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ADOLESCENT MEDICINE:
THE REQUISITES IN PEDIATRICS

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This book is dedicated to lifelong students of adolescent medicine, regardless of level, career phase, or years of experience.

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Foreword

The specialty of adolescent medicine evolved from the incubator of general pediatrics. Emergency medicine is another example of a non-organ–based subspecialty. As one reads the eighth volume of **The Requisites in Pediatrics,** it is clear why adolescent medicine is so important and is a subspecialty in pediatrics.

In this carefully edited volume, Dr. Gail Slap paints a clear picture of the issues that confront the adolescent patient in a time of dramatic physical, cognitive, emotional, and social growth. The authors repeatedly make the point that addressing adolescent health issues in the context of these changes is vital to providing outstanding care. Furthermore, Dr. Slap and the authors have, whenever possible, made recommendations that are evidence-based.

The volume starts off with "Normal Growth and Development," which outlines cognitive, social, and physiologic changes during adolescence. The statement "20% of adult height and 50% of adult skeleton are accrued during the teen years" indicates the importance of the fourth chapter on nutrition and a subsequent chapter (Chapter 11) on obesity. Other chapters in the first part of the volume are especially valuable, notably chapters entitled "Approaching Youth Violence in a Clinical Setting" (with a figure labeled "A life-saving decision tree"), "Transition to Adult Health Care," and "Consent, Confidentiality, and Privacy."

Part II of the book includes common medical problems that are present to the office, such as delayed puberty, hypertension, acne, headaches, and fatigue. Parts III and IV are outstanding sections dealing with the important issues of sexual/reproductive health and mental/behavioral problems.

My thanks and congratulations to Dr. Slap and the authors of *Adolescent Medicine.* They have produced an outstanding and easy-to-use book that provides evidence-based information on the most important questions and medical conditions confronting adolescents.

We are confident that you will find the latest volume of **The Requisites in Pediatrics** most useful.

Louis M. Bell, MD

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Preface

My decision to serve as Editor for *Adolescent Medicine: The Requisites in Pediatrics* grew out of opportunity. I have had the unique good fortune to lead two remarkable programs in adolescent medicine at The Children's Hospital of Philadelphia and the Cincinnati Children's Hospital Medical Center. As the book took shape and form, it offered a canvas on which to capture the curricular content and process of adolescent-centered care as provided at these two leading institutions. The book is the product of talented faculty whose clinical brilliance was honed under the trusting eye of their adolescent. As such, it is dedicated to the patients, families, and colleagues. Patients who keep us reaching for the highest-quality adolescent care.

The focus of this book is adolescent medicine. While it incorporates clinical material from diverse fields, including pediatric and adult medicine, behavioral and mental health, reproductive and sexual health, sports medicine, and nutrition sciences, it is written for primary-care physicians, residents, and fellows who care for adolescent-aged patients. Characteristics that set this book apart from other adolescent texts are its visual content, electronic availability, and curricular orientation. We hope that it becomes the open book and active computer screen for trainees on block rotations in adolescent medicine as well as for busy clinicians faced with complex adolescent health issues.

The book is divided into four sections: I. General Issues in Adolescent Health Care; II. Common Medical Problems; III. Sexual and Reproductive Health; and IV. Mental and Behavioral Problems. The nine chapters in Section I provide a concise, readable overview of cross-cutting issues such as normal growth and development, preventive care, and transition to adult care. The 30 chapters in Sections II–IV share a common organizational structure. Each chapter opens with an outline of its topic-specific sub-headings within the shared structure of Definitions, Epidemiology, Pathophysiology, Evaluation, Management, Major Points, and Bibliography. The text and illustrations are evidence-based or, when evidence is lacking, guided by expert opinion. To maintain high readability and portability, we decided against heavily-referenced text and long bibliographies. The reference lists therefore include print and web-based documents that are topical, timely, and readily accessible.

This book, as all books, should be a living, changing resource that reflects the science and art of our field. While many argue that a book is outdated before it appears, starting somewhere gives us a baseline for lifelong improvement. I hope this book provides a strong foundation for those who care for adolescents and work toward the continual improvement of adolescent health.

Gail B. Slap, MD, MS

Acknowledgments

Adolescent Medicine: Requisites in Pediatrics represents the concerted effort of 44 chapter authors. The content of the book reflects the breadth and depth of their clinical acumen and dedication to sensitive, evidence-based care. The form of the book and its progress through the preparatory stages are thanks to the steady guidance of many at Elsevier, including Judith Fletcher, Executive Publisher; Joanne Husovski, Former Editor; Alan Palmer, Project Manager; Bryan Hayward, Project Manager; and Martha Limbach, Associate Developmental Editor.

This book would not exist without Lynn Hanrahan, Senior Administrative Assistant in the Division of Adolescent Medicine, Cincinnati Children's Hospital Medical Center. Lynn is the organizational force and communications master behind this project. It is Lynn who monitored the detail, maintained our momentum, and kept us smiling from start to finish.

GENERAL ISSUES IN ADOLESCENT HEALTH CARE

PART I

CHAPTER 1

Normal Growth and Development

FRANK M. BIRO, MD

INTRODUCTION

Profound changes occur in the biological, cognitive, and social dimensions during the second decade of life. Although the content of these dimensions and the timing of their changes vary considerably, their overlap and interactions are hallmarks of adolescence. This chapter focuses on puberty, or maturation of the biological dimension. It opens with a review of the cognitive and social contexts within which puberty occurs. The triggers and timing of the onset of puberty are then discussed, followed by a review of its staging and dimensions. The final section presents common problems of pubertal development that present during adolescence.

COGNITIVE DEVELOPMENT

During the pre-teen and teen years, most adolescents progress from the Piaget stage of concrete thought to the stage of formal operational, or abstract, thought. They begin to understand subtleties in communication and how their current behaviors may impact future outcomes. They begin to think about thinking, both as it relates to their own thoughts and to the thoughts of others. Theoretical consequences of this reflection are the "imaginary audience" described by Elkind and the "personal fable." The imaginary audience refers to the belief that others are watching and invested in the adolescent's thoughts and action. The personal fable refers to a sense of invulnerability arising from the adolescent's perception of unique, individual attributes. Communication between adolescent patients and health care providers provides many examples of these cognitive changes. For example, an adolescent may respond to provider questions with partial answers, believing that answers obvious to the adolescent are also obvious to the provider.

When faced with stressful or emotional situations, adolescents who previously demonstrated cognitive maturity may revert to less sophisticated thought strategies. Research suggests that this reversion reflects the flux between cool, or objective, and hot, or affective, cognition. The region of the brain that integrates cognitive and affective information matures relatively late in adolescence, resulting in an intensified effect of emotional setting on decision and action.

SOCIAL DEVELOPMENT

The social tasks of adolescent development include the development of psychosexual identity, increasing autonomy from parents, and a future orientation toward adult role and responsibilities. Early adolescence (ages 11–14 years) coincides with the social transition from elementary to middle school and the associated changes in peer group, academic expectations, and teacher–student interactions. Peer influence and parent–teen conflict tend to increase during these years. Self-esteem can change dramatically and is strongly associated with gender, race, family, and school. White girls are particularly susceptible to a decline in self-image during early adolescence, with recovery by late adolescence. The decline is less in black than white girls, and self-esteem in boys tends to increase throughout adolescence.

By mid to late adolescence, conflicts between teens and parents typically diminish. Older adolescents shift

their focus to college, vocational training, and/or work as they move toward increasing self-sufficiency. Self- and sexual identity tend to stabilize, and adolescents begin to envision their roles as adults within families and communities. Although many older adolescents depend on their parents for continued financial support, personal and social expectations of independence accelerate with the completion of puberty and the achievement of physical maturity.

ONSET AND TIMING OF PUBERTY

Pubertal maturation begins with reactivation of the hypothalamic-pituitary-gonadal axis. Luteinizing hormone–releasing hormone (LHRH), also called gonadotropin-releasing hormone (GnRH), is secreted during fetal development, and the hypothalamic pulse generator remains active for 6–12 months after birth. Increased sensitivity of the hypothalamus to negative feedback from the gonadal sex steroids results in low levels of LHRH during childhood. The mechanism underlying reactivation of the LHRH pulse generator is unclear, but leptin appears to be an important mediator. Leptin is produced by fat cells, and its concentration in the serum correlates with the percentage of body fat. The administration of leptin to leptin-deficient animals has been shown to trigger puberty, and high serum levels of leptin in humans is associated with earlier pubertal maturation.

The timing and triggers of puberty have been subjects of intense study for more than 30 years. European and U.S. data on the age of menarche, dating back to the late 1800s, shows a steady downward trend through the first half of the twentieth century. Information about the ages of pubertal onset and progression is less reliable than that on menarche, and analyses regarding secular trends in the ages of pubertal onset and progression have generated considerable controversy.

In 1997, Herman-Giddens et al. published a cross-sectional study suggesting that maturation was occurring earlier in U.S. females than previously demonstrated. Using data from 17,000 visits to pediatric offices in the early 1990s, the investigators reported that 48% of black girls and 15% of white girls at age 8 years had breast or pubic hair development. Although the age of maturation was younger than expected, the mean ages of menarche for black (12.2 years) and white (12.9 years) girls differed little from the ages reported for girls in the 1970s.

A 2005 study by Sun et al. addressed the key question raised by the Herman-Giddens study: Is sexual maturity occurring earlier among U.S. children? The authors compared sexual maturity data from the 1966–1970 National Health Examination Surveys (NHES), 1982–1994 Hispanic Health and Nutrition Examination Surveys (HHANES), and the 1988–1994 National Health and Nutrition Examination Surveys III (NHANES III). Although comparison of pubertal onset is limited by the relatively high ages of enrollment at 12 years for NHES and NHANES III and 10 years for HHANES, the authors conclude that the evidence does not support a trend toward earlier maturation between the 1960 and 1990s for black boys, black girls, or white girls. The data do suggest a downward trend for white boys, Hispanic boys, and Hispanic girls. Tables 1-1 and 1-2 show the percentages of subjects who had reached Tanner stage 2 or higher at two time points in the three data sets.

The timing of pubertal maturation can have both short- and long-term effects on physical appearance and

Table 1-1 Percentages of White and Black Children in the United States Aged 12–13 Years Who Are Tanner Stage 2 or Greater

	NHES [1]	NHANES III [2]
	1966–1970	1988–1994
White girls		
Breast	94	93
Pubic hair	95	95
Black girls		
Breast	94	98
Pubic hair	90	89
White boys		
Genital	73	91
Pubic hair	68	71
Black boys		
Genital	78	89
Pubic hair	71	82

[1]National Health and Examination Surveys (NHES).
[2]National Health and Nutrition Examination Surveys (NHANES) III.
From Sun SS, Schubert CM, Liang R, et al.: Is sexual maturity occurring earlier among U.S. children? J Adolesc Health 2005;37:345–355.

Table 1-2 Percentages of Mexican-American Children in the United States Aged 10–11 Years Who Are Tanner Stage 2 or Greater

	HHANES[1]	HHANES
	1982–1984	1988–1994
Girls		
Breast	40	70
Pubic hair	7	4
Boys		
Genital	11	46
Pubic hair	90	89

[1]Hispanic Health and Nutrition Examination Surveys (HHANES) 1982–1984 and 1988–1994.
From Sun SS, Schubert CM, Liang R, et al.: Is sexual maturity occurring earlier among U.S. children? J Adolesc Health 2005;37:345–355.

psychosocial function. For example, early maturation in both males and females is associated with shorter adult stature. Among females, earlier maturation is associated with lower self-esteem and body image; earlier-onset sexual activity; increased rates of eating disorders, depression, and substance use during adolescence; and poorer adjustment skills and relationships during adulthood. Late maturation in males is associated with adolescent and adult disruptive behavior and substance abuse, whereas in females it is associated with a higher likelihood of on-time college graduation.

PARAMETERS OF PUBERTAL MATURATION

Puberty affects virtually all body systems. The most evident changes are growth in height, weight gain, and the appearance of secondary sexual characteristics. However, striking changes also occur in body composition, organ system size and function, and biochemical parameters. As shown in Figure 1-1, the patterns of growth during puberty differ for the skeletal (i.e., general), genital, lymphoreticular, and nervous systems. General and genital growth rates accelerate during puberty, lymphoreticular growth decelerates, and nervous system growth plateaus.

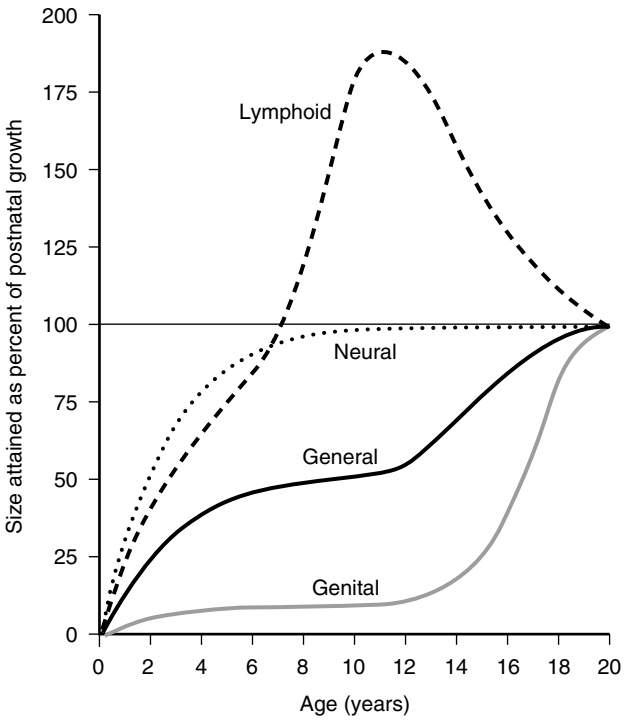

Figure 1-1 Growth curves of selected body systems, by age. From Harris JA, Jackson CM, Paterson DG, et al.: *The Measurement of Man*. Minneapolis, University of Minnesota Press, 1930.

Puberty in the individual is best described from the perspectives of its sequence, timing, and tempo. The sequence of change is commonly described by the "Tanner" stages of pubertal maturation, defined by Marshall and Tanner. Ratings of one (pre-pubertal child) to five (mature adult) are assigned separately to breast (Figure 1-2) and pubic hair development (Figure 1-3) in females and to genital (Figure 1-4) and pubic hair development in males. Since the development of the Tanner stages, estimation of testicular volume (Figure 1-5) has been shown to be a more reliable measure of male maturation than pubic hair. Figures 1-6 and 1-7 illustrate height velocity in females and males, respectively, as a function of chronological age and in relationship to other key events of puberty.

Peak height velocity (PHV) occurs relatively early in female puberty, at a mean Tanner stage of 2–3, and

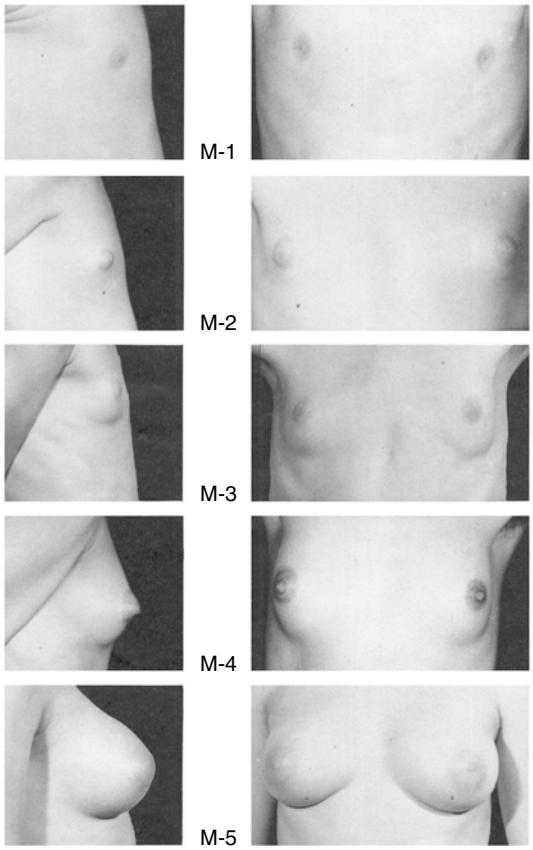

Figure 1-2 Stages of breast development in girls. Stage 1: Prepubertal, with no palpable breast tissue. Stage 2: Breast bud; elevation of the papilla and enlargement of areolar diameter. Stage 3: Enlargement of the breast, without separation of areolar contour from the breast. Stage 4: Formation of secondary mound above breast, from projection of areola and papilla. Stage 5: Recession of areola to contour of breast; papilla beyond contour of areola and breast.
From Roede MJ, van Wieringen JC: Growth diagrams 1980: Netherlands third nation-wide survey. Tijdschr Soc Gezondheids 1985;63(Suppl):1–34.

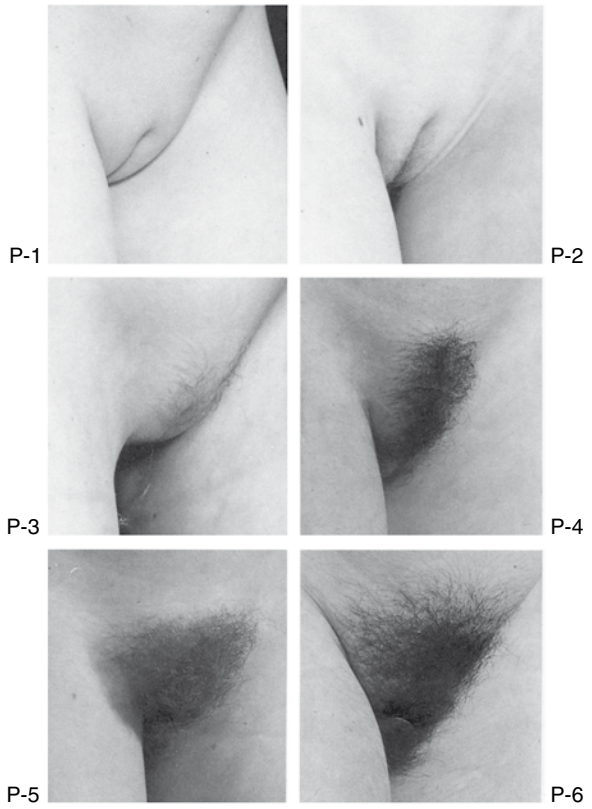

Figure 1-3 Stages of pubic hair development in girls. Stage 1: Prepubertal with no pubic hair. Stage 2: Sparse, straight hair along the lateral vulva. Stage 3: Hair is darker, coarser, and curlier, extending over the mid-pubis. Stage 4: Hair is adult-like in appearance, but does not extend to the thighs. Stage 5: Hair is adult in appearance, extending from thigh to thigh. Some describe PH6 as hair growth along linea alba.
From Roede MJ, van Wieringen JC: Growth diagrams 1980: Netherlands third nation-wide survey. Tijdschr Soc Gezondheids 1985;63(Suppl):1–34.

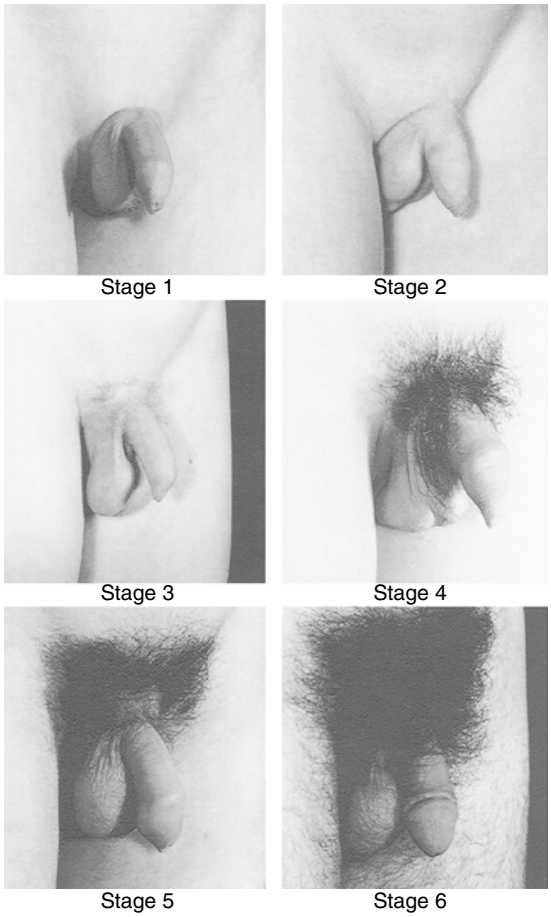

Figure 1-4 Stages of pubic hair development in boys. Stage 1: Prepubertal with no pubic hair. Stage 2: Sparse, straight hair along the base of the penis. Stage 3: Hair is darker, coarser, and curlier, extending over the mid-pubis. Stage 4: Hair is adult-like in appearance, but does not extend to the thighs. Stage 5: Hair is adult in appearance, extending from thigh to thigh. Some describe PH6 as hair growth along linea alba.
From Roede MJ, van Wieringen JC: Growth diagrams 1980: Netherlands third nation-wide survey. Tijdschr Soc Gezondheids 1985;63(Suppl):1–34.

menarche occurs relatively late, at a mean Tanner stage of 4. Body composition in girls changes rapidly after the PHV, with an increase in percent body fat. Most of the increase in female body mass index (BMI) before age 16 years is explained by an increase in lean body mass, whereas most of the increase after age 16 years is explained by an increase in body fat. The median and 95th percentile intervals between the onset of female puberty and menarche are 2.6 years and 4.5 years, respectively.

Body composition in boys changes little during puberty, and most of the increase in BMI is explained by an increase in lean body mass. PHV occurs in mid-late puberty, and the strength spurt occurs approximately 1 year later, near the completion of puberty. The earliest sign of puberty in boys is an increase in testicular volume, followed by the appearance of pubic hair approximately 6 months later.

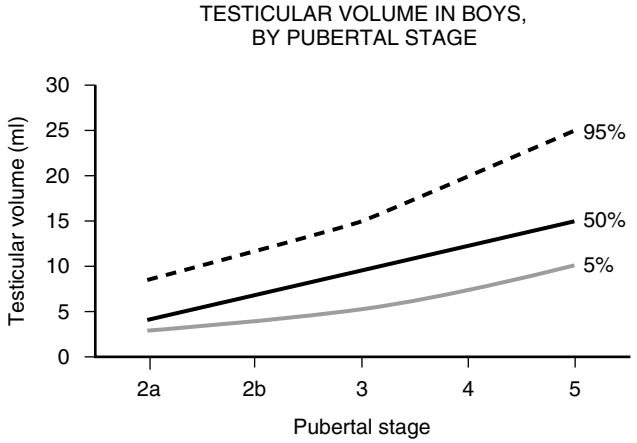

Figure 1-5 Testicular volume in boys, by pubertal stage. Stage 2a: PH1 with pubertal testicular volume; stage 26: PH2; stage 3: PH3; etc.
From Biro FM, Lucky AW, Huster GA, et al.: Pubertal staging in boys. J Pediatr 1995;127:100–102.

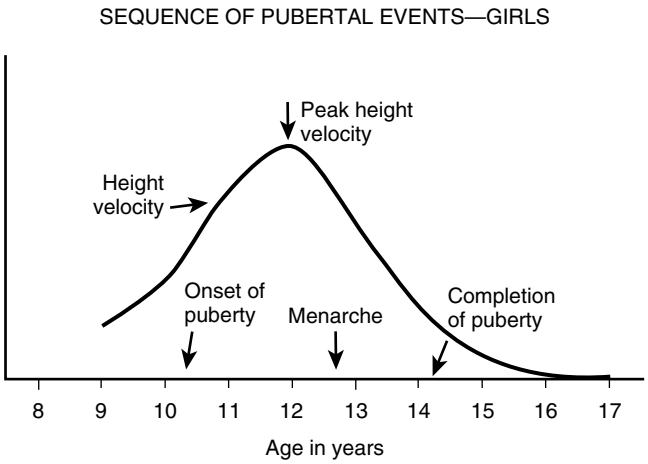

Figure 1-6 Sequence of pubertal events—girls.
Data from Biro FM, Huang B, Crawford PB, Lucky AW, et al.: Pubertal correlates in black and white girls. J Pediatr. 2006;148:234–240. Figure will appear in: Biro FM: Puberty: Whither goest? J Pediatr Adolesc Gynecol 2006; 19:163–165.

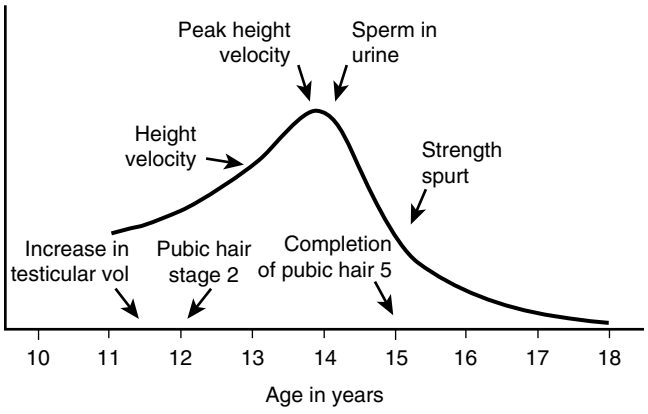

Figure 1-7 Sequence of pubertal events—boys.
Data from Biro FM, Lucky AW, Huster GA, et al.: Pubertal staging in boys. J Pediatr 1995;127:100–102. Karpati AM, Rubin CH, Sieszak SM, et al.: Stature and pubertal stage assessment in American boys: The 1988–1994 Third National Health and Nutrition Examination Survey. J Adol Health 2002; 30:205–212. Martin RJF, Dore E, Twisk J, et al.: Longitudinal changes of maximal short-term peak power in girls and boys during growth. Med Sci Sports Exerc 2004;36:498–503. Neu CM, Rauch F, Rittweger J, et al.: Influence of puberty on muscle development at the forearm. Am J Physiol Endocrinol Metab 2002;283:E103–107.

PROBLEMS ENCOUNTERED DURING PUBERTY

Issues that are statistically normative for the adolescent population are commonly viewed as abnormal for or by individual adolescents. The clinical challenge rests in differentiating pathology that requires early intervention from normal physiology that can be monitored or managed conservatively. Four examples of these issues—acne, gynecomastia, musculoskeletal symptoms, and myopia—are discussed below.

Acne may be a harbinger of normal pubertal development or may represent increased exposure or sensitivity to androgenic stimulation. It affects 85% of adolescents and resolves by young adulthood in 80% of those affected. All acne deserves clinical attention given the many therapeutic options now available, but not all acne warrants medical evaluation for underlying disorders. In males, severe acne unresponsive to topical treatment and oral antibiotics may be the only sign of hyperandrogenism. Females with acne that is accompanied by menstrual irregularity, hirsutism, excessive weight gain, acanthosis nigricans, or clitoromegaly should be evaluated for causes of ovarian or adrenal hyperandrogenism, such as polycystic ovary syndrome or congenital adrenal hyperplasia. The presentation, evaluation, and management of acne are discussed in detail in Chapter 15.

Gynecomastia, or male breast development, occurs in 50% of adolescent males and resolves spontaneously within 24 months in 90% of those affected. The probable cause is increased exposure or sensitivity to estrogenic stimulation, usually resulting from the peripheral aromatization of testosterone to estrogen. Most adolescent gynecomastia is managed by reassurance and watchful waiting, but boys with palpable breast tissue that exceeds 2 cm in diameter or persists beyond 24 months should be evaluated for hypogonadism (e.g., Klinefelter syndrome), hyperthyroidism, testicular tumors, or the use of medications associated with inhibition of androgen synthesis (e.g., ketoconazole) or receptors (e.g., cimetidine).

Musculoskeletal complaints are common during adolescence because of dynamic changes associated with the growth spurt, such as the organization of new bone, elongation of the extremities, and responsiveness of ligaments and tendons to sex steroids. Flexibility tends to decrease, resulting in muscular strains and sprains, apophyseal inflammation, and stress fractures. Many of the conditions are related to overuse and respond quickly to rest. Others are unrelated to exercise but stabilize without intervention (e.g., mild scoliosis). Chapter 3 discusses the musculoskeletal examination, and Chapter 18 discusses common problems of the back, hip, and knee during adolescence.

Myopia, or near-sightedness, typically begins or worsens during puberty. The cause is unknown, but family history of myopia and increased work requiring close vision appear to increase the risk of its development. Myopia that is readily corrected with glasses or contact lenses and that stabilizes during young adulthood typically does not require evaluation for underlying pathology. However, refractive errors during adolescence that progress beyond -6D are at risk of degenerative myopia and do warrant evaluation for underlying conditions (e.g., Marfan, Ehlers-Danlos, Stickler syndromes).

MAJOR POINTS

- Puberty refers to the biological and physical changes of adolescence that result in reproductive maturity.
- These biological changes occur within the context of cognitive and social development, resulting in abstract thought, psychosexual identity, increasing independence, and a future orientation to adult roles and responsibilities.
- Pubertal maturation begins with reactivation of the hypothalamic-pituitary-gonadal axis for the first time since fetal life. The age of pubertal onset declined in males and females during the twentieth century.
- The major parameters by which puberty is measured are the Tanner stages of sexual maturity, menarche in females, testicular volume in males, peak height velocity, and changes in body composition.
- The Tanner stages in females refer to the stages of breast and pubic hair development. The Tanner stages in males refer to the stages of genital and pubic hair development.
- In females, peak height velocity (PHV) occurs relatively early in the course of puberty. The increase in body mass index before and during the PHV reflects an increase in lean body mass, whereas the increase after the PHV reflects an increase in body fat.
- In males, PHV occurs relatively late in puberty and reflects an increase in lean body mass. Peak strength spurt occurs 1 year after the PHV.
- Developmental issues related to puberty include acne, gynecomastia, musculoskeletal complaints, and myopia. For most adolescents, these problems resolve or stabilize with the completion of puberty. A major goal of adolescent health is to differentiate between normative problems that can be managed conservatively and problems that require more aggressive intervention.

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CHAPTER 2

Preventive Health Care

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INTRODUCTION

Adolescence is a time of dramatic physical, cognitive, and emotional growth. Health care providers can play an important role in helping adolescents and their families effectively navigate these transitions and enter adulthood with a strong foundation for lifelong healthy habits. Clinical preventive services complement community-based positive development programs and public health interventions in optimizing the health of adolescents.

Most adolescents and their families progress though adolescence with few significant problems, and the rates of many risk behaviors have decreased over the past decade. On the other hand, rates of obesity and physical inactivity are increasing rapidly. Adolescents with medical and behavioral risks, as well as those with special health care needs, may be less likely than those who are low-risk to seek preventive care, making proactive screening and intervention important during all clinical contacts.

EXPERT RECOMMENDATIONS AND THE EVIDENCE BASE FOR ADOLESCENT PREVENTIVE CARE

Most expert groups, such as the American Academy of Pediatrics (AAP), the American Medical Association (AMA), the American Academy of Family Practitioners (AAFP), and the Maternal and Child Health Bureau (MCHB), make similar recommendations. The United States Preventive Services Task Force (USPSTF) has the most stringent criteria for recommending a preventive intervention. Generally, the USPSTF makes a recommendation only if there is evidence of the effectiveness of the intervention, such as for immunizations and chlamydia screening in sexually active female adolescents. If there is good evidence of lack of effectiveness or of harm, the USPSTF usually recommends against the specific intervention. For example, it explicitly recommends against routine scoliosis screening of adolescents. In many other areas, especially in screening and counseling for lifestyle or behavioral issues, evidence is lacking and the USPTF makes no recommendation.

Most other organizations will make a recommendation in the absence of evidence if it addresses a substantial public health issue (e.g., obesity) or there is evidence of effectiveness in other populations. For example, screening for tobacco use and cessation counseling have good evidence of effectiveness in adults, but little similar data are available in adolescents. The USPSTF makes no recommendation, but Bright Futures, endorsed by multiple groups, recommends tobacco screening and cessation counseling for adolescents.

Guidelines change frequently as new evidence becomes available and can be obtained online at *http://www.ahrq.gov/clinic/prevenix.htm*, *http://www.aafp.org/online/en/home/clinical/exam.html*, and *http://www.brightfutures.org*. The key elements of adolescent preventive care are summarized in Box 2-1.

ELEMENTS OF ADOLESCENT PREVENTIVE CARE

Physical Assessment

Many adolescents, parents, and clinicians expect preventive care to include a routine, annual physical examination, despite its unproven clinical value. Key components that should be performed during early, mid, and late adolescence include measurement of blood pressure, height and weight; calculation of body mass index (BMI); determination of height, weight, and BMI percentiles from age- and sex-adjusted growth charts; and determination of pubertal maturation by Tanner staging of breast and pubic hair development in females and genital and pubic hair development in males (Chapter 1). Bright Futures also recommends objective vision screening with a Snellen test during early, mid, and late adolescence, based on expert consensus. The decision about whether a parent leaves or remains during the physical examination generally should be made by the adolescent.

Behavioral Screening and Anticipatory Guidance

Evidence supporting the effectiveness of behavioral screening and anticipatory guidance is weak during adolescence as well as earlier childhood. However, screening is recommended based on its potential benefit and low risk of harm. The key behavioral screening and anticipatory guidance topics for adolescents and their parents are outlined in Box 2-2.

Box 2-1 Elements of Preventive Care for Adolescents

- Address adolescent and family concerns
- Physical assessment
- Screening
  - Development
  - Social and academic competence
  - Risky behavior
  - Violence
- Immunizations
- Preventive counseling/anticipatory guidance
- Interventions for identified problems

Box 2-2 Screening and Anticipatory Health Guidance

For Adolescents

- Normal development
  - Physical
  - Emotional
  - Social
  - Academic
  - Sexual
- Nutrition
- Physical activity
- Violence and injury prevention
- Responsible sexual behavior
- Avoidance of substances

For Parents of Adolescents

- Normal adolescent development
  - Physical
  - Cognitive
  - Academic
  - Social
  - Emotional
  - Sexual
- Parenting behaviors and styles that promote healthy development, including parental monitoring
- Role modeling healthy lifestyle and behaviors

Behavioral screening and guidance generally should be conducted with the adolescent alone, unless the adolescent requests the parent's presence. It is best to start the interview with less sensitive areas of inquiry, such as school and leisure activities, and progress to more sensitive areas such as depression and sexuality. A useful mnemonic for recalling the elements and sequencing of the psychosocial interview is HEADDS, which stands for Home, Education, Activities (social, work, sports), Drugs, Depression, Sexuality, and Safety (risk for intentional and unintentional injury). The Bright Futures materials have extensive lists of trigger questions and anticipatory guidance suggestions for each of the key areas, as well as screening checklists for parents, adolescents, and providers. Adolescent and family strengths should be sought and reinforced.

Laboratory Screening

No routine laboratory tests are universally recommended during adolescence. Consequently, laboratory screening should be tailored to the adolescent's individual risk profile. Annual chlamydia screening is recommended in all sexually active females because of its high prevalence and risk for progression to pelvic inflammatory disease. The individual benefit of screening is less clear in the adolescent male and, because of the weaker evidence

base, there is controversy about the routine screening of males for chlamydia. Gonorrhea screening is recommended by the USPSTF for high-risk females, including all sexually active females younger than age 25. Cervical cancer screening is recommended 3 years after the onset of vaginal sexual activity or at the age of 21 years. Although there is likely little value in screening young women who have never had vaginal intercourse, screening at age 21 years is recommended based on the high prevalence of sexual activity by that age and the concern that clinicians may not always obtain accurate sexual histories. Screening is risk-based for human immunodeficiency virus (HIV) (*http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5019a1.htm*), tuberculosis (*http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5412a1.htm*), and hypercholesterolemia (*http://www.guidelines.gov/summary/summary.aspx?doc_id=5453&nbr=003730&string=lipid*).

Immunizations

There is strong evidence to support the effectiveness of immunizations during adolescence. The current schedule for adolescents is outlined in Figure 2-1, and updates can be viewed at *http://www.cdc.gov/vaccines*. The schedules have changed rapidly for adolescents in recent years with the development of new vaccines, such as those protecting against meningococcus and human papillomavirus (HPV). The Centers for Disease Control and Prevention (CDC) and other groups recommend that adolescent immunization occur at the 11- to 12-year-old visit because routine visits decrease with advancing adolescent age and are more likely to take place in sites without vaccine tracking.

Counseling for Behavioral Change

There is a large theoretical and empirical literature to guide effective behavior change counseling. The ***transtheoretical model***, or stages of change theory, developed by Prochaska and DiClemente posits that interventions to motivate behavioral change must be tailored to the individual's readiness to change. Change progresses through five stages: pre-contemplation (not yet considering a change); contemplation (considering a change but ambivalent); preparation (actively making plans for the change); action (making the change); and maintenance (sustaining the change). The patient in the pre-contemplation stage should be given a clear message regarding the value of the behavior change, whereas someone in the preparation stage should be given specific assistance in setting goals and arranging the behavior change. Data pertaining to adolescents are sparse, but studies in adults demonstrate that brief advice from a physician, tailored to the patient's stage of change, doubles the rate of smoking cessation. One popular method, developed by the National Cancer Institute, is the 5 "A"s approach (Box 2-3).

Motivational interviewing is an office-based counseling technique that may be particularly useful for adolescents in the pre-contemplation and contemplation stages. Miller and Rollnick have shown that the provider

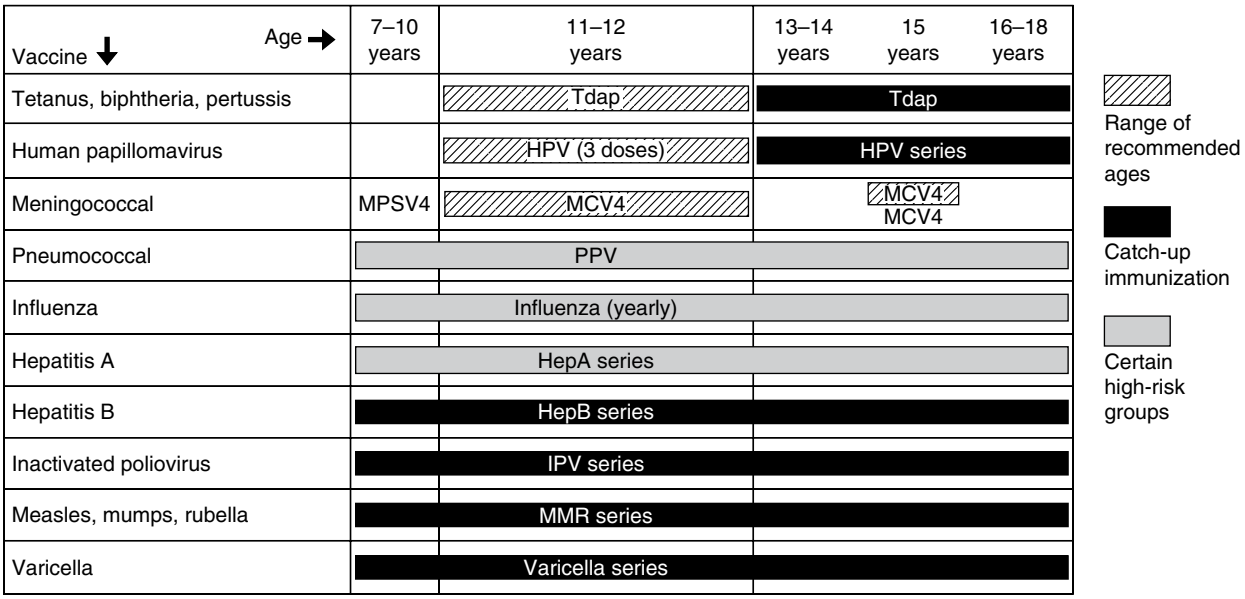

Figure 2-1 Recommended adolescent immunization schedule for persons aged 7–18 years: United States, 2007. From: *http://www.cdc.gov/vaccines*.

Box 2-3 The 5 "A"s for Brief Office-Based Interventions

Ask	Determine the presence of the behavior.
Advise	Deliver a clear, personalized message about the need to change the behavior.
Assess willingness to change	Determine whether the adolescent is prepared to change his or her behavior.
Assist the behavior change	Determine short-term, concrete actions to make the behavior change; set behavioral goals. Provide adjunct therapy as appropriate (e.g., nicotine replacement for tobacco cessation).
Arrange follow-up	Schedule a follow-up visit or phone call soon after the date set for the behavior change, ideally within 1 week.

From: Manley, M, Epps, RP, Husten, C, et al.: Clinical interventions in tobacco control. A National Cancer Institute training program for physicians. *JAMA* 1991; 266:3172–3173.

who tries to move beyond the patient's current stage of change is likely to encounter resistance. In motivational interviewing, the provider accepts the current state, expresses empathy for the patient's views and situation, helps the patient understand the discrepancy between current behavior and future goals, and supports the patient's self-efficacy to change. Most importantly, the provider rolls with, rather than opposes, resistance. Commonly used techniques include open-ended questions, reflective listening, affirmative responses, summaries of the patient's views, and elicitation of "change talk," or patient articulation of potential actions to change behavior. Although it takes time to learn and implement motivational interviewing, it may be more effective in changing behavior than brief office advice.

Office Systems to Enhance Adolescent Preventive Care

Adolescents and young adults are less likely than any other age groups to receive recommended preventive care. Within the adolescent/young adult group, the rates of preventive care are particularly low among males and ethnic minorities. Thus, all health care interactions should be considered opportunities to provide preventive services. Analyses of the National Ambulatory Medical Care Survey and the National Hospital and Ambulatory Medical Care Survey demonstrate that behavioral and lifestyle counseling is more likely to occur at acute-care visits than preventive-care visits.

Strong empirical evidence supports the value of systems-based approaches to clinical preventive services in all age groups, including adolescents. The key elements of effective office-based preventive service systems for adolescents are outlined in Box 2-4. The Agency for Healthcare Research and Quality has developed a program to help practices implement preventive services (*www.ahrq.gov/clinic/prevenix.htm*). First, the practice or organization must agree on the content of the services to be delivered. National guidelines can be adapted to local conditions. Tools such as adolescent and parent screening questionnaires, standardized preventive visit encounter forms, and preventive service flow-sheets improve efficiency and help ensure that all required areas are addressed. Electronic health records are particularly well-suited to the delivery of preventive care because of their internal prompts, reminders, protocols, and capacity for customized screening and advice.

The efficient delivery of preventive care also depends on clarity regarding the roles and responsibilities of clinical and administrative staff. Some practices have a designated preventive care coordinator. Tracking systems to record key services received (e.g., immunizations and chlamydia screening), recall strategies to contact adolescents who have missed recommended services, and system updates to meet changing public health goals are essential components of quality care.

Box 2-4 Elements of an Office-Based Preventive Care System

1. Preventive care protocols based on evidence and/or consensus
2. Use of effective tools (flow-sheets, prompts, standing orders)
3. Clear staff roles for service delivery and monitoring of results
4. Audit and feedback to providers
5. Ongoing quality improvement efforts in order to meet established local or national goals

MAJOR POINTS

- Adolescents infrequently make preventive visits, so all heath care encounters should be used as opportunities to provide preventive care.
- Office-based preventive care complements public health- and community-based approaches to improving health of adolescents.
- Preventive care for adolescents encompasses physical assessment; developmental, behavioral, and laboratory screening; immunizations; anticipatory guidance; and intervention for identified problems.
- Office-based behavioral interventions should be based on the adolescent's readiness to change and should include effective techniques such as brief advice and motivational interviewing.

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CHAPTER 3

Exercise and Sports

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INTRODUCTION

Exercise and physical activity during childhood and adolescence contribute to lifelong health and well-being. Compared with sedentary individuals, those who engage in regular physical activity are at reduced risk for obesity, diabetes mellitus, hypertension, coronary heart disease, stroke, osteoporosis, anxiety, and depression. This chapter reviews the effects of physical activity on cardiovascular, musculoskeletal, and mental health; the rates of exercise and physical activity during adolescence; recommendations from the Centers for Disease Control and Prevention (CDC) regarding amount and types of exercise during adolescence; and the prevention of injuries associated with physical activity.

DEFINITIONS

Body mass index (BMI): A measure of adiposity, expressed as weight/height^2 (kg/m^2).

Exercise: Physical activity that is planned, structured, repetitive, and for the purpose of improving or maintaining physical fitness.

Fitness: Composite measure of cardiorespiratory endurance, muscle endurance and strength, body composition, and flexibility.

Physical activity: Bodily movement associated with skeletal muscle contraction and energy expenditure.

Sufficient moderate physical activity: Activity such as walking or cycling that does not require sweating or breathing hard, lasts > 30 minutes, and occurs > 5 days per week.

Sufficient vigorous physical activity: Activity such as running or basketball that is associated with sweating and breathing hard, lasts > 20 minutes, and occurs > 3 days per week.

HEALTH BENEFITS

Cardiovascular

BMI is used to define overweight and obesity during adulthood and to identify children and adolescents who are overweight or at risk of becoming overweight (see Chapter 11). The CDC defines individuals < aged 18 years with BMI values > 95th percentile for age and sex as overweight. The 1999 National Health and Nutrition Examination Survey (NHANES) revealed that 13% of children aged 6–11 years and 14% of adolescents aged 12–19 years are overweight. This represents a 2–3% increase in overweight since NHANES III (1988–1994).

In 2004, an expert panel reviewed the effects of physical activity on health outcomes in children and adolescents. Programs of moderately intense exercise lasting 30–60 minutes and repeated 3–7 days weekly were found to decrease adiposity in overweight youth without changing adiposity in normal-weight youth. Among youth

with mild essential hypertension, 30 minutes of exercise at 80% maximal heart rate performed three times weekly was found to reduce blood pressure. Two studies in children suggest that aerobic exercise improves serum levels of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) and lowers blood pressure. In adults, sustained physical activity (i.e., 40 minutes daily, 5 days weekly, for 4 months) is required to induce and maintain improvements in serum levels of HDL-C and triglycerides.

Mental Health

Many studies have demonstrated associations of exercise with improved mood and self-concept, but the mechanisms underlying the association remain controversial. Participation in sports does appear to foster the development of healthy competitiveness, sportsmanship, self-confidence, resilience, and respect for authority. It also has been shown to decrease physical and emotional distress in healthy adolescents during high-stress times and in children and adolescents with mood disorders, attention-deficit hyperactivity disorder, learning disorders, and impaired social skills. One study of high school females demonstrated lower rates of sexual risk behaviors, pregnancy, and sexually transmitted infections among sports participants versus nonparticipants. Although it is possible that the association of exercise with improved mood and self-image is mediated by intermediate improvements in appearance, physical performance, and/or social feedback, the positive effects of physical activity on adolescent mental health are strong and consistent.

Musculoskeletal

Aerobic training increases the numbers of slow-twitch fibers and capillaries in muscle. Resistance training increases the size and recruitment of muscle fibers, which leads to the ability to exert more force (i.e., strength). Prolonged, high-intensity exercise increases both strength and the cross-sectional area of ligaments and tendons. During childhood, high-repetition, moderate-load resistance training has been shown to increase both strength and endurance and may reduce the risk of injury during participation in organized sports.

Approximately 90% of adult bone mass is attained during the first two decades of life. Optimizing bone mineral density (BMD) and strength during adolescence is believed to play a significant role in preventing osteoporosis and fractures later in life. Determinants of BMD include genetics, race, ethnicity, hormonal status, calcium intake, physical activity, and weight. Regardless of age or gender, the total number of hours of weight-bearing exercise is positively correlated with BMD. Furthermore, compared with non-weight-bearing exercises such as swimming or cycling, weight-bearing exercises such as running are associated with site-specific increases in BMD. In adolescent females, resistance training has been shown to increase BMD of the femoral neck.

EPIDEMIOLOGY

Physical Activity

Physical activity decreases during adolescence. A 2003 national survey of students in grades 9–12 revealed that student participation in sufficient vigorous activity (i.e., sweating and breathing hard > 20 minutes per day > 3 days per week) decreased 6% per year among females and 3% per year among males. Across all four grades, 33% reported insufficient vigorous or moderate (i.e., activity without sweating or breathing hard > 30 minutes per day > 5 days per week) activity and 12% reported no physical activity in the preceding week. Daily attendance in school physical education (PE) classes declined 42% between the 9th and 12th grades, and only 19% of all high school students reported > 20 minutes of physical activity in daily PE classes. Analyses by race/ethnicity and gender revealed that black students were less active than white students and females were less active than males. A 2000 CDC survey revealed that PE class was required by 50% of schools for 5th grade students but by only 5% of schools for 12th grade students (Figure 3-1).

Sports-Related Injury

Although many adolescents are not involved in sufficient physical activity, some adolescents are involved in excessive or unsafe physical activity. Athletes who participate in intense training, multiple sports per season, or year-round competition are at increased risk of acute injury in contact sports and overuse injury in noncontact sports. As athletes involved in contact sports progress through puberty, the increase in muscle mass, strength, and generated force are believed to contribute to the increasing rate of acute injury.

Contusions, strains, and sprains are the most common sports-related injuries. Ankle sprains rank first for males and females, accounting for 10–30% of all musculoskeletal sports injuries. There are an estimated 2.6 million visits to emergency departments for sports-related injuries in individuals aged 5–24 years, with a male-to-female ratio of 2:1 (48 vs. 19 visits per 1000 persons). Football causes more injuries than any other high school sport, with 41–61% of players sustaining at least one injury annually. Gymnastics ranks second, wrestling third, and boys' basketball fourth. Girls' basketball and soccer have higher

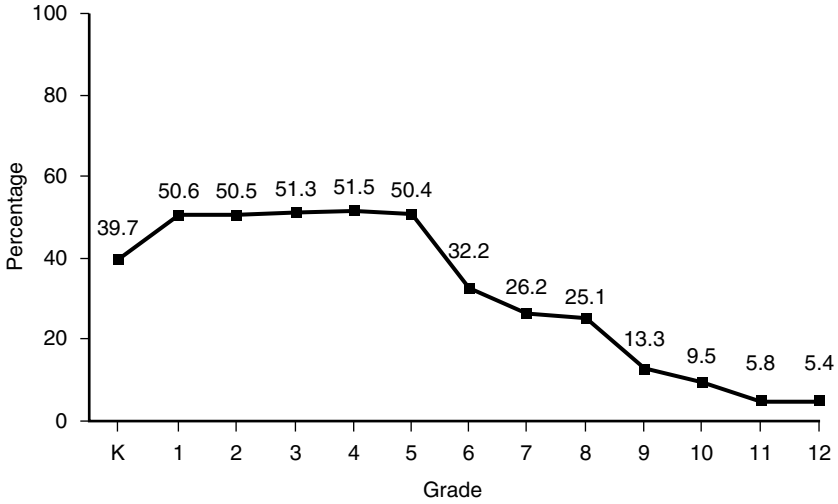

Figure 3-1 Percentage of schools that require physical education by grade. Available from: *http://www.cdc.gov/HealthyYouth/shpps/factsheets/index.htm*. Accessed May 17, 2007.

rates of knee injury and surgery than any other girls' or boys' sport, and females in general are at higher risk than males for knee injury and tears of the anterior cruciate ligament (ACL). The usual mechanism of ACL injury is a noncontact, sudden deceleration and twisting motion (i.e., cut and plant motion). Differences in female and male training, neuromuscular response, laxity, dynamic stability, hormonal influences, and lower extremity alignment may all play a role. Power, strength, balance, and core stability training show promise in decreasing the incidence of ACL injury in female athletes.

Pre-pubertal athletes are at a higher risk for heat injury than pubertal athletes due to their higher threshold for sweating and lower sweat rate. Overuse injuries, caused by repeated microtrauma, are common among both older children and adolescents (see Chapter 18). Examples include the traction apophysitis of Osgood-Schlatter disease (insertion of the patellar tendon on the tibial tubercle), Sever's disease (insertion of the Achilles tendon on the calcaneus), and Little League elbow (flexor/pronator origin on the medial epicondyle). Training errors such as a sudden increase in the frequency, volume, or intensity of training have been implicated as the most common predisposing factors for overuse injury.

In the United States, more than 300,000 sports-related concussions are reported each year. Concussions account for 90% of head injuries in sports, and most are sustained in football.

MANAGEMENT

Recommendations for Regular Physical Activity

The CDC recommends that adolescents participate in vigorous physical activity (e.g., basketball, swimming) for > 20 minutes on > 3 days per week, or moderate physical activity (e.g., fast walking, slow bike riding, pushing a lawn mower) for > 30 minutes on > 5 days per week. Most intervention studies demonstrating positive health outcomes with exercise have used supervised programs of moderate to vigorous physical activity lasting 30–45 minutes and repeated 3–5 days per week. Since usual, unsupervised physical activity is likely to be less intense than this, many experts encourage school-aged youth to participate in > 60 minutes of daily, moderate-to-vigorous physical activity that is enjoyable, developmentally appropriate, and a balance of endurance, flexibility and strength training. At least twice each week adults will benefit by performing activities using the major muscles of the body that maintain or increase muscular strength and endurance. The evidence for this is based on multiple RCTs.

Six national health objectives pertaining to adolescent physical activity are included in Healthy People 2010 (Box 3-1). These objectives call for behavioral change at the individual, family, and school levels.

Box 3-1 Healthy People 2010 Objectives

Increase the proportion of:

- Adolescents who engage in moderate physical activity > 30 minutes daily > 5 days per week
- Adolescents who engage in vigorous physical activity > 20 minutes daily > 3 days per week
- Adolescents who participate in daily school physical education
- Adolescents who spend > 50% of physical education class time being physically active
- Adolescents who watch < 2 hours television daily on school days
- Schools that require daily physical education for all students

U.S. Department of Health and Human Services. *Healthy People 2010*. Washington D.C., January, 2000. Available from: *http://www.healthypeople.gov/document/HTML/Volume2/22Physical.htm#_Toc490380803*. Accessed May 17, 2007.

Injury Prevention

Strategies for reducing the likelihood and severity of adolescent sports-related injury are summarized in Box 3-2. Examples of successful interventions include a 50% reduction in gymnastic injuries with discontinuation of competitive trampoline and an 80% reduction in softball sliding injuries with introduction of break-away bases.

The objectives of the pre-participation evaluation (PPE), as shown in Box 3-3, are not intended to replace the annual health examination. The PPE was standardized in 1992 and updated in 2004 through the combined efforts of the American Academy of Family Physicians, the American Academy of Pediatrics, the American Medical Society for Sports Medicine, and the American Orthopedic Society for Sports Medicine. The PPE should take place 4–6 weeks before the start of the sports season so that there is time to evaluate and treat musculoskeletal injuries or medical conditions.

Discussion with coaches, players, and parents should include review of warm-up, cool-down, hydration, overuse, strengthening, stretching, performance-enhancing drugs, and psychological stress associated with competition. These discussions can be held during the off-season, when coaches and families have more time.

Box 3-2 Strategies for Potentially Decreasing the Likelihood and Severity of Sports-Related Injury

- Pre-season physical examination
- Medical personnel at sporting events
- Adequate hydration during training and events
- Proper coaching and officiating
- Protective equipment
- Safe playing conditions

Box 3-3 Goals of the Pre-Participation Sports Evaluation

- To identify medical problems with risks of life-threatening complications during participation
- To identify conditions that require a treatment plan before or during participation
- To identify and rehabilitate musculoskeletal injuries
- To identify and treat conditions that interfere with performance
- To remove unnecessary restrictions on participation
- To advise athletes regarding appropriate sports in which to participate

Return to Play

"When can I play again?" is one of the first and most pressing questions an athlete asks following an injury. Even when return-to-play guidelines exist for an injury or condition, athletes tend to press for earlier return. The risks of premature return include re-injury or new injury that can have long-lasting consequences. A musculoskeletal injury typically progresses through the four phases of rehabilitation outlined in Table 3-1. Phase 1 focuses on limiting further injury and controlling acute symptoms. Phases 2, 3, and 4 introduce progressive movement of the injured structure until symptom-free function is restored. Athletes who insist on returning to play before completing Phase 4 increase their risk of additional injury. Patience on their part, as well as on the part of coaches and parents, is an essential component of the rehabilitation process.

Return-to-play recommendations following concussion are particularly controversial. The American Orthopedic Society for Sports Medicine (AOSSM) has trended away from the use of a numeric grading system and toward more individualized management. The National Collegiate Athletic Association (NCAA) does not endorse any of the current grading systems or guidelines because of their lack of scientific validity and the ongoing controversy among experts. The final decision is therefore based on clinical judgment and negotiation with the athlete.

Table 3-1 Rehabilitation Phases Following Musculoskeletal Injury

Phase	Goals	Management
1	Control pain, swelling	Rest, ice, compression, elevation
2	Improve strength, flexibility	Range-of-motion exercises
3	Improve endurance, proprioception	Resistance, endurance training
4	Return to exercise symptom-free	Progressive training without return to play

MAJOR POINTS

- Regular physical activity reduces the risk for obesity, diabetes mellitus, hypertension, coronary heart disease, stroke, osteoporosis, anxiety, and depression.
- During childhood, high-repetition, moderate-load resistance training has been shown to increase both strength and endurance and may reduce the risk of injury during participation in organized sports.
- The CDC recommends that adolescents participate in vigorous physical activity (e.g., basketball, swimming) for > 20 minutes on > 3 days per week, or moderate physical activity (e.g., fast walking, slow bike riding, pushing a lawn mower) for > 30 minutes on > 5 days per week.
- The PPE should take place 4–6 weeks before the start of the sports season so that there is time to evaluate and treat musculoskeletal injuries or medical conditions.
- Discussion with coaches, players, and parents should include review of warm-up, cool-down, hydration, overuse, strengthening, stretching, performance-enhancing drugs, and psychological stress associated with competition.
- Return-to-play following a sports-related injury should be delayed until the athlete has progressed through four phases of rehabilitation and is able to play symptom-free.

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CHAPTER 4

Nutrition

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INTRODUCTION

Nutritional evaluation and counseling are crucial elements of adolescent care. At no other time in life, except infancy, does the body experience as much growth and development. Proper nutrition and healthy eating patterns support these changes, provide energy for daily activities, and can help prevent cardiovascular disease and some types of cancer later in life. Yet appropriate nutrition is less likely during adolescence than during any other time of life. Despite the increasing rates of adolescent obesity since the 1970s, mean intakes of calcium, iron, vitamin A, and vitamin C during adolescence all remain below the Recommended Daily Allowance (RDA). The physiological and behavioral characteristics that place adolescents at risk for nutritional compromise include the following:

Growth and Development: 20% of adult height and 50% of the adult skeleton are accrued during the teen years, requiring tremendous amounts of energy and nutrients, particularly iron and calcium. The onset of menstruation puts an additional strain on iron stores in the adolescent female.

