare for the worst”). Finally, the patient will need a follow-up visit within a short period of time to discuss options and goals of treatment.

**Patient Education & Counseling**

Effective patient education serves a number of important purposes in the clinical encounter. It satisfies the patient’s desire to know about his or her condition, it improves patient satisfaction and adherence, and it relieves the patient’s anxiety. It also improves health outcomes and reduces health risks. Physicians must be acutely aware that patients misunderstand and forget much of what they hear from their physician.

The ultimate goal in patient education is to change behavior in order to improve the health of the patient. To accomplish this goal patients need to understand their illness, recognize behaviors that put them at risk, make decisions about treatment options, and adhere to their physician’s advice.

Studies show that patients commonly believe their physician does not give them enough information. Other studies show that patients commonly misunderstand or do not remember the information their physician gives them and that high levels of interpersonal skill on the part of the physician correlate with the amount of information a physician gives to a patient and the amount the patient recalls. Some situations are predictably associated with poor recall. These include discussion of many medical problems at one visit, patient anxiety, prescription of more than one medication, and relaying of new or bad news. Techniques that can be used to improve a patient’s recall of information include simplification, repetition, giving specific information, checking the patient’s understanding, discussing fewer problems, and limiting new medications. Physicians should also negotiate an agreement with the patient about the nature of and solution to the problem and explore patients’ ideas about the problem. More nonverbal immediacy such as closer interpersonal distance, more eye contact, and leaning toward the patient is beneficial. It is also important to assess what a patient wants to know.

These interventions target information giving and recall and are critical. Behavior change, however, is more complicated than simply giving information that the patient can understand and remember. Physicians need to assess patients’ understanding of the problem and assess and understand their motivation to change. Questions targeted toward the patient’s understanding of the disease such as “What do you know about your condition?” and questions directed at motivation to change such as “What are you willing to do about your condition?” are also useful.

Physicians need to present options and help patients make choices. Patients are more likely to make behavior changes successfully if they have several choices. Too many options, however, may be overwhelming. Statements such as “Your options are...” and questions such as “Which option will you choose?” or “How will you go about it?” are helpful. Some additional important areas of communication include continued offers of support from the physician, encouragement of small successes by the physician, and continued reassessment of the problem.
Family practitioners have recognized the importance of cultural competence in health care for many years. “The American Academy of Family Physicians is committed to ensuring high quality of care and patient safety by promoting access for limited English proficient (LEP) patients, cultural proficiency, expanded health workforce diversity, and reduced health disparities in the provision of medical care to our nation's LEP and racial/ethnic medically-underserved populations. Cultural proficiency is a necessary component for patient safety and adherence. All persons, regardless of race, ethnicity, or primary language deserve access to high quality health services.” (AAFP Position Paper 2008)

The AAFP is not alone, however. Knowledge and skills of cultural competence are recognized as an essential element of quality medical care for America’s diverse population by medical professions (AAFP and American Medical Association), accrediting bodies (Centers for Medicare and Medicaid Services and Joint Commission), organizations that set requirements for medical education (Association of American Medical Colleges and Liaison Committee on Medical Education), and at least five state medical licensure boards.

The US Government embraces and requires culturally competent medical care. In December 2000, the Department of Health and Human Services endorsed the National Standards for Culturally and Linguistically Appropriate Services (CLAS) as a way to achieve the national Healthy People 2010 goal to eliminate health disparities. Indeed, Title VI of the 1964 Civil Rights Act guarantees equal access to federally funded services, regardless of people’s gender, age, race, ethnicity, religion, or national origin, including people of limited English proficiency.

Multiple reports illustrate how quality care for a diverse American population requires a primary care system that is culturally competent and patient-centered. The Institute of Medicine’s (IOM) 2001 report “Crossing the Quality Chasm” documented the failures of the American medical system and asserted that the system must become equitable and patient-centered, as well as safe, timely, efficient, and effective. The following year, the IOM released Unequal Treatment, a powerful critique of how health care providers’ prejudices, biases, and stereotyping contribute to unequal treatment of racial and ethnic minorities.

Given these requirements and mandates for culturally competent quality care, this chapter addresses three topics. Why is cultural competence important? What about culture is important in medicine? And how can physicians provide culturally competent care in clinical settings?


**WHY IS CULTURAL COMPETENCE IMPORTANT?**

**Culture Influences People’s Views of Health, Illness, and Treatment**

Health, illness, and treatment are strongly influenced by cultural contexts. It may seem strange to practitioners of scientifically based biomedicine that the cultures of providers and patients are major factors in clinical encounters. It is the case, however, that all humans have been socialized from childhood to define and experience the world in ways that are shared with other members of their group. Culture provides
concepts, rules, behaviors, and meanings that are basic to and are expressed in the ways people relate to other people, to the supernatural, and to the environment. A person's culture is like a pair of glasses with just the “right prescription” that is created by socialization and life experiences. Through these cultural lenses, people interpret and categorize the events of the world, rendering the world understandable, orderly, and predictable. Culture is learned, and no single individual is a repository for his or her entire culture. Not all members of a cultural group believe, think, or act in the same manner. This point is very important for health care providers, who must avoid presuppositions about patients based on their participation in particular cultures.

### The Diverse American Population

The changing demographics of the United States provide compelling reasons for health care providers to consider the impact of cultural factors on health, disease, and health care. The population is diverse. While the 2010 census results are not yet available, the data from the 2000 census is informative. By 2000, non-Hispanic whites comprised 69.1% of the population, non-Hispanic blacks 12.1%, Hispanics 12.5%, Asians 3.6%, and American Indians 0.7%. The population as a whole will grow more slowly than it has in the past but subgroups within it will have different trajectories, such that the aggregated current ethnic minority populations will eventually outnumber the historic majority of European Americans by 2060. Differential birth and immigration rates influence the changing composition of American society. In the 2000 census, foreign-born individuals comprised 13.3% of the total population, up from 8% in 1990, and in some American cities, more than half of the residents were foreign born. (The 2010 census will soon analyze changes in the last ten years.) While the projected rate of growth in immigrants, refugees, and undocumented foreign-born residents is a highly politicized issue, for providers, it means one thing for sure—cultural differences are in the foreground of the health care arena.

Family physicians must be aware that terms such as race and ethnicity do not have universally accepted definitions. Within medicine, the term “race” usually refers to biological differences between populations that have ancient origins in geographically distinct areas in the world, while the term “ethnicity” is most commonly used to refer to cultural differences, such as beliefs about health, illness, and treatment. Within anthropology, however, race and ethnicity are understood as social categories that humans create for a variety of purposes, such as to describe, understand, influence, or control human behavior.

True, family histories and genetics have biological meaning and thus sometimes racial/ethnic categories are used as surrogate markers for genetics. However, they are rudimentary markers based on population genetics, and are not reliable for individual variations. As mapping of the human genome illustrates, there are more differences within racial/ethnic categories than differences between them. Until the era of “individual genomic medicine” arrives, physicians will have to guard against using stereotypes and assumptions that can occur when ethnic/racial categories are used as biological markers.

In addition, people in racial/ethnic categories do not necessarily share the same cultural values, beliefs, and behaviors. The variations of culture within racial and ethnic categories are staggering, so the categories must not be reified or objectified. For example, not all African Americans are Christians; not all Christians refused to use contraception; not all Middle Easterners are Muslims; not all Muslim women wear headscarves. While these examples may seem obvious, it is too easy for human beings to generalize (and physicians in particular, given biomedicine’s strong training of generalizing from pattern recognition) and to stereotype from generalities.

### Racial and Ethnic Health Disparities

People from ethnic/racial minority groups have worse health status and health care statistics than people from majority populations. Since 2003, the Agency for Healthcare Research and Quality has published annual National Healthcare Disparities Reports that clearly describe the disparities of quality health care between majority and minority populations in the United States. For instance, African Americans, Native Americans, and Hispanics have worse healthcare outcomes for diabetes, cancer, and cardiovascular disease; have more delay in receiving antibiotics for pneumonia and thrombolytic therapy for heart attacks; have higher rates of postoperative pulmonary embolism and septicemia; have more hospitalizations for uncontrolled diabetes; and report receiving less health care information from health care providers.

These ethnic/racial disparities in health are due to a complex interaction of many factors, from those that increase exposure to disease to those that decrease access to health care. One socioeconomic factor is that people without health insurance and economic resources have worse health care than people with insurance and economic resources. Another factor is that people with limited English proficiency and poor literacy skills have poor quality health care services. However, even after controlling for socio-economic class, ethnic minority groups still have worse health status than majority peoples. Institutional discrimination and individual discriminatory practices in health care settings have been cited as contributing causes, which must be addressed.

Eliminating discriminatory practices based on assumptions of racial/ethnicity categories and based on assumptions of cultural beliefs and values—many of which are unconscious—is an aim of culturally competent care.

### Patient-Centered Care Includes Culturally Competent Care

An anthropological perspective makes the distinction between disease and illness, with physicians focusing on the biological processes of disease and patients focusing on the experience of the illness. A movement toward patient-centered medical care
with emphases on improved communication, patient satisfaction, relevant health information appropriate for patients’ health literacy levels, and primary care medical homes (and hence, improved healthcare outcomes) has been built upon Engel’s bio-psycho-social model to keep patients’ human dimension in the center of medical interactions. Addressing patients’ cultural beliefs, values, and expectations, and incorporating their family and community in the therapeutic process improve health care outcomes.

The patient-centered care approach requires that physicians elicit and respectfully respond to patients’ beliefs, concerns, and experiences with their illnesses—all culturally influenced dimensions. Patient-centered care is culturally competent care.


WHAT ABOUT CULTURE IS IMPORTANT?

MT was a 72-year-old Hmong woman with a severe headache, blurred vision, and gait instability. A CT scan revealed intracerebellar hemorrhage, and evidence for early pontine herniation. Neurologists and neurosurgeons recommended a craniotomy to evacuate the clot, reduce the pressure, and save her life. The family refused an operation, and left the hospital against medical advice to perform traditional Hmong treatments.

In this situation, and similar situations when patients and physicians have different perspectives about appropriate responses to illness, exploring the cultural issues can be enlightening. This chapter describes seven concepts about the influence of culture on patients and physicians that are pertinent to providing medical care in cross-cultural settings. After the description of each concept, the information is applied to MT’s case.

A word of caution. Readers need to consider the following descriptions of general cultural beliefs and practices as information that illustrates the significance of culture in diagnosing and treating disease and illness. The information should not be interpreted as stereotypical statements about all people from any specific cultural group. Cultural beliefs and practices can vary considerably among members of any one group.

Concepts of Bodily Functions

All cultures have an internally consistent system of beliefs about how the body functions normally, how and why it can be influenced by factors that cause it to function abnormally, and how it can be restored to health. Human beings have created many systems of thought about bodily functions and malfunctions: the Chinese system of balance between yin and yang; the Aryuvedic concept of balance in nature; Western systems of biomedicine, homeopathy, and naturopathy; as well as systems indigenous to many ethnic groups. Each culture group’s beliefs about the functioning of the natural, social, and supernatural worlds are germane to its ideas about health, illness, and healing. The natural realm includes ideas about the connections between people and the earth’s elements of soil, water, air, plants, animals, etc. The social realm connotes ideas about individuals and the appropriate interaction between people of different ages, genders, lineages, and ethnic groups. And the supernatural realm includes the religious beliefs about birth, death, afterlife, reincarnation, souls, spirits, and interaction between the spiritual world and the human world.

Application to the case. Hmong people originated in China and migrated into Southeast Asia where they were involved in America’s secret war in Laos in the 1960s and 1970s. Refugees from the war, they fled into Thailand and were resettleed in Western countries. The kinship system is patrilineal, the residence pattern is patrilocal, and the system of political power is patriarchal. Hmong religion is animistic, including beliefs in reincarnation, multiple souls, and ongoing relationships between the living and the spirits of ancestors. Hmong concepts of health and disease are influenced by animism and are similar to the Chinese humoral theory of balance between yin and yang.

Classification of Diseases

Each cultural group has its own classification system of diseases. While each cultural group may recognize diarrhea or fevers, for example, the categories for classifying them vary from group to group and do not necessarily correspond with one another. This presents problems for translation of words and of ideas between systems of disease. For example, whereas physicians may be concerned about dehydration in all types of diarrhea, Pakistani mothers may be more likely to use oral rehydration solution for some types of diarrhea and less likely to use it for other types.

Entities that are recognized by certain ethnic groups and not others have been studied as folk illnesses or culture-bound syndromes. These entities are ailments with coherent concepts of etiologies, pathophysiology, and treatments, but they may also be expressions of mental and/or social distress that have social and symbolic meanings. Examples include Latino empacho, nervios, mollera caida, mal de ojo and susto; Malaysian amok; Laotian latah; African American “high blood”; and English “colds.” Some,
like American premenstrual syndrome, bulimia, and anorexia nervosa, have moved from folk illness to biomedical diagnosis. Culture-bound syndromes are part of Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), but can also be considered as disease entities in their own right, rather than subsumed under psychiatric categories.

Application to the case. The Hmong disease classification system for headache seems straightforward, as there is only one word for headache (moh taub hau), but there are multiple types of headaches based on etiology. One recognized type of headache is associated with stroke. Strokes are described by the neurologic defect (tuag tes tuag saw means dead hand dead foot) as well as by multiple etiologies. Contact with biomedicine has altered the concept of stroke for some Hmong people in the United States.

Theories of Disease Causation

Every system of health and disease considers causation—linking events in the social, natural and supernatural realms with recognized sicknesses. The finding of a cause can guide therapy prospectively; confirm actions retrospectively; and give an explanation for illnesses—thus giving solace and meaning to human suffering.

Delineating etiologies can be a complex process dependent on the interpretation of many factors. Multiple etiologies may surface during a sickness episode, and multiple etiologies, even seemingly contradictory etiologies, may remain after the event. In any given ethnic group there is likely to be overlap amongst four etiological categories: individual, natural, social, and supernatural.

Application to the case. The Hmong concepts of etiology include all four types, with natural causes being the most common, particularly for everyday nonserious illnesses. Chronic persistent sicknesses, serious illnesses, and problems occurring after social conflicts or around spiritual events, may also have social and supernatural etiologies. Supernatural and social etiologies can be discovered with various divination procedures, or during shaman’s ceremonies. Multiple etiologies can be speculated upon, can be investigated concurrently, and can coexist to cause a person’s problem.

Treatment Options

Multiple treatment options are available throughout the world, including in the United States, where allopathic medicine is well established, where alternative-complementary healing methods are growing, and where traditional healing approaches of many people from around the globe are available. Kleinman has divided types of healers into three sectors that are overlapping and interconnected rather than mutually exclusive: a popular or lay sector, a folk sector, and a professional sector. These three sectors operate continuously and concurrently. The vast majority of illnesses are treated in the lay sector, as self therapy and home therapy deal with all ailments; often it is only when this sector is unable to respond adequately to a sickness that help is sought from the folk or professional sectors. All three sectors are active in the United States. One national telephone survey estimated that one-third of all Americans use some kind of complementary medicine in the lay or folk sector, whether massage, herbs, acupuncture, vitamins, or traditional ethnic medical systems.

Application to the case. In Laos, the Hmong traditional system of healing included well-developed lay and folk sectors. In extended families, there were men and women who knew about diseases and treatments; grandparents who knew about maintaining health and preventing disease; and heads of households who had the responsibility to maintain relationships with the spirits. In villages there were experts in diagnosis and herbal medicines, rituals, and shaman ceremonies. Access to professionals (Chinese, Laotian, or Western) was limited due to their physical distance from other peoples. People had contact with biomedical personnel at refugee camps in Thailand.

Interpretation of Bodily Signs and Symptoms

The four preceding sections focus on an ethnic group’s general understanding of health and disease. The following two sections focus on how individual patients and families in such a group may deal with particular sickness within the context of their cultural beliefs and behaviors.

Initially, individuals sense a symptom or other people perceive a sign. Questions arise. Is this normal or abnormal? If it is abnormal, what does it signify? Is it serious or mild? What has caused it? What should be done about it? The answers to these questions are influenced by people’s understandings of their culture’s general approach to bodily functions and malfunctions, disease classification, etiology, and seriousness, but also may be influenced by other individual factors. Together the answers constitute what Arthur Kleinman has called an explanatory model.

Kleinman has described individuals’ “explanatory models” (EMs) of their sickness as having five aspects: the etiology of the condition, timing and mode of onset of symptoms, pathophysiological processes, natural history and severity of illness, and appropriate treatments. The sick person, family members, social network, and providers have their own explanatory models about the sickness event, and these may be complementary or contradictory. The more agreement between the EMs, the smoother the interactions among people may be, while the more disagreement between the concepts, the more conflict there may be.

Application to the case. At home, MT had had a severe headache for which her husband gave her Tylenol, a Thai pharmaceutical preparation (probably aspirin or acetaminophen), and a Hmong herbal medication. As the headache worsened, the husband called her sons. The whole family became alarmed as her gait became unstable. As their actions were not helpful, they sought assistance from the hospital. Her husband and sons believed the doctor’s interpretation of bleeding in the brain, but they were concerned about the invasive and potentially harmful nature of the proposed operation. A shaman discovered that
one of her souls had left her body and was going to be reincarnated. They knew a shamanic ritual at home was necessary to return her soul to her body. During the ceremony, the shaman discovered a longstanding intra-familial conflict that had contributed to the soul loss.

### Medical Decision Making

Once sick individuals have interpreted their signs or symptoms, they have to decide whom to consult. Given the lay, folk, and professional sectors, how do they select a healer? The decision-making process is complex, and includes cultural and social influences.

Cultural beliefs about health, sickness, and etiology influence which healers are deemed appropriate to treat the problem. After the healer has been chosen and the healing method completed, cultural factors continue to influence the healing process as sick individuals and family members evaluate the method’s effectiveness, discern the etiologies, learn from the experience, and consider need for further assistance.

Social factors also influence the process, as sick individuals’ social networks express their approval or disapproval for certain healers and healing methods. The greater the social dissonance between a healer and patient (resulting from differences in socio-economic class, language abilities, geographic location, income level, religion, etc), the less likely it is the patient will choose that healer.

Ethnic identity, the extent to which individuals and families identify with a particular ethnic group, also influences their choice of healers. While ethnic identity may be strong when people initially arrive in another country, that identity changes over time by the process of acculturation. Acculturation is an irregular, dynamic, bidirectional process that results in considerable variation for individuals, families, and communities.

People can utilize multiple healing methods without accepting a given method’s theoretical underpinnings or without wholeheartedly choosing the system as their preferred healing system. For instance, Chinese people who believe that health results from a balance of yin and yang may obtain vaccinations without accepting concepts of immunology or epidemiology and without embracing allopathic medicine. Likewise, mainstream Americans may use acupuncture without embracing the traditional Chinese concepts of qi (chi), meridians, and balance, and without rejecting allopathic medicine.

**Application to the case.** The traditional spiritual beliefs were extremely important to the couple and to their sons. They knew that the shaman’s ceremony was necessary to retrieve MT’s soul and return her to spiritual health, if she were to survive an operation. In the hospital, the family decision-making process included a discussion of the pros and cons, with the younger more acculturated members wanting the surgery and the older sons and her husband choosing the traditional ceremony. In the morning, after the shaman ceremony, the family met again, assessed that her physical condition had not improved, but recognized that her souls were intact and she could survive an operation.

### Healer/Sick Person Relations

Every cultural system has expectations about the healer-sick person/family relationship. The rules of this relationship—the preferred styles of communication, the appropriate approach to relevant topics, and the amount of the power that the healer exerts over the patient and family—are culturally influenced. Physicians in the United States learn a preferred manner of physician-patient relationships, which some patients may experience as foreign, rude, mean, or unacceptable (see examples below).

Cultural values are always present in the clinical encounter. Physicians’ biomedical and western values may conflict with values of patients from other cultures. For instance, physicians may believe in their ability to conquer problems and exert control over nature, while patients may trust their ability to live in harmony with nature; or physicians may focus on physical and psychological issues while patients expect to pursue social and spiritual issues.

There is a power differential between healers and patients that can be both helpful and harmful to patients. Biomedical physicians generally are from middle and upper socioeconomic classes, have high incomes, may be from the dominant social group, and have privileged knowledge. People have long expressed their feelings of powerlessness in relationships with health care providers in biomedical institutions. Add the dimensions of different language, different expectations of healer-sick person relations, verbal and nonverbal language barriers, and the situation is ripe for patients from various ethnic groups to feel disempowered in their encounters with biomedical health care providers.

**Application to case.** When the family had decided to take MT home, they felt the neurologists’ frustration and anger at their decision, which perplexed them. “Why should they be angry with our taking care of our mother? After all, it is up to us, her family, to make the appropriate decisions for her.” However, they felt support from the neurosurgeon; his accepting attitude that there was more at stake than the physical body and his respectful attitude toward their beliefs made it easier for them to return for the operation. And they felt the support of the shaman, who after his ceremony said that the woman was spiritually strong enough to survive the operation. Indeed, she survived the operation and went home a week later, with some residual hemiparesis.
HOW TO PROVIDE CULTURALLY COMPETENT MEDICAL CARE?