Meal Pattern and Composition: Adolescent meals, especially breakfast, are often skipped or eaten on the run. The planned family dinner may be replaced by fast foods or vending machine snacks that are high in calories, fat, sodium, and sugar and low in essential nutrients. Table 4-1 shows the nutritional information for some of the fast food items commonly selected by adolescents.

Dietary Experimentation: Adolescence is a time of experimentation in all aspects of life, including alternative diets such as vegetarianism. Although many diets do provide adequate nutrition when implemented correctly, adolescents may not have the knowledge or resources to develop healthy meal plans.

Body Image: Rapid changes in body size and composition, peer pressure, athletics, and media influences are just some of the reasons why teens often feel dissatisfied with their bodies. This may lead to fad dieting, fasting, purging, and eating disorders.

Special Circumstances: Pregnancy, substance use, chronic disease, and competitive athletics place particular strain on nutritional status during adolescence given the physiological demands of pubertal maturation.

NUTRITIONAL ASSESSMENT

A nutritional assessment should be part of every health maintenance visit and is easily incorporated into routine care. For the well adolescent, screening questions during the history, routine anthropometric measurements, and a general physical examination usually suffice. Laboratory studies to assess nutritional status are not part of the routine screen and should be prompted by findings on the history or physical examination.

Table 4-1 Fast Food Nutritional Comparison

	Calories (kcals)	Total Fat (g)	Cholesterol (mg)	Sodium (mg)
McDonald's				
Big Mac Hamburger	554	30	80	1010
Regular Hamburger	265	9	30	530
Pizza Hut				
Meat Lover's Pizza, 1 slice	300	13	35	760
Veggie Lover's Pizza, 1 slice	220	6	15	490
Taco Bell				
Beef Burrito Supreme	440	18	40	1330
Tostada	250	10	15	710
Burger King				
French Fries, King Size	603	29	0	1075
French Fries, Small Size	230	11	0	410
Subway				
Meatball Sandwich, 6-inch	560	24	45	1610
Turkey Sandwich, 6-inch	280	5	20	1020
Wendy's				
Chicken BLT Salad with dressing and croutons	680	47	130	1315
Chicken BLT Salad without dressing and croutons	330	18	105	840
Smoothie King				
Chocolate Smoothie, "The Hulk," 20 oz.	846	29	102	626
Berry Punch Smoothie, 20 oz.	350	0	0	110

History

Questions such as the following help guide the nutritional history: *Tell me everything that you ate and drank yesterday from the time you woke up until the time you went to sleep. Are there any types of foods that you do not eat? How often do you eat fast food? What do you usually drink? How often do you eat fruits and vegetables? Do you take vitamins, minerals, or other supplements? How often do you skip meals? Have you made any changes in your diet? Do you want to weigh more, less, or the same as you weigh now? What do you do to achieve that goal? What questions or concerns do you have about your nutrition?*

The high incidence and prevalence of eating disorders during adolescence have prompted the development of brief screening tools for anorexia nervosa and bulimia. Anstine and Grinenko found the following four-question screen to be both sensitive and specific for the identification of older adolescent females with eating disorders: *How many diets have you been on in the past year? Do you feel you should be dieting? Do you feel dissatisfied with your body size? Does your weight affect the way you feel about yourself?* More than two diets to lose weight in the past year, a perceived need to diet, dissatisfaction with body size, and an effect of weight on self-esteem are associated with anorexia nervosa, bulimia nervosa, and other eating disorders.

If the screening history raises nutritional concerns, the adolescent should be asked to keep a detailed food diary and to meet with a trained dietician who can both obtain and analyze intake data.

Physical Examination

Table 4-2 summarizes the physical findings associated with nutrient deficiency and excess. Although these findings may provide important clues to specific nutritional problems, the standard anthropometric measures described next remain the cornerstones of any nutritional assessment.

Weight: Body weight responds within days to a change in energy (i.e., kilocalorie) intake and therefore is a short-term indicator of nutritional status. At every adolescent health care visit, weight should be measured on a calibrated standing scale with the patient barefoot and undressed. The measurement should be plotted on an age- and gender-adjusted weight curve available from the National Center for Health Statistics (*http://www.cdc.gov/growthcharts*).

Height: Until the completion of puberty, growth in height is a long-term indicator of nutritional status. It should be measured at least annually throughout childhood and adolescence and more frequently (every to 6 months) during periods of illness or known nutritional deficiency. The most accurate and reliable measurements of height are obtained using a wall-mounted stadiometer. The

Table 4-2 Signs of Nutrient Deficiency and Excess on Physical Examination

System	Nutrient or Condition	Physical Finding
Mouth	Deficient riboflavin, niacin, biotin, B_6, B_{12}, folate, iron, zinc	Glossitis
	Deficient riboflavin, niacin, biotin, vitamin B_6, iron	Angular stomatitis, cheilosis
	Deficient vitamin C	Gingivitis and gingival bleeding
	Bulimia nervosa	Parotid hyperplasia, dental erosions
Eyes	Deficient vitamin A	Night blindness, photophobia, xerosis, corneal ulceration
	Vitamin A toxicity	Diplopia
	Deficient thiamin	Nystagmus, lateral gaze palsy
	Deficient vitamin B_{12}	Optic nerve atrophy, blindness
	Deficient vitamin E	Retinitis pigmentosa, visual deficits
	Excess copper	Kayser-Fleischer ring
Skin	Deficient vitamin B_6, zinc	Seborrheic-like dermatitis
	Deficient vitamin C, zinc	Impaired wound healing
	Deficient niacin	Rash in sun-exposed areas
	Deficient vitamin C	Perifollicular petechiae, hemorrhage
	Deficient vitamin K	Easy bruising
	Deficient essential fatty acids	Dry flaky skin
	Protein-energy malnutrition	Depigmentation
	Excess carotenoid	Yellow or orange discoloration
	Deficient iron, vitamin B_{12}, folate	Pallor (due to anemia)
Nails	Deficient iron	Koilonychia (spoon-shaped nails)
	Excess selenium	Discolored or thickened nails
Hair	Protein-energy malnutrition	Discoloration, dullness, thinning
	Deficient biotin	Alopecia
	Excess vitamin A	Alopecia
Cardiovascular	Thiamin deficiency	Congestive heart failure, tachycardia
	Selenium deficiency	Cardiomyopathy, heart failure
Gastrointestinal	Niacin deficiency	Stomatitis, proctitis, esophagitis
Musculoskeletal	Deficient vitamin D	Weakness, bone, bony tenderness, fracture
	Protein-energy malnutrition	Muscle wasting
	Hypocalcemia	Carpopedal spasm
Neurologic	Deficient vitamin B_6, vitamin E, thiamin	Peripheral neuropathy
	Excess vitamin B_6	Peripheral neuropathy
	Deficient vitamin B_{12}	Sensory neuropathy
	Deficient thiamin, B_6, B_{12}, niacin, biotin	Mental status changes, delirium
	Deficient B_{12}, thiamin, niacin	Dementia

Adapted from Saltzaman E, Mogensen KM: Physical assessment. In Coulston AM, Rock CL, Monsen ER (eds): *Nutrition in the Prevention and Treatment of Disease.* San Diego, CA, Elsevier, 2001, pp. 48–49.

measurement should be plotted on an age- and gender-adjusted height curve available from the National Center for Health Statistics (*http://www.cdc.gov/growthcharts*).

Body Mass Index (BMI): Adiposity can be estimated above the age of 2 years by calculating the BMI as weight in kilograms divided by height in meters squared (kg/m^2) or weight in pounds divided by height in inches squared, multiplied by 703 ($lbs/in^2 \times 703$). As described previously for weight and height, BMI should be plotted on an age- and gender-adjusted curve available from the National Center for Health Statistics (*http://www.cdc.gov/growthcharts*). An adolescent with a BMI greater than the 85th percentile is considered at risk for overweight, and an adolescent with a BMI greater than the 95th percentile is considered at risk for obesity. Although a high BMI usually indicates excess adiposity, an elite athlete may have an elevated BMI due to high lean muscle mass and low body fat. Other measurements, such as those described next, are helpful in these circumstances.

Waist Circumference and Waist–Hip Ratio: Waist circumference is a reliable test of adiposity in adolescents and adults. Top normal cut-points are 78.0 cm for adolescent females, 83.5 cm for adolescent males, 88.0 cm for adult females, and 102.0 cm for adult males. The waist–hip ratio, calculated as waist circumference divided by hip circumference, provides a reliable estimate of truncal adiposity in adults but does not correlate well with truncal fat mass in children and young adolescents. Complications of obesity are associated with a waist–hip ratio greater than 1.0 in adult men and greater than 0.8 in adult women.

Skin Fold Measurements: Skin folds, measured with specialized calipers at the triceps, biceps, subscapular

area, and abdomen have shown to correlate well with body fat in adults, adolescents, and children. However, the reliability of intra- and inter-observer measurements are low and the technique has only been studied in Caucasian populations.

Laboratory Evaluation

The history and physical examination guide the laboratory component of a nutritional assessment. The evaluation of an overweight or obese adolescent is discussed in Chapter 11. Serum levels of specific vitamins or minerals can be measured in adolescents with suspected excessive or deficient intake. In other situations, the laboratory evaluation can identify nutritional problems before clinical findings emerge. Examples include the use of red cell indices to detect iron deficiency anemia or anemia of chronic disease, hypophosphatemia to monitor refeeding after a period of malnutrition, and prealbumin and albumin as indicators of protein and energy intake during the preceding 1- and 3-week periods, respectively.

NUTRITIONAL REQUIREMENTS

Definitions

In 1989, the United States and Canada adopted a set of nutrient and energy guidelines called the Recommended Daily Allowances (RDAs) and Recommended Nutrient Intakes (RNIs), respectively, in a joint effort to prevent nutritional deficiency across the lifespan. In 1997, a revised set of standards called the Dietary Reference Intakes (DRIs) were adopted to promote lifelong health and prevent nutritionally related deficiency, toxicity, and chronic illness. The DRI consists of four reference values. The Estimated Average Requirement (EAR) is the daily intake required by half the healthy individuals in a given group. The Recommended Dietary Allowance, or updated RDA, is the daily intake required by nearly all the healthy individuals in a group. Adequate Intake (AI) is reported for a nutrient when there is insufficient scientific evidence to support an EAR or RDA. Finally, the Tolerable Upper Intake Level is the highest daily intake that poses no risk of adverse health effects to nearly all healthy individuals in a group. Table 4-3 lists the updated

Table 4-3 Recommended Daily Dietary Allowances (RDAs) or Daily Adequate Intakes* for Selected Nutrients at Ages 9–13 Years, 14–18 Years, During Pregnancy, and During Lactation

	Ages 9–13 Years		Ages 14–18 Years		Pregnant	Lactating
	Males	Females	Males	Females	Females	Females
Energy (kcal)[1]	2279	2071	3152	2368	2708[2]	2733[3]
Carbohydrate (g)	130	130	130	130	175	210
Total Fiber (g)	31	26	48	26	28	29
Protein (g/kg)	0.95	0.95	0.85	0.85	1.1	1.3
Vitamin A (µg)	600	600	900	700	750	1200
Vitamin C (µg)	45	45	75	65	80	115
Vitamin D (µg)[2]	5*	5*	5*	5*	5*	5*
Vitamin E (mg)	11	11	15	15	15	19
Thiamin (mg)	0.9	0.9	1.2	1.0	1.4	1.4
Riboflavin (mg)	0.9	0.9	1.3	1.0	1.4	1.6
Niacin (mg)	12	12	16	14	18	17
Vitamin B_6 (mg)	1.0	1.0	1.3	1.2	1.9	2.0
Folate (µg)	300	300	400	400	600[3]	500
Vitamin B_{12} (mg)	1.8	1.8	2.4	2.4	2.6	2.8
Calcium (mg)	1300*	1300*	1300*	1300*	1300*	1300*
Fluoride (mg)	2*	2*	3*	2*	3*	3*
Iron (mg)	8	8	11	15	27	10
Magnesium (mg)	240	240	410	360	400	360
Phosphorus (mg)	1250	1250	1250	1250	1250	1250
Selenium (µg)	40	40	55	55	60	70
Zinc (mg)	8	8	11	9	13	14

Adapted from the *Reports of Dietary Reference Intakes (DRIs)*, Food and Nutrition Board, The National Academies of Sciences. Available at *http://www.nap.edu*. Accessed May 17, 2007.

*Daily Adequate Intake is shown when there is insufficient data to support RDA.

[1]Energy requirement at the median age within the given age range and at an active level of physical activity.

[2]2368 during the first trimester; 2708 during the second; 2820 during the third.

[3]2698 during the first 6 months; 2768 during the second 6 months. Evidence links low folate intake with neural tube defects in the fetus; therefore it is recommended that all women capable of becoming pregnant consume 400 µg from supplements or fortified foods in addition to intake of food folate from the diet.

RDAs or AIs by age and gender for energy and for select macronutrients, vitamins, minerals, and other food components (fiber).

Energy

Energy, expressed in kilocalories (kcals), is the chemical fuel that drives all physiological functions. The minimum daily energy required to maintain vital body processes, or resting energy expenditure (REE), can be estimated from the individual's gender, weight, height, and age (Table 4-4). To estimate actual energy expenditure, the REE is multiplied by an average daily activity factor that ranges from 1.0 when asleep to 7.0 for activities such as heavy manual labor, basketball, or soccer.

Dietary energy is provided by carbohydrates, protein and fat. The DRIs recommend that carbohydrates (4 kcal/g) make up 45–65% of energy intake; protein (4 kcal/g), 10–30%; and fat (9 kcal/g), 25–35%. Dietary fat should come primarily from sources of polyunsaturated and monounsaturated fatty acids, such as fish, nuts, and vegetable oils. Trans fats, found in hydrogenated oils used primarily in bakery products, should be avoided altogether because they increase serum levels of low-density lipoprotein-cholesterol (LDL-C). Dietary intake of total cholesterol, found in animal products, should be limited to 300 mg/day.

Vitamins and Minerals

Vitamin and mineral requirements increase during the adolescent years. Although the guidelines are readily met by a well-balanced diet rich in fruits and vegetables, the average adolescent's intake of several key nutrients is substandard, as described next.

Calcium and Vitamin D: Achieving peak bone mass depends on adequate calcium and vitamin D intake during adolescence. Yet the 1999–2000 data from the National Health and Nutrition Examination Survey revealed that neither adolescent males nor females consumed the recommended 1300 mg/day. Median intake is 1081 mg/day for males and 793 mg/day for females. Adolescents who consume little or no dairy products should be encouraged to choose other calcium-rich foods (Table 4-5) or to take calcium supplements. In addition to low calcium intake, adolescents who do not drink vitamin D–fortified milk or who live in northern latitudes (particularly if their skin pigmentation is dark) are at risk for vitamin D deficiency.

Iron: In addition to its transport of oxygen and carbon dioxide within the red blood cells, iron contributes to energy production and immune function. Dietary requirements for iron increase during adolescence because of increased muscle mass and blood volume in males and females and menstrual blood loss in females. Iron-rich foods include meat, spinach, kidney beans, and fortified cereals. Vitamin C can enhance the absorption of non-heme iron from plant sources.

Zinc: Zinc is essential for growth, sexual maturation, immune function, and wound healing. Good sources of zinc include animal products such as meats, seafood, eggs, and milk; dried beans; and unrefined cereals.

Table 4-4 The Harris-Benedict Equation for Resting Energy Expenditure, in kcal/day

Males	66.47 + 13.75(WT) + 5.0(HT) − 6.76(AGE)
Females	655.1 + 9.56(WT) + 1.85(HT) − 4.68(AGE)

Adapted from Johnson RK, Coward-McKenzie D: Energy requirement methodology. In Coulston AM, Rock CL, Monsen ER (eds): *Nutrition in the Prevention and Treatment of Disease.* San Diego, CA, Elsevier, 2001, p. 34.

WT, body weight in kilograms; HT, standing height in centimeters; AGE, chronological age in years.

Table 4-5 Calcium Content of Selected Calcium-Rich Foods

Food and Serving Size	Calcium (mg/serving)
Dairy Products	
Yogurt, nonfat plain, 1 cup	452
Milk, skim, 1 cup	306
Swiss cheese, 1 oz.	224
Mozzarella cheese, part skim, 1 oz.	207
Cottage cheese, 1% milk fat, 1 cup	138
Calcium-Fortified Foods	
Soy milk, calcium added, 1 cup	300
Orange juice, calcium added, 1 cup	200
Total cereal, 1 cup	250
Fruits and Vegetables	
Collard greens, ½ cup, cooked	180
Figs, dried (5), 3.3 oz.	135
Kale	90
Orange, 1 medium	56
Broccoli, ½ cup, cooked	36
Legumes, Nuts, and Other	
Tofu, firm (calcium-set), ½ cup	258
Black-eyed peas, 1 cup	212
Navy beans, 1 cup	128
Almonds, ¼ cup	94
Blackstrap molasses, 1 tbsp	172

U.S. Department of Agriculture, Agriculture Research Service, USDA Nutrient Data Laboratory, 2002. *USDA National Nutrient Database for Standard Reference*, Release 17. Available at: http://www.nal.usda.gov/fnic/foodcomp. Accessed August 29, 2005.

NUTRITIONAL SUPPLEMENTATION

In general, all vitamin and mineral needs can be met with a well-balanced diet that includes fruits, vegetables,

low-fat dairy products, and whole grains. The American Dietetic Association recommends that nutrients for healthy adolescents should come from food rather than supplements. The American Academy of Pediatrics (AAP) agrees, with the exception of fluoride supplementation for children living in areas with nonfluoridated water. The AAP recommends that additional supplementation be considered for adolescents who are neglected or abused, pregnant, chronically ill, and deficient in specific food groups or nutrients.

NUTRITIONAL COUNSELING

Nutritional counseling ranges from brief endorsements of healthy eating habits to lengthy discussions of malnutrition or disordered eating. In the latter situations, a registered dietician who understands adolescent nutritional needs becomes an important member of the health care team.

The following general recommendations can be used to guide the nutritional counseling of most adolescents who are seen in the primary care setting:

- Explain why good nutrition is important: energy for school, work, sports, and fun; a healthy appearance; growth and pubertal development.
- Encourage regular meals, especially breakfast. Research shows that adolescent girls who eat breakfast have a higher intake of calcium and fiber and a lower BMI.
- Promote family meals. Frequency of family meals has been inversely associated with tobacco, alcohol, and marijuana use; low grade-point average; depressive symptoms; and eating-disordered behaviors.
- Discuss the food pyramid (Figure 4-1). The 2005 version, available at *http://www.mypyramid.gov*, allows the adolescent to create a personalized set of nutritional recommendations based on age, gender, and activity level. The web site also includes information

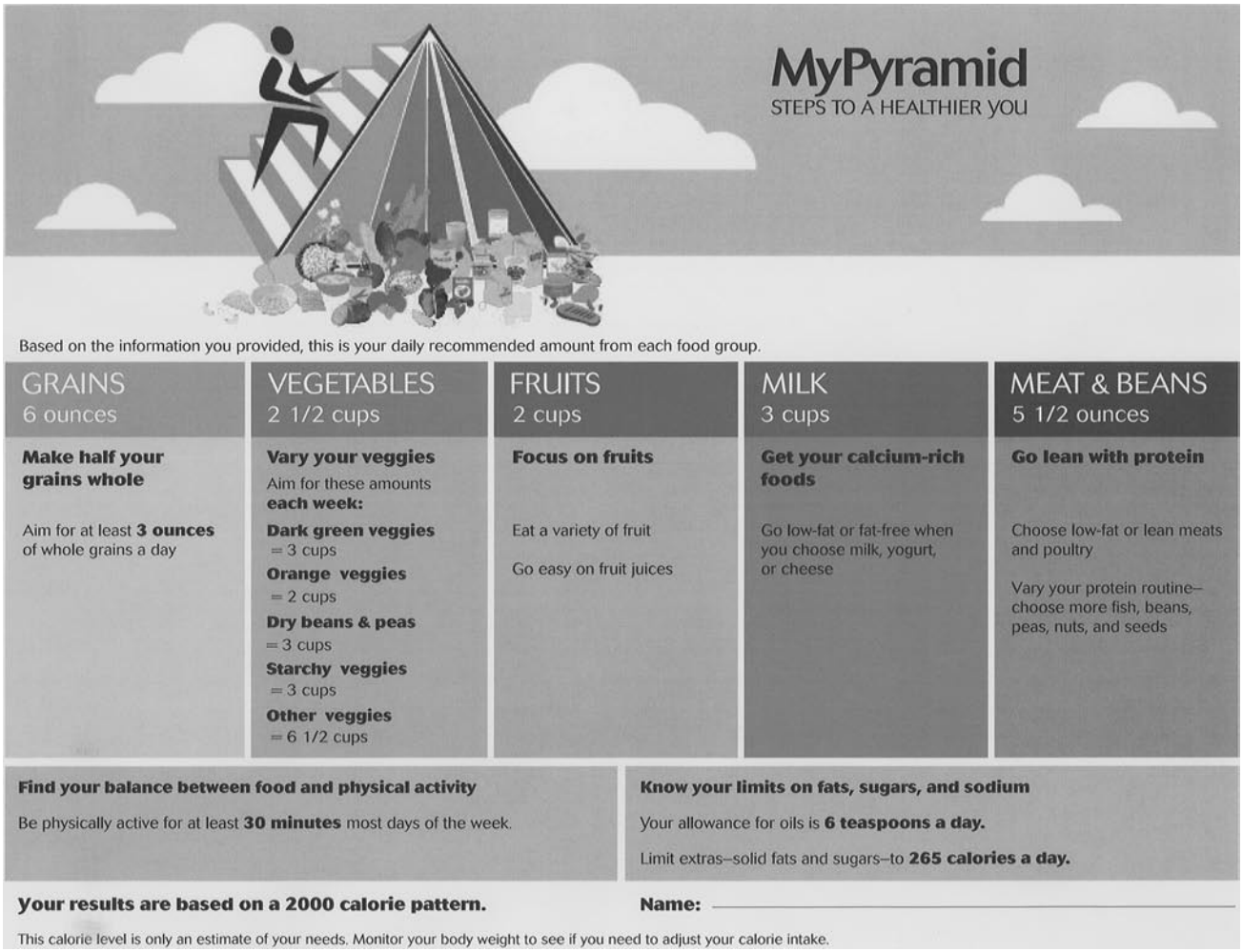

Figure 4-1 Food guide pyramid. This is the food pyramid for a 15-year-old female who gets 30–60 minutes of exercise per day, as obtained from *http://www.mypyramid.gov.*, U.S. Department of Agriculture, Center for Nutrition Policy and Promotion, April, 2005.

for health professionals and materials that can be downloaded for use as patient handouts.
- Explain how to read nutrition labels (Figure 4-2).
- Discuss serving size. Giving understandable size comparisons may help the adolescent with portion control. For example, 3 oz. of meat is the size of a deck of cards, 1½ oz. of cheese is the size of four stacked dice, and ½ cup of ice cream is the size of a tennis ball. The Department of Health and Human Services posts a wallet-sized card with similar examples at *http://hin.nhlbi.nih.gov/portion/keep.htm.*
- Encourage daily exercise. For adolescents who do not play sports, suggest ways to incorporate activity into their daily lives, such as taking stairs instead of the elevator, getting off the bus a few stops early, taking a walk with a friend, or dancing to their favorite music.
- Consider cultural differences. Food beliefs and practices vary widely among social, religious, and ethnic groups.
- Help adolescents set specific and obtainable goals to improve their nutrition. Examples include preparing a family meal that is baked or broiled instead of fried; eating breakfast before school; decreasing carbonated beverages by one serving per day; making healthier choices at fast food restaurants; planning healthier snacks; and removing the salt shaker from the table.

NUTRITION FOR ATHLETES

Intense physical activity increases energy and water requirements but rarely increases the need for specific nutrients. Adolescent athletes are aware that nutrition affects performance but are often misinformed about how to optimize their intake. Counseling athletes, families, and coaches about healthy and unhealthy nutritional practices therefore is an essential component of the sports examination. Caloric requirements vary widely by level of training and activity, as well as by gender, body size, body composition, and stage of growth. The energy recommendations shown in Table 4-3 account for some of these variables, but an adolescent athlete whose growth is delayed or whose weight deviates more than expected might require further adjustment of daily kilocalories.

Adolescent athletes, parents, and coaches should be reminded that thirst is a late indicator of fluid deficit. For intense physical activity, the athlete should drink 10 to 14 oz. 1 to 2 hours before the event, 10 to 12 oz. 20 to

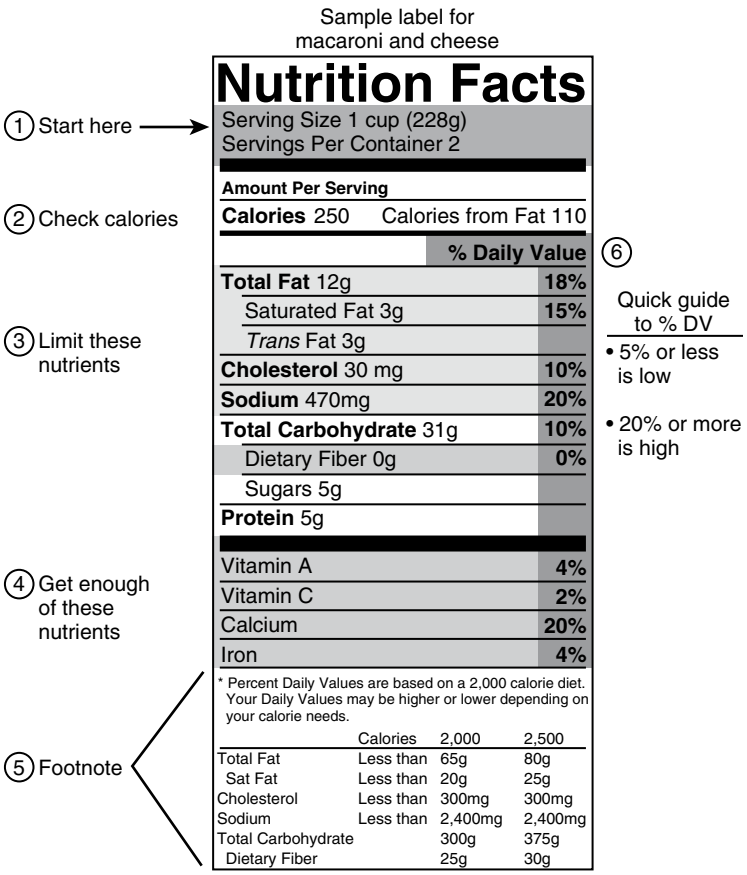

Figure 4-2 How to read a nutrition label. From U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2000. *Dietary Guidelines for Americans*, 5th ed., Home and Garden Bulletin No. 232. Washington, D.C., U.S. Government Printing Office. Available at: *http://www.cfsan.fda.gov/~acrobat/foodlab.pdf*. Accessed May 17, 2007.

30 minutes before the event, 6 to 12 oz. every 15 to 20 minutes during the event, and 16 to 24 oz. for every pound of weight lost after the event. Cool fluids are best as they are rapidly absorbed and contribute to body cooling. Plain water is generally adequate, unless the event is especially long and intense. For events lasting more than an hour, beverages containing some carbohydrate are recommended. For events lasting more than 3 to 4 hours, beverages containing both carbohydrate and sodium are recommended. Menstruating females involved in endurance sports are at increased risk for iron deficiency and should have a screening hemoglobin and hematocrit performed for anemia. Zinc deficiency often accompanies iron deficiency, and the adolescent should be counseled about good dietary sources of iron and zinc.

Many athletes want to lose weight or are encouraged to do so. Restrictive eating is a particular problem among dancers, gymnasts, figure skaters, runners, and wrestlers. All athletes should be screened for disordered eating behavior and should be referred immediately for further evaluation and management if an eating disorder is suspected.

Some athletes, usually males, may want to gain weight to improve performance. Care should be taken to ensure that the athlete is gaining lean muscle mass rather than excess body fat and that the increase does not reflect the illicit use of drugs or hormones.

NUTRITION DURING PREGNANCY

Nutritional requirements increase during pregnancy and lactation, in both the adolescent and adult female (Table 4-3). A prenatal vitamin and mineral supplement that contains iron and folate (1 mg) should be prescribed for all pregnant and lactating females, as well as for those who are planning to conceive. During pregnancy, the weight gain goal should be 25 lbs. for the overweight or obese adolescent and up to 40 lbs. for the underweight adolescent. Nutritional counseling should be a routine and repeated component of adolescent prenatal care and should continue after delivery for both mother and baby.

VEGETARIANISM

A well-balanced vegetarian diet can have health benefits, including needed reductions in weight, blood pressure, and serum lipids. It also can increase daily intake of vitamins A, E, C; folate; calcium; iron; magnesium; and fiber. Growth and pubertal development are normal for adolescents on vegetarian diets, so long as adequate nutritional intake is maintained. Understanding the type of vegetarian diet the adolescent follows is crucial for appropriate nutritional counseling. Table 4-6 summarizes the types of foods comprising different vegetarian diets. Detailed information is available from the Vegetarian Resource Center at *http://www.vrg.org*.

The most common micronutrients that are deficient in vegetarian diets are iron and zinc. Plant-based, non-heme iron is not as readily absorbed as the heme iron found in meat, poultry, and fish. Sources of non-heme iron include soybeans, lentils, dried apricots, wheat germ, blackstrap molasses, and fortified cereals. Absorption is enhanced by consuming iron with vitamin C and by cooking with cast-iron cookware. Absorption is inhibited by polyphenols found in coffee and tea, calcium-rich foods, calcium supplements, fiber, and phytates found in whole grains and legumes. Zinc is primarily found in animal products, including dairy products. Legumes, whole grains, nuts, and seeds are rich in zinc but also contain phytates, which limit zinc absorption. As with iron, calcium inhibits zinc absorption and acidic foods enhance absorption.

Vegetarians who consume poultry, fish, eggs, and/or dairy products typically have no difficulty meeting nutritional requirements. Vegans can meet protein requirements with soy, nuts, beans, and some grains, but are at risk for vitamin B_{12} and vitamin D deficiency. Vitamin B_{12}

Table 4-6 Types of Vegetarian Diets

	Plant-Based	Dairy	Eggs	Seafood	Poultry	Red Meat
Semi-vegetarian	+	+	±	±	±	–
Lacto-ovo-vegetarian	+	+	+	–	–	–
Lacto-vegetarian	+	+	–	–	–	–
Ovo-vegetarian	+	–	+	–	–	–
Vegan	+	–	–	–	–	–
Macrobiotic	Organic	–	–	±	–	–
Raw foodist	Fruit, nuts, seeds	—	–	–	–	–

is found naturally only in foods of animal origin, but can be obtained through oral supplements or fortified cereals, soy milk, and rice milk. Some soy and rice milks are fortified with vitamin D; otherwise, it can be obtained through oral supplements.

Riboflavin deficiency has been reported with severely restrictive macrobiotic diets but is not a problem with other forms of vegetarianism. Sources of riboflavin include wheat germ, tofu, whole grains, broccoli, spinach, and strawberries. Raw foodist diets limited to fruits, nuts, and seeds are not recommended for adolescents.

MAJOR POINTS

- Physiological and behavioral characteristics of adolescents put them at risk for nutritional inadequacy and disorders.
- A nutrition assessment should be part of every health maintenance visit.
- The DRIs provide reference values for evaluating nutrient intake levels both for immediate and long-term health.
- Variety, moderation, and portion control are central to maintaining healthy eating behaviors.
- The primary care physician should aid adolescents in generating practical nutritional goals to improve or enhance their diets.
- Certain groups of adolescents, such as athletes, vegetarians, and pregnant teens, have special nutrition needs that should be addressed early and frequently.

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CHAPTER 5

Approaching Youth Violence in a Clinical Setting

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INTRODUCTION

Violence is the third leading cause of death among U.S. youth aged 14–21 years. Although the primary prevention of violence has become a public health imperative, secondary prevention at the individual level has lagged behind. Clinicians commonly describe inexperience and discomfort with adolescents who are perpetrators or victims of violence. In part, this reflects the limited research on office-based interventions for youth violence. However, there is an evolving literature on community interventions that can help guide clinicians in their effort to reduce violent injury among youth.

The strategies offered in this chapter are based on the available evidence. The goal is to promote clinician discussion of violence with adolescent patients and stimulate clinician demand for violence prevention strategies that are effective, efficient, and respectful of youth assets and needs. The chapter is divided into three sections. The first approaches violence prevention from the perspective of resilience rather than risk. The second reviews strategies for office-based violence screening. The third section gives specific examples of brief office interventions designed to decrease the likelihood of subsequent violent injury.

RESILIENCE-BASED PREVENTION

The classic approach to adolescents at risk for violence is to assess their behaviors and educate them about the associated dangers (Box 5-1). This risk approach may work for youth who are highly motivated to change their behaviors but may frustrate, offend, shame, or alienate those who lack the tools or context for such change. The focus on risk utilizes a deficit model in which individual and environmental problems are highlighted. Although corrective strategies usually are discussed, the adolescent considers these strategies from the perspective of inadequacy, or weakness, rather than strength.

Proponents of resilience-based prevention believe that it avoids the negative social and psychological consequences of risk-based prevention, boosts adolescent self-efficacy, and encourages an appreciation of youth assets (Box 5-2). The resilience, or positive youth development, paradigm poses the following questions:

- Why do some adolescents from adverse environments thrive while their peers fail?
- What are the individual strengths an adolescent can employ to negotiate challenging environments?
- How can adults help adolescents apply individual strengths in safe, pro-social strategies rather than high-risk, survival strategies?
- What are the contextual supports (e.g., family, school, church, neighborhood) that will protect the adolescent during the transition to pro-social behavior?

The resilience model begins with an appreciation of what adolescents are doing *right* within their environments. For example, a gang member understands and manifests loyalty. An adolescent who discusses gang participation with a clinician has the capacity and the desire to engage a caring adult. Acknowledging these

Box 5-1 Risk Factors for Youth Violence

Individual Risk Factors

- History of violent victimization or involvement
- Attention deficits, hyperactivity, or learning disorders
- History of early, aggressive behavior
- Involvement with drugs, alcohol, or tobacco
- Low IQ
- Poor behavioral control
- Deficits in social, cognitive, or information-processing abilities
- High emotional distress
- History of treatment for emotional problems
- Anti-social beliefs and attitudes

Family Risk Factors

- Authoritarian childrearing attitudes
- Harsh, lax, or inconsistent disciplinary practices
- Low parental involvement
- Low emotional attachment to parents or caregivers
- Low parental education and income
- Parental substance abuse or criminality
- Poor family functioning
- Poor monitoring and supervision of children
- Exposure to violence and conflict in the family

Peer/School Risk Factors

- Association with delinquent peers
- Involvement in gangs
- Social rejection by peers
- Lack of involvement in conventional activities
- Poor academic performance
- Low commitment to school, and school failure

Community Risk Factors

- Diminished economic opportunities
- High concentrations of poor residents
- High level of transiency
- High level of family disruption
- Low levels of community participation
- Socially disorganized neighborhoods

Available at: *http://www.cdc.gov/ncipc/factsheets/yvfacts.htm*. Accessed May 17, 2007.

Box 5-2 Protective Factors Against Youth Violence

Individual Protective Factors

- Intolerant attitude toward deviance
- High IQ or high grade-point average
- Positive social orientation
- Religiosity

Family Protective Factors

- Connectedness to family or adults outside of the family
- Ability to discuss problems with parents
- Perceived parental expectations about school performance are high
- Frequent shared activities with parents
- Consistent presence of parent during at least one of the following: when awakening, when arriving home from school, at evening mealtime, and when going to bed
- Involvement in social activities

Peer/School Protective Factors

- Commitment to school
- Involvement in social activities

Available at: *http://www.cdc.gov/ncipc/factsheets/yvfacts.htm*. Accessed May 17, 2007.

competencies early in the conversation may help the clinician align with the adolescent.

The strength-based approach can be incorporated into daily clinical interactions with youth. When adolescents report violence, they usually do so with some explanation of context. For example, *"I punched her because she said...."* For the adolescent, the cause is primary and the behavior is secondary. The clinician, however, tends to respond primarily to the behavior and secondarily to the cause. Furthermore, adults rarely ask adolescents for permission before expressing opinions or offering recommendations. The simple act of recognizing the adolescent's predicament and strengths conveys respect and trust in the adolescent's capacity for change. Thus, instead of opening with a statement about the fight, the clinician might respond,

> *"Thank you for sharing this with me. It takes courage to stand up for something you believe in… But I am worried that fighting may get you hurt or get in the way of your success. I would like to be someone who can help you get to a place where it doesn't happen again and your future is as good as you deserve. Can we talk about this?"*

A statement such as this expresses concern without assigning blame. It allows the adolescent to join with the clinician in exploring safer coping strategies through either problem-focused or emotion-focused responses. For example, learning conflict resolution is a safer, problem-focused response to a violent environment than the emotion-focused response of rage. Venting frustration through exercise is a safer, emotion-focused response than fighting. Some adolescents may have the cognitive maturity and impulse control to develop problem-focused responses, whereas others may need to rely on emotion-focused responses that control stress without inflicting risk. In either case, adolescents can learn to recognize

the emotional and physical discomfort induced by stress and, with guidance, can plan pro-social channels that help relieve the discomfort (Figure 5-1).

EVALUATION

Annual Comprehensive Visit

Screening questionnaires for violence-related attitudes and behaviors exist, but they are neither designed nor validated for use in clinical settings. The comprehensive psychosocial assessment described in Chapter 2 as part of the annual adolescent examination therefore remains the primary means of identifying adolescents who are victims or perpetrators of violence. Before asking personal questions of the adolescent, it helps to explain the reasons for the questions, how the answers will be used, and the confidentiality limits imposed by suicidal, homicidal, or abusive behavior.

Four components of the comprehensive assessment are central to the identification of adolescents at risk for violence: home safety, relationship safety, substance use, and mental health. Asking the adolescent, *"Is home a safe place for you?"* can circumvent a crisis before it occurs. Parent–teen conflict occurs in most homes at some time during adolescence, but physical aggression between parent and teen should always raise concern that tempers are flaring out of control. Social support or family therapy can halt the escalation by offering coping strategies other than verbal or physical aggression. If the adolescent does not feel physically safe at home, social service should be contacted immediately to help with temporary placement until further evaluation is completed.

Adolescents are also at high risk for partner violence. They may misinterpret pathological control or possessiveness as innocent jealousy. Those who are accustomed to physical aggression as an acceptable coping strategy for anger may not understand that healthier, safer approaches can help them deal with relationship conflict. Questions such as *"Does he (she) treat you well?"* and *"Does he (she) get jealous?"* allow discussion of the relationship without assigning blame.

Drug use and drug dealing are major risk factors for violent injury. Once an adolescent admits to drug use, the following is an important follow-up question: *"Some people use drugs for fun, but most people use drugs to forget about some kind of uncomfortable feeling, like being sad, nervous, or stressed. How about you? Why do you use (name of drug)?"* Framing the discussion in this manner acknowledges the stress in the adolescent's life and lets the adolescent know that the negative feelings associated with the substance use will not be ignored.

The association of violent injury with mental health disorders is bidirectional. Victims of violent injury are at increased risk for the development of major depressive disorder and post-traumatic stress disorder (PTSD), and perpetrators are more likely to have mental health problems that preceded the violent behavior. Self-inflicted injuries such as nonsuicidal cutting and suicide attempts manifest even stronger associations with underlying mental health problems, such as major depressive disorder and impulsivity. Patients with suicidal ideation or intent who are unable to contract for safety (see Chapter 36) must be held under protective watch until hospital admission or another safe, therapeutic environment can be arranged.

Interim Visit

Whether the care is acute or routine, every visit can be used to screen for and educate about violence. The parent who expresses concern about an adolescent's obsession with violent media or video games may be describing an inappropriate coping strategy in which violence has become escapism, fantasy, and desensitized. The patient so used to violence that it is seen as normative or who sees it as the appropriate way to handle stress or conflict is clearly at risk. A parent who had been disciplined violently may know no other way to raise children and will not be prepared to handle the disagreements of adolescence. The clinician can help adolescents, the parents of adolescents, and adolescents who are parents understand that discipline is meant to teach. It is not intended to punish and should never intend to inflict pain.

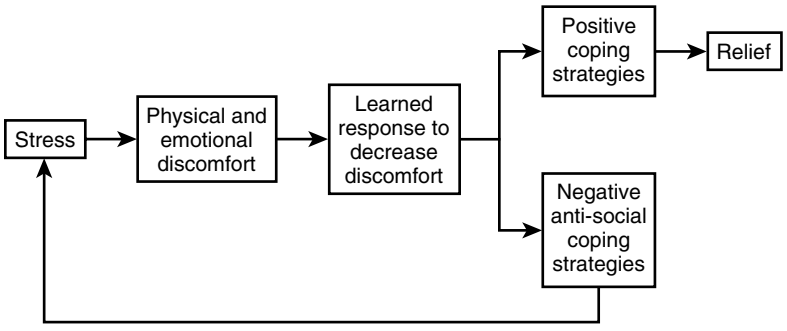

Figure 5-1 Building strength through the development of positive coping strategies.

In addition to exploring safety at home, the adolescent should be asked questions such as *"Do you feel safe at school? Are there many fights at your school? Do people bring weapons to school? What do you do to keep yourself safe?"* The adolescent who responds, "I'm fine" or "Don't worry about me" may be unprepared to divulge his or her behavior or fear of someone else's behavior. A possible response could be *"Is someone watching your back, or do you carry something for protection?"* Some youth respond, "No, I can fight for myself. People have learned not to mess with me." Others divulge gang affiliation or weapon carrying. Many, however, remain silent. If it seems appropriate, ask *"Do you think a knife or gun would make you safer? Do you carry one?"* An adolescent who carries a weapon often believes that it confers protection without risk and that his or her life is of value and to be protected. Before discussing the high risk of death associated with carrying a weapon, which is essential, the clinician can acknowledge the importance of self-protection to and for the adolescent.

Visit for Violence-Related Injury

It is imperative to know whether the adolescent treated for an acute violence-related injury is in a cycle of retaliation. Before the adolescent leaves the health care setting, questions such as the following should be asked: *"What is going to happen now? Is this over? Are you going to get even? Are people still after you?"* Some adolescents feel compelled to display bravado, even after serious injury; for these youth, avoiding the words "fear," "afraid," or "worried" may allow them to share their expectations without threatening their self-esteem. Clinicians are required to report patients who threaten the lives of others to the appropriate law enforcement authorities.

Conflict avoidance depends, in part, on understanding one's threshold for fighting. Adolescent conflict usually progresses through four stages. The first is verbal insult or disrespect directed toward the adolescent. The second is generalization of the insult to the adolescent's family, friends, gang, etc. The third is invasion of personal space, *"getting in my face,"* or *"stepping up to me."* The fourth is physical contact. Thresholds vary among individuals and across settings for a given individual. For example, an adolescent provoked on a street corner may feel compelled to fight rather than walk away. The same adolescent in an institution with zero tolerance for fighting might walk away, saying *"You're not even worth it."*

Asking the adolescent questions such as the following can help identify the threshold for fighting: *"What do you usually do when you are really mad or frustrated? Do you get in fights? Are you able to walk away from fights? How do you do that? What makes you mad enough to fight?"* Once the threshold is identified, strategies can be implemented well before it is reached.

INTERVENTION

The success of any violence intervention depends on its alignment with the adolescent's cognitive maturity, readiness for change, social context, and threshold for fighting. Each of these characteristics is discussed next, along with case histories that exemplify interventions matched to specific characteristics.

Cognitive Maturity

Cognitive maturation during adolescence involves a gradual transition from concrete to abstract thinking. However, it is always better to deliver information in small, simple bites than to talk beyond the adolescent's level. For example, consider a discussion about the risks of carrying a gun: possible injury, death, incarceration, etc.—all in the future. Words such as "possible" or "future" are abstractions that may have little meaning to a cognitively immature adolescent who views the world and people as good or bad. Concrete thinkers have difficulty looking beyond actions for underlying motivations and are easily fooled by flattering facades. Abstract thinkers can see shades of gray, consider future consequences, and evaluate underlying motivations.

The key to helping concrete thinkers grasp consequences of current behaviors is to break down abstract concepts into multiple concrete steps, delivered one at a time. A question is posed, an appropriate silence ensues, and the adolescent works step-by-step through a realization of consequences. Instead of the lecture-style discussion about the gun noted previously, consider an intervention such as the following: "*Let's pretend that I am you. I have a gun in my right hip pocket. Let's pretend you are another guy and that you have a gun. We're in each other's face, and a conflict is about to happen. I reach into my right hip pocket. What would you do?"* In nearly all cases, the adolescent responds, "*I would shoot you first*." The clinician can then simultaneously reinforce the teen's answer and point out the inherent risk: *"Exactly. Remember, we are pretending that I am you. Do you see that carrying a gun made you much more likely to be killed?"* Breaking down the action in this way may help the adolescent grasp consequences previously unconsidered.

Readiness for Change

According to the Trans-Theoretical Model of Behavioral Change, an individual's readiness to shift from negative to positive behaviors progresses through the five stages outlined in Table 5-1. The adolescent in the pre-contemplation stage denies the need for change and has no desire or intent

Table 5-1 Trans-Theoretical Model of Behavioral Change

Pre-Contemplation	Individual has no intention to change or denies need for change.
Contemplation	Individual is considering change and is weighing perceived costs and benefits.
Preparation	Individual is actively planning to change.
Action	Individual is making an attempt to change.
Maintenance	Individual is solidifying change and resisting relapse.

to change. An adolescent who perceives gun-carrying as survival cannot yet see the gun as risk and therefore has no reason to relinquish it. If other skills are developed that reduce the sense of vulnerability, the adolescent might progress to contemplation, in which the risk-benefit balance begins to shift. Preparation is actively planning to leave the gun at home, and the action is leaving home without it. Maintenance is the set of ongoing efforts to keep the new behavior intact, such as getting rid of the gun completely.

Social Context

An adolescent who agrees with a suggested behavioral change may still worry that the change will be ridiculed or undermined by the peer group. The suggested change therefore should be accompanied by a plan to "save face," or maintain pride. For example, the adolescent in the midst of escalating gang violence is likely to say that leaving town will be interpreted as cowardice. Asking *"How do you think this will play with your friends? Will they back you?"* gives the adolescent a chance to think through the peer response. As potential blocks to the change emerge, an alternate strategy can be devised. For example, the adolescent whose safety depends on leaving town can prepare an explanation other than fleeing violence, such as *"I had to go down to take care of my grandmother. She's real sick."* Face-saving maneuvers often involve shifting the blame to parents or disciplinarians. For example, *"My mother said if I get suspended one more time, I will…,"* or *"The principal says if I cut class one more time, he will expel me. That would kill my mother, and you know she has high blood pressure."*

Threshold for Fighting

The adolescent's threshold for fighting can help guide the development of alternate coping strategies. For example, individuals who answer that name-calling is enough to make them lash out physically are often impulsive and act before they have time to think. Teaching these adolescents about slow, deep breathing and silent counting to 10 may calm them enough to gain time. Others may be able to use humor to help them out of situations. When the name-calling is directed at a relative (e.g., mother) or friend, ask the adolescent, *"Does the person know your mother? How will your mother feel if you get killed just because someone called her a name?"* Adolescents who report that they are likely to fight when their physical space is invaded can be taught to avoid feeling cornered by turning sideways, keeping a leg extended in front, or sitting down. Those with the highest threshold are unlikely to strike until they have been struck. The safest approach for these youth is to avoid settings where fights are likely to happen, because even bystanders can be drawn into escalating violence.

Preventing Retaliation

The good news about an adolescent who communicates a retaliation plan to a clinician is that there is often time for intervention. This situation usually involves planning and, as a result, time for intervention. Working through a visual decision tree exposes the adolescent to consequences previously unconsidered. By acting out different scenarios and writing down possible outcomes, the patient might be better able to consider pro-social rather than anti-social strategies for coping with the anger. For example, consider the decision tree illustrated in Figure 5-2. The patient is a 15-year-old girl seen in the office after a fist fight that began when a classmate insulted her mother. When asked what would happen next, the patient responded, "I'm going to kill her." When asked how that would make her feel, she answered, "Good." When asked how long she would feel good, she responded, "All day." The decision tree led her to consider other consequences of pulling the knife, such as death, incarceration, and family grief.

Even an adolescent who is speaking of retaliation often wants to avoid fighting but cannot escape the social context in which the fight is expected to happen. In some cases, diverting the energy and attention of their peers can prevent the fight. Ask the adolescent what he or she does together with others out of school, when there is no fighting. For example, if they play basketball or smoke marijuana when there is nothing else to do, teach the adolescent to always carry a basketball. When this fails, teach the adolescent to shift the blame for escape to his or her parents. If the parent receives a call in which the teen uses an agreed-upon code word, it signals the parent to demand that the teen return home immediately. The goals are to provide a strategy that the adolescent will use and to remove the adolescent as soon as possible from a high-risk setting.

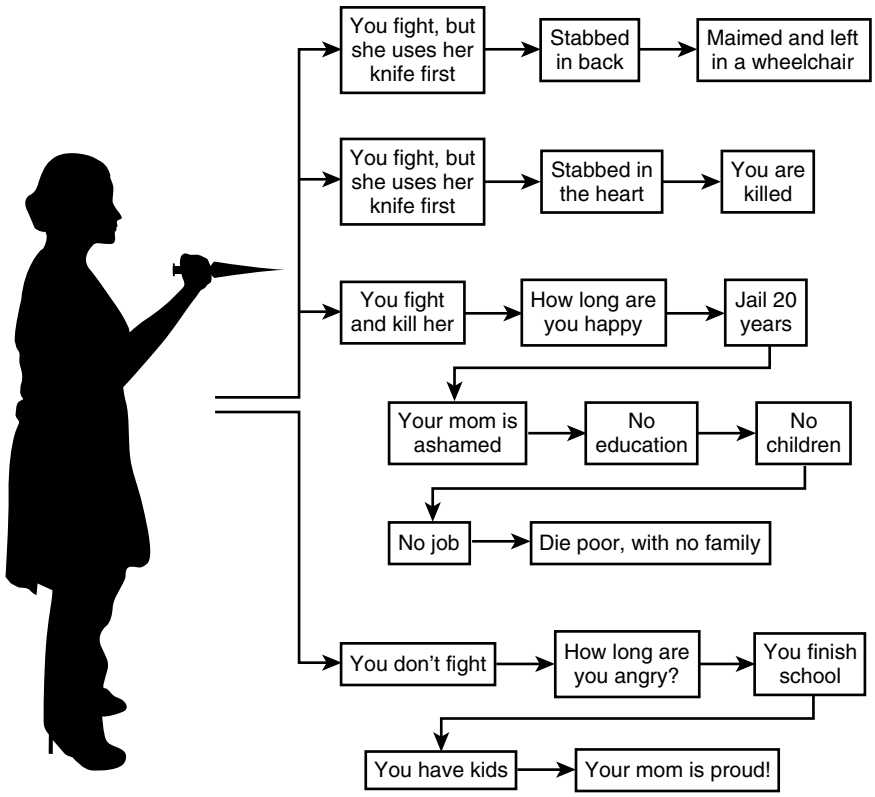

Figure 5-2 A life-saving decision tree.

MAJOR POINTS

- Resilience-based prevention begins with an appreciation of youth assets and utilizes these strengths to develop pro-social strategies in response to social stress.
- Four components of the psychosocial assessment are central to the identification of adolescents at risk for violent injury: home safety, relationship safety, substance use, and mental health.
- Visits for violence-related injury should always include discussion of planned retaliation.
- Violence intervention should be adapted to the adolescent's cognitive maturity, readiness for behavioral change, social context, and threshold for fighting.
- The use of a visual decision tree can help adolescents consider potential outcomes to fighting that were previously denied.

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CHAPTER 6

Chronic Health Conditions

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INTRODUCTION

Chronic health conditions that limit activity or increase health care utilization affect 12% of children and adolescents in the United States. Poverty, developmental delay, and psychiatric illness increase the likelihood of functional limitations which, in turn, reduce quality of life. Recent studies indicate that most individuals with chronic conditions in the United States do not receive appropriate, effective care due to inadequate time and training on the part of clinicians and poor self-management skills on the part of patients.

Systems of planned, organized care that link outpatient, inpatient, and rehabilitation services with community supports have been shown to improve health outcomes for patients with chronic health conditions. Box 6-1 outlines the characteristics of a model health care system for adolescents with chronic conditions. The cornerstones of the model, developed by Wagner and refined by a national panel of experts, are organized, efficient systems for the delivery of health care, the management of clinical information, guidelines for decision-making, and supports for self-management. Targets for quality improvement and program evaluation include patient safety, cultural competency, care coordination, and case management.

The objectives of this chapter are to review the responsibilities of the primary care provider in the care of adolescents with chronic conditions, resources that contribute to a supportive care network, and strategies for promoting the self-efficacy of adolescents with chronic health conditions as they transition to adulthood.

ROLE OF THE PRIMARY CARE PROVIDER

Medical Home

The primary care provider (PCP) plays a pivotal role in the care of adolescents with chronic health conditions. The level of involvement depends, in part, on patient and family preference, the availability of disease-specific sub-

Box 6-1 Characteristics of a Model Health Care System for Adolescents with Chronic Conditions

- Structured, evidence-based care that incorporates guidelines, pathways, and other clinical tools
- Clinical information system that monitors health care processes and health outcomes at the individual patient and population levels
- Education and support to promote management of the condition by the adolescent and family
- Developmental approach that supports transition to adult roles and success in the adult health care system
- Active partnership of health care providers, adolescent, and family
- Feedback and reminders to health care providers, adolescent, and family
- Supportive community services
- Adequate payment systems

specialists, and disease severity, but PCP constancy over time offers a medical home for the coordination of comprehensive care. Close, ongoing communication between the PCP, specialty team, community providers, and family has been shown to reduce health care error and cost while improving patient satisfaction and outcome.

In addition to coordinating effective care for the chronic condition, PCPs generally assume responsibility for general health care services. In the United States, adolescents as a group receive suboptimal preventive care. Although data are sparse, it appears that adolescents with chronic conditions are even less likely to receive needed preventive care than are those without chronic conditions, despite their more frequent health care contacts.

Box 6-2 summarizes the major responsibilities of the PCP to the adolescent and family. The tasks apply broadly to all chronic health conditions and consider current and future developmental needs. Disease-specific management goes hand-in-hand with these broader goals and may fall within the purview of the PCP and/or subspecialist. For example, the PCP may choose to manage asthma alone and co-manage cystic fibrosis. Regardless of the delineation, common goals should be the coordination of disease-specific care and the provision of comprehensive primary and preventive care. The PCP can help prevent duplications and omissions by clarifying the responsibilities of involved providers.

Advocacy

The PCP can be invaluable in helping the family identify community-based resources as their child develops (Box 6-3) and in educating parents and adolescents about the rights of individuals with disabilities. The federal Individuals with Disabilities Education Act (IDEA) requires a public school to maintain a written Individualized Educational Plan (IEP) for a student with an eligible learning disability. The IEP should be developed and annually reviewed by parents, student, and school personnel and must include a transitional plan from age 14 years to high school graduation. Section 504 of the Rehabilitation Act requires a written individual health plan (IHP) for students with functional limitations due to physical or mental health conditions. The IHP must provide reasonable accommodations in the school setting for the student, such as mobility assistance, speech therapy, or alternative class schedules (*http://www.ideapractices.org*).

Box 6-2 Role of the Primary Care Provider in the Care of Youth with Chronic Conditions

- Provide planned, comprehensive care for adolescents with common chronic conditions (e.g., asthma, attention-deficit hyperactivity disorder).
- Provide primary and preventive health care, including anticipatory guidance.
- Know areas of increased need in preventive care for this population.
- Know resources available in the community for adolescents and young adults with chronic conditions and disabilities.
- Coordinate care with specialists and community-based resources.
- Prepare the adolescent and family for transition from child-oriented to adult-oriented health care.
- Assist the adolescent with self-management and with adherence to medical regimens.

Box 6-3 Community Resources for Youth with Chronic Conditions

- State Bureau of Vocational Rehabilitation
- The ARC (formerly the Association of Retarded Citizens), (*http://www.thearc.org*)
- County and city agencies serving persons with mental retardation, developmental disabilities, and mental health disorders
- Disease-specific advocacy and support organizations such as the Juvenile Diabetes Research Foundation (*http://www.jdrf.org*) and Children and Adults with ADHD (CHADD®) (*http://www.chadd.org*)
- General family advocacy and referral organizations such as Family Voices (*http://www.familyvoices.org*)

Risk Assessment

Although earlier studies suggested that adolescents with chronic conditions or disabilities were less likely to engage in risk behaviors than those without, more recent studies suggest the reverse. For example, analyses of the National Longitudinal Study of Adolescent Health (ADD Health) revealed that adolescents with asthma were more likely to smoke cigarettes than those without asthma. Consequently, current recommendations call for comprehensive behavioral screening for all adolescents, regardless of their medical histories.

Anticipatory guidance about risks for cardiovascular disease, which remains the leading cause of adult morbidity and mortality, is as important for adolescents with chronic conditions unrelated to the heart as it is for other adolescents. Establishing lifelong habits for regular exercise and healthy eating may require adaptive equipment or support services. Diabetes mellitus, systemic corticosteroids, and some psychiatric medications increase the risk of disordered eating and difficulty with weight management. Recognizing these risks, adjusting medications, and involving registered dieticians in the care team can help young patients establish eating and exercise habits that decrease cardiovascular risk.

Adolescents with and without chronic conditions should be screened through individual and family history for psychiatric illness. There is considerable controversy in the literature about the psychosocial adjustment and potential psychiatric comorbidity of adolescents with chronic conditions. In general, family connectedness, school connectedness, and a supportive health care team appear to promote emotional and behavioral health both in youth with and without chronic conditions. However, some conditions clearly increase the risk of psychosocial difficulty. For example, obesity has been associated with social stigma and more difficulty in school and at work. Severe acne is associated with poor self-esteem and depressive symptoms. The prevalence of these conditions during the adolescent years does not diminish their chronicity and the adverse effects they can have on psychosocial function.

Monitoring Growth and Development

Chronic conditions may alter the timing and tempo of growth and pubertal development. For example, spina bifida and McCune-Albright syndrome are associated with the early onset of puberty. More often, chronic conditions are associated with pubertal delay (Chapter 10). This may occur as a consequence of poor disease control, as in diabetes mellitus; malnutrition, as in inflammatory bowel disease or cystic fibrosis; or hypogonadotropic hypogonadism due to chronic physiological stress. Anticipatory guidance, evaluation, hormonal intervention when appropriate, and strategies for coping with off-timing should occur during late childhood and throughout puberty.

Sexual and Reproductive Health Care

Sexuality and reproductive health present specific challenges for adolescents with chronic conditions. Cognitive, motor, or social limitations may result in less exposure to peer- and school-based education about the development of secondary sex characteristics, menstruation, and personal hygiene. Parents may be uncertain when or how to broach the subjects with their young adolescents. The PCP can help by providing early counseling and by suggesting strategies for managing personal hygiene as the adolescent grows, menses, etc. Counseling about sexual feelings and behavior is essential for all adolescents and should include discussion of appropriate and inappropriate touching, contraception, and sexually transmitted infection.

Asymptomatic adolescents who are not sexually active generally do not require pelvic examination. The American College of Obstetrics and Gynecology recommends that the first examination and Papanicolaou (Pap) test be performed at age 21 years or 3 years after onset of sexual intercourse, whichever is earlier. For adolescents who cannot tolerate the examination, providers and families will need to balance the value of cervical cancer screening against risks that may be associated with sedation or anesthesia. Sometimes a needed pelvic examination can be performed when the adolescent is sedated for another procedure, such as dental work.

Immunizations

Finally, immunizations are particularly important for adolescents with chronic conditions, as they often are at increased risk for diseases that can be prevented by vaccination. Essentially all adolescents can receive killed or recombinant vaccines. At-risk groups, such as those with kidney failure, diabetes mellitus, asthma, and other pulmonary conditions, should receive an influenza immunization each fall. Those who are immunocompromised should not receive live vaccines, such as measles-mumps-rubella (MMR) or varicella.

PROMOTING SELF-EFFICACY

The development of self-management skills is a critical task for all adolescents, regardless of health status. Box 6-4 outlines factors that support these skills, such as patient and parent training in problem solving. Children and adults with good problem-solving skills have been shown to have higher self-efficacy or confidence in their abilities to manage their own health conditions. A meta-analysis of 32 studies involving children and adolescents with asthma demonstrated that interventions designed to enhance skill as well as knowledge related to asthma improved

Box 6-4 Factors That Promote Self-Management

- Adolescent and family share responsibility in managing the adolescent's health.
- Responsibility adjusts to the developmental needs and changes of adolescence.
- Strategies are used that are known to be effective in enhancing adolescent self-efficacy, such as the following:
  - Assessing adolescent and family needs and preferences
  - Setting specific behavioral goals
  - Action planning
  - Problem solving
  - Motivational interviewing
  - Active follow-up
- Peer and community resources are incorporated into a supportive care network.

Table 6-1 Risk Factors for Self-Management Problems

Domain	Risk Factor
Family	Family dysfunction
	Other activities reduce treatment supervision
	Low education
Adolescent	Adjustment or coping problems
	Cognitive impairment
	Lack of belief in the benefit of treatment
Disease and regimen	Fluctuating course
	High regimen complexity
	Side effects of regimen
	Treatment of asymptomatic disease
	Cost of medication and co-pays
Health care	Poor provider–family communication
	Lack of access to care/inadequate follow-up

self-efficacy, pulmonary function, daily activities, and school attendance. In contrast, interventions that focused on knowledge alone, psychological treatment, or written management plans demonstrated little or no efficacy.

Skill development consists of specific learned strategies for success, such as taking medications at the same time each day or parent–teen review of the day's blood sugar log each evening. Asking *"What makes it difficult for you to take your medicine?"* can be a first step toward solution. When the patient or family is ready to make a behavior change, helping them set a reachable goal, such as walking 20 minutes per day, may allow them to begin the change process. Concrete, short-term goals that the adolescent believes are achievable are more likely to be successful than larger goals.

Although self-management is the ultimate goal for an adolescent with a chronic condition, it involves a process of change rather than a moment of transition. A study of adolescents with diabetes mellitus demonstrated the importance of adjusting the level of responsibility to the adolescent's maturity and ability to self-manage. Those subjects who were transitioned prematurely to adult care had poorer outcomes than subjects who transitioned later. Until adolescents are ready to manage their health and health care independently, parents should be encouraged to monitor, reinforce positive behaviors, provide consistent consequences for significant negative behaviors, and ignore small infractions that are unlikely to affect outcome.

Risk factors for self-management problems are outlined in Table 6-1. For adolescents with numerous risk factors or when simpler, office-based interventions have proven ineffective, a multidisciplinary approach, including persons with expertise in behavior change, should be employed.

MAJOR POINTS

- Systems of planned, organized care that link outpatient, inpatient, and rehabilitation services with community support have been shown to improve health outcomes for patients with chronic health conditions.
- Close, ongoing communication between the PCP, specialty team, community providers, and family has been shown to reduce health care error and cost while improving patient satisfaction and outcome.
- Adolescents with learning disabilities are eligible for support at school through the federal Individuals with Disabilities Education Act. Those with physical and mental health disabilities are eligible for reasonable accommodations of the school environment through Section 504 of the Rehabilitation Act.
- Primary and preventive care services should encompass the same domains for youth with and without chronic conditions (e.g., risk behaviors, cardiovascular health, mental health, sexual health, immunizations, growth and development).

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CHAPTER 7

Transition to Adult Health Care

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INTRODUCTION

Advances in health care have led to increased life expectancy for U.S. children with special health care needs (SHCN). More than 90% now survive to adulthood, and an estimated 500,000 transition each year to adult health care. This transition is one of six priority goals for children with SHCN included in Healthy People 2010. In an effort to achieve seamless quality care for young people with SHCN, the federal government and professional organizations have issued guidelines for training and service delivery. The Maternal and Child Health Bureau has charged that all pediatricians should understand the rationale for transition, how to facilitate it, and when it is indicated. The American Academy of Pediatrics, American Academy of Family Physicians, and American College of Physicians have identified the six steps shown in Box 7-1 as critical to a smooth transition.

This chapter discusses the process of transition from child-oriented to adult-oriented health care from a patient-centered, or developmental, perspective.

DEVELOPMENTAL APPROACH

Transition between the pediatric and adult health care systems should be a process rather than an event. It encompasses all domains of adult life (Box 7-2) but, for the patient with a chronic condition, may hinge on the balance between health and illness. Clinicians can help adolescents assume and parents relinquish responsibility for health management. They also can prepare patients and parents for the cultural and navigational differences

Box 7-1 Critical Steps to Successful Transition from Child-Oriented to Adult-Oriented Health Care for Youth with SHCN

1. Ensure that an identified clinician assumes responsibility for health care and planning for youth with SHCN during the transition period so as to provide uninterrupted, comprehensive care.
2. Incorporate into physician training and certification the core knowledge and skills to provide developmentally appropriate transition services to youth with SHCN.
3. Maintain a portable, accessible, up-to-date medical summary to facilitate collaboration during the transition.
4. Write a transition plan by age 14 years with the patient and family that outlines services, providers, and payment. Review and update the plan annually and at the time of transfer.
5. Adhere to standard guidelines for primary and preventive care, recognizing that youth with SHCN may require more resources to optimize their health.
6. Ensure the continuation of affordable health insurance that provides appropriate compensation for transition planning and coordination for youth with SHCN.

Adapted from American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians–American Society of Internal Medicine: A consensus statement on health care transitions for young adults with special health care needs. Pediatrics 2002;110(6 Pt 2):1304–1306. Available from: *http://aappolicy.aappublications.org/cgi/content/full/pediatrics;110/6/S1/1304*. Accessed May 17, 2007.

Box 7-2 Domains of Transition

- Health care
- Education
- Vocation and career
- Social and recreation
- Housing and transportation
- Financial management

From Britto MT: Chronic illness in the adolescent. In Osborn L, DeWitt T, First L, et al. (eds): *Pediatrics*. 1st ed. Philadelphia, Elsevier Mosby, 2004, pp. 1435–1438.

they are likely to experience as they move from child-oriented to adult-oriented settings. Adolescents may find adult providers less tolerant of non-adherence, and parents may feel less welcome during office visits.

Specific issues that should be addressed during the transitional process are outlined in Box 7-3. All of these issues require developmental readiness on the part of the adolescent. Cognitive maturation correlates poorly with chronological age and varies widely among individuals. Furthermore, the ability to abstract into the future, which affects most transitional issues, develops relatively late in the maturational process. Individuals will therefore differ in the ages at which they feel ready to move between health care settings, and a given individual may feel ready to explore some domains or issues (e.g., education) before others (e.g., financial management). Patience with the adolescent and the evolving nature of the transition are key to its ultimate success.

PLANNING THE TRANSITION

Pediatricians and parents differ in their perceptions of when to begin teaching children with SHCN about self-management of their health care. The mean age identified by pediatricians is 9.5 years, whereas that identified by parents is 12 years. Young adolescents describe self-management as a gradual process in which they are included in decision making and information sharing and their privacy is respected, yet their parents remain informed and involved. Including the older child or young adolescent in a discussion about readiness for self-management may therefore help bridge any gaps that may exist between physician and parent.

Box 7-3 Issues to Address During Health Care Transition

- Changes in health insurance
- Identification of an adult-oriented primary care provider
- Identification of an adult-oriented subspecialist
- Need for disability-based services
- Capability for self-management
- Skills in health care advocacy
- Health promotion and disease/injury prevention

From Britto MT: Chronic illness in the adolescent. In Osborn L, DeWitt T, First L, et al. (eds): *Pediatrics*. 1st ed. Philadelphia, Elsevier Mosby, 2004, pp. 1435–1438.

Mastering normal developmental tasks, such as household chores or an after-school job, can help boost the self-confidence and independence of a young adolescent with SHCN. As the child begins to manifest more autonomy, a clinical checklist updated on each visit prompts review and discussion of the patient's progress toward self-management and eventual transition. An example of such a checklist is provided in Table 7-1. The National Center on Transitions of the U.S. Department of Health and Human Services provides other checklist examples at its web site entitled "Healthy & Ready To Work" (*http://www.hrtw.org*).

By middle adolescence, the patient usually assumes responsibility for medications and may be ready to manage refills and appointment schedules. Time alone with health care providers is important during this phase, both to encourage autonomy and to discuss adolescent risk behaviors. Discussions of sexual and reproductive health should occur on nearly every visit with the adolescent and/or parent, depending on the cognitive capability and confidentiality requests of the adolescent. Parents of pre-adolescents with mental retardation often are anxious about puberty and can be reassured when clinicians prompt open discussion of what to expect and how to handle issues such as menstrual hygiene.

In addition to health care, clinicians should ask patients and parents about educational and vocational planning. SHCN place youth at increased risk for school drop-out and under-employment. Although physicians may not have the expertise or resources to lead this planning, they can steer families toward guidance while adolescents are still in school and considering career options. The Individuals with Disabilities Education Act (IDEA) mandates that schools begin transition planning by age 14 years for any student with an Individualized Education Plan (IEP). The transition plan should counsel the student and/or family about entry into post-secondary education, vocational training, employment, continuing education, and independent living arrangements.

Students with impairments that limit at least one major life activity but who do not qualify for school services under IDEA may be entitled to receive assistive technology interventions, supported employment, and transition

Table 7-1 Transition to Adult Care Developmental Activities Checklist

Please note: The following checklist is related to the child's developmental age and/or ability. These recommendations are based on issues related to transition to adult health care, career/work, finances, personal goals, and socialization.

	Care Coordinator Initials and Date			
Parents/Guardians Are Informed of the Need to:	**Introduced**	**Reinforced**	**Completed**	**N/A**
13–18 Years Old:				
Continue to assist and encourage your teen's attempts to do self-care.				
Discuss sexuality with your teen, including how his or her disability may affect future health, career options, marriage, and the ability to have children.				
Continue to assess your teen's knowledge and perception of his or her disability while providing additional information as needed.				
Discuss a plan for adult living, including health care services. Begin to look for adult care providers while allowing your teen to participate in the decision-making process. Discuss adult health care financing with your teen.				
Obtain information about your teen's state vocational rehabilitation program and school transition program.				
Apply for SSI and Medicaid, if appropriate, at age 18, if previously denied for financial reasons.				
Encourage your teen to do volunteer work or find part-time employment.				
Encourage your teen to speak freely with health care providers.				
Continue to assign chores and discuss the importance of family responsibilities.				
Help your teen keep a record of appointments, medications, and medical history (surgeries, treatments, hospitalization, allergies).				
Allow your teen to make his or her own appointments and call for medication refills and supplies.				
Teach your teen how to have medical information sent.				
19 Years and Older:				
Assist the young adult with finalizing adult health care financing and insurance options.				
Identify an adult health care provider with your young adult.				
Assist your young adult to schedule an appointment with adult care provider while still under pediatric care to ensure that the transfer to adult care will be uninterrupted and complete.				
Transfer medical record to the adult care provider.				
Remain as a resource, support system, and safety net for your young adult as he or she assumes the responsibility of self-care.				

Adapted by permission of Shriners Hospitals for Children. Available from: *http://www.brtw.org/tools/documents/PC1SHC_Chicago_Provider_transition_checklist.doc*. Accessed May 17, 2007.

into vocational rehabilitation programs under Section 504 of the Rehabilitation Act. The Americans with Disabilities Act guarantees equal employment opportunities and requires employers to make reasonable accommodations for employees with disabilities.

TOOLS FOR TRANSFER

The age at which actual transfer of care occurs depends on clinical resources as much as patient readiness. Patients in rural areas or those with rare pediatric conditions may have difficulty identifying adult-oriented providers who are comfortable managing their care. This is one of the most important reasons to begin planning well before the point of desired transfer. The family is better able to explore health care options if time is allowed to do so. Once an adult-oriented clinician is identified for either subspecialty or general medical care, that clinician can help the patient link to others within the adult-care network.

Medical Summary

A letter from the pediatrician or child-oriented health care provider to the adult-care provider is an important tool for transfer. The letter should summarize the patient's medical history and should be copied to members of both the pediatric and adult health care teams. In addition to establishing communication and identifying all involved clinicians, the medical summary becomes a portable document for the patient in times of emergency.

Before preparing a summary, the primary care provider should investigate whether the patient's subspecialist is preparing a statement, whether there is a transition center at a local medical center that can assist with the transfer of care, and whether an electronic medical record will be used by the adult-care providers.

Examples of portable medical summaries are available at *http://www.hrtw.org*. The usual elements of the summary are the problem list, medications, allergies, procedures, immunizations, feeding plan, and health care providers with contact information. Other items to consider are hospital medical record numbers and admission dates; growth charts; medical equipment specifications; and contact information for pharmacy, guardian, and case manager.

Health Insurance

Private parental insurance typically ends at age 18–23 years, depending on student status. Public state funding from Title V Programs for Children with SHCN ends at age 21 years, regardless of student status. Some states offer continued coverage for specific diseases (e.g., sickle cell disease), and some young adults qualify for Supplemental Security Income (SSI) benefits, Medicaid, and/or Medicare. Those already receiving SSI benefits undergo a redetermination process at age 18 years, when eligibility standards in many states change to reflect ability to work.

The variability in eligibility and covered services results in confusion and often delay in ensuring a continuation of health insurance. As a result, older adolescents and young adults represent the age groups at highest risk for uninsurance and under-insurance. Review of their policies well before termination allows time to purchase health insurance, seek employment with insurance benefits, arrange short-term Consolidated Omnibus Budget Reconciliation Act (COBRA) coverage through their parent's insurance, or explore their eligibility for public programs.

Flexibility

When ill, patients with SHCN may wish to revert back to the pediatric system for care. They may seek the opinions and reassurance of familiar pediatricians and may vacillate between the pediatric and adult systems for a period of time. Patients and their families should be supported by both the pediatric and adult health care teams as they make their way through the final transfer to adult health care. Acknowledgment of successful milestones by the pediatrician, such as high school graduation or the development of a relationship with an adult-care provider, can help bolster the adolescent with SHCN and reassure the parents that their child's physician remains interested and concerned.

MAJOR POINTS

- Factors that improve transition to adult care for youth with SHCN include the identification of a clinician who assumes responsibility for care during the transition period; a portable, updated medical summary; and a written transition plan that outlines services, providers, and payment.
- Private parental insurance typically ends at age 18–23 years, depending on student status, and public state funding from Title V Programs for Children with SHCN ends at age 21 years, regardless of student status. Some young adults qualify for Supplemental Security Income (SSI) benefits and Medicaid coverage. Adolescents already receiving SSI benefits undergo a redetermination process at age 18 years to assess their ability to work.
- SHCN places youth at increased risk for school drop-out and under-employment. The Individuals with Disabilities Education Act (IDEA) mandates that schools begin transition planning by age 14 years for any student with an Individualized Education Plan (IEP). The transition plan should counsel the student and/or family about entry into post-secondary education, vocational training, employment, continuing education, and independent living arrangements.
- Students with impairments that limit at least one major life activity but who do not qualify for school services under IDEA may be entitled to receive assistive technology interventions, supported employment, and transition into vocational rehabilitation programs under Section 504 of the Rehabilitation Act.
- Patients who have transitioned to adult care may wish to consult their pediatricians during times of illness. Pediatric and adult health care teams should work together during these times to reassure patients as they complete the final transfer to adult health care.

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CHAPTER 8

Consent, Confidentiality, and Privacy

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INTRODUCTION

Consent, confidentiality, and privacy are the legal cornerstones of adolescent health care. The shift from predominantly two-way communication between the parent and clinician about a child's health care to three-way communication between the adolescent, parent, and clinician presents new challenges as well as opportunities for a smooth transition to adult care.

After centuries in which minors had no status or legal protection, the last 40 years in the United States have witnessed constitutional, federal, and state laws that recognize the rights of minors and promote their access to health care. The objectives of this chapter are to describe the legal context of adolescent care from the clinician's perspective. The chapter focuses on defining who must consent before a clinician can deliver care to an adolescent and who has the right to information about that care.

DEFINITIONS

Confidentiality: Protection of shared information against unauthorized disclosure.

Emancipated minor: A person younger than 18 years who is legally freed of parental custody, control, and responsibility. In all states, marriage and joining the armed forces confers adult legal status. Other criteria and procedures for emancipation vary among states.

HIPAA: The 1996 Health Insurance Portability and Accountability Act (HIPAA) required the U.S. Department of Health and Human Services to develop regulations that control the access to and release of confidential medical information.

Informed consent: The legal process in which an individual voluntarily agrees to certain actions based on an understanding of the risks, benefits, and alternatives to those actions. The individual must be capable of understanding the implications at the time consent is granted.

Judicial bypass: An alternative procedure to a state's requirement for mandatory parental involvement for a minor who seeks abortion. The minor can seek a court order allowing her to decide without parental involvement if she is deemed mature enough to do so. Otherwise, the court makes the decision.

Mature minor doctrine: A minor is deemed capable of understanding the risks, benefits, and alternatives of specific health services and may consent to those services without parental permission.

Minor: A person younger than 18 years in most states of the United States.

HISTORICAL TRENDS IN THE RIGHTS OF MINORS

In the Middle Ages, the term "infant" was applied legally and socially to any individual younger than 21 years. Adult status depended on physical maturity, which was defined as the ability to bear arms and wear armor. From a legal standpoint, "adult" implied a male who was older than 19–21 years of age. Women, children, and adolescents had no legal status, rights, or protection.

In the United States, parental "ownership" or "sovereignty" of the minor child persisted until the mid-1800s, when the Industrial Revolution drew adolescents from family farms to urban factories. Although these young workers legally remained the property of their parents until age 21, employers assumed increasing control of their lives. Exploitation of minors was common, and harsh penalties were inflicted for disobedience and minor offenses. Immigration and urbanization in the United States during the late 1800s led to increasing public awareness of the need for youth services and protection. State laws began to appear that required school attendance, restricted child labor, separated the juvenile and adult justice systems, protected children from abuse and neglect, and regulated maternal and child health services. New Deal legislation in the 1930s further improved child services and enforced the protection of youth in the workplace.

The 1960s and 1970s in the United States witnessed a dramatic change in societal attitudes about children and youth. In 1967 the Supreme Court ruled that juveniles were entitled to due process, and the 26th Amendment to the U.S. Constitution lowered the voting age to 18 years in 1970. Forty-seven of the 50 states ratified the Amendment by lowering the age of majority to 18 years. Although the 1980s–1990s were more restrictive regarding the rights of minors, in 1992 the Supreme Court confirmed an adolescent's right to abortion. The Court allowed, however, that states could require parental notification prior to adolescent abortion so long as judicial bypass was available.

INFORMED CONSENT

Informed consent requires the cognitive and emotional capacity to understand the pros and cons of treatment. The law generally assumes that this capacity does not mature before the age of 18 years. However, the laws in all 50 states recognize that exceptions to this generalization exist for certain types of medical care. In most states, minors can provide their own consent for services related to family planning, pregnancy, sexually transmitted infections, human immunodeficiency virus (HIV), sexual assault, substance use, and emergencies. The rationale for selective medical emancipation of minors is two-fold. First, individual privacy is guaranteed by the U.S. Bill of Rights. Second, public health depends on access to and utilization of health care services. Laws that permit minors to consent on their own increase the likelihood that conditions threatening public health, such as sexually transmitted infections, will be diagnosed and treated.

Understanding the importance of selective emancipation helps parents to accept it and clinicians to utilize it. Understanding its limitations is reassuring to parents and to adolescents who may not be ready to accept responsibility for all aspects of their health care. Discussing consent and confidentiality with the adolescent and parent on the first visit begins the process of contract negotiation, before a moment of crisis. A welcome letter that explains the office policies regarding a minor's right to confidential care helps introduce the topic and usually shortens the subsequent discussion. In some offices, the parent or guardian is asked to sign the letter, indicating agreement to abide by the policy. Excerpts from sample welcome letters and parent/clinician contracts are shown in Box 8-1.

A common question that arises is whether such contracts are meaningful if statutes already exist that grant minors the right to consent for their own care. In general,

Box 8-1 Examples of Clinical Consent Forms

I authorize CCHMC and the doctor(s) participating in the care of my child to use any treatment or procedures that may be deemed necessary in the medical care and that may be reasonably expected to be part of the normal service. This shall include… preventive medicine procedures.

(*Excerpt from Cincinnati Children's Hospital Medical Center's Consent for Medical Treatment, July, 2004.*)

I hereby give permission for my child to be seen in the Teen Health Center without being accompanied by a parent or guardian.

(*Excerpt from Cincinnati Children's Teen Health Center Authorization Form, July, 2005.*)

We will spend time talking to your teen about "sensitive" topics, ensuring that your teen is safe and healthy while respecting your family's values. When we talk to your teen alone, we can keep our discussion confidential (just between your teen and us). Remember, we always encourage open communication between teens and their parents…. Some matters may be discussed that your teen prefers to keep in confidence. We may even provide certain examinations, treatments and medications confidentially. Many years of research have shown that this approach helps build trust between teens and their health care providers, making sure that the teens answer questions honestly in order to keep them healthy… Of course, any serious problems or issues will be shared with the parent/guardian… The Teen Health Center is committed to family-centered health care. We believe that the most important factor in a teen's life is an involved and caring adult. Staff at the Teen Health Center encourages communication between teens, their families, and other important adults in their lives.

(*Excerpt from Cincinnati Children's Teen Health Center Welcome Letter, June, 2005*).

the informed consent agreement between the parties supersedes the statute for several reasons. First, the typical statute guarantees that the minor's right to consent will be upheld in clinical sites that receive public funding but does not guarantee that the right will be upheld in sites that are privately funded. Informed consent agreements, not statutes, define whether minors can exercise the right in such private sites. Second, statutes usually do not guarantee that the right to consent will be accompanied by confidentiality from parents.

CONFIDENTIALITY AND PRIVACY

Confidentiality in adolescent health care implies that information will not be disclosed to others without the knowledge and agreement of the adolescent. Although the implication is clear, the specifics are often vague and controversial. As noted previously, state statutes guaranteeing a minor's right to consent for care do not necessarily guarantee that information about that care will be withheld from parents or legal guardians, even when reporting is not essential to the adolescent's well-being. Mandatory reporting of conditions deemed harmful to the adolescent or others (e.g., physical or sexual abuse, suicidal or homicidal intent) supersedes any pre-existing agreement of confidentiality. These exceptions to confidentiality should be discussed with adolescents prior to treatment and, whenever possible, adolescents should be informed when disclosures are necessary. Clinicians should be cautious about promising more confidentiality than they can provide. For example, adolescents covered by their parents' health insurance may experience disclosure to parents by insurers that laboratory tests were performed or prescriptions were filled.

The federal Health Insurance Portability and Accountability Act (HIPAA) of 1996 added both weight and complexity to the protection of adolescent confidentiality. The HIPAA Privacy Rule, published in the Code of Federal Regulations, prohibits providers from disclosing the protected health information of a minor to a parent when it is expressly prohibited to do so under state or other law. If the law is silent or unclear about parental access to the information, disclosure depends on the discretion of the provider and any pre-existing agreement between the provider, patient, and parent.

HIPAA specifies four situations in which the parent is not entitled to health information about the minor and parental consent is not required for the minor to obtain specific health care services: (1) a state does not require parental consent for a service and the minor consents to the service; (2) a court authorizes someone other than the parent to make decisions for the minor; (3) a parent agrees that the relationship between the minor and the physician shall remain confidential; and (4) a physician believes that the minor would be endangered by the disclosure of information to the parent.

Many of the issues of confidentiality and privacy arise when the provider feels conflicting obligations to the adolescent and others who may have a legitimate interest in the adolescent's well-being, such as family members, case workers, school personnel, and law enforcement officers. In most situations, the clinician can resolve apparent conflicts by encouraging and mediating communication between the adolescent and other parties. In other cases, clinicians can remind parents of agreements to honor confidentiality.

STATE STATUTES

The Center for Adolescent Health and the Law (*http://www.adolescenthealthlaw.org*) publishes a monograph that reviews state laws pertaining to minor consent. The monograph is updated regularly and organizes the laws by minor group (e.g., emancipated minors) and service type (e.g., treatment of sexually transmitted infection). It includes summary charts of the state laws; discussions of consent, confidentiality, and disclosure; and resource lists.

MAJOR POINTS

- Informed consent requires the capacity to understand the risks, benefits, and alternatives for a proposed health care service. Most states assume this capacity begins at age 18 years.
- All states allow selective medical emancipation in which minors can consent to health care services related to family planning, pregnancy, sexually transmitted infections, HIV, sexual assault, substance use, and emergencies.
- Discussing consent and confidentiality with the adolescent and parent on the first visit begins the process of contract negotiation, before a moment of crisis.
- State statutes typically guarantee that the minor's right to consent will be upheld in clinical sites that receive public funding but do not guarantee that the right will be upheld in sites that are privately funded. Informed consent agreements, not statutes, define whether minors can exercise the right in such private sites.
- The HIPAA Privacy Rule prohibits health care professionals from disclosing the protected health information of a minor to a parent when it is expressly prohibited to do so under state or other law.
- Health care professionals usually can resolve apparent conflicts involving confidentiality and privacy by encouraging and mediating communication between the adolescent and parent(s).

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CHAPTER 9

Adolescent Participation in Research

LORAH D. DORN, PhD

INTRODUCTION

Evidence-based medicine depends on research that is scientifically sound and clinically relevant. Although this book strives to present information that is data-driven, published research on the health and health care of adolescents is sparse compared with that on adults and children. For example, little of the research on pharmacokinetics or adherence to pharmacotherapy has included adolescent subjects. Health care providers can help strengthen the scientific base of adolescent medicine through their critical appraisal of the literature, involvement as investigators, and endorsement of adolescent participation in research. This chapter addresses six key issues relevant to research involving adolescents: its importance, challenges, ethical principles, regulations, guidelines, and oversight. Understanding these issues can make adolescent participation in clinical research more comfortable for subjects, families, investigators, and clinicians.

IMPORTANCE OF RESEARCH WITH ADOLESCENTS

For decades, adult males were the subjects of most clinical research studies. Findings from these studies were applied clinically to women and children, with little empirical evidence that such generalization was safe or effective. An awareness of the associations between age, gender, pathophysiology, and outcome led to increasing research involving women and subsequently children.

In 1997, the U.S. Congress passed the Food and Drug Administration (FDA) Modernization Act to encourage pediatric testing of new drugs by the pharmaceutical industry. This was followed by the 2002 Best Pharmaceuticals for Children Act to promote pediatric testing of already-approved drugs and the 2003 Pediatric Research Equity Act that required pediatric testing of certain drugs and biological products.

All federal grants supporting clinical studies now require either the inclusion of children or scientific/ethical justification for their exclusion. This justification typically seeks to minimize risk to children by first conducting studies in adults.

CHALLENGES OF RESEARCH WITH ADOLESCENTS

Developmental Maturity

All aspects of research with adolescents are affected by developmental maturity, from subject recruitment to data collection to the interpretation of results. Clinicians who understand development and apply this knowledge in their care of adolescents are invaluable members of the research team. These clinical investigators generate hypotheses at the bedside, help recruit adolescent subjects, and

conduct data collection with sensitivity to adolescent needs and expectations.

Informed Consent

Obtaining informed consent poses a particular challenge in research involving adolescents. Institutional Research Boards (IRBs) usually require that a parent or legal guardian consent to an adolescent's participation in research. Although adolescent assent, or agreement to participate, often is obtained along with parental consent, only the consent is legally binding. The reason stems from the relatively late development of abstract reasoning during adolescence. Along with the capacity to abstract comes the integration of "hot" and "cool" cognition, as described by Dahl. Hot cognition takes place when emotion is strong. Cool cognition takes place at calmer times, when the adolescent can weigh the positives and negatives of a situation. In a study of subjects aged 7–22 years, knowledge about the research was positively associated with feelings of control, negatively associated with anxiety, and more strongly associated with emotional than cognitive factors.

Studies exploring child and adolescent understanding of the informed consent process have yielded conflicting results. When presented with hypothetical situations of research participation, Weithorn and Campbell found that adolescent cognitive capacity by age 14 years resembled that of adults. Susman and colleagues reported that children and adolescents participating in research grasped concrete concepts such as voluntary participation, duration of participation, and benefits to self, but usually did not understand abstract concepts such as the scientific vs. therapeutic purposes of the research. Schwartz found that only 6 of 19 subjects hospitalized to participate in a research study understood the reason for admission.

Box 9-1 summarizes practical issues to consider when obtaining parental informed consent and adolescent assent for research participation.

Box 9-1 Practical Aspects for Writing and Obtaining Informed Consent/ Assent for Adolescents

- Follow guidelines of your institution. Many have standard paragraphs for certain areas (e.g., risks, confidentiality), and some require an assent form in addition to a consent form.
  - Write the nonstandardized paragraphs at an age-appropriate level. Many consider the best reading level to be at the 6th- to 8th-grade level. This is true for both parents and adolescents.
  - Often IRBs or web sites will have glossaries of terms used to explain standard medical procedures.
- Utilize word processing packages that offer options to check readability scores (e.g., Flesch-Kincaid Grade Level Scoring).
- If the protocol is complex, consider using a chart or flow diagram to describe the timeline and procedures.
- Prior to IRB submission, have a lay person read your consent form to see whether he or she understands what is being done in the protocol.
- If your protocol includes a wide age range of adolescents (e.g., 10–18 years), have adolescents of different ages within the range read the form prior to use.
- Consider sending the consent form home prior to explaining the protocol and obtaining consent.
- When obtaining consent/assent from adolescents and/or parents, reiterate issues that could be problematic for an adolescent (e.g., exceptions to confidentiality in cases of certain dangerous behaviors and pregnancy tests, parent's knowledge of study results). Reiterate that participation is voluntary.
- Offer opportunities for questions. Consider asking the adolescent questions to determine comprehension.
- If the study involves a patient, be certain the adolescent and parent understand the difference between clinical care and research procedures.

Confidentiality

State laws pertaining to adolescent confidentiality in the clinical setting might not apply to the research setting. In fact, most states do not have specific statutes or guidelines pertaining to adolescent confidentiality in the research setting. Yet confidentiality can affect the recruitment, responses, and follow-up of adolescent subjects. When parental consent is required for adolescent participation, one approach is to state in the consent form that information provided by the adolescent will not be shared with the parent. This protection of adolescent confidentiality should be explained verbally to the adolescent and parent prior to obtaining signed informed consent and should be reiterated at each follow-up research visit.

As in the clinical setting, confidentiality should not be assured or upheld when protection from harm becomes an issue for the adolescent (e.g., suicidal ideation, abuse) or others (e.g., homicidal ideation). Exceptions to confidentiality should be explained to adolescents and parents during the consent process and written into the consent form. The research protocol should also include the steps to be taken if incidents such as these arise during the study. The life-threatening nature of these incidents demands adherence to protocol even though the data collected may be adversely affected. For example, when Lothen-Klein and colleagues were required to breach confidentiality regarding suicide intent, the proportion of

subjects reporting intent dropped from 8% before the disclosure to 1% after the disclosure.

Compensation

Compensation to adolescents for their participation in research raises controversial questions about the type of compensation (e.g., monetary, vouchers, gift certificates), the amount, and real or perceived coerciveness on the part of investigators. To help guide decisions about subject compensation, the Intramural Program of the National Institutes of Health developed a standardized compensation scale that suggests $20 for the first hour or part of the study and $10 per hour or part thereafter, adjusted for the level of inconvenience. Boxes 9-2 and 9-3 summarize guidelines developed by the Institute of Medicine for the compensation of research subjects who are minors.

Clinician Role and Responsibilities

The role and responsibilities of a clinician can be confusing to an adolescent when that clinician also functions as an investigator. The IRB may recommend that someone other than the clinician discuss the research participation and informed consent with the adolescent and guardian. This suggestion is congruent with the recommendations of the 1964 Declaration of Helsinki.

Box 9-2 Compensation of Adolescents Participating in Research

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Box 9-3 Recommendations for Compensation of Children and Adolescents

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ETHICS, REGULATIONS, AND GUIDELINES OF RESEARCH WITH ADOLESCENTS

Ethical Principles

The last 30 years have witnessed a steady increase in federal regulations pertaining to the ethical conduct of human research. In 1974, the U.S. Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report,* issued by this Commission in 1979, remains the most widely cited statement of ethical principles for the protection of human subjects. Box 9-4 summarizes the five key principles defined by *The Belmont Report*: respect for persons, beneficence, nonmaleficence, proportionality, and justice. These principles hold for all human subjects, regardless of age.

Rules and Regulations

Following publication of *The Belmont Report*, the U.S. Department of Health and Human Services (DHHS) developed regulations for research with human subjects that were included in Title 45, Part 46 of the Code of Federal Regulations. Subsequent changes to Part 46 included the addition of subparts addressing specific concerns for vulnerable populations. Subpart D pertaining to children and adolescents (see below) was added in 1983 and revised in 1991.

Consent and Assent: Federal regulations specify the elements of informed consent that are required for DHHS-related research (Box 9-5). However, investigators should

Box 9-4 Ethical Principles for Conducting Research

RESPECT FOR PERSONS: Duty to respect the self-determination and choices of autonomous persons, as well as to protect persons with diminished autonomy (e.g., young children, mentally retarded persons, and those with other mental impairments).

BENEFICENCE: Obligation to secure the well-being of persons by acting positively on their behalf and, moreover, to maximize the benefits that can be attained.

NONMALEFICENCE: Obligation to minimize harm to persons and, wherever possible, to remove the causes of harm altogether.

PROPORTIONALITY: Duty, when taking actions involving risks of harm, to balance risks and benefits so that actions have greatest chance to result in the least harm and the most benefit to persons directly involved.

JUSTICE: Obligation to distribute benefits and burdens fairly, to treat equals equally, and to give reasons for differential treatment based on widely accepted criteria for just ways to distribute benefits and burdens.

Fletcher JC, Dorn LD, Waldron P: Ethical considerations in pediatric oncology. In Pizzo PA, Poplack DG (eds): *Principles and Practice of Pediatric Oncology*. Philadelphia, Lippincott-Raven, 1997. Reproduced with permission from Lippincott Williams & Wilkins.

follow institution-specific guidelines when preparing consent forms because the content and language of each element can be specified by the individual IRB.

Although parents typically provide consent for their adolescents' research participation, many adults are uninformed about the participation and do not understand terms such as randomization or placebo. Understanding has been shown to improve with the use of simple, brief documents; understandable language written at an appropriate reading level; the involvement of another family member in the consent process; sending the consent document home prior to initiation of the research protocol; provision of videotaped information; and face-to-face time.

If a parent consents but the adolescent objects to participation, the objection should be binding unless the research intervention directly benefits the adolescent and is unavailable outside the research context. A 1983 modification to the regulations requires the IRB to assure that provisions for child/adolescent assent are in place, unless the child/adolescent is incapable of providing it or there is no direct benefit. A more recent recommendation regarding child/adolescent assent, issued by the Institute of Medicine, is shown in Box 9-6.

Additional federal guidelines exist for obtaining informed consent when the research involves minors who are incarcerated, wards of the court, subject to shared parental custody, or in foster care.

Box 9-5 Elements of Informed Consent

1. State and describe:
   a. Research or nature of study
   b. Purpose of study
   c. Duration of participation
   d. Procedures to be followed
   e. Which procedures are experimental
2. Describe:
   a. Reasonably foreseeable risks
   b. Discomforts
3. Describe:
   a. Benefits to the subject
   b. Benefits to others
4. Disclose alternative procedures or treatments
5. Describe confidentiality of records identifying the subject
6. Explain if the project involves more than minimal risk:
   a. Policy on compensation for injuries due to research
   b. Availability of medical treatment for such injuries
   c. Source of further information
7. Explain:
   a. Whom to contact for questions about the research
   b. Whom to contact in event of research injury
8. State:
   a. Participation is voluntary
   b. No loss of benefits on withdrawal
   c. May withdraw at any time

Fletcher JC, Dorn LD, Waldron P: Ethical considerations in pediatric oncology. In Pizzo PA, Poplack DG (eds): *Principles and Practice of Pediatric Oncology*. Philadelphia, Lippincott-Raven, 1997. Reproduced with permission from Lippincott Williams & Wilkins.

Schools: Research conducted within a school often allows passive parental consent, in which a letter is sent home describing the study and informing the parent that the adolescent will participate unless the study personnel receive a written parental response stating otherwise. According to the Pupil Rights Amendment (i.e., Hatch Amendment), federally funded research requires active parental permission if questions focus on political affiliation; mental and psychological problems; sexual behavior and attitudes; illegal, antisocial, self-incriminating, or demeaning behavior; critical appraisals of other individuals with whom respondents have close family relationships; legally recognized privileged or analogous relationships, such as those of lawyers, physicians, and ministers; religious practices, affiliations, or beliefs of the student or student's parent; or income. The Congressional No Child Left Behind Act allows parental notification and inspection of surveys that are created by third parties and intended for student completion.

Box 9-6 Recommendations for Obtaining Child/Adolescent Assent

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Level of Risk: A study is considered minimal risk if the likelihood and magnitude of the possible harm or discomfort is no greater than that encountered in routine life. The IRB can only approve research with children if the risk/benefit category is assigned at levels 1 through 3 of 4 (see Box 9-7). If it cannot be approved by the IRB, the study may be approved by an expert panel convened by DHHS, followed by an opportunity for public review and comments.

Waiver of Parental Consent: Section 46.408(c) of the Code of Federal Regulations allows an IRB to waive parental consent if the following conditions are met: (1) the research involves no more than minimal risk; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not be conducted without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Few, if any, states have laws regarding the participation of minors in research. Consequently, IRBs frequently base decisions about consent for research participation on state laws pertaining consent for clinical care. Many states allow adolescents to receive care without parental consent for sexually transmitted infections, pregnancy, family planning, substance use, and mental health disorders. Investigators should be familiar with state-specific laws because there is considerable variability across states regarding allowable conditions, procedures, and ages of treatment. Box 9-8 summarizes recommendations of the Institute of Medicine (IOM) regarding parental consent for the research participation of children and adolescents.

Box 9-7 Levels of Research That Can Be Approved by the IRB for Child and Adolescent Research Participation

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Guidelines

A number of professional organizations have issued consensus statements regarding research with adolescents (see Box 9-9). In 2004, the IOM published recommendations for conducting research with children and adolescents. Box 9-10 summarizes the IOM guidelines for investigators pertaining to ethical conduct in pediatric research.

Box 9-8 Recommendations of the Institute of Medicine Regarding Parental Consent for the Research Participation of Children and Adolescents

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Box 9-9 Professional Organizations Providing Guidelines for Conducting Research with Children and/or Adolescents

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Box 9-10 Key Responsibilities of Investigators for the Ethical Conduct of Clinical Research Involving Infants, Children, and Adolescents

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OVERSIGHT OF HUMAN RESEARCH

Office for Human Research Protection (OHRP)

The federal OHRP oversees all research involving human subjects that is funded or conducted by DHHS. The responsibilities of OHRP include the development of

criteria for the protection of human subjects; the approval of institutional assurances of compliance on DHHS-related research; clarification and guidance about the involvement of human subjects in research; the development and implementation of educational programs and resource materials; and the enhancement of human subject protection.

Institutional Review Board (IRB)

The IRB is an administrative body that is designed to protect the rights and welfare of individuals who are approached for research participation, as well as individuals who are participating in research. The IRB has the authority to approve, disapprove, and regulate all research within an institution based on the federal guidelines mentioned previously. An IRB may exist within one institution (e.g., university, hospital, medical center) and serve only that institution, or it may exist within the private sector and serve many institutions. Different interpretation and application of the federal regulations across IRBs result in different allowable research practices across institutions. For example, some institutions never allow waiver of parental consent despite federal regulations allowing it in certain circumstances.

MAJOR POINTS

- Evidence-based health care for adolescents depends on research with adolescents that is scientifically sound and clinically relevant.
- All federal grants supporting clinical studies now require either the inclusion of children or scientific/ethical justification for their exclusion.
- Most IRBs require signed informed consent from a parent or legal guardian for the research participation of an adolescent minor.
- Confidentiality as defined by state law for the clinical setting might not apply to the research setting. In fact, most states do not have specific statutes or guidelines pertaining to adolescent confidentiality in the research setting.
- To avoid role confusion, the adolescent's clinician should not recruit or enroll that adolescent in his or her own clinical research study.
- Subpart D of Title 45, Part 46 of the Code of Federal Regulations pertains to regulations for research involving children and adolescents.
- An IRB may waive parental consent if the research involves no more than minimal risk, will not adversely affect the rights and welfare of the subjects, and could not be conducted without the waiver or alteration.
- The Office for Human Research Protection oversees research involving humans at the federal level. The IRB implements federal regulations and oversees research involving humans at the institutional level.

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COMMON MEDICAL PROBLEMS

PART II

CHAPTER 10

Delayed Puberty

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INTRODUCTION

This chapter reviews the definitions, causes, evaluation, and management of puberty that is delayed in onset or stalled in progression. It does not discuss precocious puberty or premature adrenarche, which presents in young children. Common conditions associated with normal puberty are discussed elsewhere in this book, such as anovulation due to gynecologic immaturity in Chapter 22, gynecomastia in Chapter 1, and acne in Chapter 15. The primary objectives of this chapter are to differentiate normal from abnormal puberty during the adolescent years and to facilitate the identification and treatment of conditions interfering with normal pubertal progression.

DEFINITIONS

Constitutional delay of puberty: The lack or late appearance of secondary sexual characteristics, delayed skeletal maturation as measured by the bone age, and delayed adrenarche as measured by serum concentrations of adrenal androgens.

Delayed puberty: The lack of or late appearance of secondary sexual characteristics by that chronological age at which the characteristics appear in 95% of the population. In the United States, standards published by the National Center for Health Statistics defines delayed puberty as the absence of breast development or pubic hair by age 13 years in girls and the absence of genital development or pubic hair by age 14 years in boys.

Eunuchoidal habitus refers to an arm span that exceeds height by more than 5 cm. It is usually due to hypogonadism with delayed epiphyseal closure of the long bones.

Expected adult height: Falls within 1.5 standard deviations of the mid-parental height, corrected for gender. It is determined for males by adding 6.5 cm and for females by subtracting 6.5 cm from mid-parental height.

Primary hypogonadism refers to diseases of the ovaries or testes that result in decreased secretion of estrogen or testosterone and high serum concentrations of follicle stimulating hormone (FSH) and luteinizing hormone (LH).

Secondary hypogonadism refers to impaired secretion of either pituitary gonadotropins (i.e., FSH and LH) or hypothalamic gonadotropin-releasing hormone (GnRH).

Secondary sexual characteristics refer to breast development and pubic hair growth in females and to genital development and pubic hair growth in males. Tanner staging is based on these characteristics, although testicular volume is a more accurate measure of male development than the Tanner genital stage.

Short stature: A height below the 3rd percentile for individuals of that sex and chronological age in the population.

EPIDEMIOLOGY

By definition, delayed puberty occurs in 5% of the population. Constitutional delay accounts for more than 50% of all cases, with a 2:1 ratio of males to females. A family history of delayed puberty is twice as likely in adolescents with constitutional delay as in those with normal puberty, and inheritance patterns suggest autosomal dominance with incomplete penetrance. Approximately 20% of delayed puberty is due to functional hypogonadotropic hypogonadism, in which puberty is delayed in onset but occurs spontaneously and progresses normally once begun. Permanent hypogonadotropic or hypergonadotropic hypogonadism accounts for 25% of cases (see Box 10-1).

Box 10-1 Causes of Delayed Puberty

Hypergonadotropic Hypogonadism (high FSH and LH)

- Congenital
  - Turner syndrome
  - Klinefelter syndrome
  - Anorchia
- Acquired
  - Chemotherapy
  - Radiation therapy
  - Trauma
  - Autoimmune or infectious

Hypogonadotropic Hypogonadism (low to normal FSH and LH)

- Congenital
  - Isolated GnRH deficiency
    - Kallman syndrome (with anosmia)
    - Laurence-Moon syndrome
    - Bardet-Biedl syndrome
    - Prader-Willi syndrome (with obesity)
  - Deficiencies of GnRH and other anterior pituitary hormones
- Acquired
  - Functional gonadotropin deficiency
    - Constitutional delay
    - Systemic illness (e.g., inflammatory bowel disease)
    - Malnutrition, weight loss (e.g., anorexia nervosa, starvation)
    - Excessive exercise
    - Hypothyroidism
    - Hyperprolactinemia
    - Hypercortisolism
  - Structural gonadotropin deficiency
    - Tumor (e.g., craniopharyngioma, germinoma, astrocytoma)
    - Infiltrative (e.g., histiocytosis, hemochromatosis, granulomatous)
    - Pituitary infarction

Short stature is not present in all adolescents with delayed puberty, and delayed puberty does not occur in all adolescents with short stature. By definition, short stature affects 3% of the population. The most common causes after infancy are genetic (i.e., familial) and constitutional delay of growth. Genetic short stature is associated with a bone age that is consistent with chronological age and predicts adult short stature. In contrast, constitutional delay is associated with a bone age that is delayed for chronological age and predicts normal adult stature.

PATHOPHYSIOLOGY

The age thresholds for defining delayed puberty in the United States are based on analyses of the 1988–1994 National Health and Nutrition Examination Surveys (NHANES) III, the 1988–1994 Hispanic Health and Nutrition Examination Surveys (HHANES), and the 1997 Pediatric Research in Office Settings (PROS) study (see Chapter 1). By age 13 years, at least 95% of white, black, and Mexican-American girls have achieved Tanner Stage 2 for breast and/or pubic hair development. By age 14 years, at least 95% of white, black and Mexican-American boys have achieved Tanner Stage 2 for genital and/or pubic hair development. Because there is less variability by race/ethnicity in the 95th percentile ages than in the mean ages, delayed puberty in the United States typically is defined as the absence of breast development or pubic hair by age 13 years in girls and the absence of genital development or pubic hair by age 14 years in boys.

The pathophysiology of delayed puberty involves decreased secretion of GnRH (i.e., hypogonadotropic hypogonadism) in at least 85% of cases. The cause may be functional without an apparent structural defect of the hypothalamus (e.g., constitutional delay and chronic illness), structural without an apparent genetic defect (e.g., craniopharyngioma), or genetic (e.g., Kallman syndrome). Differentiation of these categories can be difficult because all involve decreased serum levels of GnRH, FSH, LH, estrogen, and testosterone. The underlying pathologies, diagnoses, and presentations are discussed next, followed by a review of the most common causes of hypergonadotropic hypogonadism (i.e., Klinefelter syndrome and Turner syndrome).

Constitutional Delay of Puberty

Adolescents with constitutional delay of puberty present with the late onset of sexual, adrenal, and skeletal maturation. Adolescents who begin to mature on time but then stall in their development do not have constitutional delay. Thus, the presence of secondary sex characteristics excludes the diagnosis of constitutional delay and should

prompt a search for other causes of hypogonadotropic hypogonadism.

Constitutional delay of puberty always involves a decline in growth velocity relative to peers of the same age and sex. Adolescents with constitutional delay grow at the childhood rate of 5–7 cm per year, whereas their peers grow at the pubertal rate of 8–14 cm per year. However, because bone age in constitutional delay correlates better with height age (i.e., the chronological age at which the height would be average) than with the current chronological age, most adolescents with constitutional delay ultimately achieve a normal adult height. Adolescents with constitutional delay who have severely decreased pre-pubertal growth velocity (i.e., below 5 cm per year) or very late sexual maturation may not achieve the expected adult height. Growth of the long bones exceeds growth of the vertebral column in these patients, resulting in eunuchoidal proportions (i.e., arm span exceeds height by more than 5 cm) and lower-than-predicted adult height.

The psychosocial impact of constitutional delay appears greater in boys than girls. In boys it has been associated with lower self-esteem, depression, reduced peer contact, and attention-deficit hyperactivity disorder. These psychosocial correlates may explain why boys are more likely than girls to seek and receive treatment for constitutional delay of puberty.

Other Causes of Functional Hypogonadotropic Hypogonadism (FHH)

Chronic illness, impaired nutrition or weight gain, weight loss, excessive exercise, chronic use of corticosteroids, medication-induced hyperprolactinemia, and hypothyroidism are common causes of FHH. Unlike constitutional delay, which always presents as the late onset of puberty, these causes may delay the onset and/or slow the rate of pubertal development. For example, illness beginning after the appearance of early secondary sexual characteristics may stall puberty at the given Tanner stage, cause primary amenorrhea in the pre-menarcheal female, or cause secondary amenorrhea in the post-menarcheal female.

Any chronic systemic illness can interfere with growth and development. Up to a third of adolescents with new-onset Crohn's disease present with growth failure rather than gastrointestinal symptoms. The deficit in weight tends to be greater than the deficit in height, and delay or stall in pubertal development is common. Celiac disease usually presents before adolescence and is a treatable cause of short childhood stature and pubertal delay. Cystic fibrosis affects growth and puberty through decreased energy intake; increased energy requirements associated with the work of breathing; malabsorption; and chronic or recurrent infection. Hypothyroidism frequently presents as growth failure and, unlike gastrointestinal diseases, the deficit in height exceeds that in weight.

Structural Hypogonadotropic Hypogonadism

The major diagnoses in this category include hypothalamic and pituitary tumors, irradiation of the central nervous system (CNS), and congenital GnRH deficiency. Craniopharyngioma, the most common CNS tumor associated with delayed puberty, typically presents at 6 to 14 years of age with headache, short stature, polydipsia, and polyuria. Less common tumors include germinomas, prolactinomas, and chromophobe adenomas.

The most common cause of idiopathic hypogonadotropic hypogonadism is congenital GnRH deficiency, or the absence of GnRH secretion by the hypothalamus. The inheritance pattern may be autosomal dominant, autosomal recessive, X-linked, or sporadic. The age of diagnosis and clinical presentation vary widely, from infancy (e.g., cryptorchidism) to childhood (e.g., anosmia), to adolescence (e.g., delayed puberty), to adulthood (e.g., normal puberty with subsequent infertility). Anomalies associated with congenital GnRH deficiency include cleft lip or palate, unilateral renal agenesis, unilateral or bilateral cryptorchidism, and hyposmia or anosmia (i.e., Kallman syndrome). The absence of GnRH secretion cannot be established by serum assay but is supported by the absence of endogenous LH surges and the increase in serum LH induced by exogenous GnRH.

Other inherited causes of hypogonadotropic hypogonadism include Prader-Willi, Laurence-Moon, and Bardet-Biedl syndromes. Prader-Willi syndrome is an autosomal dominant condition manifested as infantile hypotonia, childhood hyperphagia and obesity, characteristic facies, small hands and feet, adolescent short stature, and delayed puberty. Micropenis is common in boys, and early adrenarche is common in boys and girls. Laurence-Moon and Bardet-Biedl syndromes are both rare, autosomal recessive conditions with hypogonadism and retinitis pigmentosa. Laurence-Moon syndrome is associated with spastic paraplegia. Bardet-Biedl syndrome is associated with polydactyly, childhood obesity, and renal dysplasia.

Hypergonadotropic Hypogonadism

Primary gonadal failure leads to hypergonadotropic hypogonadism. The two most common forms are Klinefelter syndrome and Turner syndrome, both of which are associated with abnormalities in the sex chromosomes.

Klinefelter syndrome, or seminiferous tubular dysgenesis, occurs in approximately 1 per 1000 male births. The clinical findings include small, firm testes; gynecomastia; eunuchoidal proportions; aortic valvular disease; osteoporosis; breast cancer at 20 times the baseline male rate; germ cell tumors; leukemia; and lymphoma. Most men with Klinefelter syndrome have a 47,XXY karyotype.

Although full-scale IQ is often in the normal range, the verbal IQ is typically 10–20 points lower than the mean.

Turner syndrome, or gonadal dysgenesis, occurs in 1 per 2500 female births. Sixty percent of cases have a 45,X karyotype with the classic presentation of female phenotype, short stature, and hypogonadism. Common findings include micrognathia; high-arched palate; ptosis; short, webbed neck (pterygium colli); impaired hearing (from recurrent otitis media); broad, shield-like chest; short fourth metacarpals; cubitus valgus; and genu valgum. Aortic valvular disease includes bicuspid valves, stenosis, and coarctation, and there are abnormalities in renal position, vascularization, and drainage. Autoimmune disorders are common in Turner syndrome, including thyroid disease and inflammatory bowel disease. Full-scale IQ is usually normal, but performance IQ is typically 10–20 points lower than the mean and reading scores are often higher than suggested by the full-scale IQ.

Forty percent of patients with Turner syndrome have genetic mosaicism. Those with 45,X/46,XX (the most common mosaic pattern) and 45,X/47,XXX are phenotypically female, chromatin-positive on buccal smear, and have milder clinical manifestations than do those with the classic 45,X karyotype. Those with the less common pattern of 45,X/46,XY may be phenotypically female or male and may vary in the frequency and severity of the other findings of classic Turner syndrome.

Other causes of hypergonadotropic hypogonadism include gonadal failure from chemotherapy or radiation, autoimmune gonadal disorders, biosynthetic defects, or resistance to LH (males) or FSH (females).

EVALUATION

The first step in the evaluation of delayed puberty is to determine by history and physical examination the age of onset and the progression of secondary sexual characteristics. Patients with constitutional delay of puberty have late onset without stalled progression, whereas those with other causes may have any combination of late onset and stalled progression. Although serum gonadotropin levels differentiate primary from secondary hypogonadism, no single test differentiates the most frequent causes of delayed puberty (i.e., constitutional delay and other causes of FHH). The history with review of the growth record and the physical examination are therefore important guides to the laboratory evaluation (Box 10-2).

Past medical history should include detailed questioning about congenital anomalies, eating and nutrition, chronic or recurrent illness during childhood, endocrine disorders, trauma or surgery, and medications. If systemic illness is suspected, the review of systems should seek to identify symptoms associated with the diagnoses of concern. Family history should be reviewed for late puberty or menarche in parents and siblings and heights of parents, siblings, and grandparents. If a specific inherited syndrome is suspected, parents should be questioned about manifestations of that syndrome within the extended family (i.e., anosmia in Kallman syndrome).

Box 10-2 Laboratory and Radiographic Evaluation of Delayed Puberty

Baseline
- Serum estradiol and testosterone
- Serum FSH and LH
- Serum thyroxine, TSH
- Serum prolactin
- Bone age

Follow-up
- CBC, serum chemistry panel, urinalysis, ESR, CRP
- Olfactory testing
- Chromosomal analysis
- Head MRI or CT
- Pelvic ultrasound in females
- GnRH or GH stimulation testing

The physical examination should include particular attention to sexual maturity (i.e., Tanner) ratings; the measurement of height, weight, arm span, upper body length (top of head to symphisis pubis), and lower body length (symphisis pubis to floor); calculation of body mass index (BMI); arm span/height ratio; and upper/lower (U/L) body ratio. The U/L ratio declines during childhood, reaching 0.9–1.0 by adulthood. Hypothyroidism is associated with a high ratio (> 1.0), whereas hypogonadism is associated with a low or normal ratio.

Other important findings on the physical examination include visual field cuts or papilledema; goiter; evidence of chronic lung disease; signs of congenital heart disease; hepatosplenomegaly or abdominal mass; fissures, fistulae, skin tags, or hemorrhoids on rectal examination; and neurological examination. If Kallman syndrome is suspected, patients should be referred for genetic and endocrine consultation as well as formal olfactory evaluation because office testing is unreliable.

Initial laboratory studies should include measurement of serum estradiol (females), testosterone (males), FSH, LH, thyroxine, thyroid-stimulating hormone (TSH), and bone age. Subsequent studies are determined by these results, along with the history and physical examination. Complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum chemistry profile usually are performed if chronic illness is suspected. Imaging studies of the head, such as magnetic resonance imaging (MRI) or computed tomography (CT), are indicated in the setting of neurological signs or symptoms suggesting a CNS tumor and in patients with anosmia or hyposmia on formal olfactory testing. Pelvic ultrasound is indicated to confirm the

presence of ovaries and Mullerian structures (i.e., uterus and tubes). Chromosomal analysis should be performed if Klinefelter syndrome, Turner syndrome, Kallman syndrome, or other genetic condition is suspected.

The diagnosis of growth hormone (GH) deficiency and assessment of pituitary function can be particularly difficult in adolescents with delayed puberty. Insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGF-BP-3) are secreted in response to growth hormone (GH) and mediate the effect of GH on skeletal growth. However, factors other than GH affect IGF-1 and IGF-BP-3 levels, such as malnutrition and low body weight. High levels usually exclude GH deficiency, but low or normal levels do not confirm it. If GH deficiency remains in the differential diagnosis, the patient should be referred to an endocrinologist for stimulation testing. In adolescents with severe hypogonadotropic hypogonadism, the GnRH stimulation test can help determine whether anterior pituitary function is appropriate for the level of pubertal development. The test is done best by an endocrinologist in a controlled setting.