► Learn About Self as a Cultural Being

“Culture” isn’t just a factor for “others,” “ethnic groups,” or “minority peoples”. Culture is an essential element of every human being. Physicians need to know how their personal cultural backgrounds influence their views and values about health, disease, and treatment as well as their reactions to others. In addition, family doctors need to be aware of their biomedical training. Biomedicine is a cultural system influenced by historical, social, economic, political, religious, and scientific events, with its own language and its own values that can clash with providers’ personal beliefs and with patients’ cultural beliefs and values. In addition, biomedicine trains physicians to initially categorize and recognize patterns, and then to act on those categorizations and patterns, which can easily move physicians from generalizing to stereotyping about people in cultural groups.

► Learn About Patients as Cultural Beings

Physicians need to familiarize themselves with the communities they serve. This includes important historical events, such as migration or refugee movement; social structure and function, such as which family members have more influence in making medical decisions; various religious beliefs and practices, such as a dominant religion or conflicting religious factions; prevailing health beliefs about health, disease, and treatments; use of complementary and alternative healing practices, such as herbalists, masseuses or spiritual healers; and expectations of life-cycle events, such as birth, child development, puberty, old age, and death.

Kleinman conceptualizes that all individuals—patients, family members, and healers—create cognitive explanatory models of an illness event, which change over time. The five components of explanatory models are: etiology, pathophysiology, symptom, projected course, and expected treatment. Providers need to know prevailing cultural concepts of health, disease, and treatment, prevailing medical decision making patterns, and prevailing values and ethical frameworks, so they can understand the context of patients’ explanatory models.

► Learn Culturally Appropriate Communication Skills

For optimal communication, physicians must adapt their standard interviewing techniques to fit patients’ communication styles, rather than assuming that their preferred communication style fits everyone and rather than expecting patients to adjust to physicians’ preferred styles. Difficulties delivering health care in multicultural settings may arise from patient and providers’ differences in health beliefs, expectations of life cycle events, moral values, or ethical principles. Knowing what communication style to use is a challenge. Providers cannot assume because patients are from one ethnic group that they will prefer a specific approach. However, physicians can learn general approaches from community experts, such as bilingual-bicultural colleagues, and make adaptations as they are attuned to people’s verbal and nonverbal cues. Also, physicians have to be proficient in multiple languages, and/or learn to work with interpreters (Table 60-1).

► Apply Cultural Information and Skills in Clinical Interactions

Understanding general information about the communities with whom they work, physicians are ready to apply that cultural information to specific medical encounters. One multicultural patient-centered approach to the clinical encounter is Berlin and Fowkes’ LEARN model.

Listen to patients’ perspectives. The first important step is to listen to patients’ and families’ stories about their illness experiences. Physicians must ask and display genuine desire to hear the patients’ perspectives. To elicit their perspective of their illness, or disease, or their explanatory models, physicians can try Kleinman’s questions or modifications thereof (Table 60-2).

Explain medical views. After they have completed gathering information from the patient’s story and physical findings, physicians need to explain their views of the patient’s conditions. Physicians can explain the biomedical assessment by building upon patients’ ideas, beliefs, and values, and by addressing patients’ fears and concerns.

Acknowledge similarities and differences. Physicians can acknowledge where patients’, families’, and providers’ perspectives about the illness etiology, projected course, or treatment options are similar and different.

Recommend a course of action. While explaining recommendations for diagnostic or therapeutic plans, physicians must ask permission, explain options, and ask what approaches patients want.

Negotiate plans. Depending upon how much disagreement there is between patients’ desires and medical recommendations,
physicians may need to negotiate a plan and work with patients’ perspectives about their bodies, illnesses, and desired treatments.

**Provide Linguistically and Culturally Appropriate Patient Education**

Providing patient education for diverse patient populations requires that providers first assess patients’ language preferences and health literacy skills (both in English and in other languages), and then target patient education to be compatible with patients’ language abilities, literacy levels, and cultural concepts. Utilizing multicultural and multilingual resources—from written pamphlets, to audiotapes and videotapes, to community agencies and internet sites, to bilingual bicultural patient educators and advocates—are invaluable assets to support patient empowerment.

**Deal With Cultural Conflicts**

Difficulties delivering health care in multicultural settings may arise from differing patient and provider health beliefs, expectations of life cycle events, moral values, or ethical principles. Cross-cultural ethical conflicts can challenge providers’ personal beliefs, personal morals, and professional integrity. When physicians encounter conflicting beliefs and values, it is very tempting to protect and preserve their own models by ignoring, rejecting, or disparaging other viewpoints. The costs of doing so can be the loss of patients to other providers, decreased patient satisfaction, increased noncompliance, worse patient outcomes, as well as diminished providers’ satisfaction and competence—all of which increase the health disparities. Understanding how patients’ and providers’ different cultural beliefs and values contribute to the situation is a first step in responding to specific patients in clinical encounters. Then solutions can be found, whether by compromising, negotiating alternative approaches, consulting ethics committees or community members, or referring patients to other providers.

**Do Not Abuse Power**

In the context of multicultural care, physicians have to be aware of power differences between themselves and patients, be aware of power struggles that can arise, and avoid abuse of power. To these ends, doctors need to know about their personal and professional biases and prejudices, and need to monitor their actions and emotional reactions to patients. Balint groups, physician support groups, ethics committees, and faith communities are ways to examine personal struggles. Physicians can consider “caring-in-relation” and “power-in-relation” as ways to avoid abuse of power.

**Create and Work Within Culturally Competent Institutions**

Physicians need to be active members in clinics, hospitals, and medical societies in order to create culturally competent institutions. Physicians can be powerful advocates for hiring bilingual-bicultural workers, employing trained interpreters, creating health education approaches for patients with limited English proficiency, and engaging institutions in caring for diverse patients. Physicians can champion administrative changes to improve organizational cultural competence. The more systems are constructed to empower patients and avoid prejudices and biases, the more physicians can provide culturally competent care and improve the health of all patients.

**Engage in Lifelong Learning Activities**

Learning about one’s cultural self, about people’s cultural perspectives, and applying these to clinical settings to provide culturally appropriate care is a lifetime endeavor. Cultural competence has been described as a journey, rather than a destination. As such, there are multiple local and national conferences, as well as internet resources for further information as well as CME activities. (See list below.)

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**Table 60-2. Kleinman’s questions for exploring explanatory models.**

<table>
<thead>
<tr>
<th>Question</th>
<th>Alternative Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What do you call your problem?</td>
<td>1. What do you think is wrong?</td>
</tr>
<tr>
<td>2. What do you think has caused your problem?</td>
<td>2. What are you afraid of?</td>
</tr>
<tr>
<td>3. Why do you think it started when it did?</td>
<td>3. What do you think has caused the problem?</td>
</tr>
<tr>
<td>4. What does your sickness do to you?</td>
<td>4. What have you tried to relieve the problem?</td>
</tr>
<tr>
<td>5. How severe is it? Will it have a long or short course?</td>
<td>5. What do you think would help you?</td>
</tr>
<tr>
<td>6. What do you fear most about your sickness?</td>
<td>6. What do you call your problem?</td>
</tr>
<tr>
<td>7. What chief problems has your sickness caused for you?</td>
<td>7. What are you afraid of?</td>
</tr>
<tr>
<td>8. What kind of treatment do you think you should receive?</td>
<td>8. What kind of treatment do you think you should receive?</td>
</tr>
</tbody>
</table>

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**References**

Web Sites for Assessment/Education/CME Activities


3. National Center for Cultural Competence (NCCC) has:
   b. Curricular Enhancement Modular Series: http://www.ncccurricula.info/
   d. Initiative for Decreasing Disparities in Depression: http://www.gucchdgeorgetown.net/13D/

4. Virtual Lecture Hall Delivering Culturally Competent Care: Managing Type 2 Diabetes in Diverse Populations. Case based, interactive, 9 credits. Fee required: www.vlh.com

5. Cultural Competence Online for Medical Practice: http://www.c-comp.org

Web Sites for General Information

Asian and Pacific Islander American Health Forum http://www.apiahf.org
Asian American network for Cancer Awareness, Research, and Training http://www.aancart.org/

Association for Asian Pacific Community Health Organizations http://www.aapcho.org
Bayer Institute for Health Care Communication www.bayerinstitution.org Center for Cross-cultural Health www.crosshealth.com
Center for Disease Control, TB in five ethnic groups http://www.cdc.gov/tb/publications/guidestoolkits/EthnographicGuides/default.htm
Cross Cultural Health Care Program www.xculture.org
Cultural Profiles, Center for Applied Linguistics http://www.culturalorientation.net/fact.html
Ethnomed www.ethnomed.org
Islamic Health and Human Services http://hammoude.com/Ihhs.html
National Council on Interpretation in Health Care www.diversityrx.org
National Health Law Program http://www.healthlaw.org
National Hispanic Medical Association http://www.nhmamd.org/
Provider’s Guide to Quality and Culture http://erc.msh.org
Resources for Cross-cultural Health www.diversityrx.org
Vietnamese Community Health Promotion Project http://www.suckhoelavang.org/
World Education; Culture, Health and Literacy http://www.worlded.org/us/health/docs/culture/about.html
BACKGROUND & DEFINITIONS

Ethnic and racial minorities manifest significantly poorer health status than their white counterparts. Health disparities are defined by the National Institutes of Health as “differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups in the United States.” Although these disparities have existed for more than two centuries, defining and characterizing disparities in health and health care are necessary beginnings to understanding the problem and seeking effective solutions to inequities in health status. Cardiovascular disease, cancer, and diabetes mellitus are the most commonly reported health disparities followed by cerebrovascular diseases, unintentional injuries, and HIV/AIDS. Assessing these differences requires that a variety of factors including age, gender, nationality, family of origin, religiosity, education, income, geographic location, race or ethnicity, sexual orientation, and disability be considered.

Health care disparities are defined by the Institute of Medicine (IOM) as “differences in the quality of health care that are not due to access-related factors or clinical needs, preferences, and appropriateness of intervention.” Causes of health care disparities most often relate to quality and include provider-patient relationships, provider bias and discrimination, and patient variables such as mistrust of the health care system and refusal of treatment. Although disparities in health and health care can be inextricably tied to one another, distinguishing between them increases our understanding of the complexity of the problem.

One of the most significant efforts to address disparities has been the introduction of the Healthy People goals in the late 1990s. Foundational principles of the federal Healthy People initiatives are (1) that all people are valued equally, (2) health is valued for everyone, (3) everyone should be able to achieve the highest level of health possible, and (4) the resources needed for health should be distributed fairly (http://www.healthypeople.gov/hp2020/advisory/Phase1/Phase1.pdf). The disparities evident in the health and/or health care of the US population reflect inconsistencies in implementing these principles.

Concerns regarding health and health care disparities are amplified when the dramatic changes in the population served during the last two decades of the twentieth century are considered. Between 1980 and 2000 the white non-Hispanic population of the United States increased 7.9% compared with an 88% increase in the aggregated minority (people of races other than white or of Hispanic ethnicity) population. An estimated 1 in 4 Americans (almost 70 million persons) is classified as a member of one of the four major racial or ethnic minority groups: African American, Latino/Hispanic, Native American, and Asian/Pacific Islander. By the year 2050, the US census estimates that people of color will represent 1 in 3 Americans. These populations bear a disproportionate burden of illness and disease relative to their percentage distribution in the population. Understanding the factors that contribute to inequities in health among these populations and the strategies that have resulted in improved health can inform and promote the delivery of quality health care.


HEALTH CARE DISPARITIES & THE LITERATURE

Institute of Medicine Reports

In 1999, a report from the IOM entitled Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care was
written in response to a request from Congress to the IOM to address the extent of racial and ethnic disparities in health care. Following review of more than 100 publications, the IOM study committee concluded that research findings consistently indicated that minorities were less likely than whites to receive needed services, including lifesaving procedures. The most commonly reported health care disparities were seen in cardiovascular disease, cancer, and diabetes. Other illnesses included cerebrovascular diseases, mental illness, and HIV/AIDS.

The IOM committee outlined three sets of factors that likely contributed to the complex problem of health care disparities. The first set of factors relates to minority patients’ attitudes toward health care, preferences for treatment and subtle differences in the ways that racial and ethnic groups respond to treatment, particularly pharmaceutical interventions. The second group relates to the operation of health care systems and the legal and regulatory environment in which they function. These factors include lack of interpretation services for those with limited English proficiency, lack of resources for those with limited health literacy, where care is received, and how it is delivered. The third set of factors is derived from the clinical encounter. The committee’s review suggested that provider bias, clinical uncertainty, and stereotyping or beliefs about the behavior of minorities may have a negative impact on the health outcomes of minorities. On the other side of the clinical encounter is the patient; his or her reaction to the provider’s biased or stereotyped behaviors may also contribute to disparities.

**National Healthcare Disparities Report**

With a directive from the Healthcare Research and Quality Act of 1999 (Public Law 106-129) and guidance from the IOM, the Agency for Healthcare Research and Quality (AHRQ) developed and produced two reports. The first of these, the *National Healthcare Disparities Report* (NHDR), was the first national comprehensive effort to measure differences in access and use of health care services by various populations. It incorporated a broad set of performance measures through which the data on differences in the use of services, access to health care, differences in use of services by priority populations, and impressions of quality for seven clinical conditions could be viewed and assessed. The second report, the *National Healthcare Quality Report* (NHQR), focused on safety, effectiveness, patient centeredness, and timeliness, with equity as a cross-cutting dimension. The two reports were released simultaneously in 2003 to provide a more comprehensive view of the performance of the health care system, its strengths, and areas that should serve as a focal point for future improvement. The performance measures underlying the two reports will be used to monitor the nation’s progress toward improved health care delivery. Reports have been issued annually since 2003.

The NHQR sought to analyze national disparities as both a function of health care access and quality. Disparities were related to socioeconomic position as well as to race and ethnicity. The NHQR’s key findings were that inequality in quality persists, disparities come at a personal and societal price, differential access may lead to disparities in quality, opportunities to provide preventive care are frequently missed, knowledge of why disparities exist is limited, improvement is possible, and data limitations hinder targeted efforts to provide the level necessary to measure the effect of national initiatives to reduce disparities.

In 2005, a third NHQR highlighted four key themes: disparities are pervasive and still exist, some disparities are diminishing, opportunities for improvement remain, and information regarding disparities is improving. New databases and measures were added to provide a more comprehensive assessment of disparities and new methods for tracking changes in disparities in a standardized fashion have been implemented. This allows for the identification of specific disparities that are improving and disparities that are worsening.

Agency for Healthcare Research and Quality, March 2009 report focused on quality of care and disparities in health care in America overall and AHRQ’s priority populations in particular. The 2008 National Healthcare Disparities Report found that although some of the biggest disparities in quality remain, progress has been made in reducing disparities in areas, such as dialysis, hospital admissions for perforated appendix, and childhood vaccinations. Most recently, the NHDR also reported that there are significant disparities in quality documented over the years where there has not been improvement, such as new AIDS cases (AHRQ 09-0002) (http://www.ahrq.gov/news/pubcat/c_quca.htm).

**Web Sites**


**Healthy People 2010**

Healthy People 2010 was launched in January of 2000. The program is a set of comprehensive health objectives for the nation that can be used by many different people, states, communities, professional organizations, and others to help them develop programs to improve health. The Healthy People 2010 objectives build on the 1979 Surgeon General’s report, *Healthy People*, and Healthy People 2000. All three initiatives were developed through broad consultation, backed by the best scientific knowledge available, and were designed to measure programs over time.

The two overarching goals of Healthy People 2010—to increase quality and years of healthy life and eliminate health disparities—served as a guide for developing the 467 objectives, designed to serve as a roadmap to measure progress.
The achievement of these national objectives is dependent in part on the ability of health agencies at all levels of government and on nongovernmental organizations to assess their progress.

Web Site


HISTORICAL FACTORS

Original American citizens of color bear a historical legacy that affects all aspects of their integration into society today. American Indians make up a fraction of today's citizens (0.7% in the 2000 census) but have significant health disparities. The prevalence of diabetes mellitus, obesity, alcoholism, and suicide is substantially greater in this population than in other US population groups. They are the one population with a health system that was established to help meet their medical needs. The availability of these services, however, is limited by distance for the many American Indians living in rural areas, and they may be completely inaccessible to those living in urban areas.

African Americans encompass several groups who came to the United States at different times. The impact of slavery on the original Africans cannot be minimized. Residual effects of this historical tragedy have been associated with discriminatory residential practices, educational disadvantages, and treatment practices in separate but unequal health care facilities. Later immigrants of African origin came to the United States from the West Indies where slavery was abolished well before the Emancipation Proclamation in the United States. These differing experiences have influenced the views of Caribbean Americans and result in differences between them and African Americans who descended directly from slaves on the North American continent. The final group of immigrants from African countries chose to come to the United States in recent years for both educational, economic, and political reasons. Cultural differences often exist among these three groups and include differences in customs, family roles, religious preferences, and their definition and experience of illness and disease.

Despite the fact that the foundation of the United States was a union of indigenous groups and immigrants, the preceding groups along with new immigrants bear much of the burden of disease in the nation today. The number of immigrants entering the United States during the past 15 years has increased dramatically compared with the numbers seen in the previous four decades. Political crises, natural disasters, poverty, and hunger have forced population groups of significant size to leave their homes. These migrations have resulted in loss of homes and support systems, overcrowding and overexposure, decreased access to food and medical services, and contact with new infectious agents and other toxins.

IMMIGRANTS & REFUGEES

The term immigrant has been applied to legal and illegal (undocumented) refugees and children adopted from other countries. Most immigrants reside in linguistically isolated households (those in which no one >14 years speaks English), which were identified for the first time in the 1990 census). Four percent of US households are in this category. This figure includes 30% of Asian households, 23% of Hispanic households, and 28% of all immigrant households with school-age children.

Immigrants enter the United States from many countries, but those coming from Mexico represent the largest group. Many Mexican immigrants arrive in the United States healthier than their white counterparts. However, their health deteriorates the longer they live here, possibly as a result of lifestyle changes (years of difficult labor, poverty, smoking, poor diet, and lack of attention to prevention) and a lack of health insurance. One study found that 2.6% of recent Mexican immigrants had diabetes mellitus, compared with 7.7% of Mexican immigrants who had lived in the United States for 15 years. More than two-thirds of recent Mexican immigrants and 44.8% of “long-term immigrants” have no health insurance, compared with 22.5% of Mexican-born Americans and 12.3% of US-born whites. Fewer than 10% of recent Mexican immigrants reported using emergency departments in 2000. Furthermore, more than 33% of Mexican women aged 18-64 years who were recent immigrants had not had a Pap smear in 3 years. About 37% of recent Mexican immigrants visited a health clinic instead of a physician for health care, compared with about 15% of US-born whites.

Pregnant women are of major concern because of risk for poor pregnancy outcomes. In spite of these concerns, evidence suggests that infants of Mexican immigrants have favorable birth outcomes despite their high socioeconomic risks. These favorable outcomes have been associated with a protective sociocultural orientation among this immigrant group, including a strong family unit. Yet, one-fourth of infants of immigrants in predominantly Spanish-speaking households are at high risk for serious infectious disease despite using preventive care. As these children mature beyond the neonatal period, factors predisposing to illness are large households, poor access to care, and maternal characteristics, including smoking, pregnancy complications, and employment.

Lack of understanding by health care providers of traditional remedies for common ailments can result in negative interactions between patients and clinicians, misdiagnosis, and poor health outcomes. In one study, health care providers and the population of Vietnamese immigrants for whom they cared both identified misinterpretation of patient symptoms and health care provider recommendations as major issues. The special problems of unemployment, depression, surviving torture, and obtaining assistance are all made more difficult for refugees living in small communities that lack sufficiently large ethnic populations to facilitate culturally sensitive provision of health care.
With the exception of Southeast Asian refugees, there are few clinical studies on the health problems of refugees after arrival in the United States. Tuberculosis, nutritional deficiencies, intestinal parasites, chronic hepatitis B infection, lack of immunization, and depression are major problems in many groups. The great variation in health and psychosocial issues, as well as cultural beliefs, among refugees requires careful attention during the medical encounter. In addition to a complete history and physical examination, tests for tuberculosis, hepatitis B surface antigen, ova and parasites, as well as hemoglobin measurement, are advised for most groups.


POVERTY

A greater percentage of African Americans (53%) and Latinos (59%) have incomes that are below 200% of the federal poverty line than non-Hispanic white Americans (25%) across their lifespans. Financial disadvantage has an impact on health in that mortality rates around the world decline across their lifespans. Financial disadvantage has an impact on health in that mortality rates around the world decline with increasing social class, a concept most easily associated with access to financial resources.

Poor, minority, and uninsured children are twice as likely as other children to lack usual sources of care, nearly twice as likely to wait 60 minutes or more at their sites of care, and use only about half as many physician services after adjusting for health status. Poverty, minority status, and absence of insurance exert independent effects on access to and use of primary care. Homelessness results in poor health status and high service use among children. Homeless children were reported to experience a higher number of acute illness symptoms, including fever, ear infection, diarrhea, and asthma. Emergency department and outpatient medical visits are also higher among the homeless group.


UNINSURANCE & UNDERINSURANCE

A substantial portion of the US population is medically uninsured or underinsured. A greater percentage of racial and ethnic minorities and immigrants are in this category. These numbers increase if individuals who have been without health insurance for 3 or more months in a given year are included. Underinsurance is the inability to pay out-of-pocket expenses despite having insurance and usually implies inability to use preventive services as well. The underinsured category includes unemployed persons aged 55-64 years and those not provided health insurance coverage through their jobs. These individuals are not eligible for Medicare and must pay high individual health premiums when they can obtain some form of group coverage. Lack of health insurance is associated with delayed health care and increased mortality. Underinsurance also may result in adverse health consequences. An estimated eight million children from diverse groups in the United States are uninsured. Substantial differences in both sources of care and utilization of medical services exist between insured and uninsured children.

In 2005, 34% of all nonelderly adult Hispanics living in the United States lacked health insurance coverage (either private or public), compared with 21% of African American, 19% of Asian/Pacific Islander, 32% of American Indians, and 13% of non-Hispanic white nonelderly citizens. Because Hispanics are more likely to be uninsured than any other ethnic group and because they are the fastest growing minority group in the United States, it is likely that the number of uninsured in the US population will steadily increase.

There are marked discrepancies in access to and utilization of medical services, including preventive services, between uninsured and insured children, although both groups have similar rates of chronic health conditions and limitations of activity (evidence of the general health of the children being seen). The 2002 Institute of Medicine report, Unequal Treatment, documented the widespread evidence of racial and ethnic disparities in health care. However, only 5 of the 103 published studies cited in this report addressed health disparities in children. Yet there appear to be disparities of equivalent magnitude and persistence in children as are seen in adults. Substantial gaps in insurance coverage exist among children such that 37% of Hispanic, 23% of African American, and 20% of non-Hispanic white children have no health insurance. Children of color are more likely to be insured through public programs such as Medicaid and the State Children’s Health Insurance Program (SCHIP).

Children eligible for Medicaid but who remain unenrolled are often younger than 6 years of age, live in female-headed single-parent families, or are African American or Hispanic. Not only do uninsured children lack routine medical care, they also lack appropriate well child care compared
with insured children. Children who have a chronic disease, such as asthma, face difficulties of access to care and utilize substantially fewer outpatient and inpatient services.

Parents’ utilization of health care services has a large impact on the services used by their children. Even if all children were universally insured, parental health care access and utilization would remain a key determinant in children’s use of services. Neglecting financial access to care for adults who serve as caregivers for children may have the unintended effect of diminishing the impact of targeted health insurance programs for children.

The uninsured can manifest similar psychopathology as is seen in refugees. Rates of current psychiatric disorders (including major depression, anxiety disorders, and history of sexual trauma) are extremely high in ethnically diverse women who are receiving public medical assistance or are uninsured. These women also report behaviors that pose serious health risks, including smoking (23%) and illicit drug use (2%). Fewer than half have access to comprehensive primary medical care. Young, poor women who seek care in public-sector clinics would benefit from comprehensive medical care addressing their psychosocial needs.

In the United States, the cost of health care services is a major barrier to health care access. In addition, three-fourths of persons in the United States who have difficulty paying their medical bills have some type of health insurance. Although the affordability of health care among persons without health insurance has been described, few details regarding affordability among persons who are underinsured exist.

Investigators who looked at state programs offering subsidized coverage in commercial managed care organizations to low-income and previously uninsured people found no evidence of pent-up demand or an unusual level of chronic illness between people enrolled through large employer-benefit plans and previously uninsured patients. Similarly, there was little evidence of underutilization, although dissatisfaction and reported barriers to service were more frequent among nonwhite enrollees. In another study, undocumented immigrants had more complicated and serious diagnoses on admission but a lower adjusted average length of stay than native-born populations and those with permanent residency status (insured by Medicaid or of uninsured status) admitted to the same hospital.

Although generalist physicians appear to be more likely than specialists to provide care for poor adult patients, they may still perceive financial and nonfinancial barriers to caring for these patients. Nonwhite physicians were more likely to care for uninsured and Medicaid patients than were white physicians. In addition to reimbursement, nonfinancial factors played an important role in physicians’ decisions not to care for Medicaid or uninsured patients. For example, perceived risks of litigation and poor reimbursement were cited by 60%-90% of physicians as important in the decision not to care for Medicaid and uninsured patients.


HOUSING & GEOGRAPHIC FACTORS

Racial residential segregation has been suggested as a fundamental cause of racial disparities in health. Although legislation exists to eliminate discrimination in housing, the degree of residential segregation remains extremely high for most African Americans in the United States. Williams and Collins argue that segregation is a primary cause of racial differences in socioeconomic status by determining access to education and employment opportunities. Furthermore, segregation creates conditions that hamper a healthy social and physical environment. Levels of racial residential segregation grew dramatically from 1860 to 1940 and have been maintained since then.

Recent research has linked racial segregation to higher cancer risk; the risk increases as the degree of segregation increases. Minorities living in highly segregated metropolitan areas are more than 2.5 times more likely to develop cancer from air pollutants when compared with whites. Hispanics who live in highly segregated areas are affected the most, with a risk 6.4 times that of whites. When neighborhood poverty indicators and population density are controlled, the disparities in cancer risk persist, although at lower levels.
Skinner and colleagues noted the contribution of community of residence to health disparities. The investigators suggested that black patients are concentrated in a small number of poorly performing hospitals. In this study, nearly 70% of black patients with myocardial infarctions were treated at only about 20% of regional medical centers. The majority of those with life-threatening cardiac conditions received care at smaller health care institutions that had less experience in treating these conditions. When more than one million Medicare recipients from 1997 to 2001 were examined, death rates for patients presenting with acute myocardial infarction were 19% higher at these hospitals than at facilities that saw only white patients. Because the factors contributing to health disparities are so complex, there is no one solution. However, these findings suggest that spending must be increased and quality improved at medical centers that primarily treat minorities and the poor.

Young to middle-aged residents of impoverished urban areas manifest excess mortality from several causes, both acute and chronic. African American youth in some urban areas face lower probabilities of surviving to 45 years of age than white youths nationwide surviving to 65 years of age. Minorities comprise 80% of residents of high-poverty urban areas in the United States and more than 90% in the largest metropolitan areas. The lower the socioeconomic position held, the less ability the person has to gain access to information, services, or technologies that could provide protection from or modify risks.

For most Americans, housing equity is a major source of wealth. Residential segregation in such a fashion, therefore, directly influences socioeconomic status. Income predicts variation in health for both white and African Americans, but African Americans report poorer health than whites across all levels of income. People residing in disadvantaged neighborhoods often experience a higher incidence of heart disease than people who live in more privileged neighborhoods. The quality of housing is also likely to be worse in highly segregated areas, and poor housing conditions adversely affect health. For example, research reveals that a lack of residential facilities and concerns about personal safety can discourage leisure-time physical exercise.

Disparities in mental health services have been known to exist among diverse communities for decades. Among these disparities are a high rate of misdiagnosis, lack of linguistically competent therapists, culturally insensitive diagnostic measures, and increased exposure to abuse.

The practice of psychiatry is heavily influenced by culture. The cultural identity of patients as well as providers, their perceptions of mental illness and appropriate treatment, their background, and their current environment potentially all have an impact on the psychiatric diagnosis made, the therapy selected, and the therapeutic outcome. Mental illness has been diagnosed more frequently in African Americans and Hispanics than in non–Hispanic white Americans for more than 100 years. Many of the studies reporting these data have been criticized for faulty methodology, cultural bias, and suspect racial theories.

There is some evidence that appropriate research and mental health care delivery for these populations are influenced by factors such as poor cultural validation of the Diagnostic and Statistical Manual of Mental Disorders, misdiagnosis of minority patients, and the unwillingness of many psychiatrists to acknowledge culturally defined syndromes and folk-healing systems.

General mental health screening is difficult in part because assessment of psychological health in non–English-speaking populations is impeded by lack of instruments that are language and population specific. Patients whose first language is not English most often undergo psychiatric evaluation and treatment in English. Cultural nuances are encoded in language in ways that are often not readily conveyed in translation, even when equivalent words in the second language are used. An appropriately trained interpreter will routinely identify these nuances for the monolingual clinician. When such an interpreter is not available, these nuances can be clarified through consultation with a clinician who shares the patient’s first language and culture to maximize delivery of quality health care.


In addition to cost, there are significant differences in how physicians make therapeutic decisions with respect to the minority status of the patient. Women, ethnic minorities, and uninsured persons receive fewer procedures than do affluent white male patients. Furthermore, the race and sex of a patient independently influence how physicians manage acute conditions such as chest pain. For example, women and minorities are less likely to be diagnosed with angina when presenting with comparable risk factors and the same symptoms as white men.

Illegal immigrants underutilize health services, especially preventive services such as prenatal care, dental care, and immunizations due to cost, language, cultural barriers, and fear of apprehension by immigration authorities. Further complicating efforts to provide access to health care for this group is fear for the well-being of family members who may be undocumented, even when the patient is here legally. The increasing number of immigrants entering the United States in recent years has resulted in more legislation seeking to restrict access of various refugee and immigrant groups to public services. Legislation such as Proposition 187, passed in California in 1994, prohibits people lacking legal residency status from obtaining all but emergency medical care at any health care facility receiving public funds.

This legislation has encouraged further obstacles to health care access for countless other people residing in the United States. For example, minorities who were born in the United States find that they are pressured to produce immigration documentation to receive care. Family physicians seeking to care for immigrants and refugees must recognize and effectively deal with problems in communication, establish trust regarding immigration concerns, understand cultural mores influencing the encounter, find the resources to provide necessary services, make an accurate diagnosis, and negotiate a treatment. Unfortunately, fear of these restrictive immigration laws and socioeconomic hardships combine to delay both seeking and obtaining care for these populations.

Title VI of the federal Civil Rights Act states that “no person in the United States shall, on the ground of race, color, or national origin, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity receiving Federal financial assistance.” Current federal mandates assuring access to emergency medical services and new restrictions on financing of health care for immigrants under federal programs such as Medicaid and Medicare appear to be in direct conflict. The Personal Responsibility and Work Opportunity Reconciliation Act and the Illegal Immigration Reform and Immigrant Responsibility Act specifically reaffirm federal law on delivery of emergency services without addressing the financing of that care. Unfunded mandates in an era of diminished ability to shift costs onto insured patients create a major dilemma for the institutions that provide uncompensated care. Medicaid is considered one form of insurance, although the level of reimbursement of providers has been so low that many providers will not treat patients with that coverage.


The physician-patient relationship is grounded in communication and the effective use of language. One of the first principles taught in medical school is the importance of the patient’s history. Along with clinical reasoning, observations, and nonverbal cues, skillful use of language establishes the clinical interview as the clinician’s most powerful tool.

The 2000 census found that more than 46 million Americans speak a language different than that of their clinician. In the United States, the primary “other language” is Spanish. Approximately 25% of Hispanics were born outside of the United States and Puerto Rico, but more than 77% of them note speaking Spanish as their primary language at home. Contributing to the discrepancy, the demographic profiles of the nation’s health care providers does not mirror population trends. In California, although 32% of the population is Latino, only 4% of nurses, 4% of physicians, and 6% of dentists are Latino.

Cultural competence is not necessarily associated with language fluency. The effectiveness of communication between a clinician and patient is influenced by the cultural exposure that fosters command of the meaning of the words and phrases. A patient and clinician who do not share a common language face more challenges to quality care than those who share this foundation of communication. Such language differences can have a negative impact on the clinical encounter. Parents, providers, hospital staff, and quality improvement professionals agree that language and cultural differences lead to communication issues that can have a pervasive, negative impact on the quality and safety of care children receive. There is still disagreement regarding what needs to change to improve health care delivery in a language discordant environment.

Linguistic competence refers to the capacity of an organization and its personnel to communicate effectively and convey information in a manner that is easily understood by diverse audiences, including persons of limited English proficiency, those who have low literacy skills or are not literate, and individuals with disabilities. Linguistic competency requires organizational and provider capacity to respond effectively to the health literacy needs of populations served. The organization...
must have policy, structures, practices, procedures, and dedicated resources to support this capacity (Table 61-1). Federal standards have been established for clinical practice when language discordance is present. To maintain quality of care and adhere to the federal guidelines for culturally and linguistically appropriate services (CLAS), clinicians must provide accommodation for patients in their chosen language.


Web Site

National Standards for Culturally and Linguistically Appropriate Services (CLAS) in Health Care, Office of Minority Health Resource Center: http://www.omhrc.gov/CLAS.

HEALTH CARE FOR THE DISABLED

Americans with disabilities are more than twice as likely to postpone needed health care because they cannot afford it. In addition, the National Organization on Disability has determined that people with disabilities are four times more likely to have special needs that are not covered by health insurance. Many nonelderly adults (46%) with disabilities note that they go without equipment and other items due to cost. More than a third (37%) postpone care because of cost, skip doses or split pills (36%) due to medication costs, and spend less on basics such as food, heat, and other services in order to pay for health care (36%). Those with Medicare alone (no supplemental coverage) report the highest rates of serious cost-related problems due to gaps in Medicare’s benefit package. Those receiving Medicaid fare better due to the broad scope of benefits and relatively low cost-sharing requirements of Medicaid. However, more than 20% of adults with disabilities on Medicaid reported that physicians would not accept their insurance—more than twice the percentage of patients having private insurance or Medicare.

Current data suggest that health disparities among people with and without disabilities are as pervasive as those recognized among ethnic minority groups. People with disabilities were included in the Healthy People plan to provide a broad look at the health of this population. Of the 467 objectives listed in Healthy People 2010, 207 subobjectives address people with disabilities. Some of the subobjectives focus on areas outside of the usual scope of health care or health care services, such as education, employment, transportation, and housing—all of which have a direct impact on wellness and quality of life.

In addition to examining the health of all citizens with disabilities, particular focus is directed to evaluating the health status of women with disabilities. Regardless of age, women with functional limitations were consistently less likely to have received a Pap test during the past 3 years than women without functional limitations.

The National Survey of SSI (supplemental security income) Children and Families (July 2001–June 2002) examined children with disabilities who were receiving SSI and their families. Children receiving SSI are more likely to live in a family headed by a single mother, and approximately 50% live in a household with at least one other individual reported to have had a disability. SSI support was the most important source of family income accounting for nearly half of the income for the children’s families, and earnings accounting for almost 40%.

Although the Americans With Disabilities Act was enacted 15 years ago in an effort to improve access to a broad range of services, women with physical disabilities continue to receive less preventive health screening than women with none. Furthermore, women with more severe disabilities undergo less screening than those with mild or moderate severity of disability.

Adults with developmental disabilities were more likely to lead sedentary lifestyles and seven times as likely to report inadequate emotional support, compared to adults without. Adults with physical and developmental disabilities were significantly more likely to report being in fair or poor health.
Similar rates of tobacco use and overweight/obesity were reported. Adults with developmental disabilities had a similar or greater risk of having four of five chronic health conditions compared with non-disabled adults. Significant medical care utilization disparities were found for breast and cervical cancer screening as well as for oral health care. These women also had 40% greater odds of violence in the 5 years preceding the interview, and these women appeared to be at particular risk for severe violence.

US Surgeon General Richard H. Carmona, MD, MPH, released “The Surgeon General’s Call to Action to Improve the Health and Wellness of Persons with Disabilities” on the fifteenth anniversary of the American With Disabilities Act in July 2005. The four goals of the Call to Action are to:
1. Increase understanding nationwide that people with disabilities can lead long, healthy, and productive lives.
2. Increase knowledge among health care professionals and provide them with tools to screen, diagnose, and treat the whole person with a disability with dignity.
3. Increase awareness among people with disabilities of the steps they can take to develop and maintain a healthy lifestyle.
4. Increase accessible health care and support services to promote independence for people with disabilities.

**FUTURE DIRECTIONS & CURRENT CHALLENGES**

Multiple factors contribute to the persistence of health and health care disparities in the United States today. These factors originate from the patients, clinicians providing care, and from the systems in which they must interact. Equitable, quality health care for all is achievable in an environment that values cultural competence. Cultural competence is necessary in multiple domains: values and attitudes; communication styles; community and consumer participation; physical environment, materials, and resources; policies and procedures; population-based clinical practice; and training and professional development. Only by assuming responsibility and accountability for this global problem at all levels of the health care system will there be any hope of narrowing the gap and ensuring health for all.


Smeltzer SC: Preventive health screening for breast and cervical cancer and osteoporosis in women with physical disabilities. Fam Community Health 2006;29(1 Suppl):35S-43S. [PMID: 16344635]


BACKGROUND

Who Is Lesbian, Gay, Bisexual or Transgender?

Assuming the most recent data are correct, 5%-9% of men are gay and 3%-4% of women are lesbian. Kinsey’s original reports put these numbers at 10% for men and 2%-6% for women. A recent international review notes that up to 15% of men report same-sex sexual activity at some time during their lives. An additional small percentage of the population experiences gender identity disorder or identifies as transgender. These numbers suggest that, regardless of a physician’s geographic location, or the ethnic, religious, socioeconomic, or gender demographics of their practice, and perhaps without the physician’s awareness, he or she will provide care for lesbian, gay, bisexual, or transgender (LGBT) patients on a routine basis.

ESSENTIALS OF DIAGNOSIS

The first step in providing high quality health care to LGBT patients is a thorough and sensitive sexual history. History forms can facilitate this, if items include options relevant for LGBT patients, for example, “marital status” includes options for domestic partner. Comprehensive information about behavior is necessary as a foundation for optimal education and health screening.

Taking the Sexual History

The process of taking a sexual history begins with creating a safe environment. As sexual and gender-variant minorities, many LGBT people have faced discrimination and may fear sharing the details of their sexual lives with a health care provider; in addition, many health care providers may avoid discussing these intimate details with their patients. By providing literature in the office that reaches out to LGBT patients and by displaying symbols such as a rainbow flag, physicians can help their patients feel more at ease. History forms completed by patients should be phrased to include the full range of patient responses and not have wording that ignores LGBT patients’ lives; such forms may also facilitate conversation about sensitive topics. Physicians can overcome their own discomfort by routinely taking sexual histories. Both inside and outside the examination room, physicians can also help fight entrenched prejudice by modeling tolerance and speaking out against bias with colleagues, students, and staff.

The goal of a sexual history is to identify behaviors that can affect a patient’s health. Whether a man who has sex with men (MSM) self-identifies as gay or bisexual is important for understanding his social and psychological situation, but less relevant in terms of screening for and treating organic disease processes. It is worth prefacing all sexual history taking by informing the patient that the discussion will remain entirely confidential, and that the reason that he or she must endure such probing, personal questions is so the physician can provide the best, most personalized care possible.

Physicians can help their patients be forthcoming about behaviors by guaranteeing privacy, excusing family members and partners from the room (after first receiving the patient’s consent to do so), and being mindful of the assumptions they make about their patients. For example, married heterosexual women may have sexual encounters with women, and self-identified lesbians often have had sexual encounters with men. Not all male-to-female (MTF) transgender people are sexually active with men, or at all. Many elderly patients remain sexually active well into their senior years. The

Caring for Lesbian, Gay, Bisexual, & Transgender Patients

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assumptions that health care providers make based on superficial traits can be challenged through compassionate, thorough discussion of their patients’ behaviors.

After introducing the topic, many clinicians begin the sexual history by asking, “Are you sexually active?” This question is a good starting point, but fails to address past behavior. In addition, patients may have variable definitions of what constitutes “being sexually active.” These ambiguities should be addressed by carefully listening to patients’ responses and following up with more specific questions.

The second question often used by practitioners is, “Are you sexually active with men, women, or both?” The utility of asking this is that behaviors are emphasized over labels, and no assumption is made about sexual orientation; also, providing a list of options instead of asking patients to fill in the blanks, makes it easier to give voice to important medical information and communicates the physician’s receptivity to hear any answer.

Regarding current and former partners, the distinct sexual behaviors in which the patient has participated should be elucidated. It is these behaviors (eg, penile-vaginal intercourse, receptive or insertive anal intercourse, oral-vaginal intercourse, oral-anal intercourse), and whether or not barrier protection was used during them, that will help determine screening and other management decisions. Without asking about specific behaviors, regardless of the fact that the gender of partners may be known, therapeutic decisions will be made based on potentially incorrect assumptions.