MANAGEMENT

Watchful waiting is the initial management of most adolescents with delay in the onset of puberty. If the likely diagnosis is constitutional delay and the adolescent is coping well, visits can occur at 3- to 6-month intervals until puberty begins, psychosocial problems arise, or the diagnosis of constitutional delay is in question. Hormonal treatment of constitutional delay usually is prompted by adolescent discomfort with short stature or physical immaturity and is more commonly requested by males than females. The short-term (i.e., 6-month) use of low-dose testosterone in males or estrogen in females, as outlined in Box 10-3, will induce secondary sexual characteristics and an increase in height velocity with minimal to no effect on adult height.

Most adolescents with constitutional delay will develop some secondary sexual characteristics during the 6-month treatment period and will continue to progress through puberty during the 6 months following discontinuation of the exogenous hormone. Although some patients may require a second course of treatment, failure to enter and progress with puberty increases the likelihood of a diagnosis other than constitutional delay and warrants further evaluation. Hypogonadism that persists in males or females beyond age 18 years without obvious cause suggests congenital GnRH deficiency.

It is important to note that patients with constitutional delay and other causes of isolated GnRH deficiency are not deficient in GH, despite low levels of serum IGF-1. Although there is some controversy about the use of exogenous GH in constitutional delay, the weight of the evidence does not support its use. In contrast, GH therapy is indicated for the treatment of short stature associated with Turner syndrome before beginning estrogen therapy. All patients with Turner syndrome should therefore be referred to an endocrinologist for consultation regarding the timing, type, and dosage of hormonal therapy.

Pubertal delay secondary to an underlying illness requires treatment of the illness. In some cases, specific interventions will trigger puberty even if the illness persists. Examples include hyperalimentation in inflammatory bowel disease and enzyme replacement in cystic fibrosis. In others, an intervention may be curative, as in corrective surgery for congenital heart disease. If puberty remains markedly delayed despite aggressive treatment of the underlying disease, referral to an endocrinologist is warranted.

Patients with permanent hypogonadism require ongoing hormone replacement therapy with counseling about reproductive potential and long-term follow-up for medical monitoring and support.

Box 10-3 6-Month Hormonal Therapy for Constitutional Delay of Puberty

Males	Testosterone enanthate 50 mg intramuscularly every 4 weeks
Females	Ethinyl estradiol 5–10 μg or conjugate

MAJOR POINTS

- Constitutional delay accounts for more than 50% of cases of delayed puberty, with a 2:1 ratio of males to females. Other causes of decreased secretion of GnRH account for 35%.
- Constitutional delay presents with late onset of sexual, adrenal, and skeletal maturation. Adolescents who enter puberty on time but then stall in their development do not have constitutional delay.
- Other causes of hypogonadotropic hypogonadism may delay the onset and/or slow the rate of pubertal development. Chronic illness, malnutrition, hypothyroidism, CNS tumors, and congenital GnRH deficiency are included in this category.
- Turner syndrome in females and Klinefelter syndrome in males are the leading causes of primary gonadal failure, or hypergonadotropic hypogonadism. Other causes include chemotherapy, radiation, autoimmune gonadal disorders, and biosynthetic defects.
- Evaluation of delayed puberty begins with review of the growth history, determination of the sexual maturity ratings (i.e., Tanner stages), measurement of the serum FSH and LH levels, and bone age. Additional evaluation is guided by these findings as well as the detailed history and physical examination.

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CHAPTER 11

Obesity

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INTRODUCTION

Since the mid 1980s, obesity has increased to epidemic proportions in pediatric age groups. In parallel with this trend are increases in obesity-related morbidity during childhood and premature mortality during adulthood. New treatment options do exist, such as surgery for adolescents whose severe obesity otherwise would result in certain illness and early death. However, for most obese children and adolescents, effective prevention and treatment strategies remain elusive. This chapter reviews the definitions, epidemiology, natural history, pathophysiology, evaluation, and management of obesity that begins in, or continues into, adolescence.

DEFINITIONS

Body mass index (BMI), defined as weight in kilograms (kg) divided by the square of height in meters (m^2), provides a simple, reproducible screening tool for adiposity in children and adults. BMI cut-points for levels of adiposity have been proposed by the Centers for Disease Control and Prevention (CDC) for all age groups in the United States (Table 11-1). For an adult, a BMI below 18.5 is considered ***underweight***, 18.5–24.9 is considered a ***healthy weight***, 25.0–29.9 is considered ***overweight***, and 30 or higher is considered ***obese***. For a child or adolescent, the CDC uses BMI percentile for age and gender, rather than BMI, and uses the labels "at risk of overweight" and "overweight" rather than "overweight" and "obese." The label "***at risk of overweight***" is defined as the 85th to 94.9th percentiles. The label "***overweight***" is defined as the 95th percentile or higher.

In adults, the term "***morbid obesity***" refers to BMI levels of 40 kg/m^2 or greater. In children and adolescents, there has been little research upon which to base a definition of morbid obesity. However, BMI levels of 35–40 kg/m^2 correspond to at least the 99th percentile for older adolescents and may represent a clinically useful cut-point for defining morbid obesity in children and adolescents.

EPIDEMIOLOGY AND NATURAL HISTORY

Between 1986 and 2000, the proportions of U.S. adults with obesity, morbid obesity, and BMI levels at or above 50 kg/m^2 increased two-, four-, and five-fold, respectively. Obesity among children and adolescents in the United States increased three-fold in 25 years, and the increases are two times higher in black and Hispanic than white youth. Of the 16% of children and adolescents who now meet CDC criteria for overweight, significantly more are in the highest weight percentiles compared with two to three decades earlier. The increased prevalence and severity of childhood obesity has led to increased health care costs that are both related to obesity and incurred before adulthood. A recent study estimated a three-fold increase over 20 years in the cost of pediatric hospitalizations for conditions directly related to obesity.

Even more costly are the effects of childhood weight status on adult obesity and its associated morbidity and

Table 11-1 CDC Weight Categories for Adults as Compared with Children and Adolescents[1]

Adults		Children and Adolescents	
Category	**BMI (kg/m²)**	**Category**	**BMI Percentile**
Underweight	Below 18.5	Underweight	Below 5th
Normal	18.5–24.9	Normal	5th to 84.9th
Overweight	25.0–29.9	At risk of overweight	85th to 94.9th
Obese	30 or higher	Overweight	95th or higher

[1]For adults, the labels refer to ranges of BMI, calculated as weight divided by height squared. For children and adolescents, the labels refer to ranges of BMI percentiles, adjusted for age and gender.

mortality. A 30-year prospective study demonstrated a mortality rate that was twice as high in adolescents who were obese at enrollment compared with those who were lean. In another study, the lifespan of young adults aged 20–30 years with BMI levels above 45 kg/m² was significantly shorter than that of leaner subjects. The mean number of years lost was 20 for black males, 5 for black females, 13 for white males, and 8 for white females.

COMPLICATIONS OF OBESITY

Until recently, the adipocyte, or fat cell, was considered a passive site for the storage of excess energy in the form of triglycerides. The identification of leptin, however, generated a new model of energy balance in which the adipocyte plays a more active role. Adipocytes collectively represent a secretory endocrine organ producing leptin and inflammatory cytokines (e.g., TNF, IL-6, adiponectin) that may help explain the association of obesity with disorders of many organ systems (Figure 11-1). Some of these conditions are discussed next.

Coronary heart disease (CHD). Obesity is strongly associated with adult CHD and with the development of other risk factors for CHD. During childhood, obesity carries nearly a 10-fold risk for hypertension and is associated with low HDL-cholesterol and high triglyceride levels. Nearly 30% of obese adolescents, or up to 910,000 adolescents in the United States, have a cluster of risk factors for CHD known as the metabolic syndrome (i.e., abdominal obesity, insulin resistance, hypertension, and hyperlipidemia).

Type 2 diabetes mellitus (DM). The diagnosis of Type 2 DM during adolescence increased 10-fold during the 1980s and 1990s. The epidemic of Type 2 DM has paralleled that of obesity, and the CDC projects that up one-third of all children and one-half of black and Hispanic children, born in the United States today will develop Type 2 DM during their lifetimes. The pathophysiology of Type 2 DM in children and adolescents probably begins with ß-cell dysfunction in the setting of insulin resistance. The physical finding of acanthosis nigricans, or darkly-pigmented, thickened skin of the neck or axillae, is associated with hyperinsulinemia and insulin resistance. The diagnosis of Type 2 DM depends on two separate fasting blood glucose levels above 125 mg/dl or a single level above 125 mg/dl in the presence of symptoms such as polydipsia and polyuria. Oral glucose tolerance testing is usually performed to establish the diagnosis. Although the cornerstones of clinical management are diet and physical activity, the low and delayed response rates have resulted in increasing use of metformin (see Chapter 13).

Sleep-disordered breathing. Childhood obesity is associated with a spectrum of breathing disorders during sleep involving episodes of upper airway obstruction that vary in frequency and severity. The most severe form is the obstructive sleep apnea (OSA) syndrome, in which breathing ceases for 10 or more seconds. The presenting signs and symptoms of sleep-disordered breathing include nocturnal snoring, restlessness, and frequent awakening; oxygen desaturation and hypercapnia during sleep; and daytime somnolence. In adults, OSA is associated with sympathetic overstimulation and cardiovascular hyperresponsiveness. In children, it is associated with paradoxical hyperactivity, impaired neurocognitive function, and enuresis. The long-term consequences of OSA include sustained daytime hypertension and increased cardiovascular mortality. The evaluation and management of sleep disorders in adolescents are discussed in detail in Chapter 17.

Non-alcoholic fatty liver disease (NAFLD). Children with early-onset obesity and insulin resistance are at high risk for a spectrum of liver disorders known collectively as NAFLD. The spectrum ranges from fatty infiltration of the liver alone (steatosis) to fatty infiltration with hepatocellular inflammation (steatohepatitis) to hepatocellular necrosis, fibrosis, and cirrhosis. The most

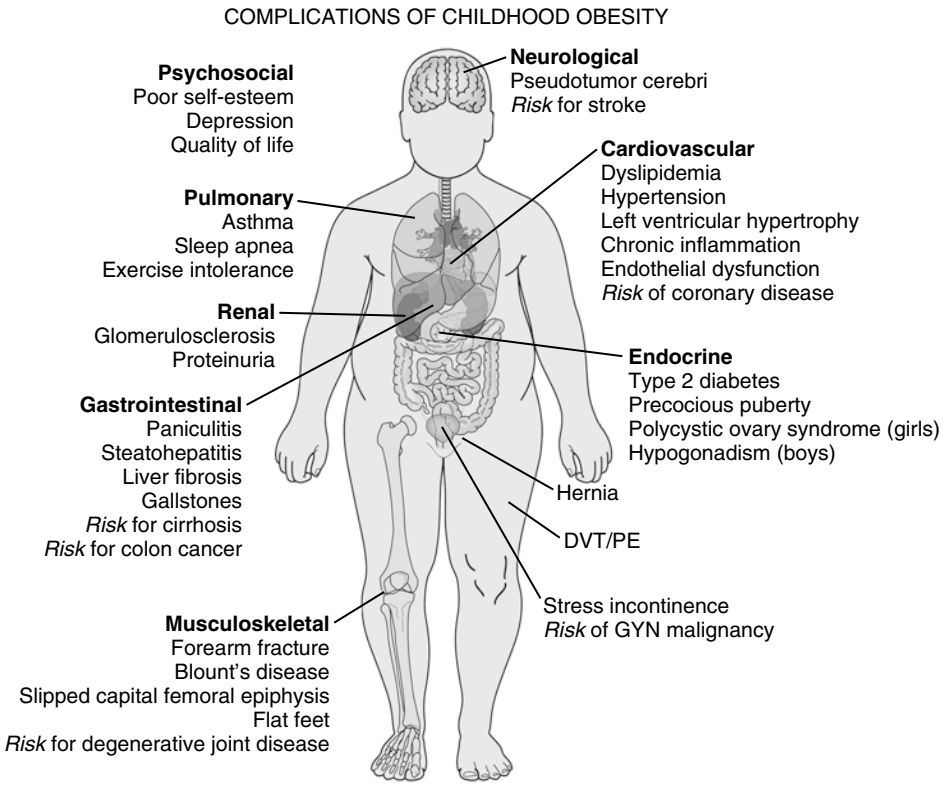

Figure 11-1 Adapted from: Xanthakos SA, Daniels SR, Inge TH: Bariatric surgery in adolescents: An update. Adolesc Med Clinics 2006;17:589–612.

advanced forms of the spectrum occur in adults with morbid obesity and Type 2 DM. Elevation of the serum transaminases can be used to screen obese children and adolescents for NAFLD, but liver biopsy is required for diagnosis and staging. The prevalence of NAFLD in obese children and adolescents who progress to liver biopsy ranges from 50–80%, with steatohepatitis in two-thirds and fibrosis in one-third. Preliminary studies demonstrate regression of steatohepatitis and fibrosis in adolescents and adults with significant weight loss following bariatric surgery.

Pseudotumor cerebri. Idiopathic elevation of the intracranial pressure, or pseudotumor cerebri, occurs in less than 1 per 100,000 children and adults. Risk factors for its development include adolescent age and obesity (30–50% of patients). There is no gender predominance in children and adolescents with pseudotumor cerebri, but adult women aged 20–44 years who are at least 20% above ideal body weight appear to be at increased risk. Presenting symptoms include headache that is often pulsatile and nocturnal; nausea and vomiting; neck pain; eye pain with extraocular movement, diplopia, and other visual change; vertigo; and tinnitus. Common findings on physical examination include papilledema (50–100% of adolescent patients); sixth nerve palsy (less than 50% of adolescent patients); visual field cuts; and nystagmus. Pseudotumor cerebri is a diagnosis of exclusion that depends on increased pressure on lumbar puncture (above 200 mm H_2O); otherwise normal cerebrospinal fluid (CSF); the absence of ventricular obstruction, deformity, or displacement on neuroimaging; and no other identifiable cause of increased intracranial pressure (ICP). An empty sella on computed tomography (CT) or magnetic resonance imaging (MRI) of the head is found in up to 70% of patients and does not exclude the diagnosis. Ophthalmology and neurology consultations are indicated for children and adolescents with pseudotumor cerebri because of the high risk of vision loss. The acute management typically includes serial lumbar punctures to lower ICP and acetazolamide to decrease CSF production. Corticosteroids, optic nerve fenestration, and lumboperitoneal shunting are reserved for patients with severe visual impairment. Ongoing therapy for obese children and adolescents centers on weight loss given the evidence that even modest reductions are associated with more rapid resolution of papilledema and visual dysfunction.

Psychosocial development. The most common complications of obesity during late childhood and adolescence may well be psychosocial. Although social stigmas associated with obesity transcend age, the negative effects can be particularly damaging to evolving self-concept, family and peer relationships, and the formation of social networks. Obese adolescents have lower self-esteem, fewer friends,

higher rates of school drop-out, and lower rates of job success than do non-obese peers. The social adversity that begins in adolescence continues into adulthood, with increased rates of psychopathology and lower levels of economic achievement. Quality of life and socioeconomic status have been shown to improve for morbidly obese adults following significant weight loss, but it remains unknown whether similar effects will be realized by children and adolescents.

EVALUATION OF OVERWEIGHT ADOLESCENTS

There is considerable controversy among health professional organizations regarding recommendations for overweight screening and evaluation in children and adolescents. All organizations agree that the problem is significant and that there is a paucity of research on the effectiveness of screening. The differences stem from how the organizations choose to apply the limited evidence that is available.

In 2005, the U.S. Preventive Services Task Force (USPSTF) updated its 1996 screening recommendations for overweight children and adolescents. Although the report acknowledges the increasing prevalence of childhood obesity and the accompanying risks to health and quality of life, it concluded that the available evidence does not support screening as a means of improving outcome. In contrast, the American Academy of Pediatrics and the Maternal and Child Health Bureau do recommend screening for family factors and health conditions associated with overweight.

In 2004, the Institute of Medicine (IOM) published recommendations for overweight screening and intervention during childhood and adolescence that were based on the best "available" evidence. The IOM acknowledged the limitations of this evidence but argued that waiting for the "best possible evidence" was not an option given the increasing rates of obesity in the United States. The recommendations that follow adhere to the approach suggested by the IOM and represent a composite from general guidelines for preventive care and specific approaches to the identification of conditions associated with adolescent obesity.

Guidelines for Adolescent Preventive Services (GAPS) and *Bright Futures: Guidelines for Health Supervision of Adolescents* (see Chapter 2) recommend annual determination of BMI and examination of the trend in BMI percentile over time. The 2004 IOM report, *Preventing Childhood Obesity: Health in the Balance* calls for routine tracking of the BMI in children and adolescents, with appropriate counseling about weight management. These recommendations for regular assessment of the BMI hold for all adolescents, regardless of weight category, and are particularly important for adolescents who meet CDC criteria for overweight.

Once the diagnosis of overweight is established, the adolescent and parent should be asked about family history of obesity, diabetes mellitus, hypertension, hyperlipidemia, and CHD. Patient and family eating behavior, caloric intake, physical activity, and efforts to lose weight should be discussed. Review of systems should include questions about symptoms associated with comorbid conditions such as insulin resistance, DM, and sleep-disordered breathing. It also should explore symptoms suggestive of disorders that may cause excessive weight gain, such as hypothyroidism.

The physical examination of overweight and obese adolescents continues along the same line as the history, with particular attention to signs suggesting comorbid or causative conditions, such as elevated blood pressure, dysmorphic features, acanthosis nigricans, thyromegaly, or hepatomegaly. The cost-effectiveness of routine laboratory testing in the evaluation of obese adolescents has not been studied, but measurement of fasting glucose and insulin levels, serum lipids, and liver function tests should be considered.

MANAGEMENT

Behavior Modification

Studies on the effectiveness of treatment strategies for overweight children and adolescents remain limited in number and variable in their findings. Although several have demonstrated significant and sustained weight loss with family-based behavioral therapy, many others reveal no weight loss and only modest, short-term effects on self-esteem. Even those studies demonstrating weight reduction suffer from selection and retention biases favoring motivated subjects and families. For example, in a recent study of obese children and adolescents participating in a family-centered behavioral program, half the subjects withdrew from the program before completing the initial 6 months. Although the drop-out rate was discouragingly high, the results for the 177 subjects who completed the program were promising. Mean reductions in weight and BMI at 6 months were 2.0 kg and 1.7 kg/m^2, respectively. Significant improvements were also found in blood pressure; serum levels of total cholesterol, low-density-lipoprotein cholesterol (LDL-C) triglycerides, and insulin; and aerobic fitness.

Pharmacotherapy

Reports in the 1990s of late adverse side effects in adult patients who had used pharmacotherapy for weight reduction slowed both the development of new pharmacological agents for the management of obesity and the testing

of these agents in children and adolescents. The recent U.S. Food and Drug Administration (FDA) approval of sibutramine and orlistat for use in the management of pediatric obesity therefore represents an important advance.

Sibutramine is a nonselective reuptake inhibitor of serotonin and norepinephrine that is approved for use in patients aged 16 years and older. Clinical trials of sibutramine plus behavioral modification in adolescents resulted in 8–10% reductions in BMI; reductions in serum levels of total cholesterol, LDL cholesterol, triglycerides, glucose, and insulin; and increases in HDL cholesterol (HDL-C). Important side effects of sibutramine, which may limit its use, are increases in blood pressure and heart rate.

Orlistat inhibits intestinal lipase activity and partially reduces intestinal absorption of triglyceride and cholesterol. Pediatric studies of orlistat have yielded mean reductions in BMI of 0.55 to 6.0 kg/m^2, side effects in 50–100% of subjects, and attrition rates as high as 33%. The typical side effects reflect fat malabsorption (e.g., oily stools, flatus with discharge, diarrhea, fecal incontinence, and abdominal cramps) and improve with restriction of dietary fat.

Bariatric Surgery

Gastrointestinal surgery has been considered a reasonable option for adults with morbid obesity since its 1991 review by a National Institutes of Health Consensus Development Conference. Outcome studies in adults have demonstrated postoperative weight reductions of 25–35% and reversal of major comorbidities such as Type 2 DM, OSA, dyslipidemia, and hypertension.

The roux en Y gastric bypass procedure (GBP) is the gold standard procedure in adults, having been used for more than four decades. It is the only procedure in which safety and efficacy have been studied in adolescents. Refinements in technique have resulted in a minimally invasive (i.e., laparoscopic) approach in which a 30-ml gastric pouch is created just beyond the gastroesophageal junction. A 75- to 150-cm roux limb of jejunum is attached to the gastric pouch using a 1.0- to 1.5-cm anastomosis, which impairs rapid emptying of the pouch. Digestive secretions from the remnant stomach and duodenum merge with the roux limb downstream to allow emulsification and enzymatic degradation of macronutrients. Most patients consume 500–700 kilocalories (kcals) daily for 3 months postoperatively, increasing to 1000–1500 kcals daily by 1 year. Mortality associated with GBP in adults is 0.5–1.0%, and morbidity includes gastrointestinal leakage, pulmonary embolism, bowel obstruction, bleeding, and micronutrient deficiencies. Long-term follow-up has revealed late weight gain in up to 15% of patients.

A second bariatric procedure, adjustable gastric banding (AGB), was approved by the FDA in 2001 for use in adults. It involves the laparoscopic placement of a prosthetic band around the proximal stomach, resulting in a small gastric pouch above the band and considerable restriction of food intake. The inner diameter of the band can be adjusted by instilling saline into a subcutaneous port. Advantages of AGB over GBP are its lower mortality rate of 0.05% and its reversibility. However, AGB carries additional risks, such as gastric erosion at the band site, gastric obstruction caused by band displacement, and complications at the subcutaneous port site.

Bariatric surgery is now considered a therapeutic option for adolescents with morbid obesity who have documentation of concerted efforts to lose weight, comorbid conditions, and family agreement about the procedure. For adolescents with BMI levels of 40–50 kg/m^2, surgery usually is not performed unless there is a severe comorbid condition such as Type 2 DM, OSA, or pseudotumor cerebri. For adolescents with BMI levels > 50 kg/m^2, surgery should be considered even if the comorbid conditions are less severe. Examples include hypertension, dyslipidemia, metabolic syndrome, polycystic ovary syndrome, stress urinary incontinence, significant impairment in activities of daily living, steatohepatitis, arthropathies in weight-bearing joints, gastroesophageal reflux disease, and significant psychosocial distress.

An adolescent who is a candidate for bariatric surgery should be referred to a specialized center with a multidisciplinary bariatric team that is capable of evaluating and managing the medical and psychological problems that commonly arise in the perioperative period. In addition, the team should provide the long-term follow-up required for both management and research purposes. The core team includes experts in surgery, pediatrics and/or internal medicine, psychology, nutrition, and exercise physiology. Consultants should be available in adolescent medicine, endocrinology, pulmonology, gastroenterology, cardiology, orthopedics, and ethics. Finally, institutional capabilities to manage morbidly obese patients must be considered, such as adequate hospital beds and radiology equipment.

A review of 65 adolescents with preoperative BMI ranging from 43–96 kg/m^2 who underwent laparoscopic GPB lost an average 2.5 kg per week over the first 6 months, after which the rate decreased. Mean weight loss was 25% at 6 months and 35% at 1 year. Body fat fell from 47% preoperatively to 36% at 1 year. Although some patients continued to lose weight up to 18 months after surgery, in most the BMI stabilized by 1 year. Baseline and 1-year laboratory results demonstrated significant decreases in serum triglycerides, total cholesterol, glucose, and fasting insulin (Table 11-2).

Preoperative polysomnographic data revealed that 19 of 34 (55%) patients had OSA by strict diagnostic criteria. Postoperatively, after a mean weight loss of 58 kg, the mean index of severity decreased 10-fold, essentially eliminating the problem.

Table 11-2 Mean Levels of Glucose, Insulin, Total Cholesterol, and Triglycerides for Adolescents with Morbid Obesity Before and 1 Year After Bariatric Surgery

	Baseline		1 Year		*p*[1]
	N[2]	Level	N[2]	Level	
Glucose (mg/dl)	22	104	24	84	0.0010
Insulin (μU/ml)	20	56	25	10	0.0044
Total cholesterol	21	170	23	151	0.0001
Triglycerides (mg/dl)	21	155	22	86	0.0003

[1]Probability value was calculated using the two-tailed Student's *t*-test for paired data.
[2]Number of patients for whom data was available at baseline and 1 year.

MAJOR POINTS

- The prevalence and severity of obesity among children and adolescents have increased dramatically in the last two decades. Prevention efforts have been ineffective thus far, and most obese children and adolescents are now developing medical and psychosocial comorbidities.
- CDC-defined weight categories differ for children and adolescents as compared with adults. The pediatric definitions are based on BMI percentile adjusted for age and gender, whereas the adult definitions are based on BMI. The pediatric categories are "at risk for overweight" and "overweight," whereas the adult categories are "overweight" and "obese."
- Severe complications of obesity seen during childhood and adolescence include Type 2 diabetes mellitus, obstructive sleep apnea, steatohepatitis, and pseudotumor cerebri. Other complications include insulin resistance, hypertension, dyslipidemia, and psychosocial problems.
- The evaluation of overweight and obesity during childhood and adolescence has two goals: the identification of conditions that contribute to obesity (e.g., hypothyroidism, family history of obesity, sedentary lifestyle, high-caloric diet) and the identification of conditions exacerbated by obesity (e.g., Type 2 diabetes mellitus, hypertension, steatohepatitis).
- Management begins with behavior modification of dietary intake and physical activity. Family involvement in the treatment program increases the likelihood of short- and long-term success.
- The FDA has approved the use of sibutramine and orlistat for the treatment of adolescent obesity. However, side effects have resulted in limited use and high rates of discontinuation.
- Since the early 1990s, bariatric surgery has been increasingly used for the management of morbid obesity in adults. Preliminary results from specialized centers indicate that surgery may provide an effective therapeutic option for adolescents with morbid obesity complicated by comorbid conditions.

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CHAPTER 12

Hypertension

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the United States, and its prevalence is increasing dramatically in countries undergoing transition to a more Westernized lifestyle. The dietary and exercise patterns of this lifestyle begin in childhood and contribute heavily to the development of cardiovascular risk factors such as obesity and dyslipidemia. Obesity is associated with hypertension, and the obesity epidemic among U.S. children and adolescents is driving the upward trend in the rates of pediatric hypertension.

This chapter reviews the definition, epidemiology, pathophysiology, evaluation, and management of adolescent hypertension. The recommendations discussed adhere closely to the *Fourth Report on Children and Adolescents of the National High Blood Pressure Education Program Working Group* (NHBPEP IV) and the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC VII).

DEFINITIONS

NHBPEP IV updates the 1987 definitions of hypertension (HTN) in children and adolescents. Unlike the adult definitions, which reflect the blood pressure (BP) levels at which treatment alters outcome, the pediatric definitions reflect the normative distribution of BP levels in the population. In normal children and adolescents, growth is associated with annual increases of 1.5 mmHg in the systolic BP and 0.7 mmHg in the diastolic BP (Figure 12-1). Rather than defining the range of normal by absolute BP, which increases with growth, NHBPEP IV definitions are based on the BP percentile, adjusted for age, gender, and height. Because an individual's BP tends to track along a given percentile with growth, the percentile can help predict the likelihood of HTN during adulthood (Tables 12-1 and 12-2). For example, in the Bogalusa Heart Study, children with BP levels > 80th percentile were 3.6 times more likely than those with BP levels < 80th percentile to have diagnoses of HTN 15 years later.

NHBPEP IV recommends the measurement of BP on three separate occasions before establishing a diagnosis of HTN. ***Normal*** is defined as BP readings < 90th percentile. ***Pre-HTN*** is defined as BP readings ≥ 90th percentile but < 95th percentile for age, gender, and height. For adolescents > 12 years and adults, this corresponds to BP readings ≥ 120/80 mmHg but < 95th percentile (Table 12-3). ***Stage 1 HTN*** is defined as BP readings ≥ 95th percentile but ≥ (99th percentile + 5 mmHg). ***Stage 2 HTN*** is BP readings > (99th percentile + 5 mmHg) and is intended to identify those patients who need prompt evaluation and treatment. The 5 mmHg addition widens the Stage 1 range from the 7-mm distance between the 95th and 99th percentiles to 12, thus allowing for more biological variability across measurements. It is important to note that the definitions of Stages 1 and 2 apply to chronic, not acute, HTN. The slower development of chronic HTN

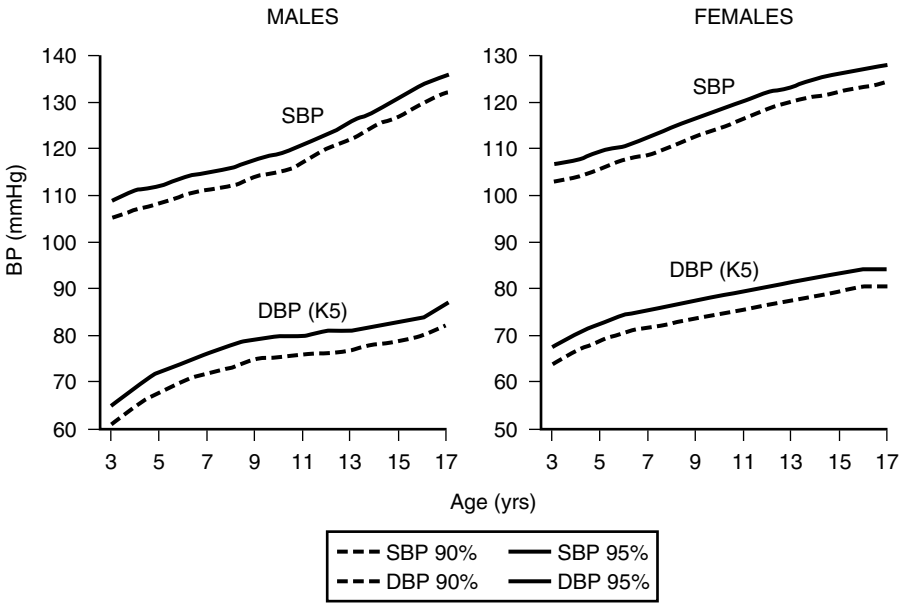

Figure 12-1 Blood pressure by age for children of average height.

results in arterial hypertrophy, which blunts the pressure effect on capillaries. Consequently, BP elevations that are considered moderate in chronic HTN may have severe consequences in acute HTN.

White-coat HTN is defined as office BP readings ≥ 95th percentile in the context of normal readings outside the office. Studies utilizing ambulatory BP monitoring (see later) suggest that up to 25% of adults and 35% of children diagnosed with HTN have white-coat HTN. Although these patients may be at increased risk for the subsequent development of sustained HTN, their risk of adult CVD is low so long as readings outside the office remain normal.

EPIDEMIOLOGY

The prevalence of HTN among school-aged children and adolescents in the United States has increased from approximately 1% in 1989 to 4.5% in 2002. In pre-pubertal children, 80–98% of HTN is secondary, or attributable to an identifiable cause. By mid-adolescence, however, at least 75% of new-onset HTN is essential, or without an identifiable cause. Essential HTN demonstrates strong, independent associations with obesity, sedentary lifestyle, high salt intake, family history of HTN, and race/ethnicity. Obesity increases the likelihood of HTN three-fold, hastens the development of left ventricular hypertrophy (LVH), and increases the risk of insulin resistance and hyperlipidemia. The adolescent and adult rates of essential HTN are significantly higher among African-Americans than either whites or Mexican-Americans, and the adult rate of hypertensive end-organ disease is highest among African-Americans.

PATHOPHYSIOLOGY

HTN during childhood and adolescence is associated with the early development of atherosclerosis, LVH, and microvascular changes in the eye and kidney. Autopsy studies of adolescents who died of causes unrelated to CVD have revealed strong associations of antemortem BP with postmortem atherosclerosis, and noninvasive vascular studies in adolescents have demonstrated an association of BP with atherosclerotic indicators such as arterial stiffness, calcification, and intimal-medial thickness. Although 40% of adolescents with HTN demonstrate concentric LVH, which is an important predictor of CVD, adult studies demonstrate regression of LVH with BP control. Hypertensive microvascular damage to the kidney can begin in childhood but usually does not cause microalbuminuria until adulthood. When microalbuminuria does present in childhood, it is an ominous marker for the early progression of CVD. However, as with LVH, adult studies have demonstrated resolution of microalbuminuria with good BP control.

The differential diagnosis of adolescent HTN is summarized in Table 12-4. Although essential HTN leads the list, it remains a diagnosis of exclusion. Factors that increase the likelihood of secondary HTN include prepubertal status, BP readings ≥ (99th percentile + 5 mmHg), negative family history of HTN, and thin body habitus. The most common causes of secondary HTN during

Text continued on p. 76

Table 12-1 Average Systolic and Diastolic BP Levels in Adolescent Males for the 50th, 90th, 95th, and 99th BP Percentiles Adjusted for Age and Height Percentile

Age (yrs)	BP Percentile	Systolic BP (mmHg) Height Percentile							Diastolic BP (mmHg) Height Percentile						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

Table 12-2 Average Systolic and Diastolic BP Levels in Adolescent Females for the 50th, 90th, 95th, and 99th BP Percentiles Adjusted for Age and Height Percentiles

Age (yrs)	BP Percentile	Systolic BP (mmHg) Height Percentile							Diastolic BP (mmHg) Height Percentile						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

Table 12-3 Fourth Report Definitions of Pre-Hypertension, Stage 1 Hypertension, and Stage 2 Hypertension in Children and Adolescents[1]

	Lower Limit	Upper Limit
Pre-Hypertension	≥ 90th percentile	< 95th percentile
Stage 1 Hypertension	≥ 95th percentile	< (99th percentile + 5 mmHg)
Stage 2 Hypertension	BP ≥ (99th percentile + 5 mmHg)	

[1]The lower and upper limits are the BP percentile adjusted for age, gender, and height.

Table 12-4 Causes and Associated Physical Findings of Secondary HTN in Children and Adolescents

Organ System	Condition	Physical Findings
Renal	Chronic renal failure	Growth retardation
	Renal artery stenosis	Epigastric/flank bruit
	Polycystic kidney disease	Palpable kidneys
	Hydronephrosis	
	Multicystic dysplastic kidney	
Cardiac	Coarctation of the aorta	Heart murmur, decreased lower extremity pulses; BP drop from upper to lower extremities
	Williams syndrome	Elfin facies
	Turner syndrome	Webbed neck, widely spaced nipples
Endocrine	Hyperthyroidism	Tachycardia, thyromegaly
	Pheochromocytoma	Pallor, flushing, diaphoresis, tachycardia
	Cushing syndrome	Truncal obesity, moon facies, acne, hirsutism, striae
	Type 2 diabetes mellitus	Acanthosis nigricans, truncal obesity
	Congenital adrenal hyperplasia	Ambiguous genitalia, virilization
	Hyperaldosteronism	Muscle weakness
	Liddle syndrome	
Immunological	Systemic lupus erythematosus	Malar rash, arthritis, mental status change
Neurological	Neuroblastoma	Tachycardia, café-au-lait spots
	Tuberous sclerosis	Adenoma sebaceum
Oncological	Wilms tumor	Mass

adolescence are exogenous (e.g., stimulant medications, substance use, hormonal contraception); renal scarring following childhood reflux nephropathy; and endocrine (e.g., hyperthyroidism). Within the renal category, renal artery stenosis is both more common and more correctable in adolescents than adults. The pathology in adolescents is fibromuscular dysplasia, in contrast to the atherosclerotic intimal hyperplasia of adults. Rare causes of secondary HTN in adolescents include pheochromocytoma, coarctation of the aorta that was not detected in childhood, neurofibromatosis, glucocorticoid-remediable hyperaldosteronism, and 17-alpha-hydroxylase deficiency. Other forms of congenital adrenal hyperplasia (CAH) that are associated with HTN present early in life, and the most common form that presents during adolescence (i.e., partial-21-hydroxylase deficiency) does not cause HTN.

EVALUATION

The evaluation of an adolescent with hypertension has four goals: confirmation of the diagnosis; identification of secondary causes; identification of other risk factors for CVD; and determination of treatment.

BP Measurement

Instruments and techniques have direct effects on the accuracy of BP measurements. Mercury sphygmomanometers are the most accurate instruments, but their use is decreasing due to concerns about release of mercury into the environment. Aneroid manometers are the recommended alternative but must be recalibrated at least twice yearly.

Oscillometric instruments are used when frequent BP readings are required or auscultation is difficult. Although more convenient than manometry, oscillometric measurements are approximately 10 mmHg higher and vary more across instruments than do manometric measurements. An oscillometric reading ≥ 90th percentile therefore should be rechecked by auscultation and manometry.

Manometry, regardless of type, requires the use of a cuff that is sized appropriately. A cuff that is too small may yield a measurement that is falsely high, whereas a cuff that is too wide may yield a measurement that is falsely low. The width of the cuff bladder should equal approximately 40% of the mid-upper-arm circumference, and the bladder should encircle at least 80% of the limb circumference. Table 12-5 lists the recommended cuff bladder dimensions for children and adults.

NHBPEP IV recommends the annual measurement of BP after the adolescent has been seated quietly for at least 5 minutes. The right arm should be positioned at heart level, and the stethoscope should be placed over the brachial artery pulse. The cuff should be inflated to a pressure 20–30 mmHg above systolic and then deflated at a rate of 2–3 mmHg per heartbeat. The pressure at which the pulse is first heard (i.e., Korotkoff Phase I) is the systolic BP. The pressure at which the pulse disappears (i.e., Korotkoff Phase V) is the diastolic BP. The measurement should be repeated at 1- to 2-minute intervals until two consecutive measurements differ by no more than 5 mmHg.

History, Physical Examination, and Laboratory Studies

The history should focus on the following: adolescent use of medications or illicit drugs associated with hypertension (e.g., stimulant therapy for attention deficit hyperactivity disorder, appetite suppressants, anabolic steroids); adolescent use of tobacco or alcohol; adolescent snoring or disordered sleep; adolescent diet and activity; and family history of HTN, CVD, and risk factors for CVD. The physical examination should include body mass index (BMI), heart rate, skin examination for café-au-lait spots, neurofibromas, or other systemic disease; fundoscopic examination; thyroid examination; cardiac examination for murmur, pre-systolic heave, and S4; peripheral vascular examination for abdominal bruit and absent femoral pulses; abdominal examination for palpable kidneys; and genital examination for findings of CAH or other conditions associated with genital and renal anomalies.

The standard laboratory evaluation of an adolescent with HTN includes measurement of serum electrolytes, blood urea nitrogen (BUN), creatinine, complete blood count, and thyroid studies; urinalysis; renal ultrasound; and echocardiogram to assess left ventricular mass. In the adolescent with obesity or a family history of early CVD, fasting plasma glucose, insulin, and lipids should also be obtained. Most adolescents will fit the characteristics of essential HTN and will require no additional diagnostic evaluation.

Table 12-5 Recommended Dimensions of BP Cuff Bladders for Children and Adolescents

		BP Cuff Bladder	
	Limb Maximum Circumference (cm)	Width (cm)	Length (cm)
Child arm	21	9	18
Small adult arm	26	10	24
Medium adult arm	34	13	30
Large adult arm	44	16	38
Adult thigh	52	20	42

MANAGEMENT

The management of Pre-HTN and HTN in children and adolescents is summarized in Figure 12-2. As noted in the algorithm, behavioral interventions to reduce the BP should precede initiation of antihypertensive medications and continue during their administration and/or taper.

Nonpharmacological Therapy

Prior to the initiation of pharmacotherapy, NHBPEP IV recommends the following lifestyle modifications for adolescents with Pre-HTN and Stage 1 HTN:

- Attainment and maintenance of a normal weight for height. In overweight children and adults, weight loss reduces systolic pressure, particularly when it is in response to a program of combined diet and aerobic exercise.
- Aerobic exercise 30–60 minutes daily. Of note, isometric exercise such as weightlifting can raise BP acutely and should be avoided until good control is achieved.
- Sedentary activity for no more than 2 hours daily.
- Restriction of daily salt intake to 3.8 gm, which corresponds to a daily sodium intake of 1.5 gm. Although the data are limited in adolescents, salt restriction in normal-weight adults with HTN has been shown to decrease BP.

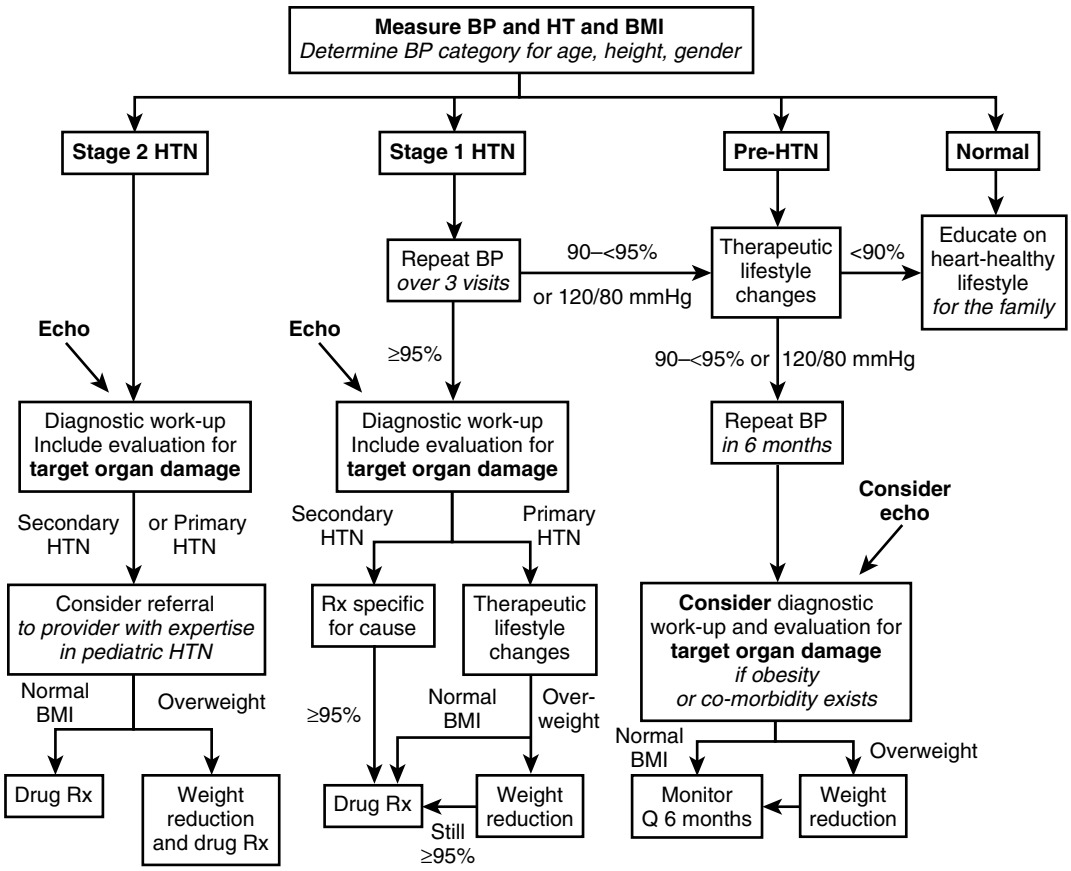

Figure 12-2 Algorithm for the treatment of HTN in children and adolescents.

- Avoidance of tobacco and alcohol. Compared with nondrinkers, adults who have more than two drinks daily are at least 1.5 times more likely to develop HTN, and the risk appears to be dose-dependent. Although chronic smoking does not increase BP, it does increase the risk of CVD.

In addition to these lifestyle changes, medications that can increase BP should be discontinued or avoided until good control is established. Although low-dose oral contraceptives are unlikely to cause HTN, they can make the nonpharmacological control of BP more difficult.

Pharmacotherapy

Antihypertensive drug therapy has not been shown to improve long-term outcome in children and adolescents with essential HTN. NHBPEP IV therefore limits its recommendations for drug therapy to children and adolescents with one or more of the following:

- Symptomatic HTN
- Stage 1 HTN in the setting of diabetes mellitus and/or other risks for CVD
- Stage 2 HTN unresponsive to nonpharmacological therapy
- HTN associated with target-organ damage (e.g., LVH, hypertensive retinopathy, microalbuminuria)

Table 12-6 summarizes the NHBPEP IV recommendations for the dosing of anti-hypertensive medications in children and adolescents, based on the available pediatric data. Because few comparative drug trials have been conducted in children, NHBPEP IV does not make specific recommendations about initial drug choice. The major drug classes used in adolescents are the following:

Thiazide diuretics in low dose (e.g., hydrochlorthiazide 12.5–25 mg daily) are unlikely to cause side effects, are as effective as high dose in reducing BP, and are considered first-line pharmacotherapy for essential HTN in adults.

Angiotensin-converting enzyme (ACE) inhibitors (i.e., enalapril) and ***angiotensin-receptor blockers*** (i.e., irbesartan, and losartan) have been approved by the FDA for the treatment of HTN in children and adolescents. These drug classes also have been shown to slow the progression of nephropathy in children and adults with Type 1 diabetes mellitus. Their use is contraindicated

Table 12-6 Anti-Hypertensive Medications with Pediatric Dosing Recommendations

Class	Drug	Initial Dose (mg/kg/day)	Maximum Daily Dose (mg/kg/day)	Dosing Interval	Evidence[1]
α agonist	Clonidine[2]	0.1 (max 0.2 mg/day)	2.4 mg/day	BID	EO
α blocker	Doxazosin	1 mg/day	4 mg/day	QD	EO
	Prazosin	0.05–0.1	0.5	TID	EO
	Terazosin	1 mg/day	20 mg/day	QD	EO
α/β blocker	Labetalol	1–3	10–12 (max 1200 mg/day)	BID	CS, EO
ACE inhibitor	Benazepril	0.2 (max 10 mg/day)	0.6 (max 40 mg/day)	QD	RCT
	Captopril	0.3–0.5	6	TID	RCT, CS
	Enalapril	0.08 (max 5 mg/day)	0.6 (max 40 mg/day)	QD–BID	RCT
	Fosinopril[3]	5–10 mg/day	40 mg/day	QD	RCT
	Lisinopril	0.07 (max 5 mg/day)	0.6 (max 40 mg/day)	QD	RCT
	Quinapril	5–10 mg/day	80 mg/day	QD	RCT, EO
Angiotensin-receptor blocker	Irbesartan	6–12 years: 75–150 mg/day	≥ 13 years: 150–300 mg/day	QD	CS
	Losartan	0.7 (max 50 mg/day)	1.4 (max 100 mg/day)	QD	RCT
β blocker	Atenolol	0.5–1	2 (max 100 mg/day)	QD–BID	CS
	Bisoprolol/HCTZ	2.5/6.25 mg/day	10/6.5 mg/day	QD	RCT
	Metoprolol	1–2	6 (max 640 mg/day)	BID	CS
	Propranolol	1–2	4 (max 640 mg/day)	BID–TID	RCT, EO
Calcium antagonist	Amlodipine[4]	2.5 mg/day	5 mg/day	QD	RCT
	Felodipine	2.5 mg/day	10 mg/day	QD	RCT, EO
	Isradipine	0.15	0.8 (max 20 mg/day)	TID–QID	CS, EO
	Nifedipine extended release	0.25–0.5	3 (max 120 mg/day)	QD–BID	CS, EO
Diuretics	Amiloride	0.4–0.625	20 mg/day	QD	EO
	Hydrochlorothiazide	1	3 (max 50 mg/day)	QD	EO
	Chlorthalidone	0.3	2 (max 50 mg/day)	QD	EO
	Furosemide	0.5–2 mg/kg/dose	6	QD–BID	EO
	Spironolactone	1	3.3 (max 100 mg/day)	QD–BID	EO
	Triamterene	1–2	3–4 (max 300 mg/day)	BID	EO
Vasodilator	Hydralazine	0.75	7.5 (max 200 mg/day)	QID	EO
	Minoxidil (< 12 years)	0.2	50 mg/day	QD–TID	CS, EO
	Minoxidil (≥ 12 years)	5 mg/day	100 mg/day	QD–TID	CS, EO

[1]CS, case series; EO, expert opinion; RCT, randomized controlled trial.

[2]Children ≥ 12 years.

[3]For Children > 50 kg.

[4]Children 6–17 years.

in pregnancy and should be avoided in adolescent females who are at risk for pregnancy.

Beta blockers have a long history of use in children and adolescents and are effective anti-hypertensive agents. However, they are contraindicated in patients with asthma, should be avoided in patients with diabetes mellitus, and are associated with troubling side effects such as fatigue and depressive symptoms.

Calcium channel blockers are effective and safe in the treatment of pediatric HTN but have been used less commonly in children and adolescents than the other drug classes.

In patients without target-organ damage, the goal of treatment is to maintain systolic and diastolic pressures levels below the 95th percentile for gender, age, and height. In patients with target-organ damage (i.e., LVH, nephropathy, retinopathy) or another risk factor for CVD (i.e., obesity, diabetes mellitus, dyslipidemia), the pressures should be below the 90th percentile for gender, age, and height. There are little data to support decisions regarding the duration of therapy in adolescents. Given the recommendation to use the lowest dose possible, gradual taper seems warranted if the BP has been well controlled and there is no target-organ damage. Regular BP checks and counseling about diet and exercise should continue during and after the taper.

MAJOR POINTS

- A diagnosis of HTN depends on the measurement of BP on three separate occasions. Normal is an average BP < 90th percentile for age, gender, and height. Pre-HTN is ≥ 90th but < 95th percentile. Stage 1 HTN is ≥ 95th but < (99th percentile + 5 mmHg). Stage 2 HTN is ≥ (99th percentile + 5 mmHg).
- White-coat HTN is office BP readings > 95th percentile with normal readings outside the office.
- By mid-adolescence, at least 75% of new-onset HTN is essential HTN. Factors that increase the likelihood of secondary HTN include pre-pubertal status, Stage 2 HTN, negative family history of HTN, and thin body habitus.
- BP should be measured at least annually in adolescents by auscultation and manometry.
- The standard laboratory evaluation of an adolescent with HTN includes serum electrolytes, BUN, creatinine, complete blood count, and thyroid function studies; urinalysis; renal ultrasound; and echocardiogram.
- Treatment of HTN begins with lifestyle changes, including attainment of normal body weight, restriction of salt intake, and daily exercise.
- Thiazide diuretics are first-line pharmacotherapy for essential HTN.

Severe, symptomatic HTN does occur in children and adolescents, particularly in the setting of renal disease, but it is far more common in adults. In the absence of hypertensive encephalopathy, prompt treatment with oral agents often yields good control of the BP and resolution of headache without the need for hospitalization. However, patients with signs of hypertensive encephalopathy (e.g., seizures, mental status change, neurological findings) must be treated in the hospital with intravenous anti-hypertensive agents that allow controlled reduction in BP by 25% over the first 8 hours followed by gradual normalization over the subsequent 24–48 hours.

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CHAPTER 13

Diabetes Mellitus

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INTRODUCTION

Diabetes mellitus (DM) comprises a group of disorders characterized by hyperglycemia. It is the sixth leading cause of death in the United States and results in $132 billion in total direct and indirect costs. Although the incidence of Type 1 diabetes has doubled over the past 30 years, the increase in Type 2 diabetes has been even more dramatic. An estimated 20–40% of cases in large pediatric diabetes centers are now Type 2, and the rates are expected to rise along with the epidemic of childhood and adolescent obesity (Chapter 11).

This chapter reviews the clinical characteristics and management of diabetes during adolescence. It emphasizes strategies for early detection, intensive treatment, and prevention of end-organ disease.

DEFINITIONS

Diabetic ketoacidosis (DKA) is a state of absolute or relative insulin deficiency characterized by dehydration, blood glucose > 300 mg/dl, serum bicarbonate < 15 mEq/L, serum pH < 7.30, ketonemia, and ketonuria.

Insulin resistance is a state of hyperinsulinemia with or without hyperglycemia in which the glucose response to a given amount of insulin is subnormal.

Macrovascular complications of diabetes include coronary heart disease and cerebrovascular disease.

Maturity-onset diabetes of youth (MODY) is a rare, autosomal dominant condition associated with the insidious onset of impaired insulin secretion in the absence of insulin resistance.

Microvascular complications of diabetes include retinopathy, nephropathy, and neuropathy.

Type 1 diabetes mellitus (T1DM) is a state of hyperglycemia and hypoinsulinemia resulting from destruction of the pancreatic beta cells.

Type 2 diabetes mellitus (T2DM) is a state of hyperglycemia and hyperinsulinemia resulting from insulin resistance.

EPIDEMIOLOGY

Diabetes affects an estimated 171 million people worldwide and 18.2 million in the United States, with projections of 366 million and 30.3 million, respectively, by the year 2030. In the United States alone, nearly 30% of

individuals with DM remain undiagnosed, untreated, and at significant risk for microvascular disease.

T1DM affects 1.7 per 1000 children in the United States. Over the past 30 years, the incidence has doubled and the mean age at diagnosis has decreased. The prevalence increases with distance from the equator, and the incidence fluctuates with season. Although the cause is thought to be primarily autoimmune, clusters resembling infectious outbreaks have been reported and the usual female predominance seen in autoimmunity is absent.

The prevalence of T2DM among adolescents has increased dramatically in recent years, along with the prevalence of obesity. It is more common among females than males and among under-represented minorities than whites. Native Americans are at particularly high risk for T2DM.

PATHOPHYSIOLOGY

T1DM involves a multifactorial interaction of genetic and environmental factors leading to autoimmune destruction of the pancreatic beta cells. Two regions in the human genome have been associated with disease transference. One region is located on chromosome 6p21 within the major histocompatibility complex. The other is located on chromosome 11p15 within the insulin gene. However, 85% of individuals with diagnosed T1DM have no family history of the disease and, even among those who are genetically predisposed, some do not progress to overt disease.

Environmental factors have been suggested as a cofactor in the pathogenesis of T1DM. For example, the "hygiene hypothesis" postulates that improved living conditions over the past century have resulted in decreased exposure to infection, impaired immunity, and increased susceptibility to atopic and autoimmune diseases. At diagnosis, 85–90% of patients with T1DM have at least one of the three autoantibodies associated with beta cell destruction: insulin antibody, anti-GAD-65, and/or islet cell antibody. Although a 40% decrease in beta cell mass is associated with detectable insulin deficiency, most patients do not reach medical attention until the beta cell mass decreases by 80–90% and insulin secretion is minimal.

The absence of insulin in TIDM impairs the cellular uptake of glucose, which in turn stimulates the secretion of counter-regulatory hormones that promote gluconeogenesis and the breakdown of triglycerides to free fatty acids. Beta oxidation of the free fatty acids produces the ketone bodies beta-hydroxybutyrate, acetoacetate, and acetone. When the blood glucose level exceeds the renal threshold of approximately 180 mg/dl, an osmotic diuresis results, with spillage of glucose, free water, and electrolytes into the urine. The patient develops the characteristic symptoms of weight loss, polyuria, polyphagia, and polydipsia. The early weight loss of DM reflects fluid loss, whereas the later weight loss reflects the catabolism of fat and muscle for the production of ketones and glucose. The excess ketones impair intra- and extra-cellular buffering mechanisms, resulting in metabolic acidosis and, if prolonged, DKA. Approximately one-third of adolescents with newly diagnosed T1DM present with DKA.

T2DM is also multifactorial, but the risk factors for disease development and the pathogenesis are different from those of T1DM. Family history is more likely to be positive in T2DM, with a 40% lifetime risk of disease if one parent is affected and a 70% risk if both parents are affected. Insulin resistance, the hallmark of T2DM, is strongly associated with obesity, which affects 80% of individuals diagnosed with T2DM. The postulated mechanism underlying the T2DM–obesity association involves fat cell accumulation of non-esterified fatty acids, glycerol, and cytokines. As these products are released into the circulation, they disrupt the normal insulin-signaling cascade mediated by tyrosine kinase, resulting in insulin resistance.

The normal action of insulin is to suppress gluconeogenesis, suppress lipolysis, and enhance glucose metabolism. Resistance to insulin results in postprandial followed by fasting hyperglycemia and increased lipolysis. The pancreatic beta cells respond by increasing insulin production, resulting in hyperinsulinemia. Initially, the beta cells can produce enough insulin to counterbalance the peripheral resistance and maintain blood glucose within the normal range. However, the rising blood glucose eventually causes oxidative damage within the pancreatic beta cells and impaired insulin production.

EVALUATION

Screening and Diagnosis

Universal screening for diabetes is not recommended. However, selected screening with random or fasting plasma glucose levels at 2-year intervals is recommended at age 10 years or the onset of puberty, whichever is earlier, for individuals who are overweight or obese and have at least two additional risk factors for T2DM. Box 13-1 lists the weight cut-points and the other risk factors that warrant screening.

The 2003 report of the Expert Committee of the American Diabetes Association (ADA) provides diagnostic guidelines for diabetes (Table 13-1) based on the fasting plasma glucose (FPG), random plasma glucose, and oral glucose tolerance test (OGTT). The patient who has a random plasma glucose = 200 mg/dl with symptoms or the patient who has an FPG = 126 mg/dl meets criteria and needs no further testing to establish the diagnosis. The asymptomatic patient who has a random plasma glucose = 200 mg/dl should have an FPG performed 8 hours after

Box 13-1 Criteria for T2DM Screening

RPG or FPG should be measured every 2 years beginning at age 10 years or the onset of puberty, whichever is earlier, if the patient has at least one of the following:

- BMI > 85th percentile for age and sex
- Weight for height > 85th percentile
- Weight > 120% of ideal weight for height

and at least two of the following:

- T2DM in a first- or second-degree family member
- Native American, African-American, Latino, Asian-American, or Pacific Islander race/ethnicity
- Signs of insulin resistance or conditions related to insulin resistance such as acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome

Table 13-1 ADA Definitions of Pre-Diabetes and Diabetes

	Pre-Diabetes	Diabetes
Random plasma glucose (mg/dl)		≥ 200 with symptoms
Fasting plasma glucose (mg/dl)	100–125	≥ 126
OGTT 2-hour plasma glucose (mg/dl)	140–199	≥ 200

last caloric intake or a plasma glucose performed 2 hours after consuming 75 grams of anhydrous glucose dissolved in water during an OGTT.

Pre-diabetes is defined as an impaired FPG of 100–125 mg/dl or an impaired glucose tolerance (IGT) at 2 hours of 140–199 mg/dl. The patient with pre-diabetes should be retested at 3 months.

T1DM vs. T2DM

The differentiation of T1DM and T2DM is an important goal of the initial evaluation because the diagnosis guides management decisions. In most cases, the correct diagnosis is apparent from the clinical presentation. Patients with T1DM are more likely to be thin and to present with the classic symptoms of diabetes, ketonemia, and ketonuria. In contrast, adolescents with T2DM usually have no evidence of ketone production and rarely present with DKA. They are more likely than adolescents with T1DM to be overweight or obese, to have acanthosis nigricans, and to have a strong family history of diabetes.

In equivocal cases, such as adolescents with obesity and ketonemia, laboratory evaluation can help differentiate T1DM and T2DM. The presence of islet cell antibody, insulin antibody, or GAD65 antibody and a low or undetectable level of plasma C-peptide level suggest T1DM. In T2DM, the level of C-peptide usually is normal or elevated.

Regardless of the type of diabetes, the patient who is symptomatic, ketotic, or has a glucose greater than 250 mg/dl requires insulin therapy. The initial use of insulin in a new-onset diabetes patient does not commit the clinician to extended use if subsequently the diagnosis suggests T2DM or MODY.

MANAGEMENT OF T1DM

Early education is a critical component of diabetes management. It must be adapted to the adolescent's cognitive maturity and should involve all potential caregivers. Discussion and teaching materials should address the causes and consequences of the type of diabetes affecting the patient, the dosing and administration of insulin and/or other medications, the importance of diet to glucose control, blood glucose testing, the symptoms and management of hypoglycemia, and "sick-day" insulin adjustment. An experienced dietitian should assist with a nutritive dietary plan that meets the individual adolescent's metabolic needs. All patients should be taught carbohydrate counting, and those with T2DM should be taught to limit and distribute carbohydrate intake throughout the day as part of a weight reduction dietary and exercise plan.

One of the first decisions following diagnosis is about inpatient versus outpatient management. The decision rests on many factors in addition to illness severity, including the comfort and collaboration of the patient, family, and clinical team. The outpatient strategy requires a team of health care providers that can share the time-intensive responsibilities of patient and family education, as well as the telephone calls and frequent visits that accompany a new diagnosis. The diabetes team at a tertiary care pediatric center typically includes a diabetes physician, diabetes nurse practitioner/educator, registered dietician, and mental health professional (see Box 13-2).

Insulin

An early decision in the management of diabetes is whether to use insulin. Nearly all adolescents who present with DKA have T1DM and require insulin. Although T1DM may enter a honeymoon phase with diminished insulin requirements for up to 1 year, pancreatic beta cell destruction continues and insulin requirements ultimately increase. Conversely, patients with T2DM typically can be managed without insulin. However, intensive short-term insulin therapy beginning at diagnosis of

Box 13-2 Diabetes Outpatient Evaluation

- History
  - Review of diabetes regimen and side effects
  - Diabetes complications (e.g. DKA, hypoglycemia)
  - Diet and exercise adherence
  - New medical conditions and medications
  - Review of annual dilated eye examination findings
  - New family history
  - Social, sexual, and menstrual history
  - Diabetes review of systems (polyuria, nocturia, hypoglycemia, weight loss, nausea, abdominal pain, vision changes, hand or foot pain, constipation)
  - Review blood glucose records
- Physical Examination
  - Vital signs
    - Blood pressure (using appropriate size cuff)
    - Height, weight, and BMI
  - General appearance and hygiene
  - Funduscopic examination
  - Thyroid palpation
  - Sexual maturity rating (annually)
  - Evaluation of pulses
  - Skin examination
    - Evidence of acne, hirsutism, or acanthosis nigricans (mainly T2DM patients)
    - Inspection of insulin injection sites for inflammation or hypertrophy
    - Inspection of fingers for evidence of blood glucose testing
    - Foot examination
  - Neurological examination
    - Sensation/monofilament testing
    - Lower extremity deep tendon reflexes
- Laboratory Evaluation
  - HbA1C (quarterly)
  - Recommended screening for complications
    - TSH (T1DM only): every 1–2 years
    - Urine microalbumin: annually
    - Fasting lipid profile: annually if LDL > 100 mg/dl, otherwise every 5 years

T2DM, particularly in patients with ketosis or blood glucose levels > 250 mg/dl, is associated with improved glycemic control 1 year later. Patients with T2DM presenting without symptoms or with blood glucose < 250 mg/dl can be managed with lifestyle modification and oral hypoglycemic medications as described below.

The various types of insulin differ in their time of onset, peak effect, and duration of action (Table 13-2). Conventional insulin therapy refers to regular and neutral protamine Hagedorn (NPH) insulin injected once or twice daily as a premixed or patient-mixed preparation. Intensive insulin therapy refers to more complex regimens in which intermediate- or long-acting insulin is given once or twice daily and rapid-acting insulin is given 15 minutes before or immediately after meals. Compared with regular insulin, lispro and aspart have a more rapid onset and shorter duration of action, allowing correction for preprandial glucose levels and coverage of consumed carbohydrates.

Treatment recommendations have called for tighter glycemic control since the Diabetes Control and Complications Trial (DCCT) demonstrated 50–76% reductions in microvascular complications with intensive compared with standard insulin therapy. Intensive therapy was defined as insulin by pump or multiple daily injections, with a target HbA1C < 6.0%. Standard therapy was defined as twice-daily insulin injections. Based on the DCCT findings, the ADA recommends preprandial blood glucose levels of 90–130 mg/dl and HbA1C levels of 7.0–7.5% for patients > 13 years with T1DM. The usual total daily dose (TDD) for new-onset diabetes is 0.3–0.7 units/kg/day. Adolescents who are thin and pre-pubertal may require less, whereas those who are heavier or at the peak of puberty may require 1.2–1.5 units/kg/day.

The TDD is divided into a basal dose (40–45%) to suppress gluconeogenesis and bolus doses (55–60%) with meals to correct preprandial hyperglycemia and to cover consumed carbohydrates. The basal/bolus regimen can be administered by multiple daily injections or by a continuous subcutaneous insulin infusion (CSII) pump that

Table 13-2 Characteristics of Human Insulin Preparations

Preparation	Action	Onset (hrs)	Peak (hrs)	Effective Duration (hrs)	Maximum Duration (hrs)
Lispro, Aspart	Rapid	0.25	1–2	2–3	4
Regular	Short	0.5–1.0	2–3	3–6	4–6
NPH	Intermediate	2–4	4–10	10–16	14–18
Detemir[1]	Long	1–2	8–11	12–20	14–22
Glargine	Long	2–4	None	20–24+	24–36

[1]Based on 0.2–0.4 U/kg dose range.

From Plank J, Bodenlenz M, Sinner F, et al.: A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. Diabetes Care 2005;28:1107–1112.

varies the basal rate over a 24-hour period. Both delivery systems, however, require patient determination of the bolus doses. Patients who are unable to manage the dosage adjustments can be managed with twice-daily injections of NPH mixed with sliding-scale regular insulin.

As shown in Table 13-3, the corrective portion of the bolus dose is equal to the difference between the actual and target blood glucose levels divided by a sensitivity factor that estimates the reduction in blood glucose induced by one unit of insulin. The sensitivity factor for rapid-acting insulin is approximately 1800/TDD. A typical target blood glucose level is 120 mg/dl, and a typical sensitivity factor is 50 mg/dl/unit. The food portion of the bolus dose is equal to the grams of carbohydrate consumed divided by a coverage factor that estimates the grams of carbohydrate covered by one unit of insulin. The coverage factor for rapid-acting insulin is approximately 500/TDD and typically ranges from 8–15 grams per unit of insulin.

Rapid growth, erratic eating, sports participation, and social pressure may complicate insulin management in the adolescent with diabetes. Some of the common problems that arise are discussed next.

Hypoglycemia

Hypoglycemia is an important complication of intensively managed T1DM. It is imperative that patients and families recognize and know how to treat it. The symptoms include diaphoresis, palpitations, tremulousness, hunger, pallor, drowsiness, confusion, aggressiveness, coma, and seizure. The conscious patient should consume 15 g of a rapidly absorbed carbohydrate (e.g., 3–4 glucose tablets) every 15–20 minutes until the blood glucose is greater than 80 mg/dl. Glucose tablets, hard candy, fruit juice, or other rapidly acting carbohydrate should always be available at home and school. The unconscious patient outside a health care setting should be given glucagon, 0.5–1.0 mg subcutaneously or intramuscularly. This will increase the blood glucose into a safe range but also causes severe nausea within 60–90 minutes that may require intravenous support. The patient within a health care setting should be given 50% dextrose, 25–50 g intravenously.

Table 13-3 Calculation of Insulin Total Daily Dose (TDD)

TDD	Basal dose + bolus doses
Bolus dose	Food dose + corrective dose
Food dose	Carbohydrate (500/TDD)
Corrective dose	(Actual blood glucose − target blood glucose) / (1800/TDD)

The risk of hypoglycemia is particularly high in the contexts of autonomic neuropathy, beta blocker therapy, excessive exercise, and eating disorders. Patients with autonomic neuropathy may lose the counter-regulatory response to hypoglycemia and, like those on beta blockers, may not manifest the symptoms of hypoglycemia until it is severe. Exercise, although recommended for all patients with diabetes, may deplete hepatic glycogen in T1DM. Blood glucose therefore should be monitored in athletes with T1DM before, every hour during, and immediately after exercise.

The optimal range for blood glucose during exercise is 150–250 mg/dl. Exercise should be avoided if the blood glucose is > 350 mg/dl or > 250 mg/dl with ketonuria. If the blood glucose is < 100 mg/dl, the adolescent should rest, consume an electrolyte sport drink containing 15 g carbohydrate, and recheck the blood glucose in 15 minutes. Athletes participating in strenuous or prolonged events typically require 15 g carbohydrate for every 30 minutes of exercise, and some may require a drop in the insulin dose before exercise. Most importantly, coaches must be aware of the adolescent's risk and must be educated about the signs and management of hypoglycemia.

Dawn and Somogyi Effects

The dawn and Somogyi effects both present as early morning hyperglycemia in patients on insulin. However, the two effects differ in their causes and treatment. The dawn effect is caused by the early morning release of cortisol, growth hormone, and catecholamines. It is managed by increasing the evening insulin dose and testing the blood glucose at 2:00 to 3:00 A.M. to avoid hypoglycemia. The Somogyi effect is rebound hyperglycemia secondary to early morning hypoglycemia. It is managed by reducing the evening insulin dose and testing the blood glucose at 2:00 to 3:00 A.M. to avoid hyperglycemia.

Sick-Day Insulin

Sick-day management is a standard component of patient and family education about diabetes. Sick days are times of physiological stress typically caused by infection, other illness, injury, and significant emotional distress. Corrective doses of rapid-acting insulin may be administered up to every 2–3 hours to control hyperglycemia. Blood glucose should be tested frequently and, if > 250 mg/dl, urine should be tested for ketones. Trace to moderate ketonuria should be treated orally with glucose-free liquids. Large ketonuria requires rapid-acting insulin in doses 10–20% greater than those given to reduce hyperglycemia. If vomiting or the underlying illness prevents oral hydration and/or glucose monitoring, the adolescent should be directed to seek medical attention.

New Therapies for T1DM

An inhaled insulin preparation with pharmacodynamics similar to rapid- and short-acting parenteral insulin is likely to be approved for use in adults with TIDM. Whole or segmental pancreas transplantation has demonstrated cure rates of 80–90% but involves major surgery and lifelong immunosuppression. Islet cell transplantation involves less risk due to its minimally invasive nature but appears less successful. Other attempts for a cure, such as beta cell regeneration and insulin gene therapy, are currently being explored.

MANAGEMENT OF T2DM

Lifestyle Modification

Weight reduction and exercise are the cornerstones of therapy for most patients with T2DM and pre-diabetes. Dietary fat and carbohydrates should comprise < 25% and 45–65% of total daily kilocalories (kcals), respectively, and total kcals should be adjusted to attain and/or maintain an ideal body weight for height. A low-carbohydrate diet (< 130 g/d) is not recommended for adolescents because of the risk of hypoglycemia. Exercise, at approximately 150 minutes weekly, is recommended because it increases calorie expenditure, facilitates glucose transport into skeletal muscle, and improves glycemic control.

The decrease in microvascular complications noted in the DCCT for T1DM was also noted in the United Kingdom Prospective Diabetes Study for T2DM. Consequently, the goals of treatment are the same as those noted above for T1DM. In general, T2DM patients with HbA1C levels > 8% after 3 months of lifestyle modification should progress to pharmacological therapy.

Table 13-4 Oral Hypoglycemic Agents

First-generation sulfonylureas	Acetohexamide
	Chlorpropamide
	Tolbutamide
Second-generation sulfonylureas	Glipizide
	Glyburide
	Glimepride
Biguanide	Metformin
Glucosidase inhibitors	Acarbose
	Miglitol
Thizolidinediones	Rosiglitazone
	Pioglitazone
Meglitinides	Repaglinide
	Nateglinide

Oral Pharmacotherapy

The classes of oral hypoglycemic agents and the drugs within each class are shown in Table 13-4. Metformin, a buiguanide, has been shown to be safe and effective for pediatric use and is considered first-line pharmacotherapy for adolescents with T2DM. In addition to increasing muscle sensitivity to insulin, metformin increases hepatic glucose production and reduces total and LDL cholesterol. Side effects are primarily gastrointestinal (e.g., nausea, diarrhea, abdominal pain) and usually resolve with continuation of therapy. Hypoglycemia is uncommon, and lactic acidosis is extremely rare. Metformin is begun at 500 mg once daily and is increased by 500 mg every 1–2 weeks to a maximum daily dose of 2500 mg. However, 80% of the hypoglycemic effect occurs at 1500 mg daily. Patients who remain hyperglycemic after 6–8 weeks at this dose should either start another oral hypoglycemic agent in addition to metformin or should be started on insulin and tapered off metformin.

Sulfonylureas and meglitinides enhance the release of insulin from the pancreatic beta cells. The key side effect of the sulfonylureas is weight gain, which may perpetuate insulin resistance, whereas the meglitinides may induce hypoglycemia if a meal is not eaten after a dose.

Glucosidase inhibitors delay the intestinal absorption of ingested carbohydrate and are given before meals to reduce postprandial hyperglycemia. Gastrointestinal side effects are controlled by slow increase of the dose and frequency, to a maximum of three times daily. The use of thiazolidinediones is controversial. In one study of adults, rosiglitazone was associated with increased risk of cardiovascular disease. They are also associated with hepatotoxicity. They are not recommended for adolescents at this time.

COMMON ISSUES IN THE MANAGEMENT OF ADOLESCENTS WITH DIABETES

The management of diabetes during adolescence involves adjustments for changes in body size and composition, energy demand and intake, and cognitive and social maturation. As development progresses, glycemic regulation typically shifts from parent to adolescent. Families that struggle with this transition may benefit from increased clinician involvement, more frequent office visits, and advance discussion about the eventual transfer of care from the pediatric to adult settings. In addition to these expected developmental processes, the management of diabetes may be complicated by comorbid conditions or behavioral issues such as those described next.

Eating disorders are more common among adolescents with than those without diabetes, and concurrent T1DM and anorexia nervosa carries a higher mortality than either disease alone. The risk may reflect hyperglycemia

secondary to the omission or reduction of insulin in an effort to lose weight; hypoglycemia secondary to inadequate intake or excessive exercise; or electrolyte imbalance secondary to purging. Regardless of body weight, all adolescents with diabetes should be screened for eating disorders (see Chapter 35). Accurate weights should be obtained at all visits, and excessive fluctuation or steady decline should trigger further evaluation. Early recognition and intervention can be life-saving, particularly in an adolescent with recurrent DKA or poor glycemic control. Whenever possible, referral should be made to registered dieticians and mental health providers who are experienced with adolescents, eating disorders, and diabetes.

Alcohol use by adolescents with T1DM may contribute to hypoglycemia by inhibiting gluconeogenesis and blunting counter-regulatory mechanisms. Alcohol is not metabolized to glucose, and alcoholic beverages should not be included in carbohydrate counting. The adolescent who does drink alcohol should consume additional carbohydrates prior to drinking, test blood glucose frequently during the subsequent 8–12 hours, and notify others about their diabetes and the possibility of alcohol-induced hypoglycemia. Drinking and driving are always contraindicated and are of heightened concern when the driver is inexperienced, inebriated, and at risk for hypoglycemia.

Driving and hypoglycemia is a dangerous combination. All patients with T1DM should test blood glucose prior to driving, have a rapid-acting source of glucose in the vehicle, and wear a diabetes bracelet or necklace.

Pregnancy in women with poor glycemic control is associated with increased rates of macrosomia and congenital anomalies. Adolescent females with diabetes should be educated about the risk of fetal malformation and the importance of planned, monitored pregnancies. Sexually active adolescent females who do not intend pregnancy should be encouraged to use hormonal contraception in addition to condoms for protection against sexually transmitted infection. If pregnancy is desired, it is recommended that glycemic control be optimized and medications such as angiotensin-converting enzyme (ACE) inhibitors/receptor blockers and statins be discontinued. The discontinuation of oral hypoglycemic agents and the initiation of insulin during pregnancy is generally recommended.

OUTCOME

Microvascular and Macrovascular Disease

Poor glucose control is a strong predictor of microvascular and cardiovascular disease both in T1DM, as discussed earlier, and in T2DM. The United Kingdom Prospective Diabetes Study demonstrated that a 1% decrease in HbA1C in patients with T2DM was associated with a 35% decrease in microvascular disease and an 18% decrease in myocardial infarction. Although macrovascular complications such as myocardial infarction and stroke are rare in the adolescent age group, predisposing conditions such as obesity, dyslipidemia, and hypertension are common and should be controlled.

In light of the strong and consistent associations between glycemic control and outcome in both T1DM and T2DM, intensive therapy is recommended for all patients with diabetes, regardless of disease type or patient age. In addition, all patients with diabetes should be screened yearly for retinopathy, nephropathy, and neuropathy. Diabetic retinopathy is the leading cause of new blindness among individuals aged 20–74 years. Nephropathy occurs in 20–40% of diabetes patients and is the leading cause of end-stage renal disease. An annual dilated funduscopic examination should be performed by an ophthalmologist experienced with diabetic retinopathy. A random urine sample or 24-hour urine collection should be screened for microalbumin. A random result greater than 30 mcg/mg creatinine or a 24-hour result > 30 mg is abnormal and should be repeated. Regardless of the presence or absence of hypertension, ACE inhibitors are the first-line therapy for adolescents with microalbuminuria. The dose should be optimized to a goal of normal microalbumin excretion, and serum potassium should be monitored for hyperkalemia. Symptomatic neuropathy (painful diabetic foot, autonomic neuropathy, gastroparesis) is uncommon in adolescents. Nevertheless, a careful history, foot examination, and neurological examination (including deep tendon reflexes and sensation) are recommended.

MAJOR POINTS

- Both T1DM and T2DM are increasing in incidence in the adolescent population.
- T1DM is primarily caused by autoimmune pancreatic beta cell destruction. T2DM is due to the effects of insulin resistance, often associated with obesity.
- Diabetes is diagnosed by a random plasma glucose greater than 200 mg/dl and clinical symptoms of diabetes; fasting plasma glucose greater than 126 mg/dl; or 2-hour post-OGTT plasma glucose greater than 200 mg/dl.
- Management depends on the presence and severity of symptoms and type of diabetes.
- Intensive insulin therapy of T1DM patients involving multiple daily injections delays the onset of microvascular complications.
- Lifestyle modification is the foundation in the treatment of T2DM. The preferred initial oral hypoglycemic agent for adolescents is metformin.
- Patients with diabetes require appropriate screening for complications and common comorbidities of adolescence, such as eating disorders and alcohol use.
- As adolescents progress into adulthood, they should gradually assume more of the responsibilities of diabetes care until they are capable of self-management.

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CHAPTER 14

Hyperlipidemia

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INTRODUCTION

Dyslipidemia is a prerequisite to the development of atherosclerotic cardiovascular disease. Only in populations with lifelong hypocholesterolemia is a near absence of clinical coronary heart disease (CHD) observed. As with blood pressure, lipid levels track through childhood. Autopsy studies have consistently demonstrated the adolescent onset of the atherosclerotic process, and the Bogalusa Heart Study has confirmed the strong association between antemortem cholesterol levels and postmortem atherosclerosis in adolescents and young adults.

The prevention of cardiovascular disease in adulthood begins with the diagnosis and treatment of dyslipidemia in childhood and adolescence. After brief reviews of the prevalence and causes of dyslipidemia, this chapter focuses on the recommendations for screening and an evidence-based approach to the management of dyslipidemia in adolescents.

PATHOPHYSIOLOGY

The classification of the dyslipidemias is transitioning from an older system based on phenotype to a newer system based on genetic or metabolic mechanism. Each system has gaps and overlaps, and the transition further complicates efforts to organize the causes and manifestations of dyslipidemia. As the pathophysiology of dyslipidemias is clarified, one system is likely to emerge in which the underlying mechanism explains the phenotypic pattern observed on lipoprotein analysis.

Most hyperlipidemia is caused by genetic polymorphism in the context of dietary and other lifestyle factors. Identifiable familial forms account for less than 2% of all hyperlipidemia yet carry the highest cardiovascular risk. Other causes, such as those listed in Table 14-1, can usually be identified by a careful history, physical examination, standard laboratory testing (i.e., thyroid, renal, and liver function studies, and urinalysis).

Familial hypercholesterolemia (FH) is due to mutations in the low-density lipoprotein-cholesterol (LDL-C) receptor gene and represents the most common single-gene disorder of lipoprotein metabolism. It has an autosomal co-dominant pattern of transmission and a population prevalence of 0.1–0.5%. Individuals who are heterozygous and homozygous for FH have LDL-C levels that are two to three and five to six times normal, respectively. FH corresponds to types IIa and IIb in the phenotypic system of classification. Cholesterol deposits are common in the tendons (xanthomas) and eyelids (xanthelasmas) in the homozygous form, but are rare before adulthood in the heterozygous form. Endothelial dysfunction begins during childhood in individuals with FH, and the risk of premature CHD during adulthood is markedly increased over the general population.

Familial combined hyperlipidemia (FCH) is characterized by genetic and metabolic heterogeneity, even among members of a single family. It has a population prevalence of 0.5–1.0%, making it a relatively common cause of dyslipidemia in children and adolescents. The usual manifestations are a modestly elevated LDL-C level, elevated very-low-density lipoprotein-cholesterol (VLDL-C) and triglyceride (TG) levels, and low high-density lipoprotein cholesterol (HDL-C). It overlaps with FH in the phenotypic classification system, presenting as IIa, IIb, IV, and rarely V.

Table 14-1 Causes of Hypercholesterolemia

Exogenous	Corticosteroids, anabolic steroids, isotretinoin, thiazide diuretics, anticonvulsants, beta blockers, estrogen, anti-retrovirals
	Alcohol
	Obesity
	Ketogenic diets
Endocrine	Hypothyroidism
	Cushing syndrome
	Hypopituitarism
	Diabetes mellitus
	Lipodystrophy
	Pregnancy
Storage diseases	Glycogen storage diseases
	Gaucher disease
	Cystine storage disease
	Tay-Sachs disease
	Neumann-Pick disease
	Acute intermittent porphyria
Gastrointestinal	Cholestasis
	Hepatitis
	Cirrhosis
	Pancreatitis
Renal	Nephrotic syndrome
	Renal failure
	Hemolytic uremic syndrome
	Anorexia nervosa
Other	Malnutrition
	Anorexia nervosa
	Idiopathic hypercalcemia
	Progeria
	Systemic lupus erythematosus

Familial hypertriglyercidemia follows an autosomal dominant inheritance pattern, but its expression is heavily influenced by diet and physical activity. The other inherited dyslipidemias, such familial defective apoB, familial lipoprotein lipase deficiency, and familial dysbetalipoproteinemia, are exceedingly rare.

SCREENING AND EVALUATION

Screening

The 1992 Report of the National Cholesterol Education Program (NCEP) Expert Panel on Blood Cholesterol Levels in Children and Adolescents provided the first guidelines for lipid screening during childhood. In 1998, the American Academy of Pediatrics (AAP) issued a Policy Statement that has served to update the NCEP Report (see Figure 14-1). Based on current evidence, children and adolescents younger than 20 years of age should have lipoprotein analysis performed after a 12-hour overnight fast if they have any of the following:

- Parent with elevated blood cholesterol ≥ 240 mg/dl.
- Parent or grandparent ≤ age 55 who had documented myocardial infarction, angina pectoris, documented coronary atherosclerosis, peripheral vascular disease, cerebrovascular disease, or sudden cardiac death. This includes parents/grandparents who had balloon angioplasty or coronary artery bypass surgery.
- Unknown family history or multiple risk factors for future cardiovascular disease (smoking, hypertension, obesity, diabetes, excessive consumption of saturated fats and cholesterol). Screening in these circumstances is at the discretion of a physician.

Although the fasting lipid panel is the best screen, it is better to obtain a total cholesterol (TC) measurement on a nonfasting sample than to obtain no sample in a patient who will have difficulty returning for the

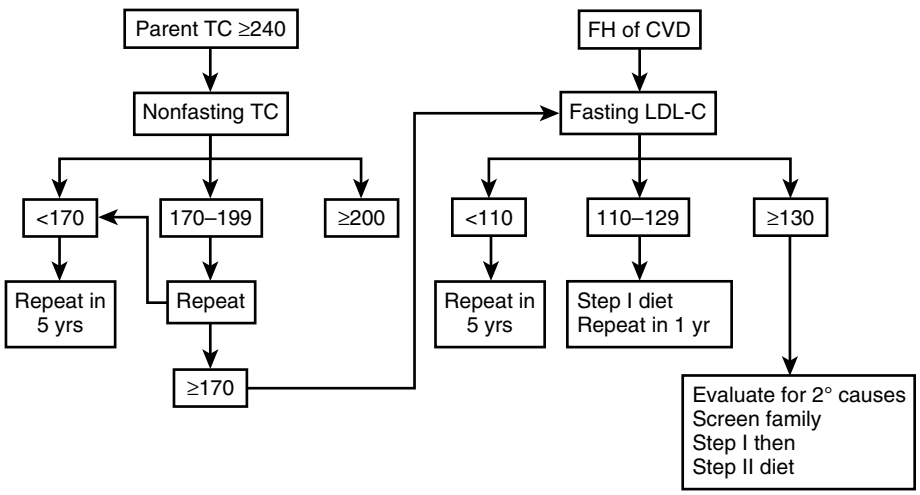

Figure 14-1 Selective lipid screening of individuals aged 2–20 years based on parent level of total cholesterol (TC) and family history (FH) of cardiovascular disease (CVD) in a parent or grandparent before age 55 years.
Levels for TC and LDL-C are in mg/dl.

best screen. Because chylomicrons from dietary fat do not affect the cholesterol measurement, a TC level below 170 mg/dl does not require further evaluation. Levels of 170 mg/dl or higher are indications for lipoprotein analysis after a 12-hour overnight fast, with measurement of TC, HDL-C, and TG, and calculation of LDL-C. If the TG level is 400 mg/dl or higher, the Friedwald equation (i.e., LDL-C = TC − HDL-C − TG / 5) is inaccurate, and the LDL-C should be measured directly by a certified laboratory.

The 5th to 95th percentiles of LDL-C levels by age are shown in Figure 14-2. The data come from the National Health and Nutrition Examination Surveys (NHANES) performed from 1988–1994. Using these data, the NCEP defined the lipid risk categories in children and adolescents, as shown in Table 14-2. The cut-points for each category are lower for children and adolescents than they are for adults. The acceptable range below age 20 years is defined as less than 110 mg/dl, borderline as 110–129 mg/dl, and high risk as 130 mg/dl or higher.

Evaluation

The identification of other cardiovascular risk factors is essential in adolescents with dyslipidemia. As shown in Figure 14-3, the number of risk factors has a significant effect on subclinical atherosclerosis as measured by distensibility of the brachial artery and intima-medial thickness of the common carotid artery. The history should explore tobacco use; past medical or family history of hypertension or diabetes mellitus; dietary intake; and physical activity. The physical examination should include height, weight, and calculation of the body mass index (BMI; see Chapter 11); Tanner stages to assess pubertal progression (see Chapter 1); blood pressure; inspection of the skin, eyes, and tendons for lipid deposition; palpation of the thyroid gland; and palpation of the liver. If the screening lipoprotein analysis reveals an LDL-C in the borderline or high range, a second fasting lipoprotein analysis should be performed and the two sets of results should be averaged.

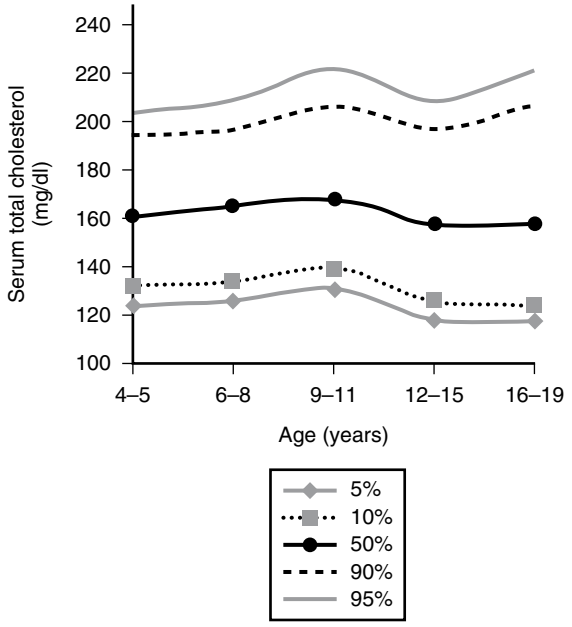

Figure 14-2 Percentiles for serum total cholesterol levels in U.S. children by age.
From NHANES III (1988–1994).

Table 14-2 Risk Categories for Children and Adolescents Less than 20 Years of Age and for Adults 20 Years of Age and Older[1]

	Total Cholesterol (mg/dl)		LDL-C (mg/dl)		HDL-C (mg/dl)
	Age < 20	Age ≥ 20	Age < 20	Age ≥ 20	Age ≥ 20
Acceptable	< 170	< 200	< 110	< 130	> 35
Borderline	170–200	200–240	110–130	130–160	
High risk	> 200	> 240	> 130	> 160	< 35

[1]As defined by the NCEP Expert Panel on Blood Cholesterol in Children and Adolescents and the NCEP Adult Treatment Panel.

MANAGEMENT

Diet and Behavior

The population-based approach to lipid levels is a primary preventive measure designed to lower the lipid levels of the entire population through recommended changes in nutrient intake and eating patterns. The guidelines apply to all facets of food delivery, including schools, health professionals, government agencies, the food industry, and mass media. The dietary recommendation to increase consumption of fruits, vegetables, complex carbohydrates, and low-fat dairy products apply lifelong after age 2 years, particularly as the Dietary Intervention Study in Children has demonstrated the safety of a low-fat diet in growing children.

On an individual basis, regardless of the cause of the dyslipidemia, lifestyle changes are the initial approach to treatment. For adolescents with an LDL-C in the acceptable range, education on heart-healthy lifestyles should include discussion of diet, exercise, tobacco, and regular blood pressure checks. For adolescents with LDL-C measurements in the borderline range, evaluation and treatment of other cardiovascular risk factors should be performed, a step-one diet should be initiated (Table 14-3), and lipoprotein analysis should be repeated at 3 months.

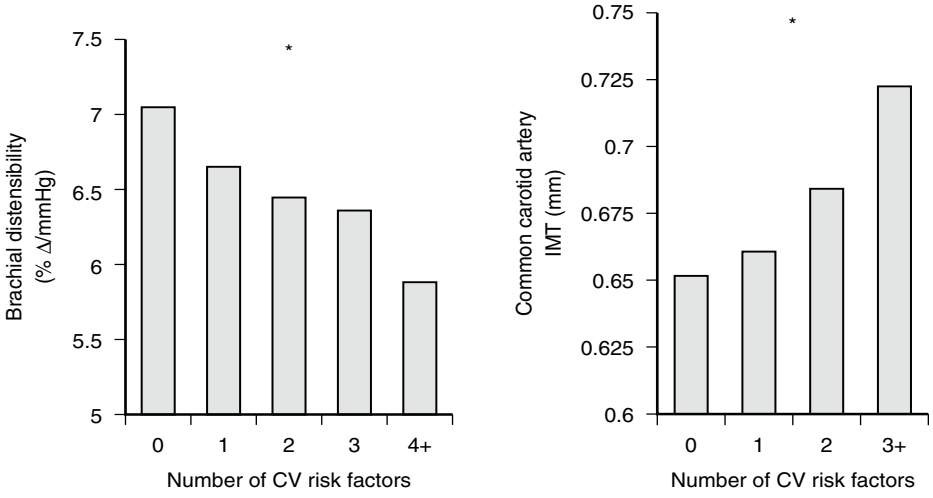

Figure 14-3 Effect of multiple cardiovascular (CV) risk factors on subclinical atherosclerosis. Brachial artery distensibility decreases and common carotid artery intima-media thickness (IMT) increases with clustering of risk factors.
*Linear trend $p < 0.02$.

If the LDL-C is in the high-risk range, a step-two diet should be prescribed. Nutritional counseling by a registered dietician is important both for adherence and to ensure adequate intake of nutrients, vitamins, and minerals. If the HDL-C is low or TGs are high, the adolescent should be encouraged to substitute complex carbohydrates for sugars and other simple carbohydrates.

Pharmacotherapy

Even with strict adherence to diet, only a 10–15% reduction of LDL-C can be expected. If the LDL-C remains 190 mg/dl or higher after 3 months of nonpharmacological measures, the NCEP guidelines suggest that drug therapy be considered. However, for the adolescent with a family history of premature cardiovascular disease or the adolescent with two or more other risk factors, medication can be initiated for persistent LDL-C levels of 160 mg/dl or greater. Repeat laboratory evaluation is recommended 6 weeks after starting drug therapy and every 3 months thereafter until LDL-C goals are reached, after which follow-ups decrease to every 6–12 months.

At the time that the guidelines were published, the bile acid sequestrants constituted the only drug class with published efficacy and safety data for the treatment of dyslipidemias in children and adolescents (Table 14-4). These agents bind bile acids in the intestine, preventing their enterohepatic re-uptake and resulting in their removal from the cholesterol pool. The starting dose is generally one packet or scoop (4 g cholestyramine or 5 g colestid) mixed in 8 oz. of liquid once or twice daily. Dosing is based on initial LDL-C level rather than on body weight (see Table 14-3). Doses greater than 8 g per day rarely improve efficacy and may increase side effects. The most common adverse effects are gastrointestinal, including constipation. These agents may increase TG levels and may interfere with the absorption of certain medications and fat soluble vitamins. Supplementation with a multivitamin and folate (1 mg daily) is therefore usually recommended. Although compliance in many studies is noted to be poor, this class of medication is quite safe and can achieve LDL-C reductions of 13–20%.

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, or statins, have become the

Table 14-3 Step-One and Step-Two Diets for Hypercholesterolemia

	Recommended Intake	
	Step One	**Step Two**
Calories	Appropriate for normal growth. Avoid energy imbalance.	
Total fat	< 30% total calories	
Saturated fat	< 10% total calories	< 7% total calories
Polyunsaturated fat	Up to 10% total calories	
Monounsaturated fat	Remainder of fat calories	
Cholesterol	< 300 mg/day	< 200 mg/day
Carbohydrates	≈55% total calories	
Protein	≈15–20% total calories	

Table 14-4 Pharmacotherapy for Dyslipidemias

Class	Drug	Starting Daily Dose	Maximum Daily Dose	Lipid Effects	Side Effects
Bile acid–binding resins	Cholestyramine	4 g or 80 mg/kg	Once daily if LDL < 195	Lowers LDL-C	Abdominal bloating
	Colestipol	5 g	BID if LDL = 195–235 TID if LDL = 236–280 QID if LDL-C > 280	Raises TG	Abdominal cramping Constipation
	Colesevelam	3750 mg	4375 mg (use in children not established)		
Nicotinic acid	Niaspan	500 mg @ HS	2000 mg (10 mg/kg/day) @ HS	Lowers LDL-C Lowers TG	Flushing Headache Pruritus Transaminase elevation
HMG CoA reductase inhibitors	Atorvastatin	10 mg	80 mg (adults) 20 mg (children)	Lowers LDL-C Lowers TG	Myositis/CPK elevation Rhabdomyolysis
	Fluvastatin	20 mg	80 mg (use in children not established)	Raises HDL-C	Transaminase elevation
	Lovastatin	10 mg	80 mg (10–40 mg in children)		
	Pravastatin	10 mg	80 mg (10–40 mg in children)		
	Rosuvastatin	5 mg	40 mg (use in children not established)		
	Simvastatin	5 mg	80 mg (5–40 mg in children)		
Cholesterol absorption inhibitors	Ezetimibe	10 mg	10 mg	Lowers LDL-C	
Fibric acid derivatives	Bezafibrate	200 mg TID	200 mg TID 5–10 mg/kg/day in children	Lowers TG Raises HDL-C	Dyspepsia Constipation, myositis, anemia
	Clofibrate	500 mg BID	500 mg QID (use in children not established)		
	Fenofibrate	48 mg	145 mg 5 mg/kg/day in children		
	Gemfibrozil	600 mg BID	600 mg BID (use in children not established)		
Omega-3 fatty acids	Omacor	2 g BID	2 g BID (use in children not established)	Lowers TG	Gastrointestinal

agents of choice for the pharmacotherapy of hypercholesterolemia in children and adults. Statins reduce LDL-C levels by inhibiting the rate-limiting step in the endogenous synthesis of cholesterol and have been shown to reduce cardiovascular mortality in adults. As shown in Figure 14-4, research has also demonstrated improvements in the vascular status of children with dyslipidemias who were treated with statins. Adverse effects are infrequent in adolescents, but liver transaminases and creatinine kinase (CK) should be monitored and patients should be aware of the risk and signs of myositis. Concomitant administration with cyclosporine, erythromycin, and gemfibrizol may increase the risk of rhabdomyolysis and should be avoided. Female patients should be advised that statins are contraindicated in pregnancy.

Nicotinic acid (niacin) is a water-soluble B vitamin that lowers cholesterol when administered in high dose. Niacin acts by decreasing liver synthesis of TG-rich VLDL-C particles, with resulting decreases in serum levels of VLDL-C, LDL-C, and Lipoprotein (a) [Lp(a)]. Although one study has demonstrated its efficacy in children, the high incidence (76%) of bothersome side effects (e.g., flushing, headache, nausea, glucose intolerance, myopathy, hyperuricemia, abnormal liver function) has resulted in limited pediatric use. Extended-release formulations diminish, but do not abolish, the vasomotor symptoms.

Fibric acid derivates, or fibrates, (i.e., fenofibrate, clofibrate, gemfibrizol) increase hepatic fatty acid oxidation, resulting in lowering TG levels, and increase production of apo-AI and apo-AII, resulting in higher HDL-C levels. Side effects are mostly minor gastrointestinal complaints, but cholelithiasis, abnormal liver function, and myopathy are associated with fibrate use. For this reason, fibrates and HMG-CoA reductase inhibitors should not be used simultaneously. Although one pediatric study demonstrated that fibrates were well tolerated and efficacious in children, the cut-points for initiating therapy are unclear. Adult guidelines recommend initiation at an HDL-C level below 40 mg/dl and/or a TG level above 200 mg/dl. However, because the major risk of TG elevation (i.e., pancreatitis) does not increase substantially until the TG

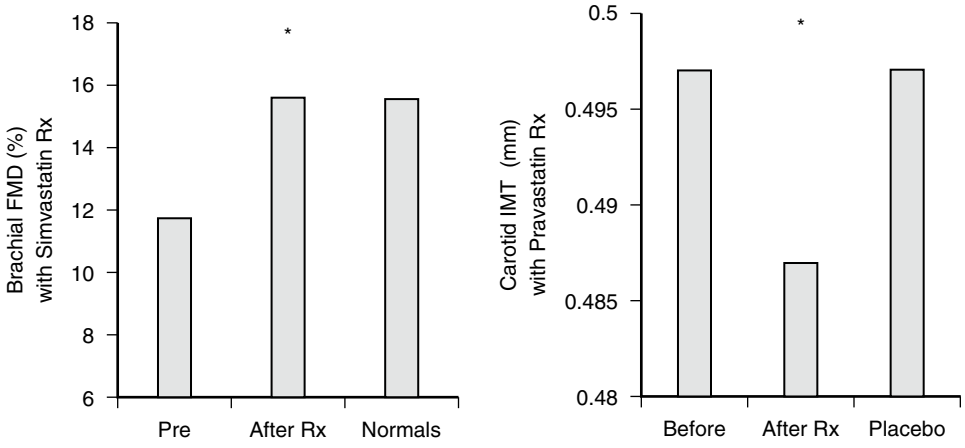

Figure 14-4 Improvement in vascular status with statin therapy in children with dyslipidemia. Treatment with simvastatin led to return of brachial flow-mediated dilation (FMD) to levels found in normal children. Pravastain, but not placebo treatment, resulted in regression of common carotid intima-media thickness (IMT).
$p < 0.05$ for difference in change from baseline.

reaches 1000 mg/dl, many experts withhold fibrate use in children until the TG is persistently above 350 mg/dl or a random level is above 700 mg/dl.

Omega-3 fatty acids, as found in fish oil, are known to reduce TG levels. Although well-tolerated in adults, pediatric data on their use are not available. The newest drug class consists of the cholesterol absorption inhibitors. Ezetimibe prevents the absorption of dietary cholesterol in the small intestine, does not appear to have side effects exceeding those of placebo, and does not increase the risk of myositis when used concomitantly with the statins. There are little data on its use in children and adolescents, but the findings in adults are encouraging.

OUTCOME

Adult studies clearly demonstrate the effectiveness of lipid-lowering therapy for the primary and secondary prevention of cardiovascular disease. However, even in adults, randomized trials have not included subjects with frequently seen lipid patterns, such as those with acceptable TC and low HDL-C levels or those with high TG levels. In the Framingham Heart Study, 40% of male and 80% of female subjects had lipid profiles that were not included in the randomized trials, and 25% of male and 66% of female subjects with CHD would have been ineligible for the trials. Although the long-term effects of treatment during childhood and adolescent remain unclear, short-term effects have been reported following medical therapy. In children with dyslipidemia, diet and exercise, antioxidants and statins, and folic acid have been shown to improve vascular function in the settings of obesity, FCH, and diabetes mellitus, respectively.

In summary, adolescents who are at increased risk for adult cardiovascular disease can be easily identified with simple measurements of anthropometrics, blood pressure, lipids, and carbohydrate metabolism. Adult treatment trials along with limited pediatric data suggest that early treatment of risk factors, including dyslipidemia, can lead to improvements in target-organ function.

MAJOR POINTS

- Dyslipidemia is a prerequisite to the development of atherosclerosis. Ongoing declines in adult cardiovascular mortality over time depend on the prevention, identification, and treatment of dyslipidemia during childhood and adolescence.
- Most hyperlipidemia is caused by genetic polymorphisms in the setting of obesity, high-fat diet, and/or sedentary lifestyle.
- Identifiable familial forms of hyperlipidemia account for 2% of all hyperlipidemia cases yet carry the highest risk of premature cardiovascular disease.
- Most causes of secondary hyperlipidemia can be identified by measurement of serum thyroid stimulating hormone (TSH), renal function, liver function, and urinalysis.
- A screening lipoprotein analysis following a 12-hour fast should be performed prior to age 20 years for individuals whose parent has a TC level > 240 mg/dl, or whose parent or grandparent has evidence of cardiovascular disease by age 55 years.
- Lipid risk categories in individuals younger than age 20 years are defined as acceptable (LDL-C < 110 mg/dl), borderline (LDL-C = 110–129); and high risk (LDL-C > 130 mg/dl).
- Management of dyslipidemia begins with changes in diet and physical activity. The step-one diet is recommended for all individuals from age 2 years onward. The step-two diet is recommended for children and adolescents in the high-risk lipid category.
- Statins are the agents of choice for adolescents with LDL-C levels > 190 mg/dl or > 160 in the presence of two or more other cardiovascular risk factors.

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CHAPTER 15

Acne

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INTRODUCTION

Acne vulgaris is the most common skin disorder in the United States, affecting 85% of adolescents and accounting for 10% of primary care visits. Along with the scarring that can follow inflammatory lesions, the adverse effects on self-esteem and psychosocial functioning that begin in adolescence can persist lifelong.

This chapter reviews the epidemiology, pathophysiology, psychosocial impact, evaluation, and treatment of adolescent acne. Effective management begins with a thorough history and physical examination and an ability to educate patients and families about the facts and fiction surrounding acne. An understanding of the factors that cause, exacerbate, and ameliorate acne allows most adolescent acne to be managed in the primary care setting.

EPIDEMIOLOGY

The prevalence of acne in the United States is an estimated 85% among individuals aged 12 to 24 years, 8% among those aged 25 to 34 years, and 3% among those aged 35 to 44 years. The mean ages of onset are 11 years in females and 12 years in males, with peak prevalence rates at 15–17 and 17–19 years, respectively. During adolescence, the prevalence and severity of acne are higher in males than females. During young adulthood, however, acne is three times more common among females than males. One-third of adult females with acne have hyperandrogenicity, and half have a family history of adult acne.

PATHOPHYSIOLOGY

Acne vulgaris develops within the pilosebaceous unit of the skin. This unit consists of the sebaceous glands surrounding the deep follicular bulb and the infundibulum that connects the sebaceous glands to the epidermis.

Acne begins with the formation of a dense, microscopic keratinous plug (i.e., microcomedo) that blocks the flow of sebum to the skin's surface. The accumulating sebum and keratin obliterate the follicular architecture and eventually form a non-inflammatory comedone on the skin's surface that is visible to the naked eye. When the surface of the comedone is closed, it appears white and may be missed unless a good light source is utilized and the skin is stretched. When the surface is open, the comedone appears black due to the oxidation of melanin and light refraction from the skin's surface.

Inflammatory acne develops in response to the colonization of the sebum-rich follicle by a gram-positive anaerobe, *Propionibacterium acnes* (*P. acnes*). The bacterium secretes a lipase that hydrolyses triglycerides in the sebum to glycerol, which is then used by the bacterium as a growth substrate. Other pro-inflammatory mediators secreted by the bacterium cause irritation and rupture of the follicular wall, with extrusion of the comedonal contents into the dermis. The early inflammatory infiltrate seen within the dermis reflects a non-immune, foreign-body response to the keratin, hair, and sebum. However, the presence of *P. acnes* and its mediators can lead to delayed hypersensitivity, cell-mediated immunity, and complement activation. Up to one-third of inflammatory lesions (i.e., papules, pustules, nodules, and cysts)

lead to scarring, and many cause post-inflammatory hyper- or hypopigmentation.

Androgens stimulate secretion of sebum and hyperproliferation of keratinocytes within the psilosebaceous unit. The sensitivity of the psilosebaceous unit to circulating androgens, as well as serum androgen levels, contribute to the development of acne. Serum androgen levels are higher in females with than without acne, and both exogenous and endogenous androgens are associated with acne. Hyperandrogenic conditions such as Polycystic Ovary Syndrome (PCOS) are discussed in detail in Chapter 23.

External factors, such as oil-based cosmetics, may exacerbate acne but do not cause most cases. Similarly, cleansers may improve the skin's appearance by removing excess sebum but do not alter sebum production and do not cure acne. Scrubbing may disrupt the skin barrier, foster bacterial colonization, and worsen inflammation. Stress and diet have both been shown to affect the course of acne, but there is no evidence that they cause or cure acne.

EVALUATION

The objectives when evaluating an adolescent with acne are to identify causative or exacerbating factors, define lesion type and severity, determine or adjust the treatment plan, and assess the response to treatment. Although the diagnosis of acne vulgaris is usually straightforward, other conditions do present with acneiform lesions. For example, ***acne rosacea*** is a disorder of adults that presents with non-comedonal papular or inflammatory acne associated with vascular dilatation of the central face. ***Acne fulminans*** is a disease of adolescent males characterized by the rapid onset of severe inflammatory acne, high fever, leukocytosis, proteinuria, elevated erythrocyte sedimentation rate, and osteolytic lesions. Dermatological consultation should be obtained, and treatment typically includes systemic corticosteroids. Pyoderma faciale, or ***rosacea fulminans,*** is acute inflammatory acne in women that follows severe stress and is treated with oral corticosteroids. ***Chloracne*** is severe inflammatory acne caused by environmental exposure to halogenated hydrocarbons such as dioxin.

When interviewing an adolescent with acne, the history should include discussion of the age of onset of the acne, association with pubertal development and menses, response to treatment, family history of acne, psychosocial function, signs or symptoms of hyperandrogenism, and use of medications associated with acne (e.g., corticosteroids, androgens, bromides, iodides, lithium, and phenytoin). Suggested questions that can help guide the interview are shown in Box 15-1.

Box 15-1 Interviewing the Adolescent with Acne

General Medical Questions:

- How much of a problem do you feel your acne has become?
- What was the age of onset of your acne, and how rapidly did it develop?
- Which products have you tried to treat the acne?
- Are you currently using any products to treat acne? If so, which?
- Do you use other prescription and/or nonprescription medications?
- Do you use cosmetics or hair greases?
- What sports do you play?
- Do you have a history of other medical problems?
- Is there a family history of severe acne?

Screening for Psychosocial Impairment:

- Are you feeling depressed, nervous, anxious, upset, confused, or scared by your acne?
- How is the acne affecting your self-esteem and self-confidence?
- Is your social life or are other activities being affected by acne?
- Is your ability to do studies or work being hindered?
- Are you preoccupied with your acne?
- Do you think about hurting yourself? Are these thoughts related to your acne?

Questions for Females:

- When was the first day of your last menstrual period? And the one before that?
- Are your periods regular? How often? How long do they last?
- Does your acne worsen before or during your period?
- Have you noticed excess hair growth on your face or elsewhere that troubles you?
- Are you sexually active? If so, what methods of birth control do you use?

The physical examination should document the location, type, and severity of acneiform lesions (Table 15-1); other skin findings such as scarring, hyperpigmentation, telangiectasias, hirsutism, or acanthosis nigricans; and signs of virilization in females such as clitoromegaly or alopecia. In a study of adult women with acne, 39% had irregular menses and, of these, 37% had PCOS. The diagnosis therefore should be considered and evaluation pursued in adolescent and adult females with acne, irregular menses, and hirsutism. If the physical examination reveals virilization, the patient should also be evaluated for late-onset congenital adrenal hyperplasia (i.e., partial 21-hydroxylase deficiency), as discussed in Chapter 23.

Table 15-1 Classification of Acne Lesions

Type	Name	Description	Size (mm)
Non-inflammatory	Closed comedone (whitehead)	Firm, slightly elevated, closed orifice	1–2
	Open comedone (blackhead)	Flat or raised, open orifice, dark color	1–5
Inflammatory	Papule	Erythematous, solid, raised	1–5
	Pustule	Firm, raised, erythematous, pus at surface	1–5
	Nodule	Firm, indurated, no visible orifice	5–10
	Cyst	Large nodule, ± fluctuance, ± abscess	> 10

MANAGEMENT

The management of acne begins with patient education about the causes of acne, general skin care, and expected response to treatment (Box 15-2). All adolescents should be taught that the affected skin should be washed gently (i.e., no scrubbing) with a mild, non-comedogenic soap or cleanser. Regardless of the treatment plan, at least 6 to 8 weeks of use is required for existing microcomedones to progress through the comedone stage and resolve. During this time, the acne may appear unchanged or even worse and the tendency is to discontinue treatment. Expecting this lag before improvement occurs may help adolescents adhere during the early treatment months. The type and severity of the acneiform lesions determine the specific medications prescribed (Table 15-2). The classes of drugs used to treat acne and their indications for use are described in Table 15-3.

Box 15-2 Myths vs. Facts about Acne Vulgaris

Myth: Chocolate, greasy foods, fast foods, soft drinks, and other foods cause acne.
Fact: There have been no meta-analyses, randomized controlled studies, or well-designed scientific trials following evidence-based guidelines substantiating a link between diet and acne.
Myth: Poor hygiene or not washing frequently enough causes acne.
Fact: Lack of hygiene has no effect on the presence or severity of acne. Frequent washing with harsh soaps may in fact irritate the skin, exacerbating acne.
Myth: Scrubbing the skin and opening comedones helps acne.
Fact: Any type of mechanical trauma to the skin may traumatize existing acne lesions, increase inflammation, delay resolution of lesions, and increase the likelihood of scar formation.
Myth: Cosmetics, but not hair products, can worsen acne.
Fact: Oil-based cosmetics and hair products both can exacerbate acne. Hair pomades are especially problematic and should be avoided. Non-comedogenic, water-based products are less likely to cause problems.
Myth: Cigarette smoking has no effect on acne.
Fact: Several studies have shown a relationship between acne severity and daily cigarette consumption.

Topical retinoids (i.e., adapalene, tretinoin, and tazarotene) are the mainstay of treatment for comedonal acne (Tables 15-4 and 15-5). They act through nuclear receptors to normalize epidermal proliferation and differentiation, leading to decreased microcomedo formation. Adverse effects such as skin irritation and dryness are least likely with adapalene and most likely with

Table 15-2 Treatment of Acne Vulgaris

Acne Type	First-Line Treatment	Alternate Treatment	Maintenance
Comedonal	Topical retinoid	Topical azelaic or salicylic acid	Same
Mild inflammatory	Benzoyl peroxide ± topical antibiotic	Topical retinoid or azelaic acid	Same
Moderate inflammatory	Oral antibiotic + benzoyl peroxide + topical retinoid	Oral isotetinoin ± estrogen/progestin for females	Discontinue oral antibiotic and oral isotretinoin after 4–6 months
Severe inflammatory	Oral isotretinoin	Oral antibiotic ± estrogen/progestin for females ± benzoyl peroxide ± topical retinoid	Discontinue oral antibiotic and oral isotretinoin after 4–6 months

Modified from Katsambas AD, Stefanaki C, Cunliffe WJ: Guidelines for treating acne. Clin Dermatol 2004;22:439–444.

Table 15-3 Topical Agents Used in the Treatment of Acne

Name	Formulation	Dose
Tretinoin	Cream: 0.01%, 0.025%, 0.05%, 0.1%, 0.4% Gel: 0.01%, 0.025%, 0.04%, 0.1% Solution: 0.05%, 0.1%, 0.2% Lotion: 0.1% Gel microsphere: 0.1% Polymer cream: 0.025%	Daily, preferably at bedtime
Adapalene	Gel, solution, cream, swab: 0.1%	Daily, preferably at bedtime
Tazarotene	0.05%, 0.1% gel	Daily
Azelaic acid	Cream: 20% cream Gel: 15%	Twice daily
Benzoyl peroxide	Topical cream: 2.5%, 5%, 10% Topical gel/jelly: 2.5%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10% Topical liquid: 2.5%, 5%, 10% Topical lotion: 2.5%, 4%, 5%, 5.5%, 8%, 10% Topical pad: 3%, 6%, 9%, 10% Topical soap: 5%, 10%	Apply daily for the first 3 days, then once or twice daily
Clindamycin	Solution, gel, lotion, foam, pad: 1%	Twice-daily solution, gel or lotion Once-daily foam, pad
Erythromycin	Solution: 1%, 2% Ointment: 2% Gel: 2%, 4%	Twice daily
Erythromycin 3% + benzoyl peroxide 5% gel		Once or twice daily
Erythromycin 4.0% + tretinoin 0.025% gel		Daily, preferably at bedtime
Erythromycin 2% + isotretinoin 0.5% gel		Daily, preferably at bedtime
Clindamycin 1% + benzoyl peroxide 5% gel		Once or twice daily
Clindamycin 1% + tretinoin 0.025% gel		Daily, preferably at bedtime

tazarotene. Tretinoin is the most commonly prescribed topical retinoid, in part because of its availability in multiple formulations (i.e., cream, gel, and solution) and potencies (0.025% to 0.1%). Although creams tend to cause less irritation than gels or solutions, the microencapsulated 0.1% gel appears to be fairly well tolerated.

Topical salicylic (1–5%) or azelaic acid is a useful alternative or adjunct to topical retinoids for the treatment of non-inflammatory acne. Both of these topical preparations have comedolytic and antimicrobial effects without the photosensitization typical of the topical retinoids.

Topical benzoyl peroxide is considered first-line treatment for mild inflammatory, or papular, acne (Tables 15-4 and 15-5). Common side effects resemble those of the topical retinoids, with skin irritation, dryness, and sun

Table 15-4 Spectrum of Efficacy of Topical Agents in Acne Therapy

Agent	Keratolytic/ Anti-comedogenic	Sebosuppressive	Antimicrobial	Anti-inflammatory
Tretinoin	+++	–	+	–
Isotretinoin	+++	–	+	+
Adapalene	+++	–	+	++
Tazarotene	+++	–	+	–
Azelaic acid	++	–	++	+
Benzoyl peroxide	+	–	+++	–
Clindamycin	+	–	+++	+
Erythromycin	+	–	+++	+
Tetracycline	+	–	+++	+

–, none; +, weak; ++, moderate; +++, strong.

Source: Krautheim A, Gollnick HP: Acne: Topical treatment. Clin Dermatol 2004;22:398–407.

Table 15-5 Adverse Drug Reactions of Topical Agents in Acne Therapy

Agent	Erythema	Scaling	Burning	Acne Flare	Bacterial Resistance	Photosensitivity	Other
Tretinoin	++++	++++	+++	+++	–	+++	–
Isotretinoin	+++	+++	++	++	–	+	–
Adapalene	++	++	++	++	–	–	–
Tazarotene	++	++	++	++	–	–	–
Azelaic acid	++	++	++++	–	–	–	–
Benzoyl peroxide	+++	+++	++	++	–	–	Bleaches hair and clothes; rarely, contact sensitivity
Topical antibiotic	+	+	–	–	++++	+ (Tetracycline)	Rarely, contact sensitivity

–, none; +, weak; ++, moderate; +++, strong; ++++, very strong.
Source: Krautheim A, Gollnick HP:Acne:Topical treatment. Clin Dermatol 2004;22:398–407.

sensitivity. Benzoyl peroxide is more effective when used in combination with topical antibiotics and/or topical retinoids than when used alone. It is available in gel, lotion, solution, and cream form and in potencies of 2.5%, 5%, and 10%. Patients should be told that it may bleach clothing and bed linens.