In addition, it may be useful to identify the number of current and past partners, whether or not those relationships were monogamous, whether or not barrier protection is always used (keeping in mind that condoms are often not used properly), and whether or not the patient and their partners have a history of sexually transmitted infection. This information is useful for approximating risk of disease exposure, and may identify ongoing risk behaviors that merit attention.

In many settings it is also helpful to understand how a patient’s sexual or gender identity affects their life at home, at work, and in the community. In addition, all LGBT patients should be screened for experiences with domestic violence or hate crime. Due to increased rates of substance abuse and dependence in some LGBT populations, the entirety of the social history should be completed, addressing the use of tobacco, alcohol, intravenous drugs, cocaine, methylenedioxymethamphetamine (MDMA or ecstasy), methamphetamine (crystal meth), prescriptions (including opiates and benzodiazepines), hormones, hallucinogens, and marijuana.

It is only by identifying behaviors that physicians can appropriately screen, risk-stratify, effectively educate, and provide optimal care for their patients. Individuals who are members of a sexual or gender-variant minority group are often less obvious in their identity than those of other types of minority groups, and human behavior does not always clearly align with gender- and sexual-identity labels.

For the purposes of this chapter and in the interest of simplicity, we will refer to gay men and lesbians as if they were single populations. However, this is a gross oversimplification of very complex and diverse human behavior. The LGBT population is heterogeneous, composed of individuals, couples, and families of all genders, ages, and socioeconomic, ethnic, religious, political, and geographic backgrounds. It is for this diversity that the rainbow flag was chosen as an LGBT symbol. This diversity also serves as the complex social context of patients’ lives that, in turn, shapes their experience of health and disease.


Who Is Gay? What Is “Bisexual”? The complexity of human sexual behavior defies simple categorization. Sexual orientation manifests as fantasies, desires, actual behavior, and self- or other-identified labels. For example, a man could think of himself and describe himself as heterosexual, engage in sex with men and women in equal numbers, and in his sexual fantasies focus almost exclusively on male images; a simple label fails to capture the reality of his sexuality. Even when considering only sexual behaviors, differences may exist between actual versus desired, past versus present, admitted versus practiced, and consensual versus forced.

In the medical setting, asking about a patient’s label (eg, “Are you gay or bisexual?”) importantly assesses her or his self perception, but may fail to identify medically significant information. Many individuals who engage in same-gender high-risk sexual behaviors do not self-identify as gay or bisexual. MSM may be at increased risk for sexually transmitted diseases (STDs) compared with men who have sex with women only. Women who have sex with men and women (WSMW) may have an increased risk for STDs and substance abuse compared with either women who have sex with women (WSW) or women who have sex with men only. Differentiation would not be possible by asking a patient only if she identifies herself as lesbian, as both WSMW and WSW may identify themselves as lesbian.
Homophobia, Heterosexism, & Sexual Prejudice

Homophobia is defined as an irrational fear of, aversion to, or discrimination against homosexuality or homosexuals. Heterosexism is the belief that heterosexuality is the natural, normal, acceptable, or superior form of sexuality. Sexual prejudice encompasses negative attitudes toward an individual because of her or his sexual orientation. In their most extreme manifestation, homophobia and sexual prejudice result in physical violence and murder. Evolving societal attitudes may diminish such threats, but homophobia and its behavioral manifestations remain a significant threat to health.

Homophobia is dangerous: one survey of physicians found that 52% had observed colleagues providing substandard care to patients because of sexual orientation. In another study, 37% of young gay men reported antigay harassment in the previous 6 months, resulting in increased suicidal ideation and diminished self-esteem. In HIV-seropositive gay men who were otherwise healthy, HIV infection advanced more rapidly, exhibiting a dose-response relationship, in participants who concealed their homosexual identity. A study of 1067 lesbians and gay men found that feelings of victimization that resulted from perceived social stigma were a significant contributor to depression. And a study of 912 Latino men found that experiences of social discrimination were strong predictors of suicidal ideation, anxiety, and depressed mood.

Overcoming entrenched prejudices and eliminating discriminatory practices are fundamental to health care for all patients. Bias against LGBT individuals seems to respond more effectively to experiential interventions (eg, interaction with LGBT individuals) than to rational interventions (eg, information dissemination). In a clinical setting, physicians can help communicate acceptance and support via posters including diverse same-sex couples, stickers depicting a rainbow flag or pink triangle, and a visible nondiscrimination statement stating that equal care will be provided to all patients, regardless of age, race, ethnicity, physical ability or attributes, religion, sexual identity, and gender identity. Modeling tolerance and speaking out against bias are also ways in which physicians can help combat antihomosexual prejudice.


Web Sites

Gay and Lesbian Medical Association (GLMA):
http://www.glma.org
Parents, Families, and Friends of Lesbians and Gays (PFLAG):
http://www.pflag.org

Diagnostic & Management Considerations

The willingness of LGBT patients to disclose sexual orientation and details of their personal lives is strongly influenced by the perceived tolerance (or intolerance) of their physician. Because a patient’s sexual practices will modify risk for various diseases and can thus influence disease screening and the diagnostic evaluation, honest discussion of the patient’s sexual and social life is vital to promote optimal health. Failure to identify an LGBT patient may cause the treating physician to fail in counseling a patient and in considering a diagnosis, thus risking the patient’s life and the physician’s reputation. Incorrect assumptions about patients can have similar adverse outcomes (Table 62-1). Using simple conversational techniques, and mastering a very manageable amount of medical information, will allow family physicians to provide superior care to LGBT patients.

HIV/AIDS

ESSENTIALS OF DIAGNOSIS

Not all gay men are at risk for HIV, but testing for HIV is recommended for all patients aged 13-64 years seen in health care settings after the patient is notified that testing will be performed unless the patient declines.

Periodic screening (HIV blood tests) is recommended for all persons who are sexually active outside a mutually monogamous relationship.

Blood tests for HIV antibodies have sensitivity and specificity greater than 99%. HIV viral load tests (eg, HIV polymerase chain reaction) should not be used for HIV screening due to the high false-positive rate.

General Considerations

Any publication on LGBT health that omitted mention of HIV would be incomplete, but thorough coverage of the
Gay men comprise the largest number of AIDS cases in the United States. Recent literature suggests increased rates of unprotected anal intercourse (“barebacking”) among certain gay populations. This trend may in part be due to decreased fear of HIV in the era of highly active antiretroviral therapy (HAART). Young gay men, those who use the Internet to meet sexual partners, and those with substance abuse problems, particularly those who use crystal meth, ecstasy, and Viagra, are at greater risk. Increasingly, African American and Latino men are disproportionately affected. Increased stigma associated with homosexuality in ethnic minority communities may drive individuals at risk to hide, complicating efforts at diagnosis and treatment.

**Prevention**

Until an effective vaccine is available, behavioral interventions are the best means to stop the spread of HIV. Physicians should screen all patients for risk behaviors (unprotected intercourse, multiple partners, concurrent sex and substance use, injection drug use, etc) and should intervene to reduce risk and test for HIV in patients with a positive risk history, repeating testing periodically if risk behaviors continue. A “harm reduction” strategy should be pursued if it is impossible to eliminate all risk (eg, stopping needle sharing until drug abuse can be stopped, keeping condoms available when sex with a new partner is possible, etc). Because patients engaging in risky behaviors often will not volunteer information about their risk, physicians must proactively assess each patient’s risk and intervene when needed.

HIV-negative individuals exposed to HIV may benefit from postexposure prophylaxis (PEP); however, the data supporting antiretroviral treatment following either occupational exposure or sexual exposure are limited. Many experts recommend a four-week regimen of PEP initiated as soon as possible after a significant exposure to HIV; the benefit of treatment started more than 72 hours after exposure is limited. Combinations of antiretroviral agents similar to those used in treating HIV may be employed, with similar adverse effects. PEP is not 100% effective in preventing HIV seroconversion.

**Clinical Findings**

Physicians should consider and test for HIV in individuals at risk who present with routine viral infection symptoms. Patients with acute HIV infection present with symptoms that are generally indistinguishable from common viral infections, including fever (96%), adenopathy (74%), pharyngitis (70%), rash (70%), and other nonspecific symptoms (see Table 14-2). HIV viral load tests (eg, polymerase chain reaction) become positive 1-2 weeks before routine

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumption about sexual orientation: Many patients are neither exclusively heterosexual nor exclusively homosexual.</td>
<td>Learn to inquire about sexual orientation in a nonjudgmental manner that recognizes the range of human diversity and apply this learning to all patients.</td>
</tr>
<tr>
<td>Assumptions about sexual activity: Lesbian and gay male patients may have numerous different sexual partners, be in a monogamous relationship, be celibate, or vary in patterns of activity over time.</td>
<td>Take a specific, sensitive sexual history from all patients.</td>
</tr>
<tr>
<td>Assumptions about contraception: The need for contraception arises from a wish to prevent pregnancy from heterosexual intercourse, regardless of the patient’s gender identity, sexual orientation, or label.</td>
<td>Inquire about need (rather than assuming need) or lack of need for all patients. Tailor recommendations to patient’s needs.</td>
</tr>
<tr>
<td>Assumptions about marriage: Lesbians and gay men may have been, and may still be, married to persons of the opposite sex. In some states and countries, they may be married to same-gender partners and may use the terms “partner” or “husband/wife” to refer to their spouse.</td>
<td>Inquire about significant relationships for all patients. Use the terminology that your patients choose.</td>
</tr>
<tr>
<td>Assumptions about parenting: Lesbian and gay male couples are often interested in and choose to bear and raise children.</td>
<td>Inquire about parenting wishes and choices, and be prepared to discuss options.</td>
</tr>
</tbody>
</table>
(antibody-based) HIV tests and may be useful in diagnosis (as distinct from screening).

Latent HIV infection may be essentially asymptomatic for years. Generalized lymphadenopathy may persist for years; its disappearance may herald clinically significant immune system decline, marked by nonspecific symptoms such as fevers, weight loss, and diarrhea. Early immune dysfunction results in diseases such as herpes zoster or persistent vaginal candidiasis. Without effective antiretroviral treatment almost all patients will progress to one or more AIDS-defining illnesses.

**Treatment**

Patients infected with HIV require a comprehensive care plan that involves skilled physicians, ancillary health services, pharmacologic therapy, and access to social and other support services. Excellent resources exist to guide physicians in the detailed management and care of patients with HIV/AIDS (see next section). The family physician’s role in HIV care will be determined by the knowledge, skill, comfort level, and personal preferences of the physician, as well as the accessibility of referral physicians. Family physicians may serve primarily in case finding, by testing and referring patients found to be HIV positive, or may assume full responsibility for comprehensive management of HIV and its complications.


**Web Sites**

AIDS Education and Training Centers (AETCs):
http://www.aids-ed.org/

AETC Warmline/Pepline, a national HIV patient management and postexposure prophylaxis telephone consultation service: http://www.ucsf.edu/hivcnr/

InSite Knowledge Base, a comprehensive, on-line textbook of HIV disease from the University of California, San Francisco and San Francisco General Hospital: http://hivinsite.ucsf.edu/InSite?page=KB


Project Inform: http://www.projectinform.org

**SEXUALLY TRANSMITTED DISEASES**

**ESSENTIALS OF DIAGNOSIS**

- Many sexually active gay men are at increased risk for most STDs, requiring routine periodic screening.

- Suspicion or diagnosis of one STD should routinely lead to testing for concomitant HIV and syphilis.

- Although generally at lower risk for STDs, lesbians have a higher incidence of bacterial vaginosis than heterosexual women.

**General Considerations**

In the United States, causes of genital ulcer disease (GUD) in heterosexual and homosexual men are most commonly due to herpes simplex and syphilis. Other causes of GUD are less common, although epidemiology may be changing: an outbreak of lymphogranuloma venereum in MSM first reported in the Netherlands has produced cases of GUD and proctocolitis in MSM throughout Europe and the United States. Gonorrhea, chlamydia, and nonchlamydial nongonococcal urethritis (NGU) are common problems in sexually active gay men. As each of these may cause asymptomatic infection, periodic screening may be useful to detect clinically silent disease.

The enterobacteriae that commonly cause enteritis and proctocolitis may be sexually transmitted via oral-anal contact, and even organisms not commonly thought to be pathogenic, such as *Endolimax nana* and *Blastocystis hominis*, should be treated in the symptomatic patient lacking other causes of abdominal symptoms. *Giardia lamblia* should also be included in the differential diagnosis of enteritis and proctocolitis in MSM, as well as CMV in the HIV-positive patient. Unprotected receptive anal intercourse can lead to the tenesmus, rectal pain, and bleeding of proctitis, with common pathogens being *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Treponema pallidum*, and herpes simplex virus.

Kaposi sarcoma (KS) poses another health risk for gay men. Although generally associated with HIV infection, KS resulting from infection with a herpesvirus, KSHV/HHV-8, can occur in the absence of HIV. It appears that this virus is sexually transmitted, probably by receptive anal intercourse, and may be carried in saliva. Although cases of KS among gay men in the absence of coexisting HIV infection are rare and even in HIV-infected patients the incidence has decreased significantly from the early period of the AIDS epidemic, physicians should be suspicious of red or purple patches or nodules on the skin or mucous membranes, and should evaluate or refer patients for treatment when indicated.

Fellatio, commonly thought to be a “safe” sexual practice, may be an independent risk factor for urethral and pharyngeal gonorrhea and nonchlamydial NGU; has been implicated in HIV transmission; and has been associated with localized syphilis epidemics in gay men. Syphilis epidemics
have also been associated with high-risk sexual activity among HIV-positive men.

Some researchers have shown comparable rates of STDs between lesbians and heterosexual women, though the types of infections varied; genital herpes and genital warts were more common in the heterosexual women, and bacterial vaginosis (BV) was more common in lesbians. One series found a 2.5-fold increase in BV among lesbians compared to heterosexual women, often with concordance in vaginal flora between female partners. Other investigators have observed different prevalence of BV and warts between lesbians and heterosexual women, but not herpes, although the nature of the inner-city population studied may preclude generalizing these findings to all lesbians.


Fethers K et al: Sexually transmitted infections and risk behaviours in women who have sex with women. Sex Transm Infect 2000;76:345. [PMID: 11141849]

Peterman TA, Furness BW: The resurgence of syphilis among men and women (see Chapter 14 for screening recommendations and other information about STDs). If not immune, gay men should be vaccinated against hepatitis A and hepatitis B.

Prevention

Counseling has been shown to reduce risk behaviors, and patients reporting high-risk behaviors or those diagnosed with an STD should receive or be referred for individual or group counseling. Additionally, MSM patients engaging in sex outside a mutually monogamous relationship should receive periodic STD screening, as should women having sex with men and women (see Chapter 14 for screening recommendations and other information about STDs). If not immune, gay men should be vaccinated against hepatitis A and hepatitis B.

Patient Education

All patients in whom a STD is suspected or diagnosed should receive information about routes of transmission and how to reduce infection risk. Information about specific treatment, if any, as well as potential coinfection with other sexually transmissible agents should also be provided. Patients should be counseled to contact sex partners; in lieu of this, the physician or health department may notify partners.


HUMAN PAPILLOMAVIRUS INFECTION

ESSENTIALS OF DIAGNOSIS

- Human papillomavirus (HPV) causes cervical cancer in both heterosexual and lesbian women; lesbians should be offered Papanicolaou (Pap) smear screening according to the same guidelines used for heterosexual women.
- Some investigators recommend that men who have engaged in receptive anal intercourse receive anal Pap smears, especially if those men are also HIV positive.

General Considerations

HPV is a pervasive infection, manifesting in more than 100 viral types that infect various parts of the human body. HPV types that infect the genitalia carry varying risk for dysplasia and neoplasia. Ironically, the types that cause the most visually apparent warts are usually the types with least risk for dysplasia; conversely, the types causing clinically inapparent disease carry high dysplastic risk.

Prevention

Secondary prevention via Pap smear remains the cornerstone of screening. One study of lesbians revealed that 25% of respondents had not had a Pap test within the past 3 years, and 7.6% had never had a Pap test. Lesbian patients may mistakenly believe themselves to be less susceptible to cervical cancer than heterosexuals or bisexuals, even though one study showed 79% reported previous sexual intercourse with a man. Even in women reporting no prior sex with men, HPV DNA and squamous intraepithelial lesions (SILs) may be found in up to 20% of patients. Thus cervical Pap smears should be performed routinely, supplemented by HPV DNA testing if and when indicated. Individuals with abnormal screening tests should receive colposcopy or anoscopy and subsequent follow-up as indicated by findings.

A gay man’s risk of anal squamous cell carcinoma is equivalent to the historical risk of cervical cancer that women faced prior to the advent of Pap screening. Anal HPV DNA is very prevalent in gay men; in one study it was detected in 91.6% of HIV-positive and 65.9% of HIV-negative men. HIV exacerbates HPV effects, and is associated with more prevalent HPV infection and higher-grade SILs. Screening HIV-positive homosexual and bisexual men for anal SILs and anal squamous cell carcinomas with anal Pap tests offers quality-adjusted life expectancy benefits at a cost comparable with other accepted clinical preventive interventions. Because the observed increased incidence of anal cancer does not appear to be solely due to HIV infection, high-resolution anoscopy and cytologic screening of all MSM with anal condyloma and other benign noncondylomatous anal disorders is supported by current knowledge.
Experimental vaccination has been shown to prevent infection with some types of HPV commonly associated with cancer development. A quadrivalent vaccine against HPV is available and licensed for females aged 9-26 years, and studies of HPV vaccine use in boys and men demonstrate safety and efficacy, and FDA indications include use in males aged 9-26 for prevention of genital warts. Additional discussion of HPV appears in Chapter 14.


### SUBSTANCE ABUSE

#### ESSENTIALS OF DIAGNOSIS

- Substance use is more common in LGBT patients than in the general heterosexual population.
- Methamphetamine use and addiction is particularly problematic in some gay male groups.

#### General Considerations

Alcohol, psychoactive drug, and tobacco use appear more widespread in gay men and lesbians than in the general heterosexual population. Several studies suggest that lesbians and bisexual women consume more alcohol and use other psychoactive substances more than heterosexual women. A recent meta-analysis found risk ratios of 4.0 and 3.5 for alcohol and substance dependence, respectively, among WSW and WSMW as compared to WSM. Another review of tobacco use found that smoking rates among adolescent and adult lesbians, gays, and bisexuals are higher than in the general population.

Methamphetamine use has reached epidemic proportions in some gay male populations, and routine history taking should include at least a brief screen for its use.

Alcohol use has been associated with high-risk sexual behavior (ie, unprotected anal and oral intercourse). Gay men who have unprotected anal intercourse are more likely to have a drinking problem and to drink more than gay men who do not have unprotected intercourse, and unprotected intercourse after drinking is more common with nonsteady sexual partners. Drug use is also associated with increased high-risk sexual behaviors. Drugs for which this association has been demonstrated include hallucinogens, nitrate inhalants, and cocaine and other stimulants. Drug use during high-risk sex is common. However, associations between drug use and high-risk sexual behavior exist only for current use, not past drug or alcohol use. Thus, efforts to provide adequate treatment to patients with substance abuse problems can diminish their subsequent risk of acquiring HIV and other STDs.

In some venues the prevalence of illicit drug use and associated high-risk sexual activity is dramatic, with use of substances such as MDMA or ecstasy approaching 80% of the population. Men who attend “circuit parties”—a series of dances or parties held over a weekend that are attended by hundreds to thousands of gay and bisexual men—should be considered at high risk for concurrent illicit substance use and should be counseled accordingly.

Anabolic steroid use is a problem among a subset of gay men. One British study of over 1000 gay men recruited from five gymnasiums found that 13.5% of the study population used anabolic steroids, and users were more likely than never users (21% vs 13%) to report engaging in unprotected anal intercourse, increasing their risk for HIV infection.

#### Pathogenesis

Several theories have been proposed to explain the increased substance use seen in LGBT patients. The observed behavior has been variously explained as a maladaptive coping strategy to deal with societal bias against homosexuality; a consequence of bars serving as a primary social gathering place for lesbians and gay men; due to a genetic predisposition to substance abuse linked to genes coding for same-sex attraction; a coping method for dealing with stresses such as fear of HIV infection, lack of social supports, fear of discrimination in housing or employment, and rejection by family or friends on the basis of sexual orientation; or something else. Research to date has not explained causation.

Reasons for steroid use are more straightforward: to modify the patient’s musculature to conform more closely with an idealized male form. Significant social pressures may cause patients to resort to steroids as a means to achieve an idealized masculine physique, and for these patients substantial support and counseling may be required to overcome steroid abuse.