Topical antibiotics are indicated for the treatment of mild to moderate inflammatory acne and are more effective when used in combination with benzoyl peroxide or retinoids than when used alone. The combination use is thought to enhance skin absorption and decrease the development of bacterial resistance. Topical clindamycin and erythromycin are preferred over topical tetracycline because of the yellow staining that can occur with the latter. Systemic absorption of topical antibiotics is minimal, and skin irritation is less than with the other topical preparations.

Oral antibiotics (Table 15-6) are indicated for moderate inflammatory acne with scarring, hyperpigmentation, widespread involvement, and/or resistance to topical antibiotic treatment. The usual course of treatment is 4–6 months, in combination with a topical retinoid and/or benzoyl peroxide. Once the inflammation is controlled, the antibiotic should be tapered and discontinued.

By 2001, more than half of the strains of *P. acnes* in the United Kingdom were found to have antibiotic resistance. Antibiotic resistance is also fast becoming a global problem. Among antibiotics, resistance to erythromycin is greatest, followed by tetracycline, doxycycline, and minocycline. Often, *P. acnes* resistant to topical erythromycin is cross-

Table 15-6 Oral Antibiotics Used in the Treatment of Acne

Antibiotic	Name	Dose	Drawbacks
Tetracyclines	Tetracycline	250–500 mg twice daily	Gastrointestinal upset Vaginal candidiasis Need to take on empty stomach
	Doxycycline	50–100 mg twice daily	Gastrointestinal upset Photosensitivity
	Minocycline	50–100 mg twice daily 100 mg once daily (slow release)	Vertigo Hyperpigmentation of skin and oral mucosa Expensive Uncommonly, significant systemic adverse effects
Macrolides	Erythomycin	500 mg twice daily	Gastrointestinal upset Vaginal candidiasis Emergence of resistance of *P. acnes* is common
	Azithromycycin	250 mg three times a week	Gastrointestinal upset

Modified from Katsambas A, Papakonstantinou A:Acne: Systemic treatment. Clin Dermatol 2004;22:412–8.

resistant to clindamycin, and erythromycin-resistant *P. acnes* have also been found in a significant number of patients never treated with erythromycin. To date, there has been no reported resistance to benzoyl peroxide or azelaic acid.

Recommendations have been made to help decrease existing resistant *P. acnes* and to counteract selection of newly resistant *P. acnes*. Antibiotics should be avoided if non-antibiotic agents, such as benzoyl peroxide or retinoids, can be used and are effective. Topical or oral antibiotics should always be used in combination with benzoyl peroxide. Oral or topical antibiotics should be discontinued once inflammatory lesions subside, and treatment should be continued with non-antibiotic topical medications. Antibiotics should not be prescribed for longer than 6 months, and the same antibiotic should be used if retreatment is required. A trial period of a minimum of 2 months should be allowed before changing antibiotics due to poor therapeutic response. To decrease development of resistance, use of oral and topical antibiotics with chemically dissimilar properties should be avoided. Short, intervening courses of benzoyl peroxide may help reduce or eliminate resistant bacteria.

Oral contraceptives are effective in the treatment of acne in females both with elevated and normal androgen levels (Table 15-7). An estrogen combined with a low-androgenic progestin should be prescribed for a trial of at least 4–6 months. A triphasic pill containing ethinyl estradiol and norgestimate has been shown to decrease lesions nearly 30% more than placebo and has been approved for use in the treatment of female acne. Although oral contraceptives are considered first-line therapy for females with PCOS, control of the acne and hirsutism often requires metformin, as discussed in Chapter 23.

Oral isotretinoin is used for the treatment of severe inflammatory acne unresponsive to the measures described previously. It decreases sebum secretion for up to 1 year after completion of therapy, with a resultant decline in *P. acnes*, comedogenesis, and inflammation. Adverse effects, including spontaneous abortions and severe congenital malformations, are common. Physicians prescribing isotretinoin and pharmacies dispensing it must be registered with the U.S. Food and Drug Administration (FDA), and physicians must document their expertise with the drug and familiarity with its risks. The FDA requires that all sexually active female patients have two negative pregnancy tests before treatment, use two contraceptive methods during treatment, have monthly pregnancy tests during treatment, and be enrolled in an electronic database of the FDA. In addition to the teratogenicity, all patients experience dose-dependent skin irritation, desquamation, cheilitis, and photosensitivity. Liver function studies, lipids, and CBC should be monitored monthly for hepatotoxicity, hypertriglyceridemia, and bone marrow suppression. Patients also may experience arthralgias, myalgias, and decreased night vision. Although there are reports of depression and suicidal behavior with isotretinoin use and the FDA recommends that patients be monitored closely for depressive symptoms, the current literature is inconclusive.

Isotretinoin is begun at 0.5 mg/kg daily and increased to a maximum of 2 mg/kg daily for very severe acne.

Table 15-7 Oral Hormonal Treatment in Acne

Agent	Indication	Dose	Drawbacks
Oral contraceptive pills (i.e., Estrostep, Orthotricyclen)	Moderate to severe acne, PCOS	1 pill daily	Vascular thrombosis Melasma Weight gain
Spironolactone	Acne with hirsutism	25–100 mg twice daily	Menstrual irregularities Breast tenderness Electrolyte abnormalities Contraindicated in pregnancy
Flutamide	Acne with hirsutism	250 mg twice daily	Hepatotoxicity, may be fatal Menstrual abnormalities if not combined with OCPs Contraindicated in pregnancy
Prednisone	Late-onset CAH	2.5–5 mg daily	Adrenal suppression
Dexamethasone	Late-onset CAH	0.125–0.5 mg daily	Adrenal suppression
Leuprolide	Acne with hirsutism	Per gynecologist or endocrinologist	Hypoestrogenism Bone loss Headaches Emotional lability Hot flashes

PCOS, polycystic ovary syndrome; OCP, oral contraceptive drug; CAH, congenital adrenal hyperplasia.

Modified from Katsambas A, Papakonstantinou A: Acne: Systemic treatment. Clin Dermatol 2004;22: 412–418.

The daily dose should be administered in 2 divided doses with food for a total cumulative dose of 120–150 mg/kg over 20 weeks. More than 80% of patients achieve remission, but more than 60% also require ongoing use of topical or oral antibiotics. Most relapses occur in patients with truncal acne and those who received less than the recommended total dose.

MAJOR POINTS

- Acne has significant negative effects on emotional well-being and social functioning.
- It is important to perform a careful history and physical examination in all patients with acne and for the physician to show empathy for the patient's distress due to acne.
- Patients with acne should be taught about gentle skin cleansing, be shown appropriate application techniques for topical therapies, have acne myths dispelled, and be helped to have realistic expectations of therapy.
- Knowledge of the pathophysiology of acne should guide individualized treatment.
- Acne is the result of hyperproliferation, abnormal differentiation, and desquamation of follicular keratinocytes; sebaceous hyperplasia with increased sebum production; follicular proliferation of *P. acnes*; and inflammation.
- Topical retinoids are the initial therapy for comedonal acne. Topical benzoyl peroxide and/or topical antibiotics may be added for papular and inflammatory acne.
- The combination of topical retinoids with antimicrobial therapy is appropriate for mild to moderate inflammatory acne.
- For more severe inflammatory acne, oral antibiotics for 4–6 months should be combined with topical retinoids.
- Hormonal therapy with an estrogen and low-androgenic progestin is effective for the treatment of acne in females both with and without hyperandrogenism. Prior to hormonal treatment, females with signs and symptoms of hyperandrogenism should be evaluated for PCOS. Those with virilization should also be evaluated for late-onset congenital adrenal hyperplasia.
- Oral isotretinoin therapy is appropriate for those with severe inflammatory acne unresponsive to other therapies. Side effects are significant, and the treatment should be prescribed and monitored by a physician experienced with the drug.

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CHAPTER 16

Headaches

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INTRODUCTION

Headache and migraine are common in children and adolescents. Up to 75% of children report having had at least one significant headache by age 15 years, and 28% meet the diagnostic criteria for childhood migraine established by the International Headache Society (IHS). This chapter reviews the classification, epidemiology, pathophysiology, evaluation, management, and outcome of headache disorders during adolescence. It focuses on the differentiation of primary from secondary headaches and on the management of migraine and tension-type headaches.

DEFINITIONS AND DIAGNOSTIC CRITERIA

Primary vs. Secondary Headache

Headaches are broadly categorized as primary or secondary. ***Primary*** headaches have no identifiable underlying cause. Diagnoses in this category include ***migraine*** and ***tension-type*** headaches. ***Secondary*** headaches are directly attributable to specific underlying conditions such as infection, tumor, bleed, trauma, toxin, and vasculitis. As noted below, a major goal when evaluating a patient with headache is to identify underlying, treatable conditions.

Migraine

The diagnostic criteria for migraine without and with aura are outlined in Box 16-1. ***Migraine without aura***, previously referred to as common migraine, consists of prodromal symptoms (e.g., change in personality, appetite, thirst) that occur several hours before the headache. ***Migraine with typical aura***, previously referred to as classical migraine, involves visual, sensory, or speech symptoms that develop gradually and resolve completely within 1 hour. If the aura includes motor weakness, the migraine is termed either ***familial hemiplegic migraine*** or ***sporadic hemiplegic migraine***. The former follows an autosomal dominant pattern of inheritance and involves mutations in three genes responsible for transmembrane sodium, potassium, and/or calcium channels. Patients with sporadic hemiplegic migraine have auras involving motor weakness but do not have first- or second-degree relatives with the syndrome. ***Basilar-type migraine*** usually begins before adolescence and is characterized by occipital headaches associated with cerebellar-type symptoms in the absence of motor weakness. The symptoms may include vertigo, tinnitus, decreased hearing, ataxia, vomiting, dysarthria, simultaneous temporal- and nasal-field visual symptoms, bilateral paresthesias, and decreased mental status.

Migraine with prolonged aura is defined as a migraine with typical or atypical aura in which a focal neurological finding persists 1 hour to 1 week beyond resolution of the headache, with no evidence of infarction

Box 16-1 Criteria for the Diagnosis of Migraine

Migraine without Aura

- ≥ 5 headache attacks that meet the criteria below.
- Headache lasts 4–72 hours in patients ≥ 15 years and 1–72 hours in patients < 15 years of age.
- Headache has ≥ 2 of the following characteristics: unilateral; interferes with daily activities; aggravated by routine physical activity.
- Headache is accompanied by ≥ 1 of the following characteristics: nausea and/or vomiting; photophobia and/or phonophobia.
- Headache is not attributable to another disorder.

Migraine with Aura

- ≥ 2 headache attacks meeting the criteria below.
- Aura consists of visual symptoms, sensory symptoms, and/or dysphasic speech; is fully reversible; and does not include motor weakness.
- Aura has ≥ 2 of the following characteristics:
  - Homonymous visual symptoms and/or unilateral sensory symptoms.
  - At least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes.
- Each symptom lasts ≥ 5 and ≤ 60 minutes.
- Not attributed to another disorder.

on neuroimaging. ***Persistent aura*** is defined as a focal neurological finding persisting more than 1 week beyond resolution of the headache, with no evidence of infarction on neuroimaging. ***Migrainous infarction*** is defined as evidence of infarction on neuroimaging in a patient who meets criteria for migraine with prolonged aura.

Childhood Periodic Syndromes

In the 2004 revision of the IHS criteria for the diagnosis of migraine, cyclical vomiting, abdominal migraine, and benign paroxysmal vertigo were categorized as childhood periodic syndromes that are harbingers of future migraine but are not defined as migraine disorders. ***Cyclical vomiting syndrome*** consists of repeated episodes of nausea and vomiting without headache that last hours to days. It usually begins in early childhood and ends by puberty. *Abdominal migraine* consists of recurrent vague abdominal pain associated with at least two of the following symptoms: anorexia, nausea, vomiting, and/or pallor. ***Benign paroxysmal vertigo*** of childhood consists of brief episodes (i.e., minutes) of recurrent dizziness and unsteadiness, often associated with nausea, pallor, photophobia, and/or phonophobia. The episodes may cluster over hours or days but tend to resolve after several attacks.

Migraine Variants

Headache with preceding or coincident visual hallucinations or delusions occurs more commonly in children and adolescents than adults. The cause is unknown, but probably reflects ischemia related to the migraine. Migraine associated with disorientation and agitation persisting beyond the headache is termed ***confusional migraine***. ***Hemisyndrome migraine*** involves hemiparesis, hemisensory deficits, visual field cuts, and/or language deficits that may begin up to 60 minutes before the headache and last several days afterward. ***Menstrual migraine*** is a migraine headache that occurs close to the onset of menses and is thought to be related to the premenstrual decline in estrogen and progesterone levels. ***Ophthalmoplegic migraine*** is headache of at least 1-week duration with the onset of a third or sixth cranial nerve palsy up to 4 days after onset of the headache. Evidence of inflammation on magnetic resonance imaging (MRI) led to the 2004 reclassification of ophthalmoplegic migraine as a cranial neuralgia.

EPIDEMIOLOGY

Large-scale studies of headache performed over the past 50 years demonstrate a steady increase in the prevalence of migraine from early childhood to late adolescence, with a shift from male to female predominance. One study of more than 2000 children and adolescents revealed a migraine prevalence of 28% in the 15- to 19-year-old group. Characteristics of this group included a strong family history of migraine in 81%, aura in 9%, and association with menses in nearly 25% of the females. Tension-type headaches have been less well studied than migraines, and prevalence estimates in children and adolescents range from 1% to nearly 75%. Of children and adolescents with migraine, more than half meet criteria for migraine without aura. Up to 30% have migraine with typical aura, and up to 19% have basilar migraine. Familial hemiplegic migraine and sporadic hemiplegic migraine are rare.

PATHOPHYSIOLOGY

The pathophysiology of migraine remains undefined. Although three genes have been identified for familial hemiplegic migraine and some of these genes may contribute to familial migraine with aura, no genes have been linked to migraine without aura. Neuroimaging studies of patients with migraine have demonstrated brainstem abnormalities in the region of the trigeminal nucleus, supporting theories that the trigeminal neurovascular system is involved in migraine pathophysiology.

The cause of tension-type headache, like migraine, remains unknown. The "continuum model" postulates

that tension-type and migraine headaches constitute one pathophysiological disorder of varying severity. The "spectrum model" postulates they are separate entities, with migraine representing a full-spectrum headache and tension-type representing a mild to moderate pain disorder. Tension-type headaches may involve muscle contraction that stimulates a feedback loop or involves central sensitization that builds pain severity.

EVALUATION

The first goal of evaluation is to determine whether the headache is primary or secondary. The history should include headache duration, severity, quality, location, and radiation; prodromal and associated symptoms; precipitating, exacerbating, and relieving factors; and psychosocial effects. Family history should be reviewed for migraine, other headache, cerebrovascular disease, and other intracranial conditions. A thorough neurological examination is the most sensitive indicator of a need for further assessment, and neuroimaging is the most sensitive tool for the detection of a treatable cause of the headache.

MANAGEMENT

The management of primary headache disorders has not been studied as thoroughly in children and adolescents as in adults. Consequently, most published recommendations are based on clinical trials in adults and clinical experience in children and adolescents. The general measures described below and the use of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and combination analgesics apply to patients with either tension-type or migraine headaches. The other abortive medications and the prophylactic medications described below are intended for patients with migraine but are often tried in patients with severe tension-type headaches that are otherwise unresponsive. Table 16-1 summarizes the medications commonly used for the management of primary headache disorders in adolescents.

General Measures

Factors identified on history that precipitate, exacerbate, or relieve recurrent headaches should be discussed in detail. The adolescent should be asked to keep a headache log that documents timing, severity, and response to intervention. Even if the history fails to identify factors, adolescents and parents should be asked to pay particular attention over the subsequent weeks to potential associations with stress, menses, sleep, and diet. Adolescents with mild or moderate tension-type headaches that do not interfere with function should be encouraged to remain in school or continue their activities as tolerated. Those with more severe headaches should be instructed to rest in a quiet, dark room and to begin abortive treatment early. Once the adolescent begins to use abortive medications, care should be taken to avoid overuse. In addition to drug-specific side effects, the likelihood of rebound headache increases with sustained overuse. If rebound is suspected, the medication should be tapered and the adolescent should be observed for several weeks before it is reinstituted.

Table 16-1 Medications for the Abortive Treatment of Headache in Adolescents

Drug Class	Drug	Dosage[1]
NSAID	Ibuprofen	5–10 mg/kg PO q 2–4 hours, not to exceed 50 mg/kg daily
	Naproxen	250–500 mg PO every 8–12 hours, not to exceed 3 doses daily
	Ketoralac	0.5–1 mg/kg IV or 0.25 mg/kg PO every 6 hours, not to exceed 1 mg/kg daily
Acetaminophen		10–20 mg/kg q 2–4 hours, not to exceed 1000 mg per dose or 3 doses daily
Combination	Midrin	2 capsules PO, then 1 capsule PRN every hour, not to exceed 4 capsules daily or 8 capsules weekly
Triptan	Sumatriptan	25–100 mg PO or 5–20 mg IN; may repeat once in 2 hours
	Zolmitriptan	2.5–5 mg PO; may repeat once in 2 hours
Anti-emetic	Promethazine	0.2–0.5 mg/kg PO, IM, PR every 8–12 hours
	Dimenhydrinate	1.25 mg/kg PO, IM every 4–6 hours
	Metoclopramide	0.13–0.15 mg/kg, not to exceed10 mg, given IV over 15 minutes
Ergot alkaloid	DHE (following metoclopramide)	DHE 0.15–0.2 mg IV, given 30 minutes after metoclopramide 5–10 mg PO. Can increase by 0.05 mg/dose as tolerated and repeat every 6 hours until 1 dose beyond headache cessation or to a maximum of 16 doses.
	DHE (following prochlorperazine)	DHE 0.5–1 mg IV, given 30 minutes after prochlorperazine 0.13–0.15 mg/kg IV and repeated every 8 hours until 1 dose beyond headache cessation. Change to another anti-emetic if nausea persists after 3 doses.

[1]PO, orally; IM, intramuscularly; IV, intravenously; PR, rectally; IN, intranasally; PRN, as needed.

Biofeedback, relaxation training, and stress management training have all been shown to reduce headache frequency and severity in children. Limitations to their use are the availability of trained counselors, health insurance coverage, and patient adherence to learned techniques.

Abortive Therapy

NSAIDs are considered first-line therapy for the acute management of headache and migraine. A crossover trial comparing ibuprofen 10 mg/kg, acetaminophen 15 mg/kg, and placebo for the acute treatment of migraine in patients aged 4–16 years showed that pain reduction was three and two times more likely with ibuprofen and acetaminophen than placebo, respectively, and pain resolution at 2 hours was two times more likely with ibuprofen than acetaminophen. Combination analgesics, such as Midrin, are commonly used in adolescents who do not respond to single analgesics. Midrin includes a mild sympathomimetic agent, a mild sedative, and acetaminophen.

Triptans represent an important advance in early, abortive therapy for migraine. All are serotonin agonists that increase vasoconstriction and therefore are contraindicated in patients with hemiplegic or basilar artery migraine. Seven triptans have been approved by the U.S. Food and Drug Administration (FDA) for use in adults with migraine. Although none is approved for pediatric use, placebo-controlled trials have demonstrated the effectiveness of oral and intranasal sumatriptan and oral zolmitriptan in adolescents with migraine. Response rates within 2 hours ranged from 58–88%, and the rates of adverse effects were lower than those reported in adults. Subcutaneous administration, as in adults, increased the risk of adverse effects and, in contrast to adults, has not been shown to be more effective than oral or intranasal administration.

Adolescents with episodic headaches unresponsive to oral analgesics or the triptans usually require treatment in the emergency department or hospital with parenteral NSAIDs (i.e., ketoralac); dopamine antagonists (e.g., phenothiazines, metoclopramide); dihydroergotamine (DHE); or anti-epileptic medications (e.g., sodium valproate). Dopamine antagonists such as prochlorperazine, promethazine, and metoclopramide initially were used only in patients who had nausea and vomiting associated with migraine. Subsequent studies, however, demonstrated their effectiveness in aborting pain when given parenterally, along with intravenous fluid loading. In an emergency department study of intravenous prochlorperazine, 50% of adolescents with migraine were pain-free and 75% had improved at 1 hour. Another trial demonstrated headache improvement in 82% of subjects receiving prochlorperazine compared with 42% receiving metoclopramide and 29% receiving placebo. Although prochlorperazine has been used in most studies, promethazine carries a lower risk of extrapyramidal side effects and therefore has become the phenothiazine of choice for the treatment of migraine in children and adolescents.

Parenteral ketorolac is often used in the emergency department as monotherapy for migraine or in combination with other drugs. Studies report improvement in 55% of subjects when ketoralac is used alone and in 93% when it is used with prochlorperazine. The 30% rate of headache recurrence within 24 hours of the ketoralac was thought to represent rebound in patients who had been overusing other NSAIDs prior to presenting to the emergency department.

Ergot alkaloids were first recognized as useful in the abortive treatment of migraine nearly 100 years ago. Of note, all ergot alkaloids are contraindicated in patients with familial hemiplegic migraine, basilar migraine, migraine with aura, and pregnancy. Ergotamine tartrate administered orally, sublingually, or rectally as monotherapy or combined therapy was commonly prescribed in adults until the early 1990s, when controlled trials showed no evidence of efficacy and high rates of nausea, vomiting, vasoconstriction, physical dependence, and rebound headache. DHE causes less arterial and more venous constriction than does ergotamine tartrate, is better tolerated, and has not been associated with dependence or rebound. A 1994 study demonstrated that 80% of children with refractory migraine improved following intravenous DHE and oral metoclopramide, and had few side effects.

Therefore, two DHE protocols have evolved for children and adolescents with migraine without aura that is refractory to other abortive regimens. As outlined in Table 16-1, both regimens call for premedication with anti-emetics to control gastrointestinal side effects. The first regimen incorporates more frequent administration at lower doses than the second regimen. The advantage of the first is a lower likelihood of side effects. The advantage of the second is a higher likelihood of rapid response.

Sodium valproate is less effective at inducing complete remission at 24 hours than DHE (60% vs. 90% of subjects), but it provides an alternative for inpatient abortive therapy when DHE is contraindicated or ineffective.

Prophylactic Therapy

The goal of prophylaxis is to reduce headache frequency and severity in patients with at least four disabling headaches monthly. Its success depends on patient and parent understanding of its purpose, the time required for titration toward an optimal dose, and the importance of dose tapering when the medication is to be discontinued. None of the medications commonly used for headache prophylaxis have been approved by the FDA for this use in children. Furthermore, the 2004 Practice Parameter of

the American Academy of Neurology concludes that there is insufficient evidence to recommend the use of any specific medication for migraine prophylaxis in children and adolescents, except perhaps one calcium channel blocker (i.e., flunarizine) that is not available in the United States. In the absence of guidelines, decisions about prophylactic therapy in adolescents are based upon the extensive literature in adults and the few studies in older children and adolescents that demonstrate probable effectiveness. The medications used most commonly for prophylaxis in adolescents are amitriptyline or nortriptyline, propranolol or atenolol, valproate, and topiramate (Table 16-2).

Propranolol and other beta blockers have a long history of use for migraine prophylaxis. Although studies in children have yielded conflicting results, studies in adults have demonstrated improvement in 60–80% of subjects. Side effects (e.g., fatigue, depressive symptoms, bradycardia, orthostatic hypotension) are common, and beta blockers should be avoided in patients with asthma, diabetes mellitus, and depressive disorders.

Tricyclic antidepressants have been used since the 1970s for the prevention of migraine headache in children and adults. Amitriptyline is the most widely used and best-studied drug in the antidepressant class. However, studies of its effectiveness for migraine prophylaxis in children have not been placebo controlled, and most have been open-label. Headache frequency and severity are reported to decrease in 50–80% of children with titration over 8–10 weeks. Side effects include anticholinergic symptoms, weight gain, and arrhythmia at higher doses.

Valproic acid and divalproex sodium (valproic acid plus sodium valproate) are oral medications approved in adults for migraine prophylaxis. Studies of divalproex sodium have demonstrated that 76% of subjects aged 7–16 years experience at least a 50% reduction in headache frequency and significant improvements in headache severity. Side effects include weight gain, fatigue, lightheadedness, tremor, teratogenicity, and hepatotoxicity. Although the optimal serum concentration for migraine has not been established, a reasonable goal is 50–100 mg/dl. Drug levels and liver function tests should be monitored every 2–3 months in patients on valproate.

Topiramate was shown to be more effective than placebo in a large-scale, open-label study but reached only borderline significance ($p = 0.06$) in a double-blind randomized trial. The trend toward significance and the wide variation in placebo response has led many clinicians to recommend its use in older children and adolescents. To achieve an effective daily dose and minimize side effects such as fatigue and cognitive slowing, topiramate should be started at a low dose of 25 mg daily and increased slowly over an 8- to 10-week period.

Cyproheptadine has antihistaminic, antiserotonergic, anticholinergic, and calcium channel blocking properties. Evidence of its effectiveness for migraine prophylaxis is based on a few small, retrospective, uncontrolled studies. In addition, side effects (i.e., appetite stimulation, weight gain, and fatigue) are common and poorly tolerated during adolescence.

OUTCOME

Headache, regardless of type or cause, can have a significant impact on function and quality of life. National surveys in the United States suggest that migraine alone accounts for 3 million missed work days monthly among adults and more than 300,000 missed school days monthly among children. Quality of life measures are lower in adults with migraine than adults with hypertension, diabetes mellitus, or heart disease, and lower in children with migraine than children with rheumatological, oncological, or cardiac disease.

Several tools have been developed to assess outcome in adults and children with migraine. In adults, the Migraine Disability Assessment (MIDAS) measures headache-related disability at work, home, and socially over the preceding 3 months. It is a clinically useful tool that has been

Table 16-2 Medications for the Prophylactic Treatment of Headache in Adolescents

Drug Class	Drug	Dosage[1]
Tricyclic antidepressant	Amitriptyline or nortriptyline	Begin 10 mg PO at HS, increase by 0.25 mg/kg/day every 2 weeks to a maximum of 50 mg PO daily
Beta blocker	Propranolol	Begin 10–20 mg PO TID, increase as tolerated to a maximum of 320 mg PO daily
	Atenolol	Begin 50 mg PO daily, increase as tolerated to a maximum of 150 mg PO daily
Anti-epileptic	Valproate	Begin 250 mg PO BID, increase as tolerated to a maximum of 1000 mg PO daily
	Topiramate	Begin 25 mg PO daily, increase as tolerated over 8–10 weeks to a maximum of 100 mg PO BID
Antiserotonergic	Cyproheptadine	0.2–0.4 mg/kg PO daily

[1]PO, orally; HS, at bedtime; BID, twice daily.

incorporated into the Stratified Care Model for the management of adult migraine. A pediatric version incorporates questions about school, home, and social function and increasingly is used to assess treatment strategies.

Although disability with migraine can be high, the overall prognosis for children and adolescents with migraine is good. Long-term follow-up studies suggest that migraine frequency decreases in at least half of patients, severity decreases in a third, and less than 15% of those with childhood onset require adult prophylaxis.

Studies exploring the risk of ischemic stroke in adults with migraine yield relatively low rates, ranging from 0.8–19 per 100,000 per year. In a study of young adults with acute infarction, migraine accounted for 14%. Of all adults with ischemic strokes, migraine accounted for less than 1%. A 2004 meta-analysis of eight studies revealed that the relative risk of ischemic stroke was 2.9 for adults who had migraine with aura and 1.6 for adults who had migraine without aura.

MAJOR POINTS

- The major goal of evaluation is to determine whether the headache is primary or secondary. A thorough neurological examination is the most sensitive indicator of a need for further assessment, and neuroimaging is the most sensitive tool for the detection of a treatable cause of the headache.
- Adolescents with mild or moderate tension-type headaches that do not interfere with function should be encouraged to remain in school or continue their activities as tolerated. Those with more severe headaches should be instructed to rest in a quiet, dark room and to begin abortive treatment early.
- Once the adolescent begins to use abortive medications, care should be taken to avoid overuse. If rebound is suspected, the medication should be tapered and the adolescent should be observed for several weeks before it is reinstituted.
- NSAIDs and probably acetaminophen are effective abortive therapy for headaches and should be considered first-line medications for home use.
- Triptans have not been approved by the FDA for use in children and adolescents but appear to be effective when administered orally and intranasally.
- Inpatient abortive therapy includes intravenous ketoralac, DHE, and sodium valproate. Although not approved for pediatric use, all appear effective in halting or decreasing the headache and associated symptoms.
- Prophylactic therapy should be reserved for adolescents with at least four headaches monthly that interfere with normal function. Although not approved for pediatric use, tricyclic antidepressants, beta blockers, and antiepileptic medications appear effective in preventing or decreasing recurrent headache.

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CHAPTER 17

Fatigue and Sleep Disorders

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INTRODUCTION

Sleep is a complex process influenced by both biological and behavioral factors. Historically, it was thought that teenagers had volitional control over their habitually late bedtimes and resultant sleepiness. Recent evidence, however, highlights the central role of biology in the adolescent sleep/wake cycle and the contributing effects of sociocultural factors such as homework, after-school employment, delayed curfew, and in-bedroom television and computer use. The interaction between the biological and sociocultural determinants of sleep results in a developmental vulnerability for sleepiness during the teenage years. In addition, the prevalence of certain health conditions during adolescence, such as obesity, increases the risk for clinically significant sleep disorders.

The goals of this chapter are to review the physiology of sleep, the impact of inadequate sleep, the evaluation of fatigue, and the management of sleep disorders during adolescence.

DEFINITIONS

Delayed sleep phase syndrome (DSPS): Asynchrony between the internal circadian pacemaker and external time that manifests as difficulty falling asleep at bedtime and awakening in the morning.

Dyssomnias: Sleep disorders that cause either insomnia or daytime sleepiness; excludes parasomnias.

Extreme daytime sleepiness: Interferes with alertness and vigilance; usually associated with obstructive sleep apnea or narcolepsy.

Insomnia: Ongoing difficulty with the onset, duration, or quality of sleep, despite sufficient opportunity for sleep, and associated with daytime impairment.

Narcolepsy: Dysregulation of REM sleep involving depletion of a neuropeptide.

Non–rapid eye movement (NREM) sleep: Includes four stages of sleep, from transitional or light sleep characterized by slow, regular brain activity on polysomnography (Stage 1) to slow wave or deep sleep characterized by stable respiration and minimal response to environmental stimuli (Stages 3 and 4).

Obstructive sleep apnea (OSA): Repeated episodes of pharyngeal collapse during sleep with resulting hypoxia and hypercarbia.

Parasomnias: Physical disorders that occur during sleep.

Periodic limb movement disorder (PLMD): Periodic episodes of repetitive, highly stereotyped limb movements during sleep that lead to partial arousal or awakening.

Polysomnography (PSG): Record of electrical brain activity, eye movement, and muscle tension during sleep.

Rapid eye movement (REM) sleep: Deep and light stages of sleep associated with dreaming, high-frequency brain activity, rapid eye movements, irregular breathing, and rapid heart rate.

Restless legs syndrome (RLS): Unpleasant sensation in the legs during rest, relieved with movement and interfering with sleep.

Sleep architecture: Distribution of sleep stages as measured by PSG.

Tiredness: Daytime fatigue that usually does not impact alertness or vigilance.

Ultradian process: Alternating NREM and REM sleep.

EPIDEMIOLOGY

Research on the prevalence and patterns of adolescent sleep disorders is both sparse and methodologically limited by differences in definition and measurement. Although large-scale epidemiological studies of sleep disturbances in adolescents are lacking, there are accumulating data on the rates of specific sleep disorders and symptoms. For example, reported prevalence rates for symptoms of insomnia and diagnoses of insomnia in adolescents range from 5–35% and 4–13%, respectively. Among adolescents with insomnia, 7% are reported to have a circadian disorder in which the internal sleep/wake cycle is asynchronous with external cues.

Studies of adolescents in the general population have revealed snoring in 26–29% and diagnoses of OSA in 0.1–3%. Narcolepsy is much less common, with an estimated prevalence across all ages of 4–10 per 10,000.

PATHOPHYSIOLOGY

Sleep Physiology

Laboratory studies suggest that circadian and homeostatic systems are responsible for regulating the sleep and wake processes (Figure 17-1). The circadian pacemaker in the anterior hypothalamus is entrained to the 24-hour day and receives its strongest external cues through phototransduction along the retinohypothalamic tract. The circadian system therefore drives light- or clock-dependent wakefulness. In contrast, the homeostatic system drives sleep propensity, architecture, and duration. Slow wave sleep (SWS), which is proportionally highest when sleep need is greatest, appears to be a marker of homeostatic drive.

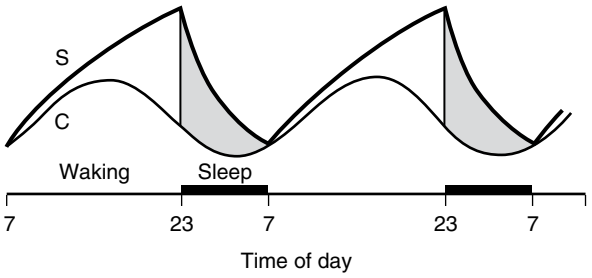


Figure 17-1 Two-process model of sleep regulation: time course of homeostatic process (S) and circadian process (C). Recreated from: Borbely AA, Acherman P: Sleep homeostasis and models of sleep regulation. In Kryger MH, Roth T, Dement WC (eds): *Principles and Practice of Sleep Medicine*. Philadelphia, Saunders, 2000, pp. 377–390. Modified from: Borbely AA: A two-process model of sleep regulation. Hum Neurobiol 1982;1:195–204.

Total daily sleep time and the ratio of NREM to REM sleep decrease steadily across the human lifespan, as shown in Figure 17-2. Children ages 9–10 years sleep approximately 10 hours daily regardless of weekday or weekend, whereas adolescents 14–18 years of age sleep an average of 7.5 hours daily on school days. Despite the decline in sleep time with adolescence, Carskadon and colleagues have demonstrated that 9 hours of sleep daily are required from ages 10 to 17 years. Furthermore, even when sleep duration is held constant in older and younger adolescents, the drive (i.e., need) to sleep appears to be greater in older than in younger adolescents. Developmental trends in sleep behavior during adolescence are summarized in Box 17-1.

Environmental Factors Affecting Sleep

Family, school, extracurricular activities, and work affect sleep pattern and quality. Only 5% of high school students report a set bedtime on school nights, and 85% require an alarm or parent to wake them on school mornings. Early start times for high school are the norm nationwide, with more than a third starting before 7:30 A.M. Several studies have demonstrated that earlier start times are associated with shorter daily sleep times and more daytime sleepiness as measured objectively by the speed of falling asleep in a controlled setting. Other studies of after-school work have demonstrated that high school students employed 20 or more hours weekly have shorter daily sleep times and higher rates of oversleeping in the morning, falling asleep in school, and substance use than students employed less than 20 hours weekly.

Effects of Inadequate Sleep

The literature on inadequate sleep differentiates excessive daytime sleepiness from tiredness or fatigue. Both excessive daytime sleepiness and tiredness are consequences of insufficient or poor-quality sleep, but excessive daytime sleepiness is more severe than tiredness and is more common in adults than adolescents. Excessive daytime sleepiness interferes with alertness and vigilance and is usually associated with clinical syndromes such as narcolepsy and OSA. Tiredness or fatigue may lead to

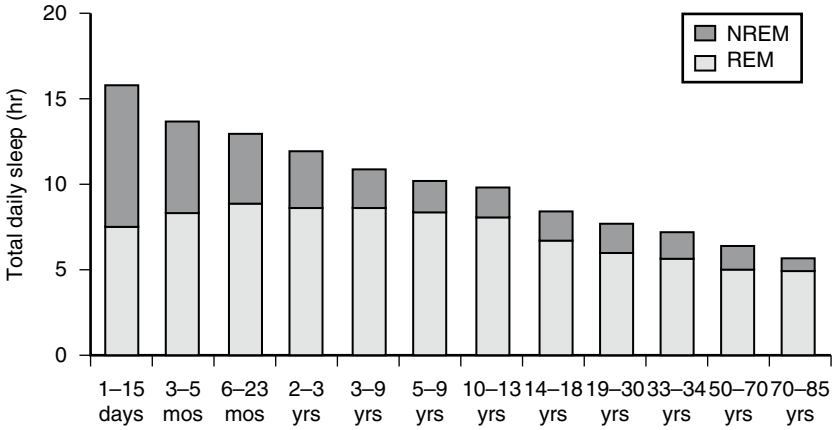


Figure 17-2 Changes in total daily sleep, REM sleep, and NREM sleep with age.
Recreated from: Anders TF, Sadeh A, Appareddy V: Normal sleep in neonates and children. In Ferber R, Kryger M (eds): *Principles and Practice of Sleep Medicine in the Child*. Philadelphia, Saunders, 1995, pp. 7–18. Anders and colleagues state this figure is based on the previously published data source: Roffwarg HP, Munzio JN, Dement WC: Ontogentic development of human sleep-dream cycle. Science 1966;152: 604–619.

adverse long-term sequelae but tends to have limited impact on daytime alertness and vigilance.

Research in adults has demonstrated that insufficient sleep is associated with declines in cognitive function, task performance, vigilance, and mood stability. Studies in adolescents have demonstrated that later bedtimes and shorter sleep times are associated with decreased academic performance, poor concentration, increased daytime tiredness, and sleeping in school. Evidence supports a bidirectional association between adolescent sleep disturbance and mood disorders. In other words, adolescents with sleep problems appear to have diminished mood regulation and adolescents with depression are at increased risk for disordered sleep.

Many studies have explored a potential association of attention-deficit/hyperactivity disorder (ADHD) with sleep problems. Although lack of sleep has clearly been shown to cause decreased attention in controlled settings and parents commonly report sleep problems in children with ADHD, objective measures have not demonstrated consistent differences in the sleep patterns of children with and without ADHD. More recent studies suggest that the inconsistencies may reflect varying adjustment for factors such as pharmacotherapy (e.g., stimulant medications) and comorbid conditions (e.g., depression, anxiety).

Drivers aged 16–29 years constitute the age group with the highest rate of motor vehicle crashes caused by falling asleep at the wheel. The likelihood of a sleep-related crash is nearly five times greater for drivers who sleep less than 5 hours nightly than for those who sleep 8 or more hours nightly.

Box 17-1 Developmental Trends in Adolescent Sleep Practices

- Bedtimes delay over the course of adolescence, especially on weekend nights.
- Rise times delay on weekends but are held in check on weekday by early school start times.
- Total sleep time decreases more on weekdays than weekends.
- The discrepancy between weekday and weekend sleep increases as adolescence progresses.
- The magnitude of this discrepancy is linked to problems such as impaired school performance and depressed mood.

Source: Carskadon MA, Acebo C: Regulation of sleepiness in adolescents: Update, insights, and speculation. Sleep 2002;25:606–614.

EVALUATION AND MANAGEMENT

The adolescent history and physical examination should include an assessment of sleep quality, quantity, and consequences. Owens and Dalzell developed a pediatric screening tool called the "BEARS" that divides sleep-related problems into five broad categories (Box 17-2) and provides sample questions within each category.

When a sleep disorder is suspected, the *International Classification of Sleep Disorders*, 2nd Edition (ICSD-2)

Box 17-2 "BEARS" Pediatric Sleep Assessment

B Bedtime problems
E Excessive daytime sleepiness
A Awakenings during the night
R Regularity and duration of sleep
S Sleep-disordered breathing

Source: Owens JA, Dalzell V: Use of a pediatric sleep screening tool in the primary care setting: A pilot study. J Dev Behav Pediatr 2000;21:389–390.

provides a tool to aid clinical assessment and an organizational system for classification (Box 17-3). This system divides sleep disorders into eight categories based on common complaint, presumed etiology, or organ system from which the problems arise. ICSD-2 defines insomnia as the almost-nightly or nightly complaint of too little sleep or not feeling rested after a night's sleep. Parasomnias are not disorders of sleep/wake regulation but rather are physical phenomena that primarily occur during sleep.

The following sections discuss sleep disorders that are particularly common or important during adolescence: psychophysiologic insomnia, delayed sleep phase syndrome, obstructive sleep apnea, restless legs syndrome, and periodic limb movement disorder.

Psychophysiologic Insomnia (PI)

As outlined in Box 17-4, PI is a conditioned sleep disorder characterized by somatic tension and learned associations that prevent sleep. The patient typically describes a cycle of trying to fall asleep; overconcern about not sleeping; and agitation, which in turn interferes with falling asleep. Without treatment, PI can persist for decades.

The combination of psychological arousal and learned behavioral response has led to clinical trials exploring the efficacy of cognitive behavioral therapy (CBT) for the management of PI. CBT seeks to modify both the dysfunctional attitudes about sleep and the sleep-related practices associated with those attitudes. Well-controlled clinical trials have demonstrated that CBT alone is more effective in the long-term management of PI than CBT plus pharmacotherapy or pharmacotherapy alone. In the short term, CBT plus pharmacotherapy may lead to greater improvement.

There are currently no sleep medications labeled for use in children or adolescents by the U.S. Food and Drug Administration (FDA). In addition, there are no controlled clinical trials examining the efficacy of medication for the treatment of adolescent insomnia. Important issues to consider when prescribing sleep medications for adolescents are potential abuse of the medication and/or interaction with alcohol, marijuana, or other drugs.

In adults, non-benzodiazepines that function as benzodiazepine receptor agonists (NBRAs) are now considered first-line pharmacotherapy for insomnia. Compared with benzodiazepines, NBRAs (e.g., zolpidem, zaleplon) have shorter half-lives, shorter durations of action, and lower rates of abuse.

Box 17-3 ICSD-2 Classification Outline

I	Insomnias
II	Sleep-Related Breathing Disorders
III	Hypersomnias of Central Origin
IV	Circadian Rhythm Sleep Disorders
V	Parasomnias
VI	Sleep-Related Movement Disorders
VII	Isolated Symptoms, Apparently Normal Variants and Unresolved Issues
VIII	Other Sleep Disorders

Source: American Academy of Sleep Medicine: *The International Classification of Sleep Disorders: Diagnostic and Coding Manual*, 2nd ed. Westchester, IL, American Academy of Sleep Medicine, 2005.

Box 17-4 Diagnostic Criteria for Psychophysiologic Insomnia

A conditioned sleep problem and/or arousal in bed characterized by one or more of the following manifestations:

- Excessive focus on and heightened anxiety about sleep.
- Difficulty falling asleep at the desired bedtime or during planned naps, without difficulty falling asleep during monotonous activities when not intending to do so.
- Ability to sleep better away from home than at home.
- Mental arousal in bed characterized either by intrusive thoughts or a perceived inability to volitionally cease sleep-preventing mental activity.
- Heightened somatic tension in bed reflected by a perceived inability to relax the body sufficiently to allow the onset of sleep.

Source: American Academy of Sleep Medicine: *The International Classification of Sleep Disorders: Diagnostic and Coding Manual*, 2nd ed. Westchester, IL, American Academy of Sleep Medicine, 2005.

Delayed Sleep Phase Syndrome (DSPS)

A circadian rhythm disorder called DSPS is thought to be the cause of insomnia in 7% of adolescents, compared with 0.7% of adults. The underlying mechanism is asynchrony between the internal pacemaker and external time. Bedtime is delayed until 2:00 to 6:00 A.M., and wake time is delayed until 10:00 A.M. to 6:00 P.M. Daytime function is characterized by oversleeping on school days, falling asleep in class, poor school performance, after-school naps, and catch-up sleeping on weekends. When the adolescent is allowed to sleep on the preferred schedule, sleep quality is normal and sleep complaints resolve.

The treatment of DSPS always involves a change in the timing of sleep in an effort to synchronize the circadian rhythm with the desired sleep/wake schedule. When sleep onset is delayed by 3 hours or less, treatment involves "phase advance," in which sleep and wake times move earlier by 15 minutes daily until the desired bedtime

is achieved (Figure 17-3). In some cases, setting the wake time at the targeted goal from the beginning of treatment promotes bedtime sleepiness and hastens the phase advance. When sleep onset is delayed by more than 3 hours, phase delay (i.e., chronotherapy) is recommended. Although this approach takes advantage of the tendency for an adolescent's endogenous pacemaker to delay sleep, staying awake becomes increasingly difficult. The success of chronotherapy depends on adolescent motivation and parental support.

Phototherapy and low-dose (1–3 mg) melatonin are adjunctive interventions for DSPS. Patients with mild DSPS may improve with morning exposure to natural sunlight and evening avoidance of bright lights. Those with moderate or severe DSPS usually require bright-light (e.g., 10,000-lux) exposure via a light box or therapeutic lamp 20–30 minutes daily for 2–4 weeks. Regardless of the treatment, success depends on daily adherence to the new sleep and wake times.

Obstructive Sleep Apnea (OSA)

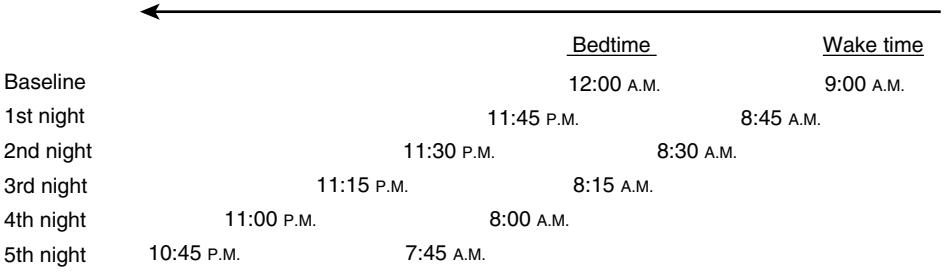
Sleep-disordered breathing (SDB) refers to the continuum of respiratory conditions ranging from primary snoring to OSA (Figure 17-4). OSA is characterized by repetitive episodes of partial or complete obstruction of the upper airway during sleep that results in hypoxemia, hypercapnia, and/or respiratory arousals. Multiple arousals resulting from apneic events lead to sleep fragmentation and daytime dysfunction. The prevalence of childhood OSA is highest at 2–6 years when lymphoid hyperplasia peaks and during adolescence. The adolescent surge in OSA also reflects the rapid weight gain of puberty and resulting obesity for many youth. SDB is four to five times more common in obese than non-obese children.

The mechanisms for pediatric OSA include adenotonsillar hypertrophy; increased upper airway resistance associated with fatty tissue in the throat, neck, and chest wall; alteration of the central ventilatory drive; and craniofacial anomalies causing upper airway narrowing and decreased neuromuscular tone. Daytime symptoms of OSA may include excessive daytime sleepiness, difficulty waking in the morning, mood dysregulation, externalizing behavioral problems, inattention, poor concentration, and distractibility. There is accumulating evidence suggesting that OSA and/or poor-quality sleep increase the risk for obesity and cardiovascular morbidity in children and adolescents.

The treatment of OSA depends on its cause. Tonsillectomy and adenoidectomy (T&A) is indicated for patients with adenotonsillar hypertrophy. Although this usually results in resolution of the OSA, close postoperative monitoring is essential because 32% of subjects with PSG-documented OSA develop acute complications such as hemorrhage or respiratory decompensation. Nasal continuous positive airway pressure (CPAP) should be considered for patients who do not respond to T&A or for whom surgery is not indicated. Although several studies have demonstrated its efficacy for the treatment of pediatric OSA, side effects are common and limit compliance

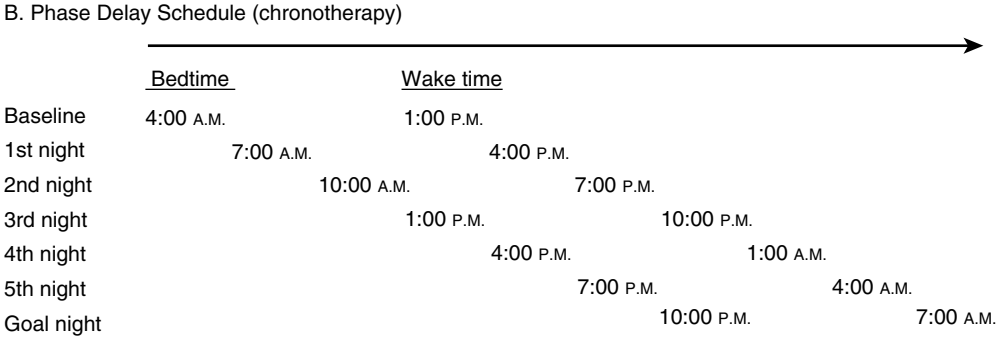
Figure 17-3 Circadian rhythm treatment.

A. Phase Advance Schedule



(Advance bedtime/wake time by 15 minutes nightly until desired schedule is reached)

B. Phase Delay Schedule (chronotherapy)



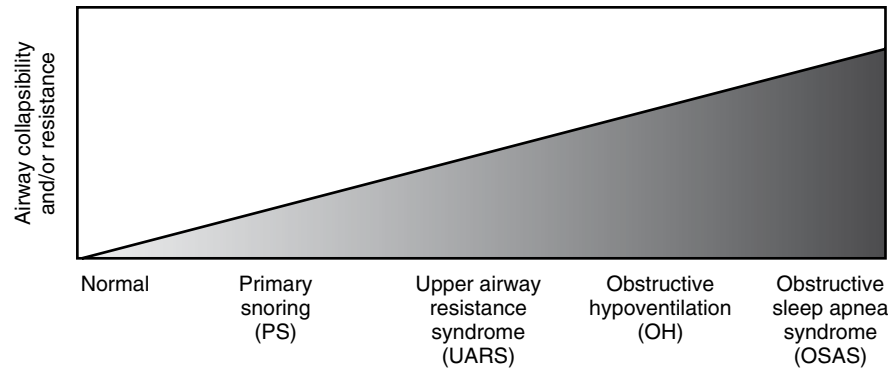


Figure 17-4 Spectrum of sleep-disordered breathing in adolescents.
Recreated from: Katz ES, Marcus CL: Diagnosis of obstructive sleep apnea syndrome in children. In Sheldon SH, Ferber R, Kryger MH, et al. (eds): *Principles and Practice of Pediatric Sleep Medicine*. Philadelphia, Elsevier Saunders, 2005, pp. 197–210. Katz et al. adapted this figure from Loughlin GM: Obstructive sleep apnea syndrome in children: Diagnosis and management. In Loughlin GM, Carroll JL, Marcus CL (eds): *Sleep and Breathing in Children: A Developmental Approach*. New York, Marcel Dekker, 2000, pp. 625–650.

with nightly use. Common complaints include nasal congestion, dryness, and rhinorrhea; eye irritation; facial dermatitis; claustrophobia; and difficulty exhaling. Desensitization training and/or work with a behavioral psychologist may improve adherence. Although weight loss is routinely recommended for all obese adolescents, there is little published research regarding its effectiveness in the treatment of adolescent OSA. Oral appliances have been used effectively in adults with mild OSA and in those who could not tolerate CPAP, but there is little evidence to support their use in children and adolescents. Nasal steroids may help mild OSA in children, but pharmacotherapy generally is of limited benefit.

Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD)

RLS is described as unpleasant sensations in the legs at night that are relieved by leg movement and that interfere with sleep. PLMD is characterized by periodic episodes of repetitive, stereotypic movements of the legs and/or arms that occur during sleep and often lead to partial or full awakening. The minimum diagnostic criteria for PLMD include documentation on PSG of limb movements with the following characteristics: duration of 0.5–5 seconds, amplitude > 25% of toe dorsiflexion during calibration; more than four movements in sequence; episodes separated by an interval > 5 seconds and < 90 seconds; more than five episodes hourly in children; and disturbed sleep and/or daytime fatigue. More than 90% of children with PLMD in a clinically referred sample met the criteria for ADHD.

Patients with RLS and low serum ferritin have been shown to improve with iron supplementation. Symptom management of both RLS and PLMD in adults typically includes pharmacotherapy with agents such as carbidopa-levodopa, pergolide, pramipexole, benzodiazepines, or gabapentin.

Narcolepsy

Narcolepsy is a chronic neurological condition that is characterized by dysregulation of REM sleep and extreme daytime sleepiness. Classic symptoms include cataplexy, or the sudden loss of muscle tone triggered by strong emotion (e.g., laughter, surprise, anger, sadness); auditory, visual, and/or sensory hallucinations during the transition to/from sleep; sleep paralysis, or the inability to move or talk during the transition to/from sleep; and sleep attacks when sedentary and understimulated. Untreated narcolepsy can lead to high levels of functional impairment associated with extreme daytime sleepiness.

The treatment of narcolepsy includes stimulant medications such as methylphenidate and dextroamphetamine. More recently, agents promoting alertness, such as modafinil, have been successfully used to treat narcolepsy. When cataplexy is severe and causes functional disability or places an individual at risk for injury, REM-suppressant agents such as tricyclic antidepressants and serotonin reuptake inhibitors may be used. However, because there are no randomized clinical trials of medication efficacy in adolescents with narcolepsy, caution must be taken when using pharmacological treatment. In addition to medication, treatment should also include patient education and psychosocial support, maintenance of appropriate sleep hygiene, use of short restorative naps when indicated, and avoidance of activities that may pose a safety risk (e.g., driving).

MAJOR POINTS

- The interaction between the biological and sociocultural determinants of sleep results in a developmental vulnerability for sleepiness during the teenage years.
- Children ages 9–10 years sleep approximately 10 hours daily regardless of weekday or weekend, whereas adolescents 14–18 years of age sleep an average of 7.5 hours daily on school days. Despite the decline in sleep time during adolescence, 9 hours of daily sleep are required from ages 10–17 years.
- Studies in adolescents have demonstrated that later bedtimes and shorter sleep times are associated with decreased academic performance, poor concentration, increased daytime tiredness, and sleeping in school.
- Psychophysiologic insomnia is a conditioned sleep disorder characterized by somatic tension and learned behavioral associations that prevent sleep. Cognitive behavioral therapy has been shown to be effective for long-term management.
- Delayed sleep phase syndrome is asynchrony between the internal pacemaker and external time. Treatment involves resetting the internal clock through incremental change in sleep and wake times and/or phototherapy.
- Obstructive sleep apnea is characterized by repetitive episodes of partial or complete obstruction of the upper airway during sleep that results in hypoxemia, hypercapnia, and/or respiratory arousals. Treatment depends on underlying cause, such as T&A for tonsillar hypertrophy and CPAP.
- Restless legs syndrome consists of unpleasant sensations in the legs during rest that are relieved with leg movement and interfere with sleep. Usual treatment in adults includes pharmacotherapy.
- Narcolepsy is characterized by dysregulation of REM sleep and extreme daytime sleepiness and is typically associated with cataplexy, sleep attacks, sleep paralysis, and hallucinations when transitioning to/from sleep. Treatment includes psychostimulant medication.

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CHAPTER 18

Back, Hip, and Knee Disorders

JAMES R. EBERT, MD, MBA

INTRODUCTION

The spine, hips, and knees are greatly affected by the acceleration in growth during adolescence. Activation of key growth plates in the vertebrae, femur, and tibia are responsible for the normal skeletal elongation as well as many of the musculoskeletal problems that characterize adolescence. This chapter focuses on conditions of the back, hip, and knee that present during adolescence. The first section reviews scoliosis, kyphosis, lordosis, and back pain. The second section reviews slipped capital femoral epiphysis, Legg-Calvé-Perthes disease, and hip fracture. The third section reviews the common causes of acute and chronic knee pain in adolescents. The common developmental anomalies are defined, and strategies for early detection and appropriate referral are discussed.

DISORDERS OF THE BACK

Vertical growth of the spine accelerates early in puberty and continues at a slower pace up to age 25 years. Normal spinal elongation depends on synchrony between the superior and inferior growth plates located within each vertebral body, as well as on the structural integrity of the vertebral bones and disc spaces. Asynchrony in vertebral growth or alignment therefore can result in accentuated spinal curvature laterally (i.e., scoliosis), posteriorly (i.e., kyphosis), or anteriorly (i.e., lordosis) (Table 18-1). These developmental anomalies are described next, followed by an approach to the evaluation and management of adolescents with back pain.

Scoliosis

Scoliosis refers to abnormal alignment of the vertebral bodies in the anteroposterior, or frontal, plane. Most scoliotic deformities detected during the second decade of life are idiopathic. However, scoliosis can be secondary to leg-length discrepancy or congenital anomalies of vertebral structure; neuropathic disorders such as cerebral

Table 18-1 Direction of the Convexity and Spinal Regions Affected in Scoliosis, Kyphosis, and Lordosis

Term	Convexity	Regions
Scoliosis	Lateral	Thoracic, lumbar
Kyphosis	Posterior	Thoracic
Lordosis	Anterior	Cervical, lumbar

palsy, spinal cord tumor or trauma, and poliomyelitis; and myopathic disorders such as muscular dystrophy. Leg lengths that differ by as little as 0.5 cm can produce pelvic tilting toward the shorter side and spinal convexity toward the longer side. Any adolescent with leg-length discrepancy who is still growing should be referred for orthopedic evaluation. Congenital scoliosis usually presents before adolescence and is commonly associated with spinal cord (40%), genitourinary (20%), and cardiac (10%) malformations. Although congenital scoliosis typically presents before age 10 years, it progresses in 75% of patients during the rapid growth phase of adolescence. Neuromuscular scoliosis tends to progress steadily and should be treated early and monitored closely with periodic radiographs.

Idiopathic scoliosis has no known cause, tends to be milder than secondary scoliosis, and is characterized by its age at onset. Adolescent idiopathic scoliosis begins at age 11 years, is far more common than juvenile and infantile scoliosis, and is more likely to occur and to progress in girls than boys. Family history is positive in 30% of adolescents with idiopathic scoliosis, but no specific gene or pattern of inheritance has been identified. Right thoracic curves are most common, followed by combined right thoracic, left lumbar, and isolated left lumbar.

Screening asymptomatic adolescents for scoliosis through school programs and primary care visits is common in North America despite limited evidence of its cost-effectiveness. In adolescents aged 11 years and older, prevalence estimates are 2.5% for curves of at least 10 degrees and 0.1–1.0% for curves greater than 20%. Using the forward bend test (see below) as a screen for scoliosis, referral rates for positive tests range from 3–30%. The variability in false-positive rates and the concern about unnecessary treatment of mild scoliosis led the U.S. Preventive Services Task Force (USPSTF) to recommend against the routine screening of asymptomatic adolescents. The USPSTF wrote that it had not found good evidence that screening was associated with earlier detection of idiopathic scoliosis and that it had found at least fair evidence that the harms of screening may outweigh the benefits. In Guidelines for Adolescent Preventive Services (GAPS), the American Medical Association concurs with the USPSTF and makes no recommendation for routine scoliosis screening. In contrast, both the American Academy of Pediatrics and the U.S. Maternal and Child Health Bureau recommend annual screening of adolescents during routine primary care visits (see Chapter 2).

The physical examination for scoliosis begins with visual inspection of the back, waistline, and shoulders while the adolescent is standing with the feet together and the arms by the sides. The adolescent then should bend forward with the head and hands hanging toward the floor, and the back should be inspected for lateral curvature of the spine, elevation of the hemithorax, and protrusion of the scapula (Figure 18-1).

If the forward bend test, with or without a scoliometer, reveals evidence of scoliosis, standing posteroanterior and lateral radiographs of the entire spine should be obtained. The Cobb method can then be used to estimate the angle between the most tilted vertebrae at both ends of the curve (Figure 18-2). Lines perpendicular to the proximal end-plate of the upper vertebra and the distal end-plate of the lower vertebra are drawn. The angle of their intersection estimates the degree of curvature. This radiographic examination is considered the standard for quantifying the scoliotic curve.

The management of idiopathic scoliosis depends on the magnitude of the curve and the likelihood of progression, which in turn depends on curve magnitude, curve location, and skeletal maturity. Ossification of the iliac crest apophysis on the spinal radiograph, rated by Risser sign from zero (no ossification) to five (complete ossification), provides a reliable measure of skeletal maturity. The likelihood of curve progression during adolescence increases with lower Risser sign, younger age, premenarcheal status in girls, larger curve angle at diagnosis, thoracic location, and double curve pattern. Once skeletal maturity is achieved, the major determinants of progression during adulthood are a Cobb angle above 50 degrees, vertical rotation above 30 degrees, and thoracic location. Adult sequelae of untreated adolescent idiopathic scoliosis include the psychological impact of the spinal deformity, chronic back pain, and restrictive lung disease for curves above 100 degrees.

Orthopedic consultation for adolescents with idiopathic scoliosis is recommended if the curvature exceeds

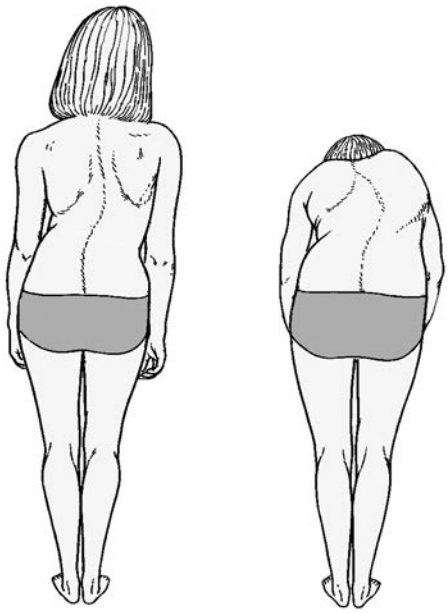


Figure 18-1 Examination of the spine.

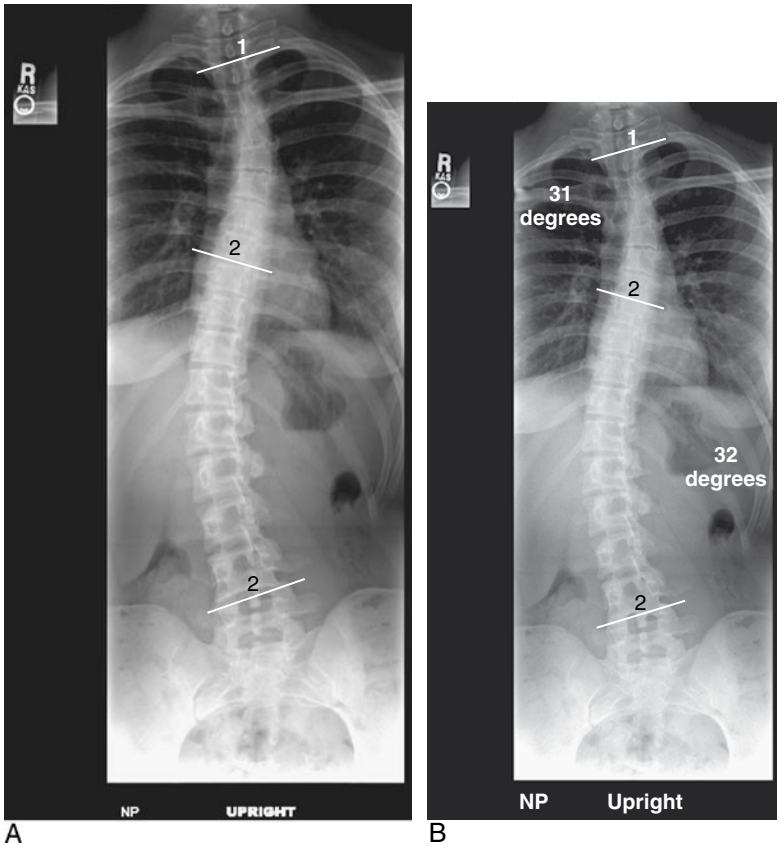


Figure 18-2 **A.** Posteroanterior radiograph of the spine showing adolescent idiopathic scoliosis. **B.** Radiographic determination of the Cobb angle in the same patient.

10 degrees or progresses at least 5 degrees between examinations. Curves less than 25 degrees are followed by serial examination alone. Although bracing typically is recommended for curves of 25–40 degrees, there is no evidence that it results in long-term correction of the curvature. Surgery is reserved for patients with idiopathic scoliosis exceeding 45 degrees. The usual procedures are implantation of internal fixation rods and fusion of the affected vertebrae.

Kyphosis

Kyphosis is posterior curvature of the thoracic spine that exceeds the normal range of 20–45 degrees. Scheuermann kyphosis is characterized by anterior wedging of the vertebral bodies and irregularities of the vertebral end-plates at three or more levels, with consequent inability to correct the round back by active hyperextension. This is in contrast to postural round back, which is characterized by normal vertebrae and disc spaces, temporary correction with active hyperextension, and long-term improvement with hyperextension exercises of the back. The prevalence of Scheuermann kyphosis is 4–8%. Males are twice as likely to be affected as females, and the risk of severe disease appears particularly high in tall males. The cause remains unknown, although there is some evidence that transient osteoporosis following prolonged immobilization may result in vertebral compression fractures with subsequent wedging.

Pain is the usual presenting complaint of patients with Scheuermann kyphosis. It is gradual in onset, has no clear precipitating event, is worse with activity, and improves with rest. When the adolescent bends forward at the waist, examination from the side reveals sharp angulation of the thoracic spine. The most commonly affected vertebrae are T7–T9 and T10–T12. Radiographic examination of the entire spine should be performed with standing lateral and posteroanterior views. Oblique views should also be considered because of the association of Scheuermann kyphosis with spondylolysis (see below). All patients with Scheuermann kyphosis warrant orthopedic consultation. Observation may be all that is required for adolescents with non-progressive curves that are less than 50 degrees. Bracing or surgery is indicated for larger or rapidly progressive curves to prevent chronic pain and impaired pulmonary function.

Spondylolysis and Spondylolisthesis

The words spondylolysis and spondylolisthesis are derived from the Greek *spondylos* (vertebra), *lysis* (break), and *listhesis* (slipping). Spondylolysis is a unilateral or bilateral defect in the pars interarticularis, which is the narrow neck of bone between the superior and

inferior articular processes that extend posteriorly from the vertebral body. Spondylolisthesis is the forward slippage of one vertebra on the vertebra below it. The severity is expressed as a percentage, ranging from grade I (0–25%) to grade V (more than 100%). The percentage is calculated as 100 times the ratio of the forward displacement to the vertebral width. The forward displacement is the misalignment of the superior to inferior vertebrae, measured in millimeters. Vertebral width is the anteroposterior width of the inferior vertebra.

In children and adolescents, the most common causes of spondylolysis and spondylolisthesis are congenital dysplasia of the articular processes and acquired deformities of the pars. Activities involving spinal impact and hyperlordosis, such as gymnastics and wrestling, increase the risk of acute fracture, chronic separation, and elongation of the pars. Spondylolysis and spondylolisthesis are more common in adolescent males than females, but progressive slippage is more likely in females than males.

The signs and symptoms of spondylolysis and spondylolisthesis are back pain, tight hamstrings, bent-knee gait, bent-hip gait, and nerve root impingement with higher-grade slippage. If the oblique, anteroposterior, and lateral radiographs of the spine are unremarkable, bone scan or CT scan should be considered (Figure 18-3).

Asymptomatic spondylolysis requires no treatment. If pain is present, activities involving impact and hyperextension should be discontinued. Physical therapy can help with exercises to stretch tight hamstrings and strengthen anterior spinal and abdominal muscles.

The treatment of spondylolisthesis is determined by the adolescent's symptoms and the radiographic measure of slippage (Figure 18-4). Asymptomatic patients with grade I spondylolisthesis are followed with observation alone. Patients with painful grade I slippage are candidates for bracing. Surgery is indicated for patients with slippage that is progressive or grades III–V and for those with nerve impingement. The usual procedure involves fusion of the L4 and L5 vertebrae to the sacrum.

Back Pain

Back pain is more likely to have a discernable etiology in adolescents than adults. Although self-limited muscle strain is the most common cause, the developmental conditions discussed earlier in this chapter and the inflammatory, infectious, and neoplastic processes summarized in Box 18-1 should always be considered. Psychogenic back pain is a diagnosis of exclusion, particularly when the pain awakens the adolescent at night or is associated with neurologic findings, fever, weight loss, or other systemic signs of illness.

Adolescents are much less likely than adults to have degeneration of the disc with herniation of the nucleus pulposus. When degenerative disc disease does occur in adolescents, it often follows acute trauma or is precipitated by an underlying developmental anomaly such as Scheuermann kyphosis.

Infectious causes of back pain in adolescents include vertebral osteomyelitis, epidural abscess, paraspinal muscle abscess, pyelonephritis, pelvic inflammatory disease, and pneumonia. Discitis probably represents a low-grade, self-limited bacterial infection of the intervertebral disc space. The incidence peaks in early childhood and is rare in adolescence. Although the etiology of discitis remains uncertain, the limited data that are available suggest that the high vascularity of the disc space in young children contributes both to hematogenous seeding and an aggressive immune response that contains the local infection. Fever is reported in fewer than 25% of patients, the white blood cell count typically is normal, and blood cultures are negative. In more than 90% of patients, however, the erythrocyte sedimentation rate is elevated. Magnetic resonance imaging (MRI) often shows changes in the vertebral end-plates in addition to the expected inflammatory changes of the disc, suggesting an association between discitis and early vertebral osteomyelitis. Despite its uncertain cause, discitis usually is treated with intravenous antibiotics until the pain diminishes, followed by several weeks of oral antibiotics.

Spondyloarthropathy is an important consideration in the adolescent with persistent back pain. The term refers to a group of arthritides that begin during the second decade of life and involve the sacroiliac joint and/or large joints of the lower extremities. Specific diagnoses within this group include juvenile ankylosing spondylitis, Reiter syndrome, psoriatic arthritis, and the axial arthropathy associated with inflammatory bowel disease. The history should include questions about morning stiffness, weight loss, abdominal pain, diarrhea, and blood per rectum. Physical examination may reveal limitation on flexion of the waist or hips and asymmetrical arthritis of the knees or ankles. Erythrocyte sedimentation rate may be normal or elevated, and antinuclear antibodies may be positive in patients with psoriatic arthritis. Rheumatoid factor is typically negative. MRI is the most sensitive study for the detection of early sacroiliitis. If spondyloarthropathy is diagnosed or suspected, referral to a rheumatologist is warranted.

DISORDERS OF THE HIP

Adolescents with problems related to the hip usually present with pain. Its location can be misleading, however, because the first symptom of hip disease may be pain referred to the knee. Similarly, patients with disorders of the lumbosacral spine may present with pain referred to the hip or knee. Any adolescent with hip pain, knee pain, or limp should therefore have a careful examination performed of the spine, hips, and knees.

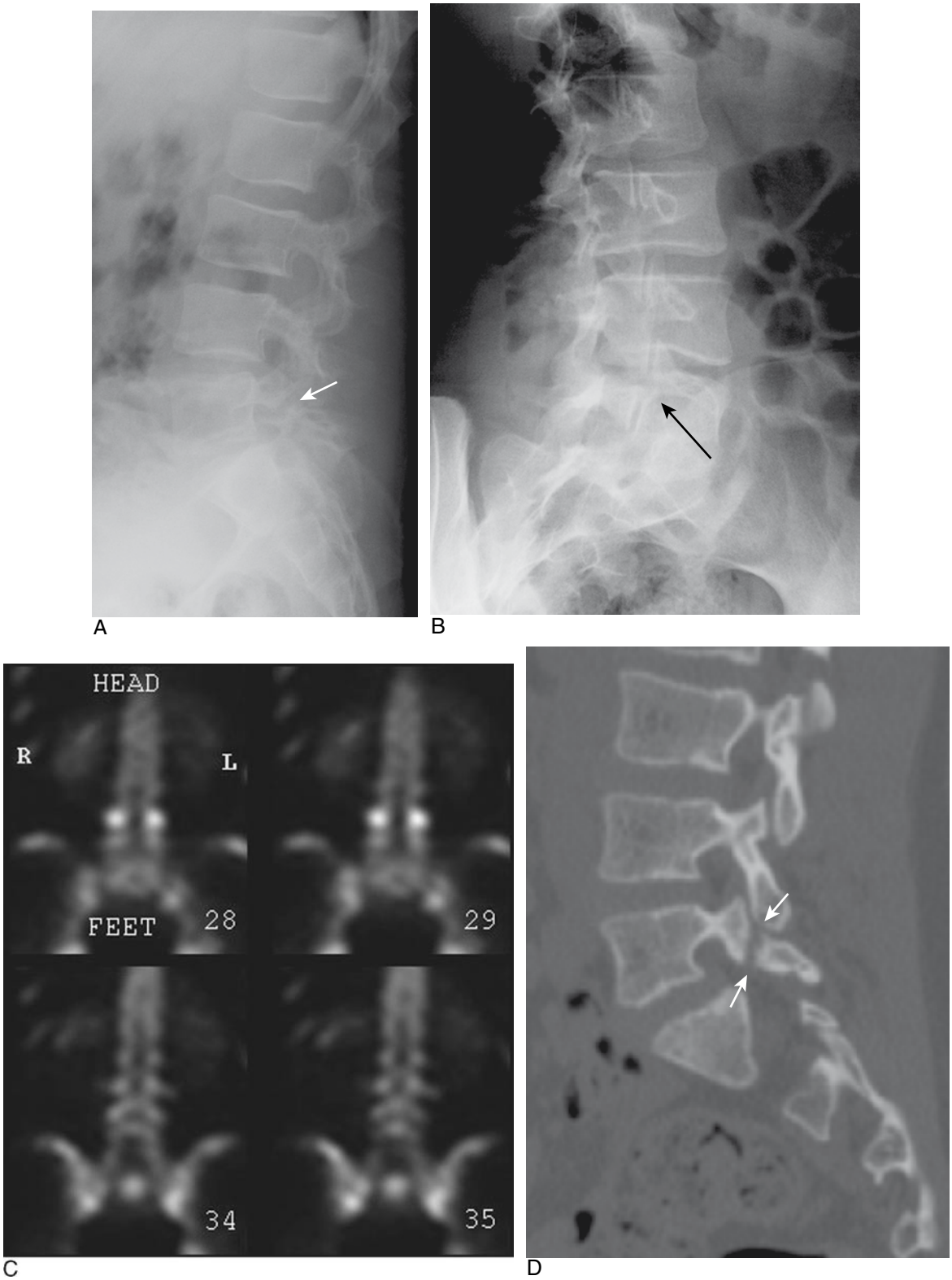


Figure 18-3 **A.** Radiograph of spondylolysis with arrow pointing to lysis of pars interarticularis. **B.** Oblique view in the same patient. **C.** SPECT scan demonstrating L5-S1 spondylolysis. **D.** Computed tomography with arrows demonstrating spondylolysis.

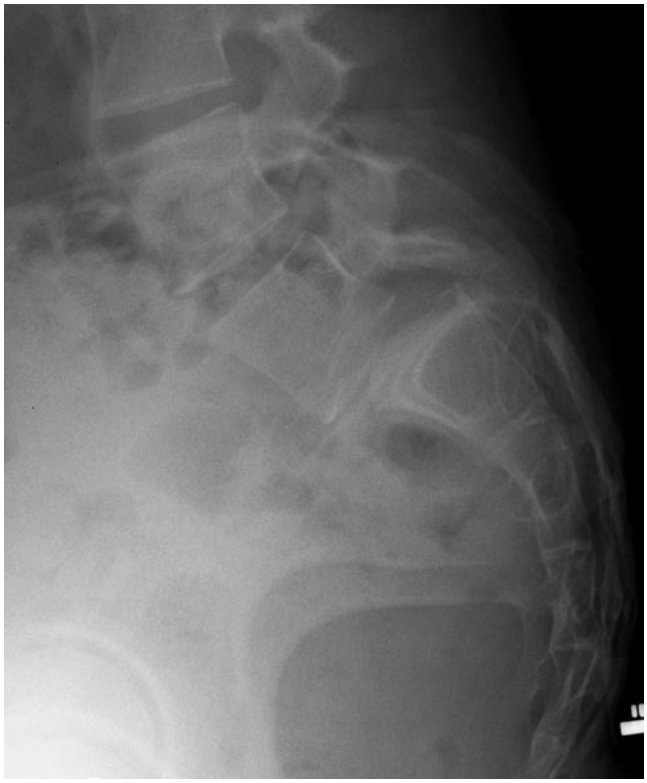


Figure 18-4 Lateral radiograph of the spine showing nearly 50% slippage in an adolescent with grade II spondylolysthesis.

Examination of the adolescent's gait is essential when a hip disorder is suspected. Unilateral disease may result in a tendency to lean over the affected hip (Trendelenburg gait) or to unload the affected leg more quickly than the unaffected leg (antalgic gait). The clinician also should examine hip range of motion when the adolescent is in the supine position. If pain is elicited when the clinician holds the thigh and rolls the entire leg in and out (log-roll test), the hip is the probably source of the pain.

Slipped Capital Femoral Epiphysis

Slipped capital femoral epiphysis (SCFE) is a hip disorder of early to mid-adolescence in which the normal alignment of the femoral head and neck is disrupted by slippage at the epiphyseal plate. The name of the disorder is misleading because the femoral head remains in the acetabulum while the femoral neck moves proximally and anteriorly. The onset of SCFE correlates with the peak height velocity at approximately ages 10–13 years for girls and 12–15 years for boys. Although the left hip is more commonly involved than the right, bilateral involvement occurs in at least 20% of cases. The annual incidence of SCFE ranges from 0.2 per 100,000 in Japan to 10 per 100,000 in the northeastern United States. Males outnumber females at a ratio of 1.4 to 1.0. The major risk factor for SCFE is obesity, and the age of presentation is younger for obese than non-obese children.

Box 18-1 Differential Diagnosis of Back Pain in Adolescents

- Mechanical and Developmental
  - Acute muscle strain
  - Overuse injury
  - Fracture
  - Herniated nucleus pulposus
  - Spondylolysis
  - Spondylolisthesis
  - Scheuermann kyphosis
  - Advanced scoliosis
- Inflammatory and Infectious
  - Juvenile rheumatoid arthritis
  - Ankylosing spondylitis
  - Other rheumatological conditions
  - Discitis
  - Vertebral osteomyelitis
  - Tuberculous spondylitis
  - Pneumonia
  - Pelvic inflammatory disease
  - Appendicitis
  - Pyelonephritis
  - Retroperitoneal abscess
- Neoplastic
  - Leukemia/lymphoma
  - Ewing sarcoma
  - Spinal cord and meningeal tumors
  - Rhabdomyosarcoma
  - Metastatic tumors
  - Benign tumors
- Psychogenic

The presentation of SCFE is highly variable. The pain may be sudden or insidious in onset; constant or intermittent; and may localize to the hip, knee, or thigh. In 90% of cases there is no history of trauma or temporal association with a particular event. Inability to walk indicates severe slippage and risk for subsequent osteonecrosis. More commonly, the patient presents with a waddling gait and lateral rotation of the affected leg. On physical examination, the log-roll test produces pain with lateral rotation of the thigh and marked limitation of motion with medial rotation. Importantly, isolated movement of the knee when the thigh and hip are stabilized causes no pain.

When SCFE is suspected, radiographic examination of the hip should be obtained with anteroposterior (AP) and lateral views in the frog-leg position. The AP view demonstrates widening of the physis and displacement of the femoral neck proximally and anteriorly. The lateral view demonstrates posterior displacement of the epiphysis relative to the femoral neck (Figure 18-5).

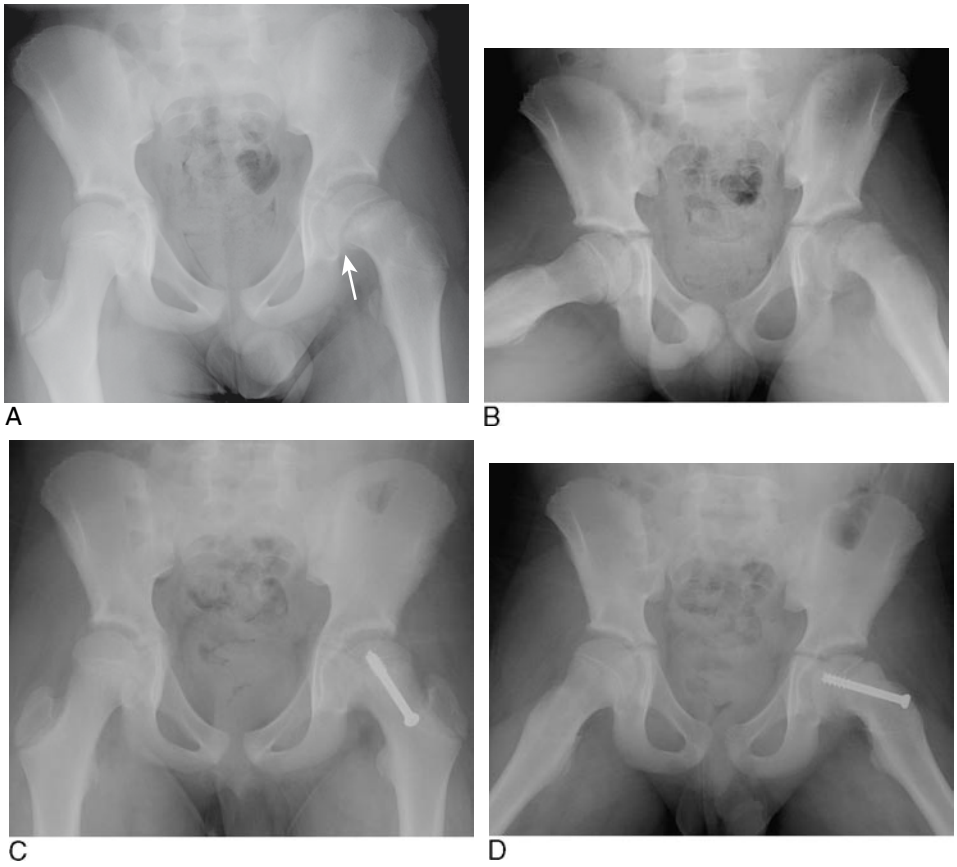


Figure 18-5 **A.** Anteroposterior radiograph of the hip showing slipped capital femoral epiphysis with arrow pointing to the site of slippage. **B.** Frog-leg view of the same patient. **C.** Anteroposterior view of the same patient following in-situ screw fixation. **D.** Frog-leg view of the same patient following in-situ screw fixation.

SCFE is an orthopedic emergency. The patient should be hospitalized and restricted to bed rest upon diagnosis. The operative procedure of choice is single-screw fixation to prevent further slippage. Intentional reduction of the existing displacement increases the risk of osteonecrosis and should not be attempted. A second procedure can be performed later, when the physis has closed, if limited mobility or pain persists.

The outcome of SCFE is related to the degree of slippage and the operative success of stabilization. The major adverse outcomes are osteonecrosis and chondrolysis, or dissolution of the cartilage of the hip joint. Improvements in operative technique have led to decreases in the rates of both complications.

Legg-Calvé-Perthes Disease

Legg-Calvé-Perthes disease is most common in children between the ages of 4 and 8 years. It is mentioned in this chapter because it can present as late as age 12 and carries a poorer prognosis for adolescents than younger children. Legg-Calvé-Perthes disease involves a temporary decrease in blood flow to the femoral head, with subsequent remodeling and structural deformity. The pathophysiology is divided into four phases: (1) synovitis, lasting up to 3 weeks; (2) osteonecrosis, lasting up to 1 year; (3) fragmentation of the femoral head, lasting approximately 1 year; and (4) revascularization and remodeling, lasting up to 3 years. The cause of Legg-Calvé-Perthes disease is unknown, but its association with hypercoagulation disorders (e.g., deficiencies of protein C or S) suggests that impaired venous drainage and increased pressure in the femoral head may cause the transient decrease in arterial supply. The variability in age of onset and phase duration leads to variability in presentation. Limping and pain tend to be most severe in phases 1 and 3. Once the permanent flattening of the femoral head occurs in phase 4, there may be shortening of the affected leg.

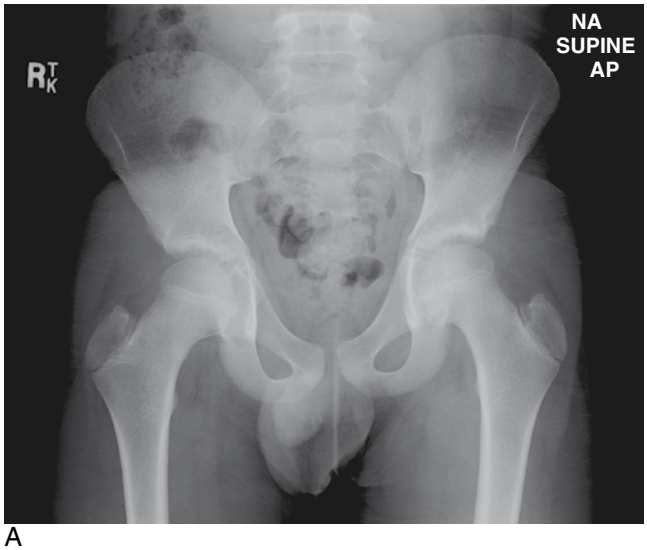
The evaluation of patients with suspected Legg-Calvé-Perthes disease includes AP and frog-leg radiographic views of the hip. Once the diagnosis is confirmed, laboratory studies should be performed to exclude coagulopathy and other causes of osteonecrosis, and the patient should be referred for orthopedic evaluation. Milder cases can be managed with bed rest, traction, crutches, physical therapy, bracing, and/or casting. More severe

cases require surgery to obtain better containment of the femoral head within the acetabulum.

Stress Fracture

Stress fracture of the femoral neck is the most serious overuse injury involving the hip and is usually associated with distance running. Stress fractures of the inferior pubic ramus, superior pubic ramus, and ischial ramus are less common overuse injuries, usually seen in females with amenorrhea. The incidence of stress fracture, regardless of site, increases with age. The pathophysiology involves repeated loading of the bone with accumulated microtrauma resulting in the development of a bony defect.

Stress fractures of the hip and pelvis present with pain in the hip, groin, or knee that worsens with physical activity and improves with rest. With femoral neck fracture, there may be tenderness of the groin and hip range of motion is decreased. With pelvic stress fracture, hip range of motion may be normal but there usually is pain on palpation of the affected bone and difficulty standing on one leg. Radiographs may not reveal small or early stress fracture. If the diagnosis is strongly suspected, bone scan or MRI is indicated (Figure 18-6).



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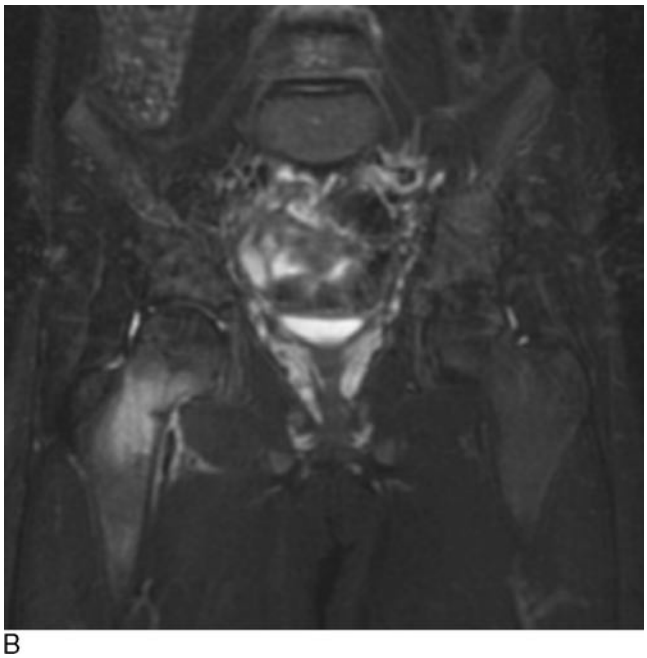

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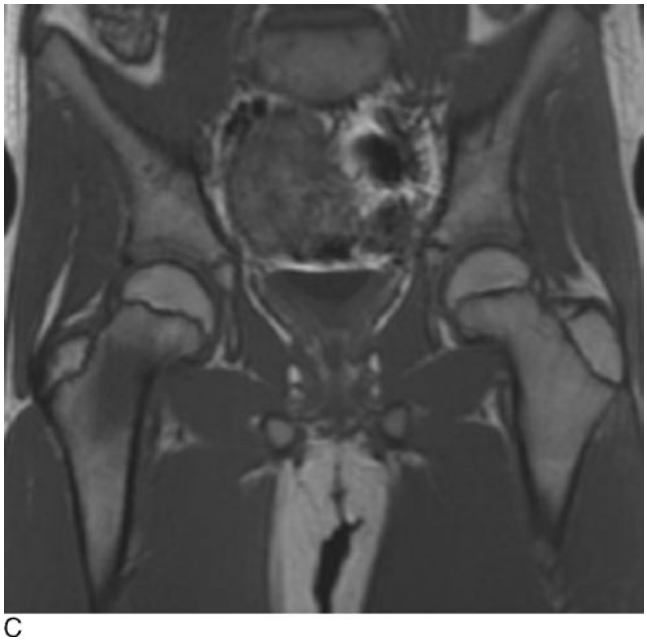

C

Figure 18-6 **A.** Anteroposterior radiograph showing a stress fracture in the neck of the right femur. **B.** T1-weighted magnetic resonance imaging of the same patient. **C.** T2-weighted magnetic resonance imaging of the same patient.

Treatment depends on the location of the fracture. Stress fracture of the superior femoral neck may require surgical repair to prevent complete fracture and displacement. Fractures involving other portions of the femoral neck or pelvis may heal adequately with restriction of activity until the patient is free of pain.

Avulsion Fractures of the Pelvic Apophyses

Pelvic avulsion fracture peaks during the adolescent growth spurt and is caused by the forceful contraction of a muscle against an immature apophysis. The three most common types involve the anterior superior iliac spine, where the sartorius muscle originates; the anterior inferior iliac spine, where the rectus femoris originates; and the ischial tuberosity, where the hamstrings and adductors originate (Table 18-2).

Hip or groin pain is the usual presenting symptom, with tenderness or swelling over the involved apophysis. Plain radiographs may appear normal until compared with radiographs of the unaffected hemipelvis or may show obvious displacement at the fracture site (Figure 18-7 and Figure 18-8). Normal radiographs in the patient with persistent pain suggest traction apophysitis without fracture and warrant bone scan or CT scan.

The treatment of pelvic avulsion fracture begins with crutches until callus is evident radiographically, followed by limited weight-bearing and positioning so as to minimize traction of the muscle on the injured apophysis. Avulsions with displacement of 2 cm or more may require open reduction and internal fixation.

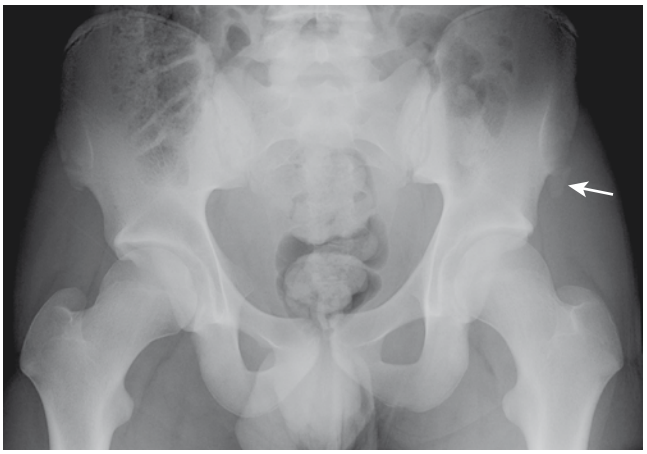

Figure 18-7 Anteroposterior radiograph of the pelvis showing an avulsion fracture of the anterior inferior iliac spine. Arrow indicates the site of fracture.

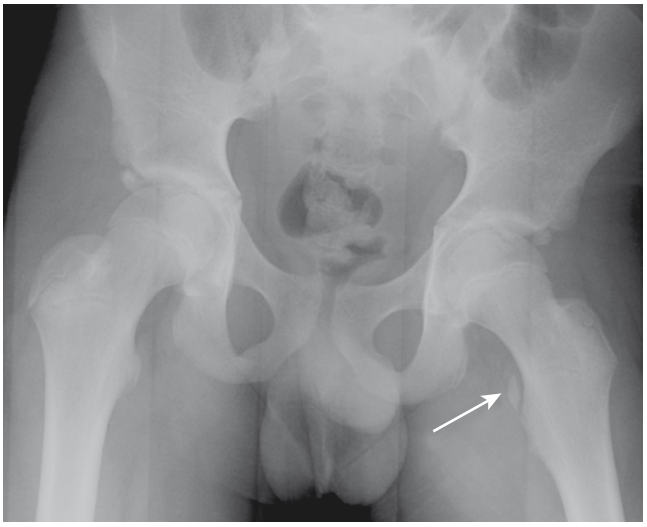

Figure 18-8 Anteroposterior radiograph of the pelvis showing an avulsion fracture of the lesser trochanter of the left femur.

DISORDERS OF THE KNEE

Knee disorders during adolescence typically involve the interface between bone, cartilage, and tendon. The rapid skeletal growth during puberty coupled with the athleticism of many teens increases the likelihood of both overuse and acute injury to the knee. The initial evaluation of an adolescent with knee pain should focus on identifying those conditions that warrant prompt surgical intervention. General indications for immediate orthopedic consultation are inability to bear weight within minutes of an injury, increasing effusion or hemarthrosis within hours of an injury, gross structural deformity of the knee, and evidence of neurovascular compromise. It is important to remember that up to two-thirds of knee fractures and most injuries involving tendon and cartilage are not apparent on plain radiographs of the knee. The history and physical examination therefore are particularly important in narrowing the differential diagnosis in an adolescent with knee pain.

Table 18-2 Bone–Muscle Groups Involved in Pelvic Avulsion Fracture and Apophysitis

Bone	Muscle
Anterior superior iliac spine	Sartorius
Anterior inferior iliac spine	Rectus femoris
Ischial tuberosity	Hamstring, adductors
Lesser trochanter of the femur	Iliopsoas
Iliac crest	Abdominal obliques
Greater trochanter of the femur	Piriformis

The discussion that follows is divided into two sections. The first section reviews acute disorders of the adolescent knee, usually associated with single injuries. The second section reviews chronic disorders, usually associated with overuse injuries.

Acute Knee Pain

Sudden-onset knee pain can be caused by fractures (Figure 18-9 and Figure 18-10), bony contusions (Figure 18-11), dislocations (Figure 18-12), ligamentous and meniscal injuries, muscle and tendon strains, and chondral lesions. Common causes of acute knee pain during adolescence are described below.

Knee dislocation usually is caused by high-velocity trauma, such as a motor vehicle accident, and involves anterior or posterior dislocation of the tibia relative to the femur. Damage to the popliteal artery and peroneal nerve occur in one-third and one-quarter of patients with knee dislocation, respectively. Immediate orthopedic consultation should be obtained.

Anterior cruciate ligament (ACL) sprain or tear is caused by twisting or hyperextension of the knee while the foot is planted. It occurs most commonly in female basketball and soccer players and, in 50% of cases, is associated with injury to the medial collateral ligament (MCL) or the menisci. Acute ACL injury is associated with sudden-onset pain, a popping sensation in the knee, and trouble walking. Patients with ACL sprains may be able to bear weight and walk but avoid twisting, pivoting, or changing the direction of the gait. Physical examination demonstrates an effusion and positive Lachman test. Initial treatment consists of rest, ice, compression, and a knee immobilizer. All ACL injuries warrant orthopedic referral.

Medial collateral ligament (MCL) sprain or tear is caused by a side impact, or valgus force, to the extended knee. It is common in skiing and tackling injuries and may be accompanied by injury to the lateral meniscus.

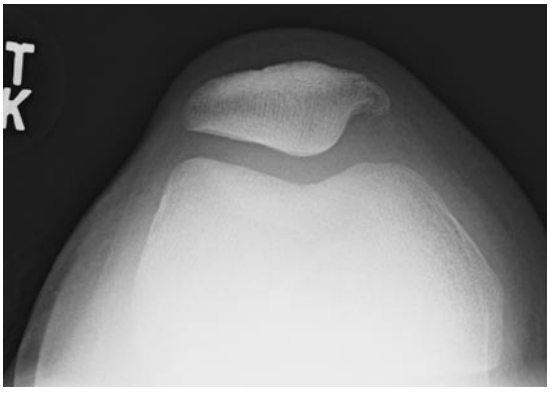

Figure 18-9 Sunrise-view radiograph of a lateral patellar fracture.

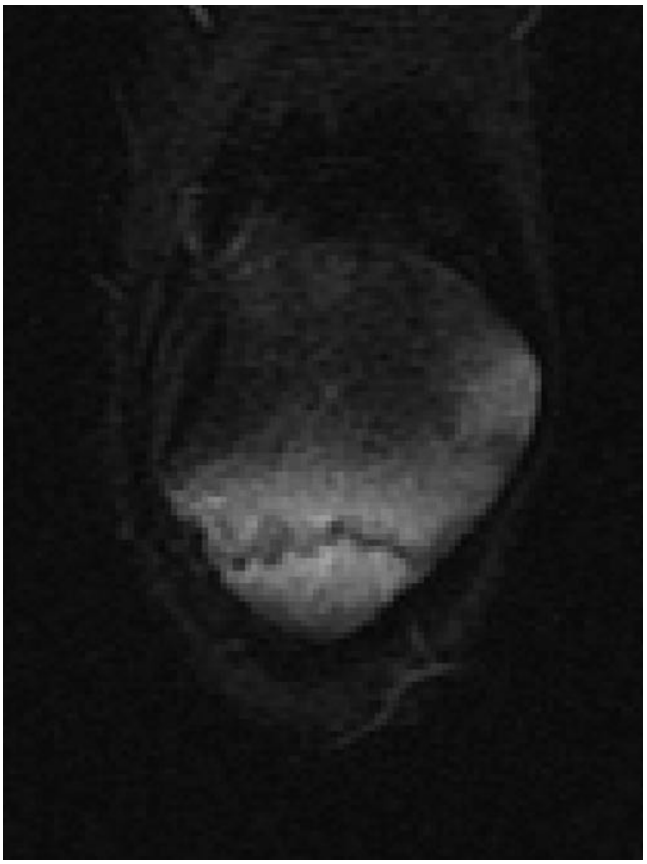

Figure 18-10 T2-weighted coronal magnetic resonance imaging showing a fracture of the inferior pole of patella.

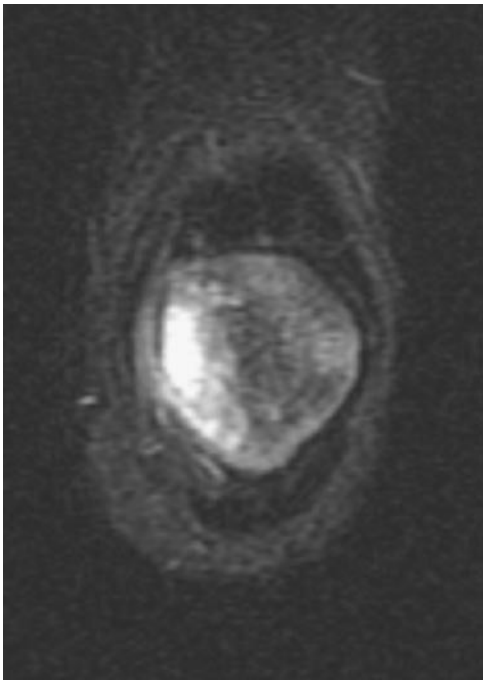

Figure 18-11 T2-weighted magnetic resonance imaging showing a contusion of the medial patella.

The patient may experience a tearing sensation in the knee followed by pain, swelling, stiffness, and instability. Physical examination reveals tenderness on palpation of the MCL and pain with valgus stress at 30 degrees flexion. Pain and instability with valgus stress at full extension suggests both MCL and ACL injury. Tenderness along the distal femur suggests an associated physeal fracture and warrants radiographic examination in all patients who are still growing. The management of isolated MCL sprains includes rest, ice, compression, and a hinged knee brace. Rehabilitation should begin early to preserve muscle strength and joint motion. Surgical reattachment of the MCL generally is unnecessary, even in cases of complete rupture.

Meniscal tear is caused by rotation or twisting of the knee as it bears weight (e.g., landing from a jump). The symptoms of acute meniscal injury include pain, locking, popping, and clicking. Physical examination reveals tenderness along the joint line, effusion, and painful clicking on the McMurray test. Although plain radiography does not confirm the diagnosis, it should be performed with AP, lateral, sunrise, and tunnel views to exclude fracture and osteochondritis dissecans. MRI often will demonstrate a meniscal tear, and the size and location of the tear can help guide the decision about arthroscopic repair. Referral to an orthopedic surgeon is recommended for all suspected meniscal injuries.

Posterior cruciate ligament (PCL) sprain or tear is caused by trauma to the upper, anterior tibia when the knee is in the flexed position. Common settings are dashboard impact to the passenger's flexed knee during a motor vehicle accident and a fall onto the flexed knee from a bicycle. The acute pain tends to be less severe with PCL than ACL or MCL sprain. Physical examination, however, usually reveals positive posterior drawer and posterior sag tests.

Lateral collateral ligament (LCL) sprain or tear is caused by an outwardly directed blow (varus force) to the medial knee, usually sustained in a motor vehicle accident. Physical examination reveals tenderness along the LCL and painful instability on varus testing at 30 degrees flexion. Instability on varus testing at full extension suggests injury to multiple ligaments.

Muscle strain or tear around the knee most commonly involves the hamstring, rectus femoris, gastrocnemius, and adductor longus. When the injury is acute, hematoma may accompany the muscular pain and tenderness is noted on palpation.

Chronic Knee Pain

Chronic knee pain during adolescence is usually associated with overuse injury from repeated activity or failure to rehabilitate a previous acute injury. Causes unrelated to sports or injury must also be considered, however. These causes include developmental disorders of the hip (e.g., SCFE), knees (e.g., genu valgum), or feet (e.g., pes planus); rheumatological disorders; infection of the bone or joint; and benign or malignant tumors of bone. The most common causes of chronic knee pain during adolescence are discussed below.

Patellofemoral syndrome accounts for up to 80% of chronic knee pain in adolescent females and up to 30% in adolescent males. It is caused by overuse injury at the articulation of the patellar and femoral bones and is

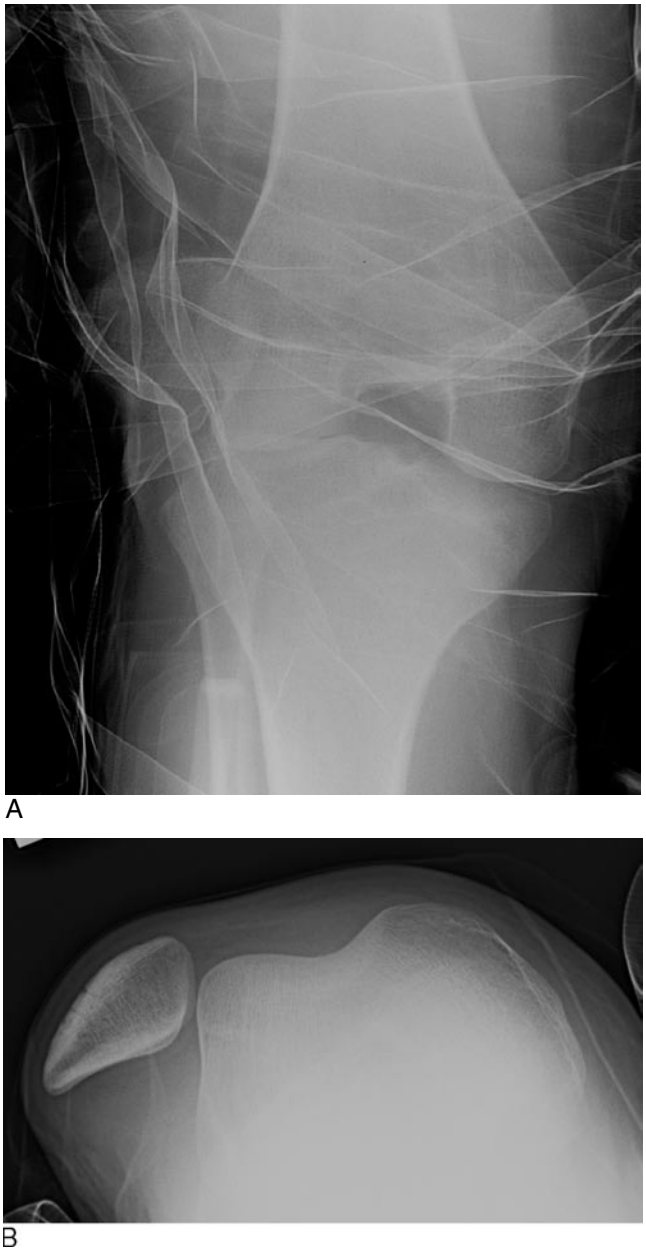

Figure 18-12 **A.** Tunnel-view radiograph of dislocated patella. **B.** Sunrise view radiograph of same patient.

usually associated with impact activities such as running and jumping. Anomalies of patellar alignment (i.e., shift laterally or superiorly), size, and shape increase the risk of patellofemoral syndrome. Lateral drift may be caused by weakness of the quadriceps femoris muscles, variant attachment of the vastus medialis muscle, femoral neck anteversion, or genu valgum.

The patellofemoral syndrome presents with the insidious onset of pain around or behind the knee that increases with flexion-extension activities such as walking stairs and arising from prolonged sitting. Physical examination of the knee reveals pain with medial or lateral traction and with compression of the patella into the femoral groove. Range of motion is normal, but joint effusion may be present and flexion or extension may elicit crepitation if the syndrome has advanced to degeneration of the articular cartilage (i.e., chondromalacia patellae). Radiographs help to exclude other conditions but usually contribute little to the diagnosis of patellofemoral syndrome. When ordered, radiographic examination should include AP and lateral views, as well as a tangential view of the patellofemoral joint (i.e., merchant or sunrise view).

The management of patellofemoral syndrome begins with restriction of activities such as running, jumping, and squatting; nonsteroidal anti-inflammatory agents for pain and swelling; and physical therapy with the development of a home rehabilitation plan. Orthotic shoe inserts and knee bracing may be helpful for selected patients but should not replace the program of joint rest followed by muscle strengthening. The outcome in patellofemoral syndrome is related to the severity of misalignment, adherence to physical therapy, and the intensity or frequency of the exacerbating activity.

Patellar dislocation can be a recurrent complication of the patellofemoral syndrome, unassociated with acute injury. Reduction usually occurs spontaneously. However, persistent dislocation should be manually reduced by flexing the patient's hip, extending the knee, and gently returning the patella to the femoral groove. Radiographs are usually taken to exclude fracture and are normal following reduction. Pre-reduction radiographs are shown in Figure 18-12. When obtained, an MRI may demonstrate injury to the articular cartilage. Treatment of recurrent patellar dislocation includes a cast or knee immobilizer for 2–4 weeks followed by physical therapy to strengthen the vastus medialis oblique and improve range of motion. Orthopedic referral is recommended for all patients with dislocation of the patella.

Osgood-Schlatter disease is a unilateral or bilateral apophysitis of the anterior tibial tubercle that coincides in onset with the adolescent growth spurt. Rapid growth of the femur and tibia during this period can cause tightness of the hamstring and quadricep muscles, traction of the patellar tendon against the tibial tubercle, repeated microtrauma to the tubercle, and ultimately inflammation of the apophysis. Most adolescents with Osgood-Schlatter disease have histories of overuse related to running and jumping activities, but acute trauma to the tibial tubercle in the absence of overuse can also cause the apophysitis.

The presenting symptom of Osgood-Schlatter disease is anterior knee pain exacerbated by activity and relieved with rest. Physical examination typically reveals tenderness of the tibial tuberosity and, less commonly, swelling or warmth over the tuberosity. An important prerequisite to the diagnosis is a normal examination of the knee joint. Although radiographs of the knee may demonstrate fragmentation at the anterior tibial tubercle, the characteristic history and physical findings usually make radiographic examination unnecessary for the diagnosis of Osgood-Schlatter disease (Figure 18-13).

The management of Osgood-Schlatter disease begins with reassuring the adolescent and family of its benign course. In nearly all patients, the pain resolves with completion of growth. During the growth phase, the pain responds to limitation of the exacerbating activity,

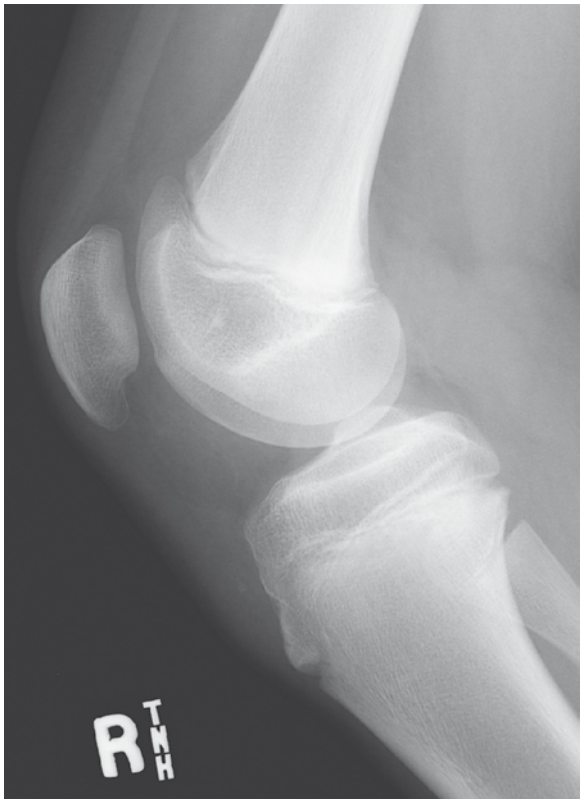

Figure 18-13 Radiograph showing Osgood-Schlatter disease with soft-tissue swelling.

the use of nonsteroidal anti-inflammatory agents, and flexibility exercises to stretch the hamstrings and quadriceps. As patients return to sports participation, knee pads can be worn to prevent reactivation by contact injury. Persistent pain may require the use of an immobilizing brace for a few weeks to enforce limitation of activity. Corticosteroid injection into the tibial tubercle is contraindicated for Osgood-Schlatter disease as it may result in weakening and rupture of the patellar tendon.

Sinding-Larsen-Johansson syndrome is a traction apophysitis of the lower pole of the patella. Like Osgood-Schlatter disease, it can recur throughout adolescence until the physis fuses and presents as knee pain associated with activity. Unlike Osgood-Schlatter disease, physical examination reveals tenderness of the inferior patella rather than the tibial tuberosity. Although unnecessary for diagnosis, radiographic examination may show fragmentation of an ossicle at the inferior pole of the patella. Treatment is the same as described for Osgood-Schlatter disease, and full recovery is the usual outcome.

Osteochondritis dissecans is a condition involving the articular cartilage and subchondral bone of the femoral condyle. A fragment of cartilage or bone separates from the joint surface of the medial, or less commonly, the lateral femoral condyle. It can occur at any age, but most cases present between ages 13 and 17 years. The pathophysiology is thought to involve genetic factors, repetitive microtrauma, and compromised blood supply to the affected bone. The major presenting symptom is the insidious onset of knee pain that increases with strenuous activity and extension movements. Physical examination of the knee when flexed to 90 degrees reveals tenderness of the femoral condyle. Other findings may include swelling, locking, or a palpable free body in the joint. Plain radiographs usually confirm the diagnosis (Figure 18-14), but grade and prognosis may be influenced by the appearance of the cartilage on MRI. Management varies from reduced sports participation to knee immobilization by casting or bracing. If serial radiographs demonstrate progressive fragmentation despite these interventions, surgery may be indicated to remove or secure fragments and improve circulation to the affected condyle.

Cruciate ligament insufficiency and meniscal injury can present together as chronic knee pain, swelling, and instability. Chronic meniscal injuries alone present as intermittent pain along the joint line and swelling, without joint instability.

Iliotibial band syndrome is a condition of runners that presents as pain over the lateral femoral condyle, where it is crossed by the band of connective tissue that extends from the ileum to the fibula. Contributing factors include band shortening, varus alignment of the knee, and excessive or high-impact running. The physical examination reveals local tenderness over the lateral femoral condyle, occasional clicking over the condyle, and an otherwise normal knee.

MAJOR POINTS

- Screening for scoliosis in early adolescence reduces the need for surgery. Treatment is determined by the degree of curvature and the stage of skeletal maturity.
- Scheuermann kyphosis is a deformity of the spine that may present as back pain during adolescence. Improvement with physical therapy is unlikely, in contrast to postural round back.
- Spondylolysis indicates a defect in the pars interarticularis, and spondylolisthesis indicates actual slippage of one vertebra on another. Both are caused by repeated hyperextension and loading of the lower spine.
- Back pain in adolescence increases in incidence with age. Although psychogenic back pain occurs, an identifiable source is more common in teens than in adults. Adolescents presenting with back pain deserve a careful history, a thorough physical examination, and radiographs and laboratory studies as indicated.
- Knee pain in adolescents may be caused by hip pathology. Although much more common in early childhood, Legg-Calvé-Perthes disease can still present in early adolescence.
- Slipped capital femoral epiphysis is an orthopedic emergency. Bilateral involvement occurs about 20% of the time, and the opposite side may be asymptomatic. Obesity is a commonly associated factor.
- Osgood-Schlatter disease is a common apophysitis that almost universally resolves with closure of the physis.
- Patellofemoral syndrome is a common source of knee pain in adolescence. Its incidence is nearly three times greater in girls than boys. An increased Q-angle, femoral anterversion, genu valgum, external tibial torsion, and anatomical variations of the patella may be contributing factors.
- Osteochondritis dissecans of the knee is appearing at younger ages. Onset is usually insidious, and there may be a history of knee "locking."
- Mechanism of injury is important in taking the history of an injured knee. The sensation of a "pop" or "snap" during injury is significant and can suggest ligament sprain. ACL injuries can occur in combination with MCL injuries, and mensical injuries can occur in combination with ACL or MCL sprains.

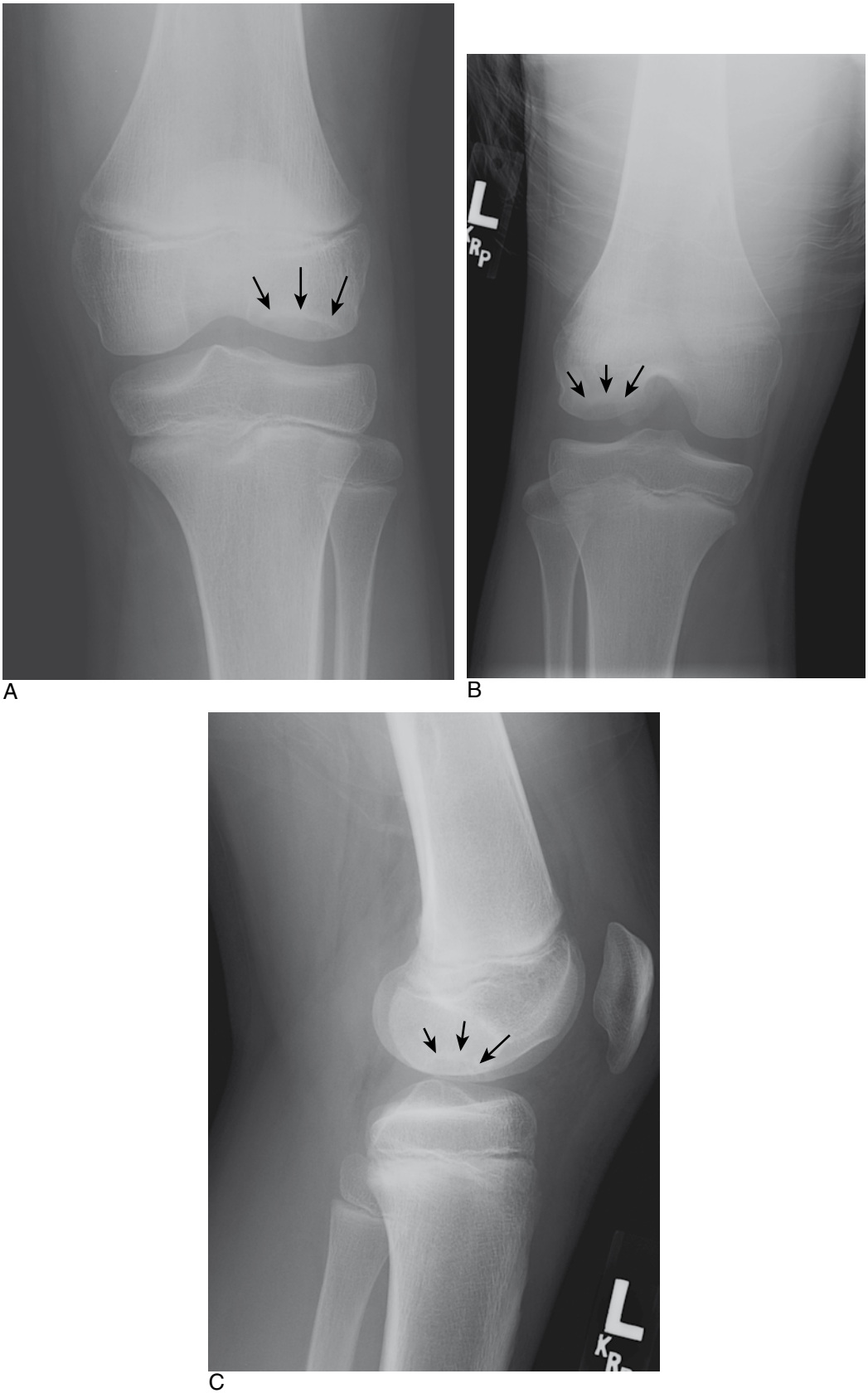

Figure 18-14 **A.** Anteroposterior radiograph of the knee showing osteochondritis dissecans involving the lateral femoral condyle. **B.** Tunnel radiograph of the same process. **C.** Lateral radiograph of the same process.