#### Prevention & Treatment

By and large, prevention, clinical findings, complications, and treatment of substance abuse in LGBT populations are similar to these management considerations in heterosexual populations (see Chapter 56 for further discussion). However, modification of standard treatment approaches to reflect LGBT culture may enhance treatment effectiveness. Differences to consider with this population include the prevalence of methamphetamine use, and its association with high-risk sexual behavior among some groups of gay men; concomitant use of sildenafil (Viagra) or other treatments for erectile dysfunction; and “club drugs” (eg, MDMA or ecstasy, amphetamines, γ-hydroxybutyrate, ketamine). Erectile dysfunction treatments, either with or without other substance use, are associated with high-risk sexual behavior.

One study of lesbians considered predictors of depression and looked at relationship status, relationship satisfaction, social support from friends, social support from family, “outness” (degree to which the woman publicly shared her sexual orientation), and relationship satisfaction. Lack of social support from friends, poor relationship satisfaction, and lack of perceived social support from family were significant predictors of depression.

**Prevention**

Well-being is enhanced during later stages of gay identity development, suggesting that helping to facilitate an individual’s synthesis of his or her gay identity may alleviate depressive symptoms. Conversely, in HIV-positive men, concealment of homosexuality is associated with lower CD4 counts and depressive symptoms, lending further support to the idea that facilitating gay identity development may alleviate or prevent depression in some patients, and in so doing, better equip them to maintain their health.

**Clinical Findings**

Symptoms and signs of depression in lesbian and gay male patients are very similar to those in heterosexual populations (see Chapter 52). Although depression is often associated with decreased sexual activity, one study of gay men revealed 16% had heightened sexual interest while depressed. Predictors of depression in lesbians (eg, social support from friends, relationship status satisfaction, and perceived social support from family) are similar to predictors for heterosexual women.

**General Considerations**

Feelings of being stigmatized, internalized homophobia (the direction of society’s negative attitudes toward the self), and actual experiences of discrimination or violence contribute to gay men’s distress. In a study of HIV-infected men that may have relevance for all gay men, it was found that men who did not demonstrate traditional gender identity were more likely to have current symptoms of anxiety and depression and to have had a lifetime history of depression. Depression has also been linked to the AIDS epidemic, and particularly to being a caregiver for someone with AIDS, regardless of whether the caregiver is infected with HIV or not.

Well-designed studies with valid sampling techniques have demonstrated that suicidal ideation, attempts at suicide, and completed acts of suicide are more common in gay, lesbian, and bisexual youth than in their heterosexual counterparts. Population-based research demonstrates significantly higher rates of suicidal symptoms and suicide attempts among men who reported same-sex partners than among men who reported exclusively opposite-sex partners. A recent meta-analysis indicates a four-fold increase in lifetime suicide attempt prevalence among gay and bisexual men as compared to heterosexual men. Other investigators have demonstrated similar findings (eg, in a study of twins in which one brother reported same-sex partners after age 18 and the other did not). Suicidality has been linked to the process of “coming out,” or revealing one’s homosexual orientation to others. Thus, physicians caring for gay adolescents or adults disclosing their sexual orientation to others should be especially sensitive to symptoms or signs suggesting any increase in suicide risk.

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**DEPRESSION**

**ESSENTIALS OF DIAGNOSIS**

- Depression and anxiety are more prevalent in lesbians and gay men than in the general population.
- Suicidal ideation, attempts at suicide, and completed acts of suicide are more common in gay, lesbian, and bisexual youth than in their heterosexual counterparts.
- Suicide risk seems to be increased around the time an individual “comes out” (reveals his or her gay or lesbian identity to others).
- Lack of social supports, lack of family support, and poor relationship quality are significant predictors of depression.

**Cancer Screening**

LGBT patients require the same age- and gender-appropriate cancer screening as heterosexual and non-gender-variant patients. As discussed above, cervical cancer screening should be offered to lesbian women, and anal cancer screening to men with a history of receptive anal intercourse, particularly if they are coinfected with HIV, though there remains insufficient evidence to universally recommend the anal Pap at this time.

Breast cancer may be more common in nulliparous or uniparous women and thus may be more common in lesbians,
but well-designed, prospective studies are lacking. One study compiling survey data from almost 12,000 women found lesbians had greater prevalence rates of obesity and alcohol and tobacco use, and lower rates of parity and birth control pill use. Another study confirmed higher prevalence of nulliparity, and also found higher prevalence of other health risk factors, including high daily alcohol intake, higher body mass index, and higher prevalence of current smoking.

In transgender patients, it is important to screen based on current anatomy as well as use of hormonal therapy. For example, many male-to-female (MTF) transgender patients are at risk for both prostate and breast cancers, and female-to-male (FTM) transgender patients often require screening for breast, uterine, cervical, endometrial, and ovarian cancers. As in any patient population, tobacco and alcohol use among LGBT patients increase risk for malignancy.


Erectile Dysfunction

Studies have demonstrated that erectile dysfunction is more common in homosexual than in heterosexual men, although overall prevalence was still less than 4%. Associated with this observation, gay men also report higher levels of performance anxiety (eg, are more likely to agree with the statement “If I feel I’m expected to respond sexually, I have difficulty getting aroused”) than do heterosexual men; this was true even when men reporting erectile dysfunction were excluded from analysis. Erectile dysfunction is more common in HIV-positive homosexual men than in HIV-negative homosexual men. Declines in serum testosterone have been associated with HIV infection, suggesting one possible etiology for his difference.


Contraception & Reproductive Health

Physicians who assume that all women of reproductive age need contraception risk alienating lesbian patients, who may consequently decline to disclose their sexual orientation. However, lesbians who are sexually active with men may be interested in obtaining contraceptives.

Lesbian patients may also be, or wish to become, mothers and so may welcome a discussion of reproductive options.

Parenthood options available to lesbians and gay men include adoption, artificial insemination, surrogacy, or heterosexual intercourse. Existing evidence suggests that gay men and lesbians have parenting skills comparable to heterosexual parents. Special considerations that may arise for lesbian and gay parents include the children’s awareness of lesbian and gay relationships, heterosexism, and homophobia. When compared with children of heterosexual parents, children of gay men and lesbians seem to be no different in significant variables measured, including their sexual or gender identity, personality traits, and intelligence. Despite this, gay men and lesbians may face unjustified barriers in their attempts to become foster and adoptive parents. Issues that warrant physician awareness include parental legal rights and durable power of attorney; gestation and pregnancy; choice of surrogate, sperm, or egg donor; possible HIV risk; and routine preconception and prenatal care. Physicians caring for lesbians and gay men wishing to become parents should maintain information about appropriate referrals to facilitate this process.


ESSENTIAL FEATURES

Transgender Patients

Rather than assume, physicians should determine how patients wish to be addressed and understand how they conceptualize their gender.

Sex reassignment in adolescence may be indicated for carefully selected patients.

Sex reassignment should be managed by multispecialty teams with experience caring for this population.
transgender individuals as suffering pathology, in a manner similar to the characterization of homosexuality prior to the American Psychiatric Association’s 1973 revision of the DSM. Increased knowledge and changing societal attitudes may alter this characterization at some future time.

A. Terminology

Terminology can be problematic when describing transgender individuals, reflecting evolving knowledge. “Transgender” can be used as an umbrella term for a diverse group of individuals who cross or transcend culturally defined categories of gender in some way. In other usage, the term transgender serves as an umbrella for patients experiencing discordance between their physical gender and their gender identity. “Transsexual” often refers to an individual who has undergone partial or complete sex reassignment surgery (SRS). Intersex individuals are born with both male and female sexual characteristics and organs, such that unambiguous assignment of male or female sex at birth is not possible.

The term male-to-female (MTF) describes individuals born with male genitalia who may undergo treatment to create a female-appearing body; the reverse is true for female-to-male (FTM) individuals. Additional ways to characterize the biological, social, psychological, and legal identity of transgender individuals have been described. In caring for an individual patient, the best approach for physicians is to determine how patients wish to be addressed and to understand how they conceptualize their gender.

In the spectrum of gender identity disorder, individuals who experience the strongest feelings of dissonance between their gender identity and their physical appearance believe the quest for full hormonal and surgical sex reassignment is vital because they actually feel “trapped” in an anatomically wrong body. Currently, the transgender movement includes cross-dressers, female and male impersonators, transgenderists and bigender persons (who identify as both man and woman), as well as transsexuals who have undergone or desire to undergo sex reassignment therapy. Limited research into the etiology of gender identity disorder suggests that it may be multifactorial; there may be anatomic brain differences between transsexual and nontranssexual individuals, as well as differences in parental rearing. Regardless of the etiology or classification, the needs of transgender patients are increasingly recognized as valid, authentic, and deserving of attention from health care educators, researchers, policy makers, and clinicians of all types.

B. Treatment

Perhaps the most important element of treatment is to have a multidisciplinary team experienced with transgender care available to guide therapy. Some patients choose partial medical or surgical treatment of their gender dysphoria, finding that a physical existence with components of both genders best addresses the dissonance caused by their birth physiology. Others wish to use surgery and hormonal treatment to manifest physically their “internal” gender as fully as possible. The literature describing the health needs of transgender patients focuses principally upon psychologic and psychiatric evaluation and treatment, surgical modification or SRS, and hormonal therapy. Although common practice is to delay initiating sex reassignment therapy until the patient is at least 18 or 21 years of age, treatment in adolescence is well tolerated for carefully selected individuals, does not lead to postoperative regret, and may forestall psychopathology seen in transgender individuals forced to delay therapy. Initial treatment of a patient considering SRS should include a complete psychological evaluation by a therapist experienced in working with this population.

Intensive psychological counseling, hormonal treatment, and living in the role of the desired gender for a period of at least 1 year should precede surgical treatment. Surgical treatment can involve the breasts, genitalia, and larynx. Interestingly, even in health systems funded by government support, courts have found that transsexuals have the right to SRS. Because of individual psychological and anatomic variations, surgical approaches must be tailored to individual patients, and patients seeking SRS should be referred to teams experienced with these procedures.

Hormonal treatment is often employed in both genders. Hormones induce feminization or virilization and suppress the hypothalamic-pituitary-gonadal axis. Cross-sex hormonal treatment may have substantial medical side effects, so the smallest doses needed to achieve the desired result should be used. Outcome studies suggest that known complications of hormonal therapy such as galactorrhea and thromboembolic events occur, but that the incidence of complications can be held to acceptable levels with careful attention to regimens used. Extensive experience with hormonal therapies in transsexual patients indicates that hormonal therapy, particularly if transdermal formulations are used, does not cause increased morbidity or mortality; monitoring luteinizing hormone levels in MTF transsexuals may increase the benefit-to-risk ratio by limiting hormone-related bone loss.
Adolescents

Lesbian and gay adolescents growing up in a loving, supportive environment develop and mature in a manner similar to that of their heterosexual counterparts. However, lesbian and gay adolescents may be vulnerable to parental wrath and withdrawal of support upon disclosure or suspicion of their homosexual orientation. In certain instances, this can initiate a chain of events that leaves the youth homeless and vulnerable. Lacking employable skills, some homeless gay youths may resort to prostitution or “survival sex” to support themselves.

Gay youths have an increased risk for suicide compared with their heterosexual peers, and gender nonconformity may be particularly detrimental to boys. In addition, population-based surveys of adolescents indicate that lesbian and gay adolescents report being physically abused up to twice as often as their heterosexual peers, and sexually abused up to 10 times as often as heterosexual adolescents. Despite this, homosexual adolescents are generally more similar to than different from their heterosexual peers, face many of the same challenges, and mostly grow up healthy and happy.

Physicians caring for families need to be aware of the possibility that the normal adolescent struggle to establish identity may be compounded when a teen recognizes his or her gay or lesbian identity, particularly when this occurs in a potentially hostile environment. Physicians can play a vital role in helping the adolescent—and his or her family—accept the patient’s sexual orientation. Parental acceptance and support can dramatically reduce the adverse effects of “coming out” and the potential risk for suicide, and can increase the likelihood of healthy psychological development and maturation.


Older Lesbians & Gay Men

Older lesbians and gay men developed and matured in a different social milieu, when society was less tolerant of homosexuality and the consequences of being gay or lesbian included even greater threats to the individual’s social and family relationships, housing, and livelihood than exist today. Thus, older patients may be even less willing to disclose their homosexual orientation to physicians, and may have special health care needs that would go unrecognized without the taking of a thorough, sensitive sexual history. Incorrect assumptions about geriatric patient sexuality may lead physicians to fail to identify risk behaviors and to implement appropriate education and/or screening tests. Physicians should be mindful that many older lesbians and gay men remain sexually active well into their lives, with older gay men reporting less condom use than their heterosexual counterparts.

Although not extensive, research suggests that many lesbians and gay men successfully navigate the aging process and remain connected and involved in life. In fact, the demands of being gay may cause individuals to face the challenges associated with aging more successfully than their heterosexual counterparts.


Family & Community

One aspect of being gay or lesbian that may be overlooked in caring for a patient’s medical needs is the role of family and social networks in providing support and sustenance to the LGBT patient. In this context, family often includes individuals unrelated by biological ties. A useful concept is that of “family of origin,” which consists of parents, siblings, and others with whom one shares a blood relation, contrasted with “family of choice,” which includes those close friendship relationships that endure over time and incorporate the same types of support and emotions often associated with idealized views of the traditional family. The family of a lesbian or gay patient, including her or his partner, is a vital part of the individual’s health and can serve as a source of both stress and support, just as with heterosexual patients. Physicians caring for gay men and lesbians need to assess the resources and stressors that exist within the family, as defined by the patient.
BACKGROUND

Homes for the dying, or as they were soon to be called, hospices, were established in Ireland and France in the nineteenth century. However, it was not until 1967 that the first truly modern hospice, Saint Christopher’s Hospice, was founded in London. There, Dr Cicely Saunders, a former nurse and social worker who had earned a medical degree, helped to establish the underlying philosophy of hospice and palliative medicine. She emphasized clinical excellence in pain and symptom management; care of the whole person, including physical, emotional, social, and spiritual needs; and the need for research in this newly developing field of medicine. Interdisciplinary team care became the norm, as it became clear that no one physician, nurse, social worker, or chaplain could address all the needs of the terminally ill person. Further, although the focus of care was clearly on the dying individual, the needs of the family were also addressed.

Florence Wald, RN, PhD, Dean of the Yale School of Nursing, invited Dr Saunders to lecture to medical, nursing, and social work students at Yale in 1963 on care of the terminally ill. Dr Wald spent 1968 at Saint Christopher’s on sabbatical and after her return to the United States helped to establish the Connecticut Hospice, the first hospice in the United States, in 1974. In 1982, the Congress created the Medicare Hospice Benefit (MHB), and in 1986, the benefit was made permanent. By 2007, 4700 hospice programs were providing health care services to the terminally ill and their families throughout the United States.

Eligibility criteria for hospice enrollment through the MHB require that patients waive traditional Medicare coverage for curative and life-prolonging care related to the terminal diagnosis and be certified by their physician and the hospice medical director as having a life expectancy of 6 months or less if the disease runs its usual course. The patient may be recertified as eligible for the MHB even if the patient has already been receiving the benefit for 6 months or longer.

The goal of hospice care is to relieve suffering and improve the patient’s and family’s quality of daily life. To achieve those goals, hospice care has come to be defined as holistic, patient, and family centered rather than disease centered. Hospice provides a team composed of those trained to care for problems in a holistic manner: physician, nurse, social worker, chaplain, bereavement counselor, nursing assistant, and volunteer. The hospice team meets weekly, under the direction of the hospice medical director, to review the care plans of all patients. Further, although the focus of care was clearly on the dying individual, the needs of the family were also addressed.

Palliative medicine has developed as a medical subspecialty in the United States over the past 20 years, bringing a “hospice-like” approach to patients with terminal or life-limiting illnesses who have a prognosis of more than 6 months or to those pursuing aggressive life-prolonging treatments. The goals of palliative care programs are similar to hospice: pain and symptom control; emotional, social, and spiritual support of patients and families; and facilitation of clear and compassionate communication regarding goals of treatment. Many models of palliative care are under development. There are palliative care consultation teams in hospitals, nursing homes, and in outpatient clinics. The growth of palliative care consultation programs over the past 10 years has been significant and mirrors the growth of hospice since 1974. The number of hospital-based palliative care consultation programs has increased linearly from 632 (15%) in 2000 to 1027 (25%) in 2003 and continues to grow annually.

Palliative medicine fellowships are undergoing rapid development as well. In the early 1990s, the first US palliative medicine fellowship was initiated. By June 2006, 49 programs offered 119 fellowships for advanced training. In September 2006, the field of palliative medicine was officially
recognized as a subspecialty by the American Board of Medical Specialties.

PAIN & SYMPTOM MANAGEMENT

Good symptom control is the cornerstone of palliative medicine. Distressing symptoms can consume patients and rob them of their will to live. Uncontrolled symptoms detract from patients’ quality of life, their interactions with loved ones, and their ability to attend to important issues at the end of life. Many studies have documented the high frequency of symptoms and the tendency for symptoms to increase in intensity as a disease progresses. The following discussion reviews management of some common symptoms. As with most medical problems, successful management of symptoms starts with a careful history and physical examination, with therapy directed at the underlying cause, if possible.

Pain

Pain can be classified physiologically as somatic, visceral, neuropathic, or of mixed type. Pain can occur from direct tumor involvement, as a consequence of cancer therapy, or from unrelated pathology. It is important to remember that pain is a subjective experience that can be influenced by psychosocial and spiritual issues.

The World Health Organization (WHO) published guidelines on pain control in 1996 (Figure 63-1). These guidelines have proven effective in large-scale studies in cancer patients, and for the majority of patients their application will lead to effective pain control. Based initially on the severity of the patient’s pain, different medications can be used and adjustments made depending on the patient’s response.

General principles of opioid administration include the following:

- Equianalgesic tables for opioids are available in most general pharmacology texts; these tables may differ slightly.
- Morphine is the most commonly used opioid and is the most versatile in terms of available formulations.
- Opioid-naive patients should be started on morphine sulfate, 5 mg immediate-release formulation, given orally every 4 hours (scheduled), and every 2 hours as needed. This regimen can then be converted to the sustained-release formulation based on the previous 24-hour dose, and titrated based on pain control.
- Chronic pain deserves around-the-clock pain medication, not just as-needed dosing.
- As-needed medications should always be provided for breakthrough pain.

▲Figure 63-1. WHO three-step pain control guidelines.
• Breakthrough doses are generally 10%-15% of the 24-hour dose.
• Breakthrough medications can be given as frequently as the time to peak onset of action: 1-2 hours for oral immediate-release formulations and 10-15 minutes for intravenous formulations.
• When pain control is inadequate, the scheduled dose should be increased by 30%-50% after 24 hours (after 48 hours for fentanyl patches). The amount of breakthrough medication used must be considered in calculating the additional amount of drug patients can tolerate—usually being able to tolerate an additional dose equivalent to the amount of breakthrough medication.
• There is no specific limit to the opioid dose; these agents should be titrated until pain control is achieved or side effects develop.
• Fentanyl patches should not be used alone for acute severe pain. Because of the delayed onset of effect (12 hours) and long half-life of this formulation, it cannot be titrated quickly for rapid pain control.
• The lowest available fentanyl patch may be excessive in patients who are opioid naive (a 12-μg/h fentanyl patch is approximately equivalent to 25-35 mg of oral morphine sulfate over 24 hours).
• Morphine sulfate, hydromorphone, and fentanyl can be administered subcutaneously for patients unable to take oral formulations and who do not have intravenous access. Subcutaneous doses are equivalent to intravenous doses.
• When pain is severe, parenteral opioids are preferable because of their quicker onset of action and ease of titration. Conversion to oral formulations can occur after pain is controlled.
• With patient-controlled analgesia (PCA), opioids can be infused at a continuous basal rate and patients control the administration of bolus doses. The total hourly dose and lockout interval between boluses are preprogrammed. PCA can be administered intravenously or subcutaneously at home with specialized syringe drivers or infusion pumps.
• With most opioids, oral and parenteral doses are not equal—parenteral morphine sulfate supplies one-third the oral morphine sulfate dose, and parenteral hydromorphone one-quarter the oral hydromorphone dose. Care must therefore be taken when converting from the oral to the parenteral form.
• When side effects develop and are not easily controlled, options include decreasing the opioid dose if pain is well controlled, switching to a different opioid, or decreasing the opioid dose and adding adjuvant pain medication.
• Because nausea and vomiting are common transient side effects of opioid therapy, metoclopramide or haloperidol is sometimes started prophylactically for the first several days of opioid therapy.
• Tolerance to the respiratory depressant effects occurs rapidly; thus, opioids can be used safely when titrated to pain control, even in patients with underlying emphysema.
• Constipation is a side effect of opioids to which patients do not become tolerant; laxatives should be included whenever patients are receiving opioids.
• Methadone has a biphasic and variable half-life; therefore, administration can be difficult and should be attempted carefully by those experienced in its use.
• Psychostimulants, such as methylphenidate, amphetamine, and modafinil can be prescribed for some patients troubled by persistent opioid induced sedation.