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The author wishes to thank Elizabeth Ey, M.D., Medical Director of Medical Imaging, The Children's Medical Center of Dayton, Ohio for her assistance in providing the radiographs used in this chapter.

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SEXUAL AND REPRODUCTIVE HEALTH

PART III

CHAPTER 19

Sexual Identity and Behavior

MICHAEL G. SPIGARELLI, MD, PhD

INTRODUCTION

Sexual identity and behavior are challenging issues for individuals, families, and society. The resulting tensions can be particularly trying when an idealized concept of normal denies the sexual variation that exists within every population. Although the formation of sexual identity is a key developmental task of adolescence, parents and clinicians rarely discuss it openly with teenagers. Parents, wanting their children to grow without undue social scrutiny or pressure, may be alarmed by any deviation from an assumed social norm. Clinicians, uncertain how to counsel or reassure, may avoid the sexual history altogether or forego those questions pertaining to sexual identity.

The goals of this chapter are to provide an evidence-based review of sexual identity and sexual behavior during adolescence. It begins with a definition of commonly used terms related to sexuality and a review of the epidemiology of sexual orientation and behavior during adolescence. The chapter focuses on the adolescent sexual history as a core component of the routine evaluation and the management of issues related to gender identity, sexual identity, and sexual behavior.

DEFINITIONS

Asexual: Lack of sexual attraction or desire.
Bisexual: Sexual desire directed toward members of both sexes.
Chromosomal sex: Classification of gender based upon chromosomal analysis.
Gender: Differentiation between male and female of a species.
Gender identity: Knowledge of being male or female.
Gender role: Outward expression of maleness or femaleness.
Heterosexual: Sexual desire directed toward members of the opposite sex.
Homosexual: Sexual desire directed toward members of the same sex.
Phenotypic sex: Classification of gender based upon the appearance of the external genitalia.
Sexual identity: Self-assessment as heterosexual, homosexual, bisexual, or asexual.
Sexuality: Interest in sexual activity or behavior.
Sexual orientation: Individual's pattern of sexual arousal toward other individuals.
Transgender: An individual who is in transition or has already transitioned to the opposite sex.
Transvestite: An individual who gains sexual satisfaction by dressing as the opposite sex.
Transsexual: An individual with a desire to live as a member of the opposite sex.

EPIDEMIOLOGY

Gender and Sexual Identity

Phenotypic sex, or the classification of male–female gender based on the appearance of the external genitalia, typically is determined at birth. An estimated 1.9 per 100 newborns have anomalies of the external genitalia that may delay gender definition, and 1 per 1500 individuals have chromosomal patterns other than XX or XY. Ambiguities of external phenotypic sex are sorted out socially, if not medically, early in life. Regardless of phenotype or genotype, many individuals

question their sexual identity, and less commonly their gender identity, during adolescence. Discussion of sexual and gender identity should be a routine part of the adolescent history. A clinician who is unable to conduct the discussion without bias or judgment should refer the adolescent to another provider or participate with other providers in the adolescent's ongoing care.

Kinsey's pioneering work on sexual behavior demonstrated that 28% of males and 17% of females reported at least one homosexual experience by age 20 years and that 10% of adults identified themselves as predominantly homosexual in orientation. A subsequent survey by Sorensen revealed that 11% of males and 6% of females aged 13–16 years and 17% of males aged 16–19 years reported at least one homosexual encounter. In a study of students aged 12–18 years, 11% reported uncertainty about their sexual orientation, 5% reported same-sex attraction, and 1% described themselves as bisexual or homosexual. Using the criteria of sexual desire, identity, and behavior to define homosexual or bisexual orientation in adults, Laumann found that all three criteria were met by 2% of men and 1% of women and that at least one criterion was met by 10% of men and 9% of women.

The prevalence of gender identity dysphoria, defined as persistent cross-gender identification and discomfort with one's assigned sex or gender role of that sex, is unknown. Estimates in adults range from 1 per 2500 for transsexuality to 1 per 30,000 males and 1 per 100,000 females who seek sex-reassignment surgery.

Sexual Behavior

The U.S. Youth Risk Behavior Survey (YRBS), conducted biannually since 1991, provides national data on the health-risk behaviors of 9th- to 12th-grade students. As shown in Figures 19-1, 19-2, and 19-3, the proportions of males and females who report sexual intercourse ever, within the past three months, and with more than four lifetime partners increase steadily between 9th and 12th grades. Factors associated with sexual initiation in early adolescence include early pubertal development; past history of sexual abuse; poverty; parental neglect; cultural or family patterns of early sexual experience; lack of school or career goals; school drop-out; and substance abuse (Figure 19-4). Factors associated with delay in sexual initiation include connectedness with parents; family stability; nonparental adult role models; peer role models; academic achievement; future aspirations; and religiosity.

Studies exploring why adolescents engage in sexual relationships indicate the importance of force, coercion, and older partners. Up to 10% of sexually active teens report at least one episode of physical force, 21% report

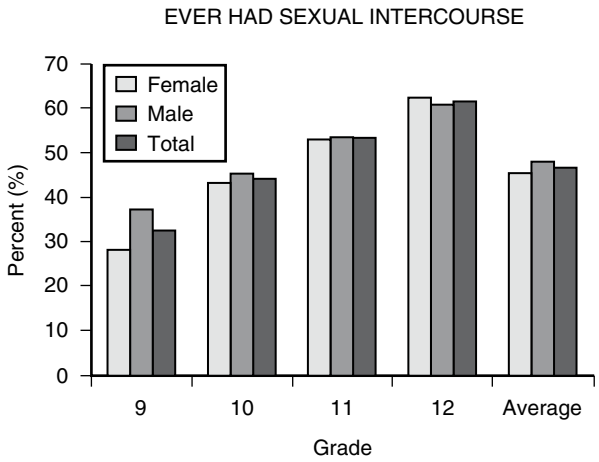

Figure 19-1 Percentage of high school students by grade reporting sexual intercourse ever. Adapted from: Centers for Disease Control and Prevention. Surveillance Summaries, May 21, 2004. MMWR 2004:53(No. SS-2).
Available from: *http://www.cdc.gov/HealthyYouth/yrbs/index.htm*. Accessed May 17, 2007.

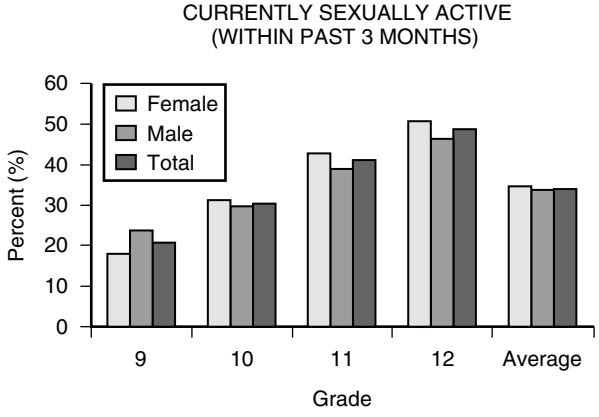

Figure 19-2 Percentage of high school students by grade reporting sexual intercourse in the past three months. Adapted from: Centers for Disease Control and Prevention. Surveillance Summaries, May 21, 2004. MMWR 2004:53(No. SS-2).
Available from: *http://www.cdc.gov/HealthyYouth/yrbs/index.htm*. Accessed May 17, 2007.

oral sex to avoid intercourse, and 30% report feeling pressured to have sex. An age discrepancy of six or more years confers a six-fold risk of sexual intercourse for a 13-year-old female and a two-fold risk for a 17-year-old female.

Adolescents who are lesbian, gay, bisexual, transsexual, or questioning (LGBTQ) are at increased risk for suicide, substance use, early sexual initiation, abuse, and multiple partners. Suicide is the leading cause of death among LGBTQ youth, and those who are LGBTQ may account for up to 30% of all youth suicides annually. More than 40% of LGBTQ adolescents report suicidal ideation, and 28% report at least one suicide attempt within the preceding year.

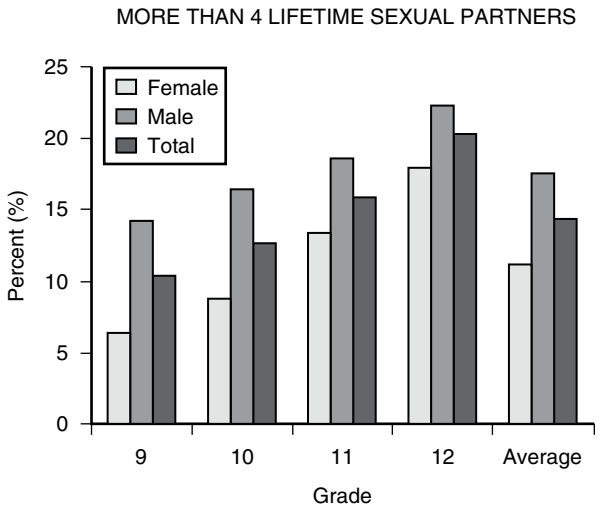

Figure 19-3 Percentage of high school students by grade reporting more than four lifetime sexual partners.
Adapted from: Centers for Disease Control and Prevention. Surveillance Summaries, May 21, 2004. MMWR 2004:53(No. SS-2). Available from: *http://www.cdc.gov/HealthyYouth/yrbs/index.htm*. Accessed May 17, 2007.

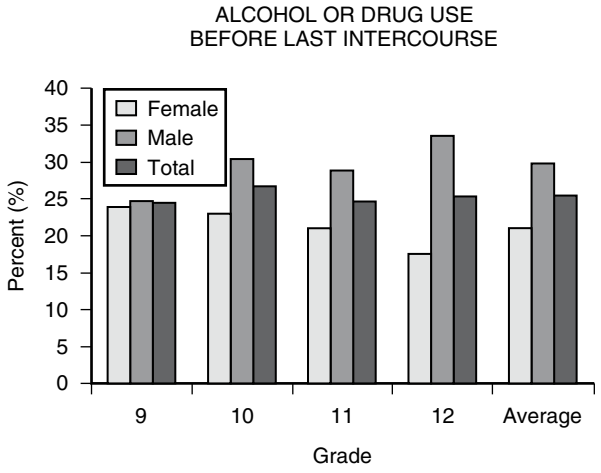

Figure 19-4 Percentage of high school students by grade reporting use of alcohol or drugs prior to last sexual intercourse.
Adapted from: Centers for Disease Control and Prevention. Surveillance Summaries, May 21, 2004. MMWR 2004:53(No. SS-2). Available from: *http://www.cdc.gov/HealthyYouth/yrbs/index.htm*. Accessed May 17, 2007.

Self-identified sexual orientation during adolescence correlates poorly with sexual behavior. In one study, high school females who self-identified as lesbian or bisexual were as likely as heterosexual females to have had sexual intercourse with a male partner and were more likely to have been pregnant. Adolescents who self-identify as LGBTQ are as likely to have been raised in a heterosexual household as adolescents who self-identify as heterosexual. This leaves many LGBTQ youth without family role models who can help them cope with the social stigma, discrimination, and attendant risk.

EVALUATION

The constant change that characterizes adolescence makes it a time when an inadvertent label or diagnosis may be both incorrect and harmful. This is especially true for labels related to sexual orientation. From a clinical perspective, the goal is to provide a confidential setting in which the adolescent can discuss sexual questions and concerns without bias or label, recognizing that the adolescent's sexual orientation and behavior may change with maturation.

The discussion of sexuality and sexual behavior is best thought of as a process rather than a question or set of questions at one point in time. Although no single interview style has been shown to be most effective, there is evidence to support the use of open-ended questions that progress from topics that are less to more personal. One such approach, summarized by the HEEADSSS mnemonic, evaluates *h*ome, *e*ating, *e*ducation, *a*lcohol, *d*rugs, *s*uicidality, *s*ex, and *s*afety (e.g., sexual abuse). Box 19-1 suggests indirect "trigger questions" that can help guide an interactive discussion of sexuality and sexual behavior.

An adolescent who is concerned about gender or sexual identity is unlikely to state that as the chief complaint when scheduling the clinical visit. The information is likely to emerge during the course of a visit or over a series of visits as trust and comfort with the clinician and in the clinical setting develop. Time can be an important deterrent to the discussion, particularly when the adolescent's disclosure comes late in the visit. Expressing respect for the adolescent's willingness to share highly personal information and appreciation of the adolescent's trust are important prerequisites to the scheduling of a subsequent visit that allows time for further discussion.

Box 19-1 Trigger Questions for Eliciting a Sexual History

- What are your thoughts about people your age having sex?
- What does "having sex" mean to you?
- What kinds of activities do you include in having sex?
- Are you involved with anyone now?
- Have you ever been involved with anyone?
- Can you tell me about your relationship(s)?
- Do your friends or parents know about your relationship(s)?
- What do your friends think about your partner(s)?
- Has anyone ever touched you in a way that made you uncomfortable?

MANAGEMENT

One of the first questions asked by parents when they suspect or learn of their adolescent's sexual orientation is "Why?" Little is known about the formation of gender and sexual identity. Theories range from the psychoanalytical Oedipal struggle described by Freud to the psychosocial crises described by Erikson to the biological mechanisms explored in recent research. Several studies have demonstrated differences between heterosexual and homosexual males in the neuroanatomy and neurohormonal activation of regions of the anterior hypothalamus. Although management may include some discussion of cause, current evidence suggests that sexual identity is multifactorial in origin. Searching for an explanation may delay progress toward acceptance without recrimination or blame.

Trust of the clinician and comfort in the clinical setting are critical aspects of all health care and are particularly important to the adolescent seeking care related to sexual health. The suggestions listed in Box 19-2 can help foster the adolescent's relationship with the health care provider and perception that the health care site is welcoming and safe. Aligning patient and provider goals should be a priority for each visit. For example, an adolescent who does not consider contraception important at the moment or a goal for the visit is unlikely to fill a prescription for the oral contraceptive pill. The visit time would be better spent managing the adolescent's presenting concern, discussing contraceptive options, and scheduling a follow-up visit to reach a contraceptive decision.

Sound medical advice about sexual risk behaviors is far more important to the adolescent's health outcome than is establishing a label for the adolescent's sexual orientation. Instead of asking, "Do you have sex with males, females, or both?" the clinician might say, "Can you tell me about your sexual partners?" Health care professionals should provide factual, current, nonjudgmental information in a confidential manner while at the same time paying attention to the special considerations associated with the care of homosexual and bisexual youth (Box 19-3).

The health care provider may be one of the first adults with whom an adolescent discusses same-sex feelings or relationships. It is important to remember that although the adolescent's feelings may not predict adult sexual orientation, the behaviors associated with those feelings may impose health risks regardless of sexual orientation. The clinical goal should be one of support and guidance rather than diagnosis. The health care provider in this scenario has an opportunity to help the adolescent consider different behavioral pathways and consequences. This may include a discussion of when and how to discuss same-sex feelings with parents. The clinician can offer to be present when the information is shared and can provide ongoing support for both the adolescent and the family.

The clinician who feels pressed by a parent to divulge confidential information should realign with the parent around the common goal of optimal health care for the

Box 19-2 Providing Health Care for LGBTQ Youth

- Establish a welcoming environment that includes LGBTQ-friendly symbols and provides lesbian and gay health information that can be accessed in a private manner.
- Provide the opportunity for an open, honest, face-to-face conversation about sexual feelings and behaviors. Use gender-neutral terms, and avoid assumptions regarding sexual or gender orientation.
- Explain that discussing sexual health and behavior is a part of quality health care. Accept that time is required to develop rapport.
- Same-sex experimentation during adolescence precedes self-identification as gay or lesbian. Avoid labels of sexual orientation unless used by the adolescent.
- Be sensitive to the risks and stressors experienced by LGBTQ youth.
- Everyone working within the health care system must understand that discrimination against LGBTQ patients or staff is unacceptable.

Adapted from: Catallozzi M, Rudy BJ: Lesbian, gay, bisexual, transgendered, and questioning youth: The importance of a sensitive and confidential sexual history in identifying the risk and implementing treatment for sexually transmitted infections. Adolesc Med Clin 2004;15:353–367. Gay and Lesbian Medical Association. Available from: *http://www.glma.org:16080/medical/clinical/lgbti_clinical_guidelines.pdf*. Accessed May 17, 2007.

Box 19-3 Special Considerations for Homosexual and Bisexual Youth

- Clinicians who are uncomfortable with issues of sexual orientation should refer the adolescent to another health care provider.
- Assure the adolescent that confidentiality will be protected.
- Discuss with the adolescent whether to include sexual orientation in the medical record.
- Explain that same-sex feelings and experiences during adolescence do not necessarily define sexual orientation.
- Identify and counsel the adolescent about sexual risk behaviors.
- Recognize the mental health risks of LGBTQ youth.
- Offer support and advice to current or anticipated conflicts with family and/or friends.
- When referring to other health care providers, ensure that they provide respectful and nonjudgmental care.

Adapted from: Frankowski BL, American Academy of Pediatrics Committee on Adolescence: Sexual orientation and adolescents. Pediatrics 2004;113:1827–1832.

adolescent. In most cases, a parent who requests information will not persist when breaking confidentiality means risking his or her child's future confidence in the health care provider. When the parent does persist, the health care provider should inform the adolescent of the parental request and suggest that parent, adolescent, and clinician meet together to answer the parent's questions. Adolescents who are unable to talk alone with their parents about sexual health issues usually are willing to discuss the issues with the clinician present, especially when they realize that their parents are likely to push for information after leaving the clinician's office.

MAJOR POINTS

- Adolescent trust and the protection of confidential information is a core component of quality health care, particularly when that care involves sexual health.
- Discussions of sexual feelings and behavior should begin with gender-neutral language (e.g., partner instead of boyfriend or girlfriend) and should avoid assumptions regarding sexual orientation.
- Sexual identity formation is a central task of adolescence. Although the sexual behaviors of adolescents have very real effects on health outcome, neither sexual feelings nor behaviors during adolescence predict adult sexual orientation.
- The prevention of sexually transmitted infections and unintended pregnancy should be discussed with all adolescents, regardless of sexual feelings, behaviors, or orientation.
- The association of substance use with sexual risk behaviors should be discussed with all adolescents.
- Health care providers can provide support and counseling for adolescents and parents when sensitive information pertaining to sexual behavior and orientation is shared.

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CHAPTER 20

Testicular and Scrotal Disorders

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INTRODUCTION

Scrotal disorders often are categorized according to the presence or absence of scrotal pain. The leading causes of acute scrotal pain during adolescence are epididymitis, torsion of the appendix testis, and torsion of the testis. The leading causes of painless scrotal swelling during adolescence are hydrocele, inguinal hernia, varicocele, spermatocele, and—rarely—testicular cancer. This chapter reviews each of these conditions, compares their clinical presentations, and suggests strategies for their evaluation and management.

DEFINITIONS

Hydrocele: Painless, soft collection of fluid located anterior to the testis, within the tunica vaginalis.
Processus vaginalis: Peritoneal diverticulum that surrounds the testis.
Spermatic cord: Connected to the epididymis and containing the vas deferens and testicular vessels.
Spermatocele: Painless, sperm-containing cyst located above or posterior to, and distinct from, the testis.
Torsion of the testis: Twisting of the spermatic cord and testis on its vertical axis, leading to obstruction of venous and subsequent arterial flow.
Torsion of the testicular appendages: Twisting of a remnant of the Mullerian duct (appendix testis) or Wolffian duct (appendix epididymis).
Tunica vaginalis: Space surrounding the anterior testicle where fluid may accumulate.
Varicocele: Tortuous collection of veins surrounding the spermatic cord that may be painless or cause mild, chronic pain and that is more common on the left than right.

TESTICULAR TORSION

Epidemiology and Pathophysiology

Testicular torsion is the most serious cause of acute scrotal pain. It affects 1 in 4000 males younger than 25 years, and 65–80% of cases occur at ages 12–18 years. Studies of children and adolescents with acute scrotal pain reveal that 14–16% have testicular torsion, 14–46% have torsion of the appendix testis, and 35–71% have epididymitis (Table 20-1).

The testis normally is positioned vertically within the scrotal sac and is covered anteriorly by the tunica vaginalis.

Table 20-1 Clinical Findings Distinguishing Testicular Torsion from Epididymitis

	Torsion	Epididymitis
Peak age, years	0–1, 12–16	8–15
Duration of symptoms	< 12 hours	12–72 hours
Similar pain in past	10%	20%
Local tenderness	20%	97%
Normal testicular lie	50%	100%
Color Doppler ultrasound	Decreased flow	Increased/normal flow
C-reactive protein	Normal	Elevated (4×)

Adapted from: Lehmann CE, Biro FM: Male genitourinary disorders. In Osborn LM, DeWitt TG, First LR, et al. (eds): *Pediatrics*. Philadelphia, Elsevier/Mosby, 2005, p. 1476,Table 227-2.

Patients with testicular torsion commonly have a bilateral "bell clapper" deformity in which the testicle does not attach at its lower pole to the tunica vaginalis. As a result, the testis is excessively mobile and tends to position horizontally rather than vertically within the scrotum. These factors, along with the increase in testicular weight that occurs with puberty, predispose to torsion, or twisting of the testis on the spermatic cord. The twisting initially causes compression of venous flow and edema of the testis and cord, followed by arterial insufficiency, tissue ischemia, and ultimately necrosis of the testis.

Evaluation and Management

The usual presentation of testicular torsion is the sudden onset of severe, colicky pain in the testicle, scrotum, groin, or lower abdomen that persists for hours and is often associated with nausea and vomiting. Up to one-third of patients with testicular torsion report at least one previous episode of scrotal pain. Testicular torsion can occur intermittently and resolve spontaneously within minutes. Consequently, even brief episodes of pain and swelling warrant urological consultation.

Physical examination of the patient with testicular torsion reveals a tender, edematous, elevated testis. The absence of the cremasteric reflex, or normal elevation of the testis that occurs when the upper medial thigh is stroked, has high sensitivity but relatively low specificity for torsion. Elevating the scrotum tends to worsen or has no effect on the pain of torsion but, like the cremasteric reflex, is not a reliable enough finding to confirm or exclude the diagnosis.

If the clinical suspicion of testicular torsion is high, surgery without radiological evaluation is indicated, particularly if the imaging will delay the intervention. If the diagnosis is uncertain, Doppler ultrasound or nuclear scintigraphy is indicated to assess testicular blood flow. Patients with torsion tend to have decreased flow, whereas those with epididymitis tend to have normal or increased flow (Table 20-1). However, up to 38% of pubertal boys without torsion are reported to have no identifiable blood flow on ultrasound, and there are case reports of normal flow in the setting of torsion. If there is any question of the correct diagnosis, urological consultation should be obtained immediately.

The testis can be salvaged in up to 98% of patients if the torsion is repaired surgically within 6 hours of the onset of pain. Salvage declines to 20% after 12 hours and is close to 0% after 24 hours. A nonviable testis after untwisting the spermatic cord should be removed because its retention carries a 20% rate of postoperative infection. If a bell-clapper deformity is present, the contralateral testis should be explored and, if necessary, scrotal fixation (i.e., orchiopexy) performed. Even when surgery appears successful, up to two-thirds of patients may develop atrophy of either testis.

TORSION OF THE APPENDIX TESTIS

Epidemiology and Pathophysiology

The testicular appendages are small, pedunculated remnants of the Mullerian duct (appendix testis) or Wolffian duct (appendix epididymis) systems that can twist on their stems, causing ischemia and pain. It tends to occur at younger ages (7–12 years) than testicular torsion, is more common, and is less severe both in presentation and natural history. Blood flow to the testis is normal or increased, and pain usually resolves spontaneously within one week.

Evaluation and Management

Unlike the generalized testicular pain and swelling of testicular torsion, the pain associated with torsion of an appendage is less severe, localized to the upper pole of the hemiscrotum, and unassociated with nausea or vomiting. Physical examination may reveal a "blue dot sign" caused by ischemia or necrosis (Figure 20-1) or a reactive hydrocele. The cremasteric reflex is usually intact. The diagnosis is usually evident on history and physical examination, but a Doppler ultrasound or nuclear scan demonstrating increased blood flow to the affected testis can help distinguish it further from testicular torsion.

Torsion of the testicular appendages is managed conservatively, with scrotal support, bed rest, and analgesics. Surgery to remove the appendage should only be performed if the pain is severe, persists beyond the usual 5–10 day period, or is recurrent. There is no need to explore the contralateral testis.

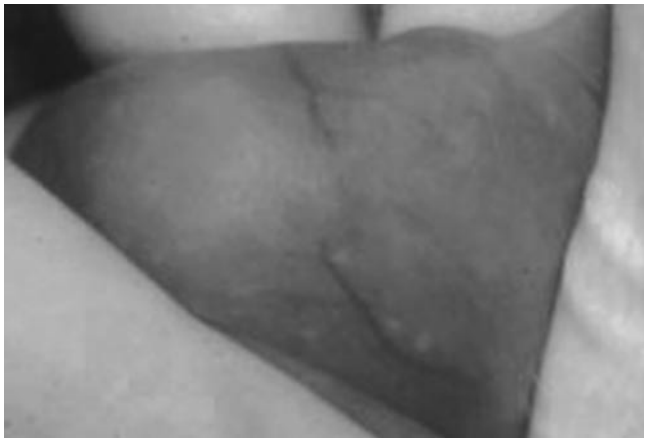

Figure 20-1 Blue dot sign of appendix testis torsion and area of point tenderness.
From Lehmann CE, Biro FM: Male genitourinary disorders. In Osborn LM, DeWitt TG, First LR, et al. (eds): *Pediatrics*. Philadelphia, Elsevier/Mosby, 2005, p. 1475, Figure 227-3.

EPIDIDYMITIS

Epidemiology and Pathophysiology

Epididymitis accounts for 35–71% of cases of acute scrotal pain in adolescents. Two-thirds of cases of epididymitis in patients younger than 35 years are caused by *Chlamydia trachomatis* (Chapter 26). Other causes include *Neisseria gonorrhoeae* (Chapter 26), *Escherichia coli* associated with urinary tract infection or anal intercourse, mycobacterial and fungal infections associated with immunocompromise, and viral infections associated with orchitis. Noninfectious epididymitis is associated with urinary reflux into the epididymis, with resulting inflammation and edema.

Evaluation

Epididymitis usually presents with scrotal pain and swelling that progresses gradually over hours to days. There often is a history of urinary urgency or frequency, dysuria, fever, and/or urethral discharge. Physical examination is variable but usually reveals scrotal edema and erythema, a normal cremasteric reflex, and pain relief on elevation of the testis. In some cases, tenderness on palpation can be localized to the epididymis. However, the physical examination may be complicated by edema of the spermatic cord, a reactive hydrocele, or associated orchitis.

Laboratory studies may include pyuria and leukocytosis, both of which may also occur in testicular torsion. Doppler ultrasound or nuclear scan typically reveal increased testicular blood flow in epididymitis, in contrast to the decreased flow observed in testicular torsion.

The Centers for Disease Control and Prevention (CDC) recommend the following laboratory studies in sexually active males with epididymitis: nucleic acid amplification testing of a urethral swab or urine sample for *C. trachomatis* and *N. gonorrhoeae* or gram stain and culture for *N. gonorrhoeae* (Chapter 26); urinalysis and urine culture; and testing for syphilis (Chapter 28) and human immunodeficiency virus (HIV) (Chapter 29).

Management

The management of epididymitis should be guided by the likely cause. In sexually active males, the CDC recommends ceftriaxone 250 mg intramuscularly once plus doxycycline 100 mg orally twice daily for 10 days. Sexual partners should also be treated presumptively for *C. trachomatis* and *N. gonorrhoeae*. When epididymitis is associated with urinary tract infection, the recommended treatment is trimethoprim-sulfamethoxazole, a cephalosporin, or a quinolone for 10–14 days.

Other measures that help control pain include scrotal support, bed rest, and nonsteroidal anti-inflammatory drugs (NSAIDs). If symptoms do not improve within 3 days, the patient should be reevaluated for structural anomalies of the urinary tract or other causes of scrotal pain and swelling, such as inguinal hernia, Henoch-Schonlein purpura, trauma, and retrocecal appendicitis.

INGUINAL HERNIA, HYDROCELE, AND SPERMATOCELE

Epidemiology and Pathophysiology

The leading causes of painless scrotal swelling in adolescents are hydrocele, inguinal hernia (Figure 20-2), varicocele (see below), and spermatocele. Less common causes include unilateral, compensatory scrotal enlargement in the setting of a contralateral undescended or rudimentary testis; bilateral macro-orchidism secondary to fragile X syndrome, leukemia, lymphoma, testicular germ cell tumors, or precocious puberty; and idiopathic painless edema of the testis and epididymis that resolves within 48–72 hours. Testicular cancer (see below) is rare in adolescents.

Indirect inguinal hernias occur at the internal inguinal ring, where the spermatic cord descends from the abdomen into the inguinal canal. Direct inguinal hernias occur at the external inguinal ring, where the spermatic cord descends from the inguinal canal into the scrotum. Normally, the inguinal rings close and the process vaginalis obliterates after the testicle descends. Patency at either site allows intra-abdominal or inguinal contents to protrude, or herniate, into the groin or scrotum.

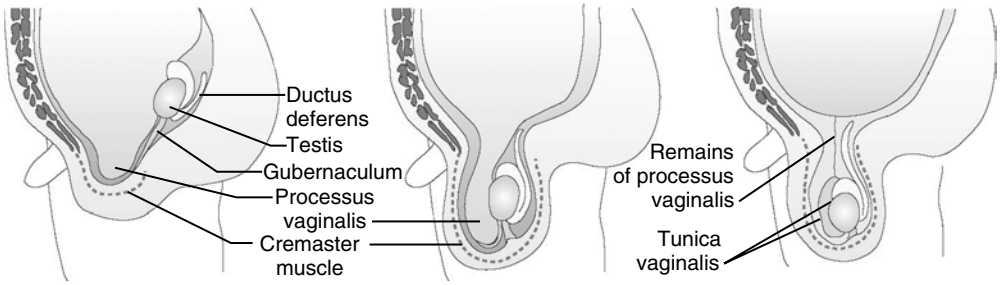

Figure 20-2 Anatomy of hernias: diagram illustrating descent of the testes.
From Lehmann CE, Biro FM: Male genitourinary disorders. In Osborn LM, DeWitt TG, First LR, et al. (eds): *Pediatrics*. Philadelphia, Elsevier/Mosby, 2005, p. 1473, Figure 227-1.

Indirect inguinal hernias are located laterally to direct inguinal hernias and are at higher risk for incarceration and strangulation.

When a patent process vaginalis allows fluid, but not tissue, to collect within the potential space of the tunica vaginalis, a communicating hydrocele forms. However, the formation of a hydrocele does not require a congenitally patent process vaginalis. In a noncommunicating hydrocele, the fluid may collect in association with torsion of the testis or testicular appendage, epididymitis, orchitis, testicular trauma, or testicular tumor.

The prevalence of spermatoceles in adolescents is unknown. Many are subclinical; they are not associated with infertility or malignancy; and surgical removal is only indicated for persistent discomfort.

Evaluation and Management

An inguinal hernia presents as a painless groin bulge, unless it is incarcerated. An indirect hernia should be distinguished from a direct hernia because of its higher risk of strangulation. The hernia orifice usually can be localized with a vigorous cough or strain. Ultrasound can help define the anatomy and can differentiate a hernia from a hydrocele or lymph nodes. Inguinal hernias should be repaired surgically because of the risk of incarceration.

A hydrocele is diagnosed on physical examination as a soft fluid collection anterior and inferior to the testis that transilluminates. A communicating hydrocele tends to decrease in size at night, when supine, and to increase in size over the course of the day. It should be repaired surgically in an adolescent because of the risk of hernia development. A noncommunicating hydrocele does not change in size with position or straining and is often associated with underlying pathology of the testis or epididymis. It usually resolves with treatment of the underlying problem or spontaneously, without surgery.

A spermatocele presents as a cyst distinct from the testis that can transilluminate or feel like a third testicle on physical examination. This is in contrast to a testicular mass, which is not separate from the testis and does not transilluminate. Once confirmed by examination or ultrasound, a spermatocele does not require surgical excision unless there is pain or discomfort.

VARICOCELE

Epidemiology and Pathophysiology

A varicocele is a cluster of dilated, tortuous veins around the spermatic cord (Figure 20-3). Varicoceles occur in 10–25% of adolescent males, and 85–90% are left-sided. The cause is unclear, but the left-sided predominance suggests that increased venous pressure is involved. The left spermatic vein joins the left renal vein at a right angle, whereas the right spermatic vein joins the inferior vena cava at an obtuse angle. Consequently, flow is less continuous and hydrostatic pressure is higher on the left than the right. When a right-sided varicocele is present, potential causes of increased venous pressure should be explored, such as situs inversus or obstruction.

Figure 20-3 Left-sided varicocele.
From Lehmann CE, Biro FM: Male genitourinary disorders. In Osborn LM, DeWitt TG, First LR, et al. (eds): *Pediatrics*. Philadelphia, Elsevier/Mosby, 2005, p. 1474, Figure 227-2.

The possible effect of a varicocele on testicular function is controversial. A study of sexually mature adolescents with varicoceles revealed abnormal semen analyses in 26% and higher gonadotropin levels in those with abnormal than with normal semen. Adult studies indicate that up to one-third of males with infertility have varicoceles but that less than 15% of those with varicoceles have problems with fertility.

Evaluation and Management

Patients with varicoceles may have no symptoms, scrotal swelling, or dull discomfort after prolonged standing (Table 20-2). The genital examination should include observation and palpation of the testis in the standing and supine positions, as well as measurement of testicular volume. The gold standard for the diagnosis of varicocele is venography, but it is only indicated for confusing presentations or in conjunction with embolization. Other diagnostic tools, such as thermography, Doppler ultrasound, and scrotal scintigraphy, carry high false-positive rates and are not relied upon for diagnosis.

The management of adolescents with varicoceles is controversial. If testicular size is normal, the patient can be followed by physical examination and ultrasound every 6–12 months to evaluate a change in size and/or by semen analysis when sexual maturation (i.e., Tanner Stage 5) is achieved. Indications for repair of a varicocele include testicular volume discrepancy of 2 ml or 20%, persistent pain, bilateral involvement, or very large varicoceles. A right-sided varicocele or a varicocele on either side that persists in the supine position suggests an obstruction to flow and warrants ultrasound evaluation to the level of the left renal vein and inferior vena cava.

Procedures for repair of a varicocele include embolization of the spermatic vein, microsurgical varicocelectomy, and testicular vein ligation. The Palomo approach (i.e., ligation of the testicular vein and artery above the inguinal ring) has a low rate of postoperative testicular atrophy but a 16% rate of varicocele recurrence. The long-term effects of testicular artery ligation are unknown, making the microsurgical varicocelectomy the procedure of choice for many surgeons. The rate of postoperative hydrocele is low (0–7%), and the 9–16% rate of varicocele recurrence due to unrecognized collaterals decreases to 6% with intraoperative venography.

Table 20-2 Grading Classification for Varicoceles

Grade	Clinical Description
0	Not palpable or visible at rest; demonstrated by imaging
1	Small; palpable only with Valsalva maneuver
2	Moderate; not visible but palpable; described as a "bag of worms" or "squishy tube" when palpating the spermatic cord
3	Large; visible from door

Adapted from: Lehmann CE, Biro FM: Male genitourinary disorders. In Osborn LM, DeWitt TG, First LR, et al. (eds): *Pediatrics*. Philadelphia, Elsevier/Mosby, 2005, p. 1474, Table 227-1.

TESTICULAR TUMORS

Epidemiology

The incidence of testicular cancer begins to increase at ages 15–19 years and peaks at ages 25–29 years. It accounts for 20% of cancers in males aged 15–35 years and 1% of cancers in males of all ages. Risk factors for testicular cancer include history of childhood malignancy, history of cryptorchidism (10% of testicular cancer cases), contralateral testicular cancer, family history of testicular cancer, androgen insensitivity, Klinefelter syndrome, Down syndrome, and infection with HIV.

Pathophysiology

Germ cell tumors comprise 75% of testicular tumors that present before puberty and 95% that present after puberty. The most common type in adolescents is seminoma, followed by embryonal cell, choriocarcinoma, teratoma, yolk sac, and mixed forms. Most testicular tumors in adolescents are considered curable with surgery and radiation therapy if detected early.

Germ cell tumors derive from the intratubular testicular germ cells. Embryonal carcinoma cells are more primitive and undifferentiated, and it is believed other germ cell tumors arise from further differentiation of the embryonal carcinoma (somatic, yolk sac, or trophoblastic lines). However, the more common seminoma does not fit into this scheme and does not have a counterpart that fits into an embryological stage or structure. Consequently, germ cell tumors are usually divided into seminomas and non-seminomas.

Evaluation and Management

Although testicular self-examination is often taught to adolescents, there are no data to support its effectiveness as a screening tool. Consequently, the recommendations of the American Academy of Pediatrics do not currently include self-examination but do include annual testicular examination of the adolescent male by the health professional.

Testicular cancer usually presents as a painless, firm nodule in the lower pose of the testis that does not transilluminate. Less commonly, the patient may complain of testicular enlargement and a dragging sensation in the

scrotum. The presence of pain has been associated with a more advanced stage and with bleeding into the tumor.

Immediate urological consultation is indicated if testicular cancer is suspected. The primary care physician can help prepare the patient for the likely evaluation and the possibility of sperm banking. Ultrasound, tumor markers, baseline laboratory work, and computerized axial tomographic (CAT) scan of the abdomen and chest are typically performed prior to treatment. Generally, the patient will undergo radical orchiectomy, followed by a combination of chemotherapy and radiation. The 5-year survival rates for testicular cancer are 92% overall and 70% for those with advanced disease at diagnosis.

MAJOR POINTS

- Testicular torsion peaks in incidence during adolescence and presents with acute pain and decreased venous and arterial flow to the involved testis. Surgical repair within 6 hours is associated with a testicular salvage rate of 98%.
- Torsion of the testicular appendages peaks in incidence at ages 7–12 years, presents as pain localized to the upper pole of the hemiscrotum, and is associated with normal or increased flow to the involved testis. Pain usually resolves spontaneously within days, without surgery.
- Epididymitis accounts for most cases of acute scrotal pain and swelling in adolescents. Two-thirds of cases in males younger than 35 years are due to *Chlamydia trachomatis.*
- The leading causes of painless scrotal swelling in adolescents are hydrocele, inguinal hernia varicocele, and spermatocele. Communicating hydroceles and inguinal hernias are managed surgically. Most varicoceles and spermatoceles do not require surgery.
- The incidence of testicular cancer begins to increase at ages 15–19 years and peaks at 25–29 years. Overall 5-year survival is 92%.

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CHAPTER 21

Breast Disorders in Females

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INTRODUCTION

Serious breast disease is rare in adolescent females. Common presenting complaints are breast pain, nipple discharge, and the discovery of a mass. Because of heightened public awareness of breast cancer, even minimal breast symptoms may cause considerable anxiety in patients and families. However, benign disease dominates the differential diagnosis and dictates a unique protocol for care in the adolescent compared with the adult patient. Many breast specialists are not adequately experienced with the young patient or familiar with the data for this population. Their adult frame of reference can lead to inappropriately high assessment of risk, diagnostics, and surgery. This chapter will present an adolescent-specific outline for the evaluation and management of common breast symptoms, as well as how to address concerns about breast cancer.

DEFINITIONS

Amastia: Absence of the breast and nipple.
Amazia: Absence of the breast with presence of the nipple.
Fibroadenoma: Benign solid tumors of the breast containing glandular and fibrous tissue.
Galactorrhea: Spontaneous discharge of milk from the nipple without breastfeeding.
Lobule: Cluster of ductules (i.e., alveoli) around a terminal end bud.
Macromastia: Extreme bilateral hyperplasia of breast tissue.
Mastalgia or ***Mastodynia:*** Pain in the breast; cyclical pain suggests fibrocystic changes.
Mastitis: Inflammation of the breast, usually caused by infection.
Morgagni tubercles: Elevations at the periphery of the areola where ducts from large sebaceous glands open.
Polymastia: Accessory nipple(s) and breast tissue.
Polythelia: Accessory nipple(s).
Stroma: Adipose and fibrous tissue that comprises most of the non-lactating breast volume.

PATHOPHYSIOLOGY

Normal Breast Architecture

The pre-pubertal breast consists of narrow, primitive ducts in the region of the nipple and areola. With puberty, estradiol stimulates branching of the ducts and the formation of terminal end buds which, in turn, form new branches called alveolar buds, ductules, or alveoli. The formation of about 11 ductules around the terminal end

bud constitutes a Type 1 lobule, which appears within 2 years of menarche. With maturation, Type 2 lobules form (i.e., about 50 alveoli per lobule) and, with pregnancy, Type 3 lobules form (about 80 alveoli per lobule). Maximal proliferation of the ductal epithelium occurs in the presence of both estrogen and progesterone. Microscopically, it is manifested by the larger-sized ductules of the Type 1 lobule. The nulliparous breast consists primarily of Type 1 lobules and epithelial cells that are estrogen receptor (ER)-positive and progesterone receptor (PR)-positive. The parous breast of a reproductive-aged women is predominantly Type 3 lobules, and the proportion of ER-positive and PR-positive cells is 10 times lower than in the nulliparous adolescent. In the post-menopausal woman, there is regression of Types 2 and 3 lobules to a predominance of Type 1 lobules. The Type 1 lobule is thought to be the site of origin for ductal carcinoma, explaining the higher risk of its development in nulliparous women.

Conditions Associated with Breast Development

Pubertal development of the breast begins with the appearance of nodular, firm breast buds beneath the areola that may be tender or asymmetrical. In one series, 45% of females younger than 18 years who were referred for the evaluation of breast masses had asymmetrical breast buds associated with normal thelarche. Biopsy is not indicated in these young girls because it can cause irreversible damage to the developing breast bud with resulting hypoplasia or amazia. Polythelia, or accessory nipple(s), is the most common breast abnormality of adolescent males and females. The accessory nipples typically occur without underlying breast tissue and may be found anywhere along the milk line that runs from the axilla to groin. Rarely, it is associated with renal or other anomalies. An estimated 25% of adolescent females have idiopathic breast asymmetry that persists into adulthood. In most cases, it is mild and without associated anomalies. Unilateral amastia or severe hypoplasia, however, usually is associated with unilateral pectoral muscle hypoplasia and, less commonly, with unilateral anomalies of the upper limb. The cause is unknown, but evidence suggests fetal abnormalities in subclavian artery flow. Juvenile breast hypertrophy is the rapid, unilateral, or bilateral overgrowth of breast tissue in adolescent females, typically beginning shortly after thelarche. Extreme bilateral hyperplasia has been termed macromastia, or gigantomastia, and is exceedingly rare. However, breast hypertrophy and significant asymmetry are neither rare nor psychologically insignificant. Adolescents with these conditions receive negative social attention and are at increased risk for low self-esteem, social isolation, and eating disorders.

Mastalgia

Breast pain, or mastalgia, is a common complaint during adolescence and is usually associated with shifts in the hormonal stimulation of the breast. In most adolescents, mastalgia does not represent fibrocystic disease. Even in adult women, fibrocystic changes are an expected component of breast maturation and do *not* represent disease, pre-cancer, or cancer. Fibrocystic breast tissue does respond to hormonal flux and typically presents as tender breast nodularity, usually in the upper outer quadrant, that worsens premenstrually. Other etiologies for breast pain include cysts, mastitis, and candida infection of the nipples. In addition, irritation of the chest wall, costochondritis, and myalgia can be misconstrued as arising from the breast.

Box 21-1 outlines the usual management of patients with breast pain associated with hormonal fluctuation. Although the oral contraceptive has been shown to decrease mastalgia over time, new users commonly complain of transient breast tenderness. Other hormonal therapies, such as bromocriptine, danazol, and tamoxifen, have been shown to decrease breast pain in 66–75% of subjects but are associated with significant side effects and rarely are indicated for mastalgia in adolescents. The effectiveness of complementary and alternative therapies, such as vitamin E and evening primrose oil, remains unproven.

Discharge

Nipple discharge is a common symptom during adolescence and is usually due to either ductal ectasia or galactorrhea. Ductal ectasia may cause a mass as well as discharge and is a benign finding in the developing breast, consisting of ductal dilation, periductal fibrosis, and inflammation. Galactorrhea, or the production of milk in a non-lactating female, is distinguishable from other causes of nipple discharge by its thin, milky character and tendency to involve both breasts. Most, but not all, patients with galactorrhea have hyperprolactinemia. Conditions associated with galactorrhea and hyperprolactinemia are listed in Table 21-1. The association of galactorrhea and amenorrhea is discussed in Chapter 22.

Box 21-1 Management of Primary Mastalgia

- Reassurance
- Smoking cessation
- Avoidance of caffeine
- Low-fat diet
- Sports bra during exercise
- Naproxen sodium or ibuprofen
- Oral contraceptive

Table 21-1 Conditions Associated with Galactorrhea and Elevated Prolactin Levels

Condition	Example
Pregnancy	
Hypothalamic lesions	Pituitary tumor, stalk compression
Prolactin-secreting tumors	Pituitary adenoma, microadenoma
Hypothyroidism	
Stress	Recent surgery
Chronic renal failure	
Local irritants	Chest wall trauma, stimulation
Medications	
Antipsychotics (neuroleptics)	
Phenothiazines	Chlorpromazine, thioridazine
Thioxanthenes	Thiothixene
Butyrophenones	Haloperidol
Atypical antipsychotics	Risperidone, molindone
Antidepressants	
Tricyclic antidepressants	Clomipramine, amitriptyline
Monoamine oxidase inhibitors	Pargyline[1]
Antihypertensive medications	Verapamil, methyldopa, reserpine
Gastrointestinal medications	
Motility agents	Metoclopramide, domperidone
Anti-nausea	Prochlorperazine
Opiates and cocaine	Morphine
Estrogen	(High dose)
Oral contraceptives	(Conflicting data—not seen with current formulations)

[1]Not currently in use.

Intraductal papillomas are a rare cause of bloody or serosanguinous nipple discharge. Montgomery's tubercles—small glands located at the outer aspect of the areola—may produce a nipple discharge that resolves spontaneously.

Breast Mass

Retrospective chart reviews indicate that biopsies of breast masses in adolescents reveal fibroadenomas in 60–70%, fibrocystic changes in 15–20%, abscess/mastitis in 1–3%, and simple cysts in 1–3%. Fibroadenomas are benign solid tumors containing glandular and fibrous tissue that most commonly occur in adolescent and young adult women. Several longitudinal studies demonstrate that 40–60% of fibroadenomas regress spontaneously and that regression is more likely in adolescents than in older women, regardless of the size or number of lesions. The use of oral contraceptives appears to decrease the risk of fibroadenomas.

As discussed previously in the section on mastalgia, fibrocystic changes are less common in adolescent than adult women. Simple cysts, arising from either obstruction of the lactiferous duct or an imbalance of fluid production and resorption, often resolve spontaneously. When persistent and painful, needle aspiration following ultrasound usually relieves the symptoms. In the adolescent, cytology of the fluid is not warranted unless it is grossly bloody.

Other etiologies such as juvenile hypertrophy, ductal ectasia, lymph nodes, accessory breast tissue, abscess, fat necrosis, papillomatosis, cystosarcoma phylloides, and metastatic cancer are seen in < 1% of cases (Table 21-2). Mastitis or breast abscess often follows minor skin trauma, is caused by skin flora, and is usually subareolar in location. Cystosarcoma phylloides is a rare tumor that tends to be large in size and to grow rapidly. Malignancy is rare, but the rate of growth warrants prompt excision for both diagnosis and treatment.

Breast Cancer

Breast cancer is extremely rare in adolescents. The combined rate of primary breast cancer and metastatic malignancy from another site is 1 per million females under age 20 years and 12 per million females at ages 20–24 years. When malignancy does occur in the young breast, it is more likely to be metastatic than primary. The risk of primary breast cancer is increased in adolescents who have had malignancies at other sites and/or have received radiation therapy to the anterior chest at least 10 years

Table 21-2 Breast Masses in the Adolescent Female

Benign		Malignant
Solid	**Cystic**	
Fibroadenoma	Fibrocystic changes	Primary: Lymphoma, neuroblastoma, sarcoma, rhabdomyosarcoma, acute leukemia
Fibrocystic changes	Simple cyst	Metastatic disease
Mastitis	Abscess	Cystosarcoma phyllodes (malignant)
Unilateral thelarche	Duct ectasia	Breast carcinoma
Lymph node	Galactocele	
Fat necrosis		
Macromastia (juvenile hypertrophy)		
Lipoma		
Hematoma		
Hamartoma		
Intraductal papilloma		
Juvenille papillomatosis		
Cystosarcoma phylloides (benign)		

earlier. As discussed further in the Management section, these adolescents may benefit from breast self-examination.

The average woman in the United States surviving to age 72 years has an 11% lifetime risk of developing breast cancer. Family history of breast cancer in a first-degree relative increases this risk two- to three-fold, and the BRCA 1 or 2 gene carries a risk of 3.2% by age 30 years and 85% by age 70 years. Other factors associated with an increased risk of breast cancer in adulthood include smoking, alcohol use, obesity, adult weight gain, high intake of sweet foods, and a sedentary lifestyle.

There is considerable confusion and anxiety regarding a potential association between oral contraceptive use and the development of breast cancer. A study of more than 4500 women demonstrated no increased risk of breast cancer for women who were past or current users of oral contraceptives compared with never-users. Two other studies demonstrated that a history of oral contraceptive use for at least 1 year decreased the risk of breast cancer by more than 70% in women with the BRCA 1 gene but had no effect on risk in women with the BRCA 2 gene.

Although pregnancy appears to decrease the lifetime risk of breast cancer, there are no scientific data to support an association between abortion and breast cancer. A meta-analysis of 44,000 women from 16 countries participating in 53 studies concluded that history of an induced abortion did not increase the risk of breast cancer later in life.

Nipple Piercing

Nipple piercing is a common practice among adolescent females and males. The 3–6 months required for healing is longer than that of other pierced sites. Complications include infection; bleeding and hematoma; allergic reaction to the ornament; keloid formation; and the potential transmission of hepatitis B, hepatitis C, and human immunodeficiency virus (HIV). Clinicians should educate patients regarding safer piercing strategies and should ensure immunization against hepatitis B and tetanus. Adolescents with metal allergies, bleeding disorders, valvular heart disease, keloids, diabetes mellitus, and immunosuppression should avoid piercing.

EVALUATION

Figure 21-1 outlines an approach to the evaluation of breast conditions in adolescent-aged patients. Regardless

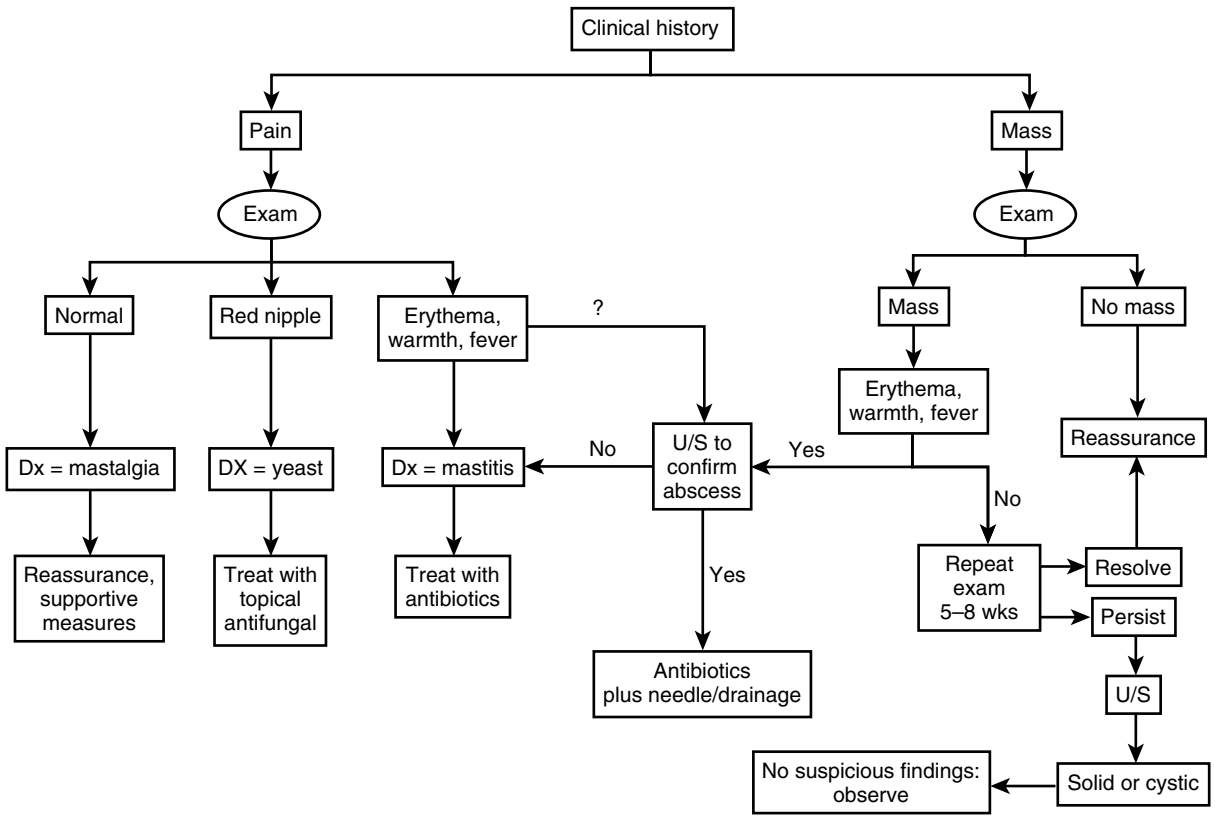

Figure 21-1 Evaluation of breast conditions in adolescent females.

of the presenting complaint, the history begins with a discussion of the problem from the adolescent and parent perspectives and a complete medical history, including personal and family risks for cancer. An issue that seems minor to the clinician and parent may have a significant effect on the adolescent's self-esteem and psychosocial function. An issue of relatively little concern to the adolescent, such as a breast nodule, may frighten the parent who considers any breast mass cancer until proven otherwise. Once the individual perspectives are understood, the evaluation can be adapted to reassure as well as to diagnose and plan management.

The physical examination should include an assessment of the Tanner stages for breast and pubic hair development (see Chapter 1). A complete breast exam should include visual inspection and palpation of both breasts with the patient sitting as well as supine. The areola/nipple complex should be gently compressed to express discharge. The axillae should be palpated to detect lymphadenopathy.

For patients with nipple discharge or galactorrhea, serum levels of prolactin and thyroid stimulating hormone (TSH) should be measured. A gram stain of the discharge can identify fat globules, which differentiates galactorrhea from other discharge. Adolescents who have galactorrhea without a breast mass and normal prolactin and TSH levels can be followed with supportive measures, such as a well-fitting bra and the avoidance of nipple stimulation.

Mammography should not be performed in adolescents. The dense fibroglandular tissue of the adolescent breast results in poor image quality, high rates of false-positive and false-negative readings, and the risks accompanying unnecessary surgery. Ultrasound can be used to differentiate solid lesions that can be followed without intervention from cysts or abscesses that warrant needle aspiration. Cytology of aspirated fluid is not warranted in adolescents unless the fluid is grossly bloody. Culture of the fluid is indicated in patients with mastitis or abscess, but antibiotics to cover skin flora are indicated prior to the final culture results. Adolescents with cystic or solid breast lesions who do not have other worrisome findings on history or physical examination may be followed without further evaluation over several menstrual cycles.

MANAGEMENT

Breast surgery before the completion of puberty can deform the developing breast and should be avoided. Indications for surgery include the following: a breast mass that enlarges rapidly, has overlying skin changes, or occurs in a patient with a previous malignancy at another site; a breast abscess that has not responded to aspiration and antibiotics; and corrective surgery for breast anomalies that will not improve with maturation and are associated with physical or psychosocial distress. Specific issues that arise commonly during adolescence are discussed below.

Breast Self-Examination

In the past, many experts recommended that adolescents be taught breast self-examinations to establish the health habit and promote an understanding of its importance in adulthood. However, there are no data to support breast self-examination during adolescence and there is concern that it may produce unnecessary anxiety, testing, and surgery. There is consensus in the literature that breast self-examination should be encouraged for all adolescents with a history of malignancy, adolescents who are at least 10 years post-radiation therapy to the chest, and adolescents 18–21 years of age whose mothers carry the BRCA 1 or BRCA 2 gene.

Reduction Mammoplasty

Surgical removal of breast tissue, or reduction mammoplasty, is indicated for adolescents with juvenile breast hypertrophy or significant breast asymmetry. More than 75% of women who had reduction mammoplasty performed during adolescence report improved self-esteem and satisfaction with the procedure, even when surveyed several years postoperatively. In one study, 94% would recommend it to a teenage friend with a similar condition. Potential complications include postoperative pain, incisional separation, scarring, sensory loss, infection, difficulty with breastfeeding, and regrowth of breast tissue.

The decision about whether and when to recommend reduction mammoplasty depends on the adolescent's physical symptoms, psychosocial discomfort, pubertal stage, and cognitive maturation. The referring physician and plastic surgeon should be confident that the adolescent has realistic goals and fully understands the limitations and risks of breast surgery. Some experts recommend postponing surgery until the breast is fully matured with no change in breast size for at least 6–12 months.

Breast Augmentation

Medical and social controversy surrounds breast augmentation during adolescence. The number of augmentation procedures performed in patients aged 18 years and younger has increased three-fold in 10 years. The U.S. Food