Unlike opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen have a ceiling effect to their analgesia. The use of opioid-nonopioid combinations therefore is limited by the dose of the NSAIDs or acetaminophen. Despite this fact, NSAIDs are effective pain medication, especially for inflammatory conditions. Their use can decrease the amount of opioids required and hence decrease the incidence of opioid side effects. Unless contraindicated, all pain protocols should include NSAIDs.

Neuropathic pain results from nerve injury. Often described as sharp, electric shock-like, or burning in nature, neuropathic pain generally occurs along specific dermatomes. Patients with neuropathic pain occasionally respond to opioids alone; however, many require the addition of adjuvant pain medications. Commonly used adjuvants for neuropathic pain include tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitors (SNRIs), anticonvulsants, and antiarrhythmics. The choice of an adjuvant is usually dictated by the individual drug side-effect profile, the potential for drug interactions, and the previous drug therapy. The secondary amines, nortriptyline and desipramine, are generally better tolerated than amitriptyline. The analgesic effects of TCAs occur at lower doses and usually within several days, as compared with the antidepressant effects. Data on use of selective serotonin reuptake inhibitors (SSRIs) for neuropathic pain are not convincing; however, recent studies suggest that SNRIs may be as beneficial at tricyclic agents for pain control. Of the anticonvulsants, gabapentin, pregabalin, carbamazepine, and valproic acid are commonly used for neuropathic pain. Carbamazepine and valproic acid are cost-effective but have a higher risk of drug interactions and toxicity compared with gabapentin and pregabalin. Gabapentin requires more frequent dosing, slower titration secondary to sedation, and dose adjustments for renal insufficiency. Antiarrhythmics, topical lidocaine, and oral mexiletine have also been used successfully for neuropathic pain. For adjuvant pain medications, standard initial dosing and titration guidelines should be followed, although lower than usual doses have been effective for pain control. In elderly patients, it is generally safer to start at low doses and titrate at a slower rate.
Corticosteroids, benzodiazepines, and anticholinergics are also used as adjuvant pain medication. Corticosteroids, by decreasing tumor-associated edema and by their anti-inflammatory effects, are useful for pain due to multiple pathologies, including bone metastasis, liver capsule distention from metastasis, and conditions in which the tumor is compressing sensitive structures. Benzodiazepines and baclofen are indicated for pain from spasticity. Anticholinergics can relieve colic due to intestinal obstruction.

In addition to drug therapy for pain control, interventions such as palliative radiation therapy for bone metastasis, nerve blocks (e.g., celiac plexus block for pancreatic cancer), palliative surgical resection, or immobilization of fractures should be considered. Before undertaking such interventions, the patient’s overall prognosis and the effectiveness of less invasive measures should be taken into consideration.

Complementary therapies are often used in hospice and palliative care for treatment of pain and other symptoms. Some of these therapies are described in Table 63-1.

Fear of addiction should not hinder the use opioids for pain control. Addiction is a rare occurrence in patients with terminal illness and in patients without a prior history of drug abuse. Psychological addiction should be differentiated from physical dependence. Patients with physical dependence develop withdrawal symptoms with the abrupt cessation of a drug or significant reduction of dosage. If the need arises for a rapid decrease in the opioid dose, administering 25% of the stable dose can prevent withdrawal symptoms. In patients previously receiving steady opioid doses, dose escalation portends disease progression rather than tolerance to opioid analgesic effects. Analgesic tolerance, like addiction, is rarely seen.

### Table 63–1. Complementary modalities used in palliative medicine.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Brief Description</th>
<th>Recommendations</th>
</tr>
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| Acupuncture        | Stimulation of defined points on the skin using a needle, electrical current (electroacupuncture), or pressure (acupressure). These points correspond to meridians, or pathways of energy flow with the intent to correct energy imbalances and restore a normal, healthy flow of energy in the body. | 1. Acupuncture may provide pain relief in terminally ill patients with cancer pain.  
2. Acupuncture may provide relief from breathlessness.  
3. Acupressure may reduce chemotherapy- and radiation-induced nausea and vomiting. |
| Aromatherapy       | Therapeutic use of essential oils, which are applied to the skin or inhaled. The impact on the emotional and psychological state is mediated through the olfactory nerve and the limbic system in the brain. | 1. Aromatherapy may be used in conjunction with other complementary therapies, such as massage.  
2. Aromatherapy may provide reduction in anxiety. |
| Massage therapy    | Manipulation of the muscles and soft tissues of the body for therapeutic purposes. | 1. Massage might provide short-term reduction in cancer pain.  
2. Massage has been shown to reduce stress and anxiety and enhance feelings of relaxation. |
| Hypnosis           | A state of increased receptivity of suggestion and direction.                     | 1. Hypnotherapy may reduce nausea and vomiting in persons receiving chemotherapy.  
2. Hypnotherapy can enhance pain relief. |
| Relaxation         | The use of muscular relaxation techniques to release tension. These techniques are often used in conjunction with meditation, biofeedback, and guided imagery techniques. | 1. Relaxation can reduce stress and tension.  
2. Relaxation techniques can improve pain control in advanced cancer patients. |
| Therapeutic touch  | A technique performed by physical touch and/or the use of hand movements to balance any disturbances in a person’s energy flow. | 1. Therapeutic touch may increase hemoglobin levels.  
2. Therapeutic touch may relieve anxiety and tens-ion and reduce the effects of stress on the immune system. |
| Music therapy      | The use of music as a therapy to influence mental, behavioral, or physiologic disorders. | 1. Music therapy may assist in the reduction of pain perception.  
2. Music therapy may reduce anxiety and help persons cope with grief and loss. |
| Support group      | The use of groups and psychosocial interventions to help persons learn how to cope better with their disease. | 1. Support groups can enhance the quality of life.  
2. Support group therapy can improve pain management and coping skills.  
3. Support group therapy can reduce anxiety and depression. |
Nausea & Vomiting

Nausea and vomiting entail a complex physiologic process. Several discrete afferent neural pathways terminate at the “vomiting center” (Figure 63-2). Stimulation of this center leads to the efferent emetic reflex; however, because multiple receptors and neurotransmitters are involved with each pathway, patients can experience nausea without vomiting and vice versa.

The list of possible etiologies of nausea and vomiting is extensive. Treatment should be directed at correcting the underlying pathology when possible. The choice of antiemetics is based primarily on the suspected afferent pathway involved. Other factors to consider include route of administration, patient’s previous antiemetic drug experience, drug side-effect profile, and cost of therapy.

Classes of antiemetics include the following:

- Butyrophenones: haloperidol and droperidol (narrow-spectrum dopamine-2 antagonists).
- Phenothiazines: promethazine, prochlorperazine, and chlorpromazine (broad-spectrum anticholinergic, antihistamine, and antidopaminergic).
- Benzamide: metoclopramide (antidopaminergic, cholinergic, and at high doses 5-hydroxytryptamine-3 [5-HT3] antagonist).
- 5-HT3 receptor antagonists: ondansetron, granisetron, and dolasetron.
- Anticholinergics: scopolamine, hyoscine, and glycopyrrolate.
- Antihistamines: meclizine and diphenhydramine.
- Cannabinoids: dronabinol.
- Corticosteroids: dexamethasone.

Drug therapy for specific causes of nausea and vomiting includes the following:

- Vestibular dysfunction (motion induced): antihistamines, anticholinergics, or both.
- Delayed gastric emptying or squashed stomach syndrome (hepatomegaly, ascites): metoclopramide.
- Drug-induced and metabolic causes (hypercalcemia, uremia): selective antidopaminergic agents, haloperidol, or dronabinol.
- Increased intracranial pressure: steroids, specifically dexamethasone.
- Chemotherapy and radiation induced: 5-HT3 receptor antagonists.
- Anticipatory nausea associated with chemotherapy: benzodiazepines.

![Figure 63-2. Vomiting pathways.](Reproduced, with permission, from Baines MJ: ABC of palliative care. Nausea, vomiting, and intestinal obstruction. BJM 1997;315:1148.)
DYSPNEA

Dyspnea can be present with or without hypoxia and, like pain, is a subjective experience. With a broad differential existing for dyspnea, reversible causes should always be considered first. The optimal therapy is aimed at the presumed etiology. Palliative therapy can involve chemotherapy, radiotherapy, thoracentesis, pericardiocentesis, and bronchial stent placement. Minor adjustments in the environment, such as providing a fan and keeping the room temperature cool, or a careful trial of supplemental oxygen can help dyspneic patients. Available palliative drug therapies include steroids, opioids, bronchodilators, diuretics, anxiolytics, antibiotics, and anticoagulants. All these drugs can be used in combination, depending on the etiology of dyspnea.

Opioids can relieve breathlessness associated with advanced cancer. The mechanism is unclear. Opioid administration, dose, frequency, and titration are the same as for pain control. The use of nebulized morphine sulfate is not more effective than placebo. Opioids can increase exercise tolerance and reduce dyspnea in patients with chronic obstructive airways. Fear of addiction or fear of respiratory depression should not preclude a trial of opioids in this population. Starting at low doses, carefully titrating the dose to achieve symptom control, and close monitoring allow for safe and effective use.

Steroids are useful for dyspnea from bronchospasm and tumor-associated edema. Specific indications include malignant bronchial obstruction, carcinomatous lymphangitis, and superior vena cava syndrome. Dexamethasone can be started at 8 mg twice daily and subsequently reduced to the lowest effective dose. Dexamethasone is more potent and has lower mineralocorticoid activity than other steroids, resulting in less fluid retention.

Some patients with dyspnea express disturbing fears of suffocation and choking. Understandably, anxiety often coexists with chronic dyspnea. Anxiety can heighten breathlessness, making symptom control more difficult. The use of anxiolytics such as benzodiazepines and pentoctothiamine can help treat dyspnea associated with a high component of anxiety. Lorazepam, 0.5–1 mg, can be tried initially. If patients show benefit, long-acting diazepam or clonazepam can then be prescribed. Low-dose chlorpromazine has also shown benefit in relieving both dyspnea and anxiety.

Anorexia & Cachexia

Anorexia (poor appetite) and cachexia (severe weight loss) are prevalent distressing symptoms in patients with advanced cancer. Factors released either by the tumor or by the host response appear to produce the anorexia-cachexia syndrome. Cytokines implicated include tumor necrosis factor, interferon-γ, and interleukins-1 and -6. The syndrome is characterized by impaired metabolism of carbohydrates, protein, and lipids. A perpetual catabolic state ensues, with loss of protein and lipid stores. Patients lose weight and appear malnourished despite adequate nutrient intake. There is an abundant amount of research in this field, but little effective drug therapy available. Medications prescribed for the anorexia-cachexia syndrome include megestrol acetate, corticosteroids, dronabinol, and anabolic steroids. Megestrol acetate, a progestin, has been shown to increase appetite and result in weight gain; doses start at 160 mg/d and can be titrated to 800 mg/d if required. Corticosteroids, such as dexamethasone, can be prescribed as an appetite stimulant for patients in whom side effects of long-term steroid use are of less concern. Beneficial effects tend to be limited to several weeks. Significant weight gain is not seen with corticosteroids in this population. Dexamethasone can be started at 2–4 mg daily, with titration to 16 mg daily as needed. The lowest effective steroid dose should always be used. Androgens and dronabinol have been effective for patients with AIDS-associated anorexia and cachexia. Investigations are ongoing with respect to the use of omega-3 fatty acids and melatonin.

Anorexia can be provoked by conditions such as delayed gastric emptying, constipation, mucositis, or thrush, or even ill-fitting dentures. Metoclopramide, a prokinetic agent, can improve anorexia associated with early satiety or nausea. It is important not to overlook reversible causes of anorexia.

Nutritional support, parenteral and enteral, has not been shown to prolong survival in patients with advanced cancer who are not candidates for disease-specific therapy. Regardless,
a role for palliative nutritional support exists. Patients who suffer from concurrent malnutrition—for example, patients with dysphagia from head and neck cancer or patients with gastrointestinal dysfunction from radiation toxicity or neuromuscular disorders—can potentially benefit from nutritional support. Consideration of artificial nutrition should be on an individual basis.

► Asthenia

Asthenia is generally described as excessive fatigue. Patients with asthenia feel tired after minimal activity or lack the energy to perform daily activities. Patients become increasingly dependent on others for basic needs. Feelings of helplessness can lead to mood disturbances and depression, symptoms that often accompany asthenia. Asthenia is pervasive in advanced disease and may result from direct tumor effects (eg, cancer cachexia, paraneoplastic neuropathy or myopathy, and tumor involvement of the central nervous system [CNS] or spine) or be a consequence of therapy (eg, steroid myopathy, chemotherapy, radiation, or drug toxicity). Unfortunately, when disease-specific therapy is not effective, asthenia is difficult to palliate.

Nondrug therapies include a trial of transfusion for anemia; optimizing fluid and nutritional status; aggressive treatment of nausea, vomiting, and constipation; oxygen supplementation for hypoxia; moderate physical therapy to improve mobility; providing appropriate assistive devices; and providing psychosocial support. Symptomatic drug therapy includes corticosteroids and psychostimulants. A short course of dexamethasone or methylphenidate can increase patients’ energy levels and improve their mood. The usual starting dose of dexamethasone is 2-4 mg once or twice daily and of methylphenidate, 2.5-5 mg twice daily. To lessen potential insomnia at night, these drugs should be administered early in the day (ie, 8 am and 12 noon).

► Key Considerations in Symptom Management

Physicians caring for patients with terminal illnesses must consider carefully the risks and benefits of all interventions in the context of the patient’s quality of life and prognosis. Whenever possible, the patient and loved ones should be included in the decision-making process. The appropriateness of interventions should be reevaluated as disease progresses.

Physicians should pay special attention to details of drug prescribing, written instructions, side-effect profile, potential drug interactions, and cost of therapy. Any of these factors can easily affect treatment outcome. The patient’s response to therapy should be assessed frequently, and trials of drug therapy discontinued if ineffective. Knowing when to consult specialists is a basic and essential part of care; as a general rule, a consult should be considered whenever a patient’s symptoms are difficult to control.

PSYCHIATRIC DIMENSIONS IN PALLIATIVE CARE

► Depression

There is a common assumption that all patients with terminal illnesses are and should be depressed. This thought promotes the underdiagnosis of depression and in turn its undertreatment. Depressive states exist on a continuum from normal sadness that accompanies life-limiting disease to major affective disorders. It is important that physicians differentiate among these levels of distress. Studies have suggested that physicians and nurses do not recognize levels of depressive symptoms and that failure to do this is worse when such symptoms are more severe.

Diagnosing depression in physically healthy patients depends heavily on the presence of somatic symptoms such as decreased appetite, loss of energy, insomnia, loss of sexual drive, and psychomotor retardation. These neurovegetative symptoms of depression are very compelling when present in the absence of physical illness but are less reliable for diagnosing depression in patients with advanced disease, in whom loss of appetite can be due to chemotheraphy, fatigue can be due to cancer, and lack of sleep can be due to unrelied pain. It is often difficult to determine whether somatic symptoms in patients with advanced disease are a result of depression or other medical causes.

Persistently depressed mood and sadness can be an appropriate response for a patient with a life-threatening disease, so the diagnosis of depression in patients with advanced cancer relies more on the other psychologic or “cognitive symptoms.” Anhedonia is a useful, if not the most reliable, depressive symptom to monitor. Cancer patients who are not depressed, although periodically sad, maintain the capacity for experiencing pleasure, and there is nothing inherent to the disease or treatment process that robs them of the ability to feel pleasure. Such patients react positively to opportunities to engage in the activities that they enjoy, even though the range of activities available to them may be diminished. Indeed, some patients with far advanced disease experience exhilaration in things such as intimacies with family or friends knowing that the experiences are among the last they might have. Feelings of hopelessness, worthlessness, excessive guilt, loss of self-esteem, and wishes to die are also among the most diagnostically reliable symptoms of depression in cancer patients.

The interpretation of even these more reliable symptoms can be difficult. Hopelessness that is pervasive and accompanied by a sense of despair or despondency is likely to present as a symptom of a depressive disorder. Suicidal ideation, even rather mild and passive forms, is very likely associated with significant degrees of depression in patients with advanced disease. Several groups, recognizing the difficulties in applying traditional diagnoses of depression from the Diagnostic and Statistical Manual of Mental Disorders in these settings, have tried to define a group of more relevant variables responsive to a range of interventions. These variables
include loss of meaning, hopelessness, loss of dignity, boredom, and demoralization.

**Anxiety**

Patients with advanced disease may present with a complex mixture of physical and psychological symptoms in the context of their frightening reality. Thus, recognizing anxiety symptoms that require treatment can be challenging. Patients with anxiety complain of tension or restlessness, or they exhibit jitteriness, autonomic hyperactivity, vigilance, insomnia, distractibility, shortness of breath, numbness, apprehension, worry, or rumination. Often the physical or somatic manifestations of anxiety overshadow the psychological or cognitive ones. These symptoms are a cue to further inquiry about the patient’s psychological state, which is commonly one of fear, worry, or apprehension. In deciding whether to treat anxiety, the patient’s subjective level of distress is the primary impetus for the initiation of treatment rather than qualifying for a psychiatric diagnosis. Other considerations include problematic patient behavior such as nonadherence, family and staff reactions to the patient’s distress, and the balancing of the risks and benefits of treatment.

In this population anxiety is a symptom that can have many etiologies. It may be encountered as a component of an adjustment disorder, panic disorder, generalized anxiety disorder, phobia, or agitated depression. Additionally, in patients with advanced disease, symptoms of anxiety are most likely to arise from some medical complication of the illness or treatment such as organic anxiety disorder, delirium, or other organic mental disorders. Hypoxia, sepsis, poorly controlled pain, and adverse drug reactions such as akathisia, or withdrawal states are specific entities that often present as anxiety. Withdrawal from benzodiazepines, for example, can present first as agitation or anxiety, although the diagnosis is often missed in cancer patients with advanced disease, and especially the elderly, in whom physiologic dependence on these medications is often unrecognized.

Although anxiety in patients with advanced disease commonly results from medical complications, psychological factors related to existential issues equally as often cause anxiety, particularly in patients who are alert and not confused. Patients frequently fear isolation and estrangement from others, and may have a general sense of feeling like an outcast. Financial burdens and family role changes are common stressors.

**Delirium & Dementia**

Delirium has been characterized as an etiologically nonspecific, global, cerebral dysfunction, characterized by concurrent disturbances of level of consciousness, attention, thinking, perception, memory, psychomotor behavior, emotion, and the sleep-wake cycle. Disorientation, fluctuation, or waxing and waning of symptoms, as well as acute or abrupt onset of such disturbances, are other critical features of delirium. Delirium is also conceptualized as a reversible process, in contrast to dementia. At times it is difficult to differentiate delirium from dementia because they frequently share such common clinical features as impaired memory, thinking, judgment, and disorientation.

Dementia appears in relatively alert individuals with little or no clouding of consciousness. The temporal onset of symptoms in dementia is more insidious or chronically progressive, and the patient’s sleep-wake cycle is generally not impaired. Most prominent in dementia are difficulties in short- and long-term memory, impaired judgment, and abstract thinking as well as disturbed higher cortical functions (i.e., aphasia, apraxia, etc.). Occasionally delirium is superimposed on an underlying dementia, as in the case of an elderly patient, a patient with AIDS, or a patient with a paraneoplastic syndrome.

Delirium is most common in patients with far advanced disease. Between 15% and 20% of hospitalized cancer patients have organic mental disorders. In one study, more than 75% of terminally ill cancer patients were found to have delirium. Delirium can be due either to the direct effects of cancer on the CNS, or to indirect CNS effects of the disease or treatments (medications, electrolyte imbalance, failure of a vital organ or system, infection, vascular complications, and preexisting cognitive impairment or dementia). Early symptoms of delirium can be misdiagnosed as anxiety, anger, depression, psychosis, or unreasonable or uncooperative attitudes toward rehabilitative efforts or other treatments. In any patient showing acute onset of agitation, impaired cognitive function, altered attention span, or a fluctuating level of consciousness, a diagnosis of delirium should be considered.

A common error among medical and nursing staff is to conclude that a new psychological symptom is functional without completely ruling out all possible organic etiologies. For example, given the large numbers of drugs patients with advanced disease require, and the fragile state of their physiologic functioning, even routinely ordered hypnotics are enough to create an organic mental syndrome. Opioid analgesics such as levorphanol, morphine sulfate, and meperidine are common causes of confusional states, particularly in the elderly and in patients with advanced disease. Except for steroids and biological response modifiers, most patients receiving these agents will not develop prominent CNS effects.

The spectrum of mental disturbances related to steroids includes minor mood lability, affective disorders (mania or depression), cognitive impairment (reversible dementia), and delirium (steroid psychosis). The incidence of these disorders ranges from 3% to 57% in noncancer populations, and they occur most commonly on higher doses. Symptoms usually develop within the first 2 weeks of treatment, but in fact can occur at any time and on any dose, even during the tapering phase. Prior psychiatric illness or prior disturbance on steroids is a poor to fair predictor of susceptibility to, or the nature of, mental disturbances during subsequent steroid treatments. These disorders are often rapidly reversible upon dose reduction or discontinuation.
CARE OF THE DYING PATIENT

At some point in a person’s illness, whether it be progressive cancer or an end-stage medical illness, it becomes clear that further attempts to treat the underlying condition are not only futile but harmful in that they expose the patient to treatments that do more harm than good, delay the important conversations that must occur around the issues of death and dying, and reduce the likelihood of good symptom control because of the focus on disease management. Family practitioners and general internists, because of their long-term patient-centered relationships, are in the best position to have conversations about the status of the illness, treatment options with attendant benefits and burdens, prognosis issues, goals of care, and the use of hospice or palliative care services.

Cary interviewed 84 terminally ill patients to understand what factors predict who best will cope with dying and what can be done by physicians and other professionals to make life more meaningful. His findings were as follows:

1. Most people want to hear the truth from their physicians. Patients with a limited life expectancy prefer to be told in person, with time allowed to express feelings and ask questions.
2. Patients want to be assured that their physician will not abandon them.
3. If the physician feels that he or she does not have the time or training to provide effective counseling for the patient or family, it is best to refer the patient elsewhere for care.
4. The proper administration of pain medication is a major factor in emotional adjustment to the terminal illness. Patients have greater peace if they know that suffering will be kept at a minimum.
5. Because of the patient’s many needs, physicians should be willing to seek and accept the help of other professionals, including clergy, social workers, and nurses.

An essential first step in facilitating the shift from the curative to the palliative mode is in communicating the terminal diagnosis. Buckman describes a six-step protocol for such a conversation:

1. Getting started: The patient and his or her support person should attend. Ensure a comfortable environment. Allot adequate time, and prevent interruptions. Know the facts of the illness and treatment to date.
2. Ask what the patient knows and assess the ability to comprehend the information.
3. Find out how much the patient wants to know, taking into account cultural, religious, social, and personal issues.
6. Next steps: treat symptoms, make referrals, plan for support, and schedule a timely follow-up visit.

Similarly, predicting the course of the illness and the patient’s life expectancy is an essential component of good end-of-life care. Most patients and family members want to have this information for emotional, spiritual, and practical reasons. Loprinzi suggests that these discussions should contain the following elements:

1. Acknowledge uncertainty.
2. Foretell a general, realistic time frame.
3. Recommend “doing the things that should be done.”
4. Provide realistic assurance that the physician will be available to help the patient through the dying process.
5. Refer the patient to other professionals for emotional and spiritual support in “dying well.”
6. Ask the patients what he or she wants to accomplish.
7. Encourage additional questions.

As death approaches the patient will develop a series of signs that predict its closeness (Table 63-2). It is important to recognize that death is approaching and share this information compassionately with the patient, if desired, and family.

Table 63-2. Signs of impending death.

1. Bed bound
2. Confusion
3. Cool/mottled extremities
4. Death rattle
5. Decreased hearing and vision
6. Decreased urinary output
7. Difficulty swallowing
8. Diminished interest in conversation
9. Diminished interest in oral intake
10. Disoriented to time
11. Drowsiness progressing to extended periods of somnolence
12. Dry mouth
13. Hallucination
14. Increasing distancing from all but a few intimate others
15. Limited attention span
16. Profound weakness
Medical care should be simplified as much as possible. Laboratory tests, radiologic procedures, and other interventions should be done only if they will result in improvement of the patient’s comfort. Nonsensational medications should be discontinued. Blood pressure medicines, for example, may be safely reduced in dosage or stopped as the patient becomes bed bound, reduces his or her activity, and reduces oral intake. Artificially provided hydration and nutrition are seldom necessary or helpful for the dying person. More often than not, administration of fluids results in progressive edema, lung congestion, oral secretions, and frequent urination with attendant discomfort and distress. Experienced hospice professionals note no increase in discomfort or suffering with the naturally occurring dehydration that accompanies the dying process. However, some authorities suggest that modest intravenous or subcutaneous fluids may be helpful for the delirious dying patient who is not responding to neuroleptics. A brief trial of fluids in this circumstance may be warranted. Family members frequently are concerned that not providing food by some route will result in increased suffering and “starvation” of their loved one. Confronting this misconception with care and compassion but directly usually provides reassurance for the concerned family that food is not necessary at the “time of dying.”

Certain medications are important to manage the symptoms that may occur during the dying process (Table 63-3). Additionally, of great importance are the following nursing interventions, which should not be forgotten:

1. Daily bathing with application of a lubricating lotion or talcum powder to the entire body.
2. Frequent cleaning of the mouth with application of lip balm.
3. Application of artificial tears and lubricating ointment to the eyes.
4. Comfortable positioning in the bed with pillows placed under the calves or for other areas of support.
5. An open window for fresh air if possible; if not, then a fan at the bedside.
6. A calm and peaceful environment.

Family members may be instructed in these nursing interventions and participate in the care of their loved one. This often is very meaningful and comforting to both the patient and family member. As the patient becomes minimally responsive or nonresponsive, family members are encouraged to gently talk to and touch their loved one.


### Table 63-3. Drugs used to control symptoms in the dying process.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Drug Class</th>
<th>Drug</th>
<th>Route*</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Nonopioid NSAID</td>
<td>Ketorolac</td>
<td>IV/SC/PR</td>
<td>15–30 mg every 6 h, 4 mg every 4 h, 15 mg every 4 h</td>
</tr>
<tr>
<td></td>
<td>Opioid</td>
<td>Morphine</td>
<td>IV/SC/PR</td>
<td></td>
</tr>
<tr>
<td>“Death rattle”</td>
<td>Anticholinergic</td>
<td>Scopolamine</td>
<td>TD</td>
<td>1 patch every 3 days, 0.2–0.4 mg every 2 h, 0.2 mg every 4 h, 0.125–0.25 mg every 4 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atropine</td>
<td>IV/SC</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glycopyrrolate</td>
<td>IV/SC/SL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyoscineamine</td>
<td>SL</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Opioid</td>
<td>Morphine</td>
<td>IV/SC/PR</td>
<td>4 mg every 4 h, 15 mg every 4 h</td>
</tr>
<tr>
<td>Restlessness/anxiety</td>
<td>Benzodiazepine</td>
<td>Midazolam</td>
<td>SC</td>
<td>2–5 mg every 2 h, 0.5–1.0 mg every 4 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lorazepam</td>
<td>IV/SC/SL</td>
<td></td>
</tr>
<tr>
<td>Agitation/hallucinations</td>
<td>Antipsychotic</td>
<td>Haloperidol</td>
<td>IV/SC/PR</td>
<td>5–10 mg every 30 min to effect, 12.5–25 mg every 6 h, 25–50 mg every 6 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thorazine</td>
<td>IV/PR</td>
<td></td>
</tr>
</tbody>
</table>

NSAID, nonsteroidal anti-inflammatory drug; IV, intravenous; SC, subcutaneous; PR, rectal; SL, sublingual; TD, transdermal.

*The oral route is not listed as it is often not a viable choice in the last 48 h.
ADVANCE CARE PLANNING

Advance directives are legal documents that allow patients to make their health care choices known. Terms for advance directive documents are not standardized from state to state but usually encompass one or more of the following options:

1. Patients appoint someone (surrogate or proxy) to make health care decisions for them.
2. Patients specify their own choices regarding various life-sustaining treatments (often called a Living Will).
3. Patients sign a form alerting emergency medical workers (EMS) that they have signed an advance directive.

Advance directive documents go into effect when a patient loses decision-making capability. Most states, through law, require the document to be witnessed and or notarized. The American Bar Association Commission on Legal Problems of the Elderly (http://www.abanet.org) suggests that patients are best served by selecting a trusted individual to serve as a surrogate and executing a Living Will to provide guidance on treatment choices. The National Hospice and Palliative Care Organization web site (http://www.caringinfo.org) urges all family members regardless of age to have meaningful discussions about end-of-life decisions.

Patients, families, and the health care system benefit from advance directives and from the decision-making process patients and their families go through to create a written document. Advance care planning (the process of arriving at an end-of-life care decision) is important to patients because they can “direct” and inform the health care system when they are no longer able to speak for themselves. Families benefit from advance directives, because they are relieved from making extremely difficult decisions that often lead to family disagreements over the patient’s wishes. Advance care planning is important to physicians because they can be assured they are following the patient’s wishes.

In 2005, this issue received national attention when the case of Terri Schiavo, a young woman who had suffered severe brain damage 15 years earlier, became front-page news throughout the United States. Schiavo’s husband Michael had requested that her gastric feeding tube be removed; her parents opposed this action. Legal battles ensued, but in the end the courts supported the right to refuse treatment based on Michael Schiavo’s argument that his wife had previously communicated her desire not to be kept alive by artificial means. The strong feelings that surrounded this case illustrate the importance of conversations relating to advance directives and the anguish and conflict that can beset families involved in such weighty decisions.

How to Start the Process

The advance care planning process should begin with physicians educating themselves about legal statutes that exist for advance directive documents and where to direct patients for further education. Hospices, senior citizen centers, and hospital social service or spiritual care departments are all good resources for obtaining documents and educational materials.

The ideal time to discuss an advance care directive is when a patient is still healthy. Such discussions should become a part of routine health care. Although advance directive documents are important, advance care planning is a process that allows for adequate time to reflect, educate, and involve family members. A physician can initiate an end-of-life care discussion with a patient, direct the patient on where to obtain information, and encourage the patient to seek additional guidance from religious or legal advisors. Patients should also be encouraged to have a discussion with their family members so that family can be made aware of their loved ones’ health care preferences. Ideally, the physician should follow up with the patient at a later date to address questions or concerns and obtain a copy of a signed advance directive document for inclusion in the patient’s medical record. Physicians who follow a patient for several years may want to have further discussions periodically to ensure that any documents on file still reflect the patient’s choices. States may or may not outline specific processes for changing an advance directive.

Numerous articles and studies have shown that the avoidance of planning for end-of-life care results in families agonizing over difficult health care decisions, costly futile care, and time-consuming lawsuits to sort out the results. Hammes and Briggs give the following common reasons why health care professionals avoid having end-of-life conversations:

1. A belief that the person is not sick enough, may become upset, is not capable enough to understand, and will be robbed of hope.
2. Lack of confidence in their own skills related to delivering bad news.
3. A perceived lack of time.
4. A belief that there are simply too many contingencies for individuals to have to consider regarding their future potential medical conditions.

Patients may also wish to avoid end-of-life conversations. Fear and a lack of understanding of medical technology prevent patients from initiating discussions with their physicians. A study conducted in 2000 by the National Hospice and Palliative Care Organization found that adult children would have an easier time discussing sex or drugs with their teenage children than having end-of-life care discussions with their aging parents. That so few individuals have signed advance care directives may in large part be a result of a combination of health care professional and patient avoidance. The need for conversation, however, could not be more critical.

Talking to the Palliative Care Patient

As the change from curative care to palliative care begins, opportunities to engage in meaningful compassionate discussions with patients will appear. Asking patients what they understand about their disease can inform physicians of patients’ perceptions and possible gaps in knowledge about the disease progression. When discussing new palliative care options, the discussion should include the goal of each treatment. Patients and their families should have a clear understanding of the benefits and the burdens of any proposed treatment.

Patients, when asked about end-of-life care choices, often use vague phrases such as “I don’t want to be a vegetable” or “I don’t want to be hooked up to machines” to convey their wishes. Such phrases, although descriptive, leave gaps in a loved one’s ability to make concrete treatment decisions if not further explored. End-of-life care discussions are often difficult because the conversation is based on patients’ and their family members’ values and beliefs. Some individuals believe that removing a loved one from a ventilator constitutes murder. Others, when asked about feeding tubes, wonder about “starving their loved one to death.” Such beliefs are often difficult to address and are clearly emotionally laden. Additionally, when the patient dies, the loved one, having felt forced to make a difficult decision may face a longer and more complicated bereavement period.

One approach to helping patients with advance directives is to guide the conversation to what would constitute a “good day” for the patient. By focusing on living each day to the best extent possible the physician can learn what is important to the patient and can help the patient weigh treatment options against the patient’s measure of a good day. Several documents exist to help patients think about what is important to them. Five Wishes, produced by Aging with Dignity, and Caring Connections, the web site maintained by the National Hospice and Palliative Care Organization, are designed to assist patients and their families by leading them through a series of questions designed to stimulate thought and conversation about quality of life issues.

Caring Connections, maintained by the National Hospice and Palliative Care Association (free, state-specific forms; an advance directive checklist, and additional information): http://www.caringinfo.org

SPIRITUAL DIMENSIONS IN PALLIATIVE CARE

Palliative care physicians observe that their patients have needs that transcend physical pain, social disruptions, and psychiatric disorders. Chochinov notes, “More ubiquitous aspects of suffering—including psychological, existential, or spiritual distress—are not necessarily well understood or researched, nor do they necessarily engender a well-considered response.”

The spiritual dimensions in palliative care include consideration of the patient’s religious practices (eg, prayer, sacraments, and rituals) but also attend to what may be called the existential concerns of the patient. Chochinov lists these as “an overwhelming sense of hopelessness, existential or spiritual angst; loss of sense of dignity; sensing oneself a burden to others; or a waning of one’s will to live and a growing desire for death . . . .” To this list can be added concerns such as the loss of a sense of meaning, a paralyzing sense of guilt and regret, broken relationships with loved ones, difficulties with one’s concept of divinity or a sense of difficulty in a relationship with a personalized deity, feelings of anger, feelings of grief, and feelings of despair. Unmet religious needs and unresolved existential concerns cause spiritual distress and can also result in psychiatric disorders such as depression or anxiety, as well as an increased sense of physical pain for the patient.

Recent studies have examined the importance of spirituality to physicians and to patients who are seriously or terminally ill, and whether and how physicians should address the spiritual concerns of these patients. (For a brief summary see Astrow and Sulmasy, 2004.) Holmes and colleagues considered the results of some of these studies, conducted a study of their own, and came to the following conclusions:

It seems patients tend to desire a sophisticated and somewhat controlled relationship with PCPs [primary care providers] around spirituality: They want their concerns cared about but not discussed or talked about, and they want to be prayed for but not with. These results indicate that, instead of discussing spiritual issues, PCPs may more appropriately “care” for the spiritual concerns of their patients by simply asking and listening . . . . and leave the more active roles to others who have specific training in this area . . . .

A study conducted by MacLean and colleagues concludes that patients’ “desire for spiritual interaction increased with increasing severity of illness setting and decreased with referring to more-intense spiritual interactions.”

Although intense intervention such as praying with a patient may not be welcome, being present, attentive, and supportive invites patients to share the physical, emotional,
and spiritual aspects of their suffering. For the physician who is comfortable going a step further with a patient who presents spiritual concerns, Puchalski and Sandoval offer a simple assessment tool, known by its acronym, FICA:

F: Faith, belief, meaning. Ask: "Do you consider yourself spiritual or religious?" “Do you have spiritual beliefs that help you cope with stress?” If the patient answers no, the physician might ask, “What gives your life meaning?”

I: Importance and influence. Ask: “What importance does your faith or belief have in your life?” “Have your beliefs influenced you in how you handle stress?” “Do you have specific beliefs that might influence your health care decisions?”

C: Community. Ask: “Are you a part of a spiritual or religious community? Is this of support to you and how?” “Is there a group of people you really love or who are important to you?”

A: Address/action in care. Ask: “How should the health care provider address these issues in your health care?” Appropriate action might involve referral to chaplains, clergy, and other spiritual care providers.

Often the presence of spiritual suffering will emerge as patients tell their stories. To attend to this suffering requires that the health care professional be aware of and attentive to his or her own spirituality. The decision to share personal insights, experiences, and resources must be done with sensitivity and compassion, and with respect for the patient’s faith tradition and practice.

Consultation with and referral to a chaplain or other faith-based community leader is often appropriate. Professional chaplains are trained to understand and respect religious and cultural diversity and to assist patients and families in dealing with a wide variety of spiritual issues. Meador notes that “the clergy member of the team brings an interpretive, liturgical, and communal sense of spiritual care from her or his pastoral formation unique to that vocational formation.”

Victor Frankl, a psychiatrist whose writings were based on his experience in a Nazi concentration camp, observed: “Man is not destroyed by suffering; he is destroyed by suffering without meaning.” Palliative care therefore extends beyond the physical dimensions of suffering to attend to the spiritual suffering that may be present. A physician can attend to this dimension of healing by offering a listening ear, a word of kindness, and a referral to a professional spiritual caregiver.


RESOURCES

Books


Journals


Supportive Care in Cancer. Senn HJ, ed. Springer-Verlag, Heidelberg, Germany.

Web Sites

ACP-ASIM End-of-Life Care Consensus Panel: http://www.acponline.org/ethics/eolc.htm

Alliance of State Pain Initiatives (ASPI): http://aspi.wisc.edu/

AMA: Education for Physicians in End-of-Life Care: http://www.epec.net/EPEC/webpages/index.cfm

American Academy of Hospice and Palliative Medicine: http://www.aahpm.org
| American Alliance of Cancer Pain Initiatives: http://www.aacpi.org |
| American Board of Hospice and Palliative Medicine: http://www.abhpm.org |
| End-of-Life Physician Education Resource Center (EPERC): http://www.eperc.mcw.edu/ |
| Growth House: http://www.growthhouse.org |
| Last Acts: http://www.lastacts.org |
| National Hospice and Palliative Care Organization (NHPCO): http://www.nhpco.org |
| Supportive Care of the Dying: http://www.careofdying.org |
The 21st century has begun with some very exciting changes for primary care and specifically for Family Medicine. In this chapter we will discuss why a new model of primary care is essential; describe past, current, and future efforts for redesigning primary care with a focus on the Patient-Centered Medical Home (PCMH); and conclude with a discussion of how to transform both medical practices and the nation's health care delivery system to take full advantage of the PCMH’s potential to improve the quality of, and access to affordable care that enhances the well-being of everyone in this country.

INTRODUCTION

The objective of any system of health care should be to improve the lives of the patients it serves, both in the quality and the length of those lives, to create an environment in which people feel better, avoid preventable medical problems, ameliorate the effects of existing disease, and enjoy the lives they have as fully as possible.

Currently in the United States of America we have too many people who do not have adequate access to care, receive care that is of less than optimal quality, get care that costs too much and has significant disparities in its provision (Institute of Medicine, 2001). We need to do things differently because we know there is a better way; a way that is based on solid scientific fact, which builds on the good of our current system and that is fair to all, a truly American way.

We must change from rewarding doing things to people, and create incentives to do things for people, from paying to do a task to paying for thinking about the task. Is a given procedure the most appropriate one for this individual at this particular time, if ever?


THE NEED FOR CHANGE

Past Attempts

A. Managed Care

In the early 1990s the idea of “managed care” was introduced into the United States, primarily as a way to increase profits and control costs by the insurance industry. This was popularly known as the “Gatekeeper” system. Patients were required to visit a primary care provider who was approved by their insurance carrier to provide services under a particular plan as an entry point for any further access to the Healthcare System. Payment was made to the physician on a capitated basis. That is, a fixed amount was paid to the physician for each member of that insurance plan who designated that doctor as his or her primary care physician. The payment was the same each month regardless of whether the patient had been seen in a particular month or not. Additionally, a preauthorization was required for most services provided outside the physician’s office. Testing and procedures done in the physician’s office were generally not compensated beyond the amount of capitation. Understandably, both patients and physicians generally despised this idea.

It deprived the patient of freedom of choice, while increasing the inconvenience of obtaining a referral, test, or most any other service. Physicians were in the unfamiliar and uncomfortable situation of being a patient adversary rather than a patient advocate. Payments were generally slow in coming and many times did not come at all, making it difficult, if not impossible, for practices to maintain financial margins sufficient to remain viable. This system was further flawed in that the physicians were selected to be the “gatekeepers” solely on the condition that he or she have a pulse, and not by specialty or any other criteria that might indicate the doctor’s ability to improve quality and control cost.
The chronic care model.

to mobilize community that promotes safe, high quality care by sup-

tant influence on the Future of Family Medicine (FFM) project

The resulting model was the chronic care model (CCM) developed by Wagner and his colleagues at the MacColl Institute (Wagner, 1998; see Figure 64-1) which was an important influence on the Future of Family Medicine (FFM) project (discussed below) and the evolution of the PCMH.

At the core of the CCM is a shift in focus from a reactive approach to chronic illness care to a proactive approach that results in improved outcomes through productive interactions between an informed and activated patient and a prepared and proactive practice team (ICIC, 2008). It is beyond the scope of this chapter to provide a detailed description of the model, but in brief the model shows that to improve the current health care system and promote high-quality chronic illness care, the system must be reorganized to include six essential elements (see Figure 64-1). These elements include a Health System that promotes safe, high quality care by supporting effective and patient centered Delivery System Design, Decision Support, and Self-Management Support strategies and Clinical Information Systems as well as collaboration with The Community to mobilize community resources to meet the needs of patients (IHI, 2008).

Since the inception of the CCM, there have been numerous intervention studies conducted that incorporate one or more elements of the CCM and there is extensive evidence to support the positive effects of CCM based interventions on both clinical processes and patient outcomes (Glasgow et al., 2001; Ouwens et al., 2005; Tsai et al., 2005; & Piatt et al., 2006) and cost-effectiveness (Bodenheimer, Wagner, & Grumbach, 2002). Each individual element of the CCM is important and can lead to improved outcomes and while no single element appears to be more effective than the other, the more CCM elements implemented the better the outcomes (Tsai et al, 2005).

Although the CCM was originally developed as a model for improving chronic illness care, most components are also applicable to the necessary redesign of primary care; hence the model serves as the foundation of the new model of primary care that has been adopted by the American Academy of Family Physicians (AAFP, 2004), it is also endorsed by The National Committee on Quality Assurance and The Joint Commission (ICIC, 2008), and is one of the most important influences on the development of the PCMH (Robert Graham Center, 2007) which builds upon CCM elements to address the needs of patients and families in the medical home. The CCM and PCMH complement each other with the CCM focusing more heavily on health care system change while the overall PCMH philosophy focuses on the patient and family to determine the best ways to support them through system change as well as other strategies.

In the year 2000, leaders in Family Medicine began an assessment of that specialty’s future role. Known as the “Future of Family Medicine Project (FFM),” this effort, along with similar projects by the AAP and the American College of Physicians (ACP), ultimately became the second major step in the development of the medical home.

During this period much independent research, both here and abroad, demonstrated that primary care was associated with higher quality care delivered at lower cost and with increased patient satisfaction. Simultaneously, IBM, aware of this research and its own experiential data from countries with primary care–based health systems, began to search for the same value in healthcare in the United States.

**Figure 64-1.** The chronic care model.
In the spring of 2006, having become aware of the now completed FFM project and it’s conclusion that the country’s family doctors needed a “new model” of practice, representatives of IBM approached leaders of the American Academy of Family Physicians (AAFP) at the World Health Care Congress held in Washington, DC, about collaboration on the issue.

Subsequently, the ACP and AAFP along with IBM convened a summit to educate and involve more businesses, insurance companies and physician groups such as the American Osteopathic Association (AOA) in the development and propagation of what came to be termed the “Patient-Centered Medical Home” (PCMH).

These groups developed and refined the principals on which the medical home would be based, formed the “Patient Centered Primary Care Collaborative (PCPCC)” with headquarters in the Nation’s Capitol to promote and disseminate the medical home idea to businesses, the public, physicians, and insurance companies as well as to federal and state governments. Currently the PCPCC has over 700 member organizations representing 333,000 primary care physicians, several Fortune 500 companies and their millions of employees, major health insurance companies, other physician groups and organizations representing patients.

In the span of just three short years the PCMH has gone from a glimmering of an idea to becoming the most important idea for health system change in the past 50 years. It can be the vehicle that finally provides quality, affordable, accessible health care for everyone in the United States.


B. PCMH Evidence

Although the concept of a patient-centered medical home has been around since the 1960s, the current definition and framework are relatively new and empirical evidence demonstrating the effects of this new model of care is still being generated. Indeed, there are currently over 100 demonstration projects evaluating the PCMH on health outcomes, patient satisfaction, processes of care and cost effectiveness Preliminary reports are encouraging (Stewart et al., 2009) and final analysis of some of these projects are just coming available at the time of this writing. The evidence is expected to be very strong since we already know that the elements of the model work as demonstrated by the extensive evidence supporting the value of primary care in improving health outcomes, patient satisfaction, resource utilization and cost effectiveness (PCPCC, 2009) and the value of incorporating CCM elements to improve cost effectiveness, patient outcomes and clinical processes (Glasgow et al., 2001; Tsai et al., 2005; and Bodenheimer et al., 2002).

C. PCMH Benefits

First and foremost the Patient-Centered Medical Home (PCMH) puts the patient and his or her interests squarely at the center of both their own health care and the health care system. What is best for the patient is also best for the health care team and the system as a whole. It moves the old adage of “first, do what is right for the patient” up to the position of primacy in the priorities of the physician and other team members as well as the health care system.

Patients will feel better, have better health, live longer more productive lives, use less expensive services, enable subspecialists to do what they are trained to do better than they do now, and provide the only model of care that can possibly deliver high quality health care at reasonable cost to every person in the United States.

The PCMH does not require inventing any new tests, treatments, or new specialties; it simply requires enough primary care physicians in the workforce, using the principles of the medical home, existing technology, and the best available evidence to do the “right thing” at the right time for the whole population.
Preventive services will be delivered more regularly, appropriately, and broadly than currently. The lower the barriers to care (ie, co-pays) in the PCMH, the more patients have incentives to use its services rather than accessing the system at another, more expensive level.

The PCMH provides the quality, accessible, cost efficient health care for everyone that has for so long eluded the United States. It will at last improve the health and well being of all our people without depriving them of choice, riches, or independence, rather it will make our country the envy of the world.

**ESSENTIAL ELEMENTS FOR A SUCCESSFUL PATIENT-CENTERED MEDICAL HOME**

**Adherence to Accepted Standards and Recognition**

The Patient-Centered Medical Home (PCMH), as defined by the National Committee for Quality Assurance (NCQA; 2009), is a “health care setting that facilitates partnerships between individual patients, and their personal physicians, and when appropriate, the patient’s family. Care is facilitated by registries, information technology, health information exchange and other means to assure that patients get the indicated care when and where they need and want it in a culturally and linguistically appropriate manner.”

To describe the essential characteristics of the PCMH, the American Academy of Family Physicians, American Academy of Pediatrics, American College of Physicians, and the American Osteopathic Association (representing approximately 333,000 physicians) developed the Joint Principles of the Patient-Centered Medical Home, which are listed in Table 64-1.

The joint principles emphasize a patient-centered, holistic approach to patient care provided by a physician led medical practice that should include collaboration with other disciplines such as nursing, pharmacy, nutrition, and behavioral science to meet the individual needs of the patients through integrated and/or coordinated care. No single individual can adequately meet all the needs of all the patients in the medical home.

### Table 64-1. Joint principles of the Patient-Centered Medical Home (AAFP, AAP, ACP, and AOA Consensus Panel, 2007).

<table>
<thead>
<tr>
<th>Personal physician</th>
<th>Each patient has an ongoing relationship with a personal physician trained to provide first contact, continuous and comprehensive care.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician-directed medical practice</td>
<td>The personal physician leads a team of individuals at the practice level who collectively take responsibility for the ongoing care of patients.</td>
</tr>
<tr>
<td>Whole person orientation</td>
<td>The personal physician is responsible for providing for all the patient's health care needs or taking responsibility for appropriately arranging care with other qualified professionals. This includes care for all stages of life; acute care; chronic care; preventive services, and end of life care.</td>
</tr>
<tr>
<td>Care is coordinated and/or integrated</td>
<td>Care is coordinated and/or integrated across all elements of the complex health care system (eg, subspecialty care, hospitals, home health agencies, nursing homes) and the patient's community (eg, family, public and private community-based services). Care is facilitated by registries, information technology, health information exchange and other means to assure that patients get the indicated care when and where they need and want it in a culturally and linguistically appropriate manner.</td>
</tr>
<tr>
<td>Quality and safety are hallmarks of the medical home</td>
<td>Practices advocate for their patients to support the attainment of optimal, patient-centered outcomes that are defined by a care planning process driven by a compassionate, robust partnership between physicians, patients and the patient's family. Evidence-based medicine and clinical decision-support tools guide decision making. Physicians in the practice accept accountability for continuous quality improvement through voluntary engagement in performance measurement and improvement. Patients actively participate in decision making and feedback is sought to ensure patients’ expectations are being met. Information technology (IT) is utilized appropriately to support optimal patient care, performance measurement, patient education, and enhanced communication. Practices go through a voluntary recognition process by an appropriate non-governmental entity to demonstrate that they have the capabilities to provide patient-centered services consistent with the medical home model. Patients and families participate in quality improvement activities at the practice level.</td>
</tr>
<tr>
<td>Enhanced access</td>
<td>Enhanced access to care is available through systems such as open scheduling.</td>
</tr>
<tr>
<td>Payment</td>
<td>Payment appropriately recognizes the added value provided to patients who have a patient-centered medical home.</td>
</tr>
</tbody>
</table>

*The Patient-Centered Medical Home (PCMH) is an approach to providing comprehensive primary care for children, youth and adults. The PCMH is a health care setting that facilitates partnerships between individual patients and their personal physicians, and when appropriate, the patient’s family. The AAP, AAFP, ACP, and AOA, representing approximately 333,000 physicians, have developed the following joint principles to describe the characteristics of the PCMH, at the core of which is a team approach to the health care of an individual.*
a practice, thus teamwork and collaboration between disciplines in a manner that utilizes the strengths that each discipline brings to the team is essential to the success of the PCMH. The joint principles also emphasize enhanced access to care and an improved payment structure that combines enhanced fee for service as well as a per-patient-per-month payment or PPPM (see below).

To be formally recognized as a PCMH, practices must meet a set of standards such as those established by the NCQA (see Table 64-2) that are aligned with the "Joint Principles" of the PCMH. Using this model, a practice would complete a self-assessment survey and submit documentation supporting the responses in the survey. The NCQA would then evaluate the practice as outlined in Table 64-3. Each practice would then receive a score based on a standardized point system (see Table 64-2). This model proposes three levels of achievement. The level a practice achieves depends on the extent to which they meet increasing numbers of the requirements for each standard (see Table 64-4). Practices that earn recognition, as a PCMH will be rewarded with higher PPPM payments with each level achieved.

For practices interested in achieving PCMH status, TransforMED is an initiative of the AAFP to help practices get there by providing a framework and tools through online resources as well as direct consultation to facilitate the necessary practice changes (Barclay, 2006). The goal of a transformed practice is to improve quality, safety and access while also increasing physician satisfaction (McGeeney as cited in Barclay, 2006).


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**Table 64-2.** NCQA PPC-PCMH standards and scoring.


<table>
<thead>
<tr>
<th>Standard 1: Access and Communication</th>
<th>Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Has written standards for patient access and patient communication**</td>
<td>4</td>
</tr>
<tr>
<td>B. Uses data to show it meets the standards for patient access and communication**</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standard 2: Patient Tracking and Registry Functions</th>
<th>Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Uses data system to basic patient information (mostly non-clinical data)</td>
<td>2</td>
</tr>
<tr>
<td>B. Has clinical data system with clinical data in searchable data fields</td>
<td>3</td>
</tr>
<tr>
<td>C. Uses the clinical data system</td>
<td>3</td>
</tr>
<tr>
<td>D. Uses paper or electronic-based charting tools to organize clinical information**</td>
<td>6</td>
</tr>
<tr>
<td>E. Uses data to identify important diagnoses and conditions in practice**</td>
<td>4</td>
</tr>
<tr>
<td>F. Generates lists of patients and reminds patients and clinicians of services needed (population management)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standard 3: Care Management</th>
<th>Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Adopts and implements evidence-based guidelines for three conditions**</td>
<td>3</td>
</tr>
<tr>
<td>B. Generates reminders about preventive services for clinicians</td>
<td>4</td>
</tr>
<tr>
<td>C. Uses non-physician staff to manage patient care</td>
<td>3</td>
</tr>
<tr>
<td>D. Conducts care management, including care plans, assessing progress, addressing barriers</td>
<td>5</td>
</tr>
<tr>
<td>E. Coordinates care follow-up for patients who receive care in inpatient and outpatient facilities</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>20</td>
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</tbody>
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<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Assesses language preference and other communication barriers</td>
<td>2</td>
</tr>
<tr>
<td>B. Actively supports patient self-management**</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standard 5: Electronic Prescribing</th>
<th>Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Uses electronic system to write prescriptions</td>
<td>3</td>
</tr>
<tr>
<td>B. Has electronic prescription writer with safety checks</td>
<td>3</td>
</tr>
<tr>
<td>C. Has electronic prescription writer with cost checks</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standard 6: Test Tracking</th>
<th>Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Tracks tests and identified abnormal results systematically**</td>
<td>7</td>
</tr>
<tr>
<td>B. Uses electronic system to order and retrieve tests and flag duplicate tests</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standard 7: Referral Tracking</th>
<th>PT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Tracks referrals using paper-based or electronic system**</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standard 8: Performance Reporting and Improvement</th>
<th>Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Measures clinical and/or service performance by physician or across the practice**</td>
<td>3</td>
</tr>
<tr>
<td>B. Survey of patients' care experience</td>
<td>3</td>
</tr>
<tr>
<td>C. Reports performance across the practice or by physician**</td>
<td>3</td>
</tr>
<tr>
<td>D. Sets goals and takes action to improve performance</td>
<td>3</td>
</tr>
<tr>
<td>E. Produces reports using standardized measures</td>
<td>2</td>
</tr>
<tr>
<td>F. Transmits reports with standardized measures electronically to external entities</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standard 9: Advanced Electronic Communications</th>
<th>Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Availability of interactive Website</td>
<td>1</td>
</tr>
<tr>
<td>B. Electronic Patient Identification</td>
<td>2</td>
</tr>
<tr>
<td>C. Electronic Care Management Support</td>
<td>1</td>
</tr>
</tbody>
</table>

**Must Pass Elements**

the physician immediately knows that several equally regrettable things have occurred. First, something the patient perceives as significant has taken place. Second, this event is likely to have been a nonspecific symptom (like chest pain) and involve several subspecialists, multiple tests (many of which may have been unnecessary if not redundant), and a whole lot of money. Third, and most dreadful of all, the physician has not the first clue as to what the patient is talking about.

It is clear from all available data that preventing this scenario is absolutely essential to controlling quality and cost. Regardless of whether an emergency department visit is avoided, or the number and type of tests a patient needs are more appropriately ordered, someone must be enabled to see that the care of a given individual is optimized. This function cannot be totally done in face-to-face encounters between the patient and his or her physician. Many types of “asynchronous” interactions will need to occur in order to achieve quality at acceptable cost. Delivering preventive services in the office, refilling prescriptions, educating patients about diet, exercise, and smoking cessation as well as making referrals, tracking consultations, handling abnormal test results, and a myriad of other tasks must be performed in a coordinated, well defined manner or the game is lost.

The time and effort devoted to such asynchronous activities by all members of the healthcare team is labor intensive and time consuming. Properly performed, these endeavors will produce significant benefits to the health and well being of individual patients, practices as a whole, and to society in general. Being central to the success of the PCMH, care coordination as well as integration of individual components of care into a unified plan and set of actions for a person’s health, there must be support and incentives for practices to take on this responsibility. The mechanism to provide such support is simple: a dollar amount paid to the medical professional (usually a primary care physician) responsible for the health care of a given individual in the Patient-Centered Medical Home (PCMH). This monthly fee is additional to any payment made to the physician for services rendered when the patient is actually seen in the PCMH, hospital, or nursing home. It is paid every month, so long as that patient is a member of that particular PCMH, whether or not the patient was seen in the PCMH in any given month. The payment must be adequate to sustain the PCMH’s fiscal ability to provide the range of asynchronous services required by its patients.

Called by many names, per-patient-per-month payment (PPPM), case management fee, disease management fee, care coordination fee, pay for reporting, pay for performance, pay for use (ie, use of a qualified electronic health record) or simply “capitation” (which it is most definitely not), such payments are better termed “Care Coordination and Integration Fees” or “CIFs” for short, so as to better describe their purpose.

Such payments cannot be inconsequential. Real change requires real money, but neither can such payments be easily earned. A given practice will need to meet and maintain a rigorous set of standards like those of the National Committee for Quality Assurance (NCQA), which designates three levels

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**Table 64-3.** PPC-PCMH recognition evaluation process.

<table>
<thead>
<tr>
<th>Level</th>
<th>Points</th>
<th>Must-pass elements (elements that a practice must pass at a 50% or greater score in order to achieve recognition)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1.</td>
<td>25-49 points</td>
<td>Must-pass elements = 5 of 10, with a performance level of at least 50%</td>
</tr>
<tr>
<td>Level 2.</td>
<td>50-74 points</td>
<td>Must-pass elements = 10 of 10, with a performance level of at least 50%</td>
</tr>
<tr>
<td>Level 3</td>
<td>75+ points</td>
<td>Must-pass elements = 10 of 10, with a performance level of at least 50%</td>
</tr>
</tbody>
</table>

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**Table 64-4.** PPC-PCMH achievement levels.

<table>
<thead>
<tr>
<th>Level</th>
<th>Points</th>
<th>Must-pass elements (elements that a practice must pass at a 50% or greater score in order to achieve recognition)</th>
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<tbody>
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</tr>
<tr>
<td>Level 3</td>
<td>75+ points</td>
<td>Must-pass elements = 10 of 10, with a performance level of at least 50%</td>
</tr>
</tbody>
</table>

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Individual Care Coordination

“I guess you know what’s happened to me since my last visit.” or some variant thereof, is among the most dreaded phrases a patient can ever utter to a family physician. Dreadful because...
that the PCMH might attain, each level having a correspondingly higher CIF.

Without the CIFs, the services mentioned above and the benefits to patients that derive from such services cannot be delivered on a consistent basis. There is simply not enough time in the day or money in the budget for the PCMH to bear the additional overhead associated with the provision of these services without them.

**Reduction of Barriers to Care and Disparities in Care**

Reducing barriers, particularly financial barriers, to care is vital to the functioning of the successful PCMH. While such reductions are also goals of the PCMH, system changes to enable the attainment of these goals are integral to providing fiscally stable entities that are ubiquitous enough to allow easy access.

Specifically, financial barriers to use of the PCMH should be as low as possible. There should be no co-pays for visits to the PCMH, although there may still be some role for reasonable deductibles. Reducing or eliminating out of pocket expenses would provide incentive for patients to use the medical home primarily, rather than accessing the system at another level where co-pays and deductibles would fully apply.

Next, the amount paid on a fee-for-service basis for visits to the PCMH must increase significantly. Cognitive services, which make up the majority of services rendered by the PCMH, have long been undervalued relative to payments for procedures.

Along with reasonable CIFs, enhanced payments for services delivered by the PCMH have several positive results. The stability of the PCMH is considerably improved. As previously noted, services provided by the PCMH would be enriched and be delivered in a more consistent manner. Due to the improved economics, more medical students will be able to choose primary care careers thereby increasing the number of medical homes and improving access to those medical homes. Evidence tells us that increased access to primary care services will reduce and may even eliminate disparities that currently exist in health care.

**How Do We Get There?**

This question has implications both for practices and the health care system as a whole. The answer is different for each. For individual practices, be they large or small, the first step is the implementation of a functional Electronic Medical Record (EMR) that has an easy to use, comprehensive disease registry (many, if not most, do not. Check before investing!). Second, a thorough study of the NCQA criteria (see Table 64-2) will provide a roadmap.

If the EMR can provide preventive care reminders to the physician at the time of a visit or at the time of chart review, true electronic prescribing (not just faxing or emailing prescriptions), automatically identify abnormal test results (requires electronic interface with lab/radiology, etc.), provide physician specific and aggregate data on performance, track referrals, and supports improvement in practice initiatives, the practice should be well on the way to qualifying as a medical home. Written policies concerning patient access/communication and an interactive website will provide the framework for achieving higher levels of qualification (see Table 64-4). Additionally, development of a certification for individual practitioners as being capable of providing services specified as vital to the PCMH, whether or not their entire practice or health system is so certified, will be crucial to having enough “medical homes” to satisfy patient demand for these services.

Changing the healthcare system to take advantage of the possibilities of the medical home can be done gradually or rapidly. The former would be less disruptive, but would achieve the improvements in quality and cost savings more gradually, while the latter would be more disruptive (it would require a mandate for everyone to have a medical home), but it would result in a more rapid realization of the “return on investment” the nation will be making in improving the populations’ health and lowering the cost of healthcare.

**CONCLUSION**

The Patient-Centered Medical Home is an entity designed to build on the strengths of the “chronic care model,” the “new model of care”; and solid scientific evidence of the quality and cost effectiveness of primary care. It does not require inventing new technologies, nor does it require creating new kinds of physicians.

The PCMH will function in any environment, and under any payment system so long as the essentials of the medical home (strict adherence to the joint principles, individual care coordination, and reduction of barriers and disparities) are not compromised.

The PCMH is the only mechanism that can transform our health care system to truly achieve quality, affordable, accessible health care for everyone. Half measures and compromises will not do. This is too important for partisan politics and power grabs. This is about people, our friends, our families, and our fellow citizens. This is the time to look objectively at the facts and act accordingly. This is the time and the PCMH is the way to finally bring longer, healthier, happier, and more productive lives to all our people. We have a rendezvous with destiny. We must not fail that rendezvous.

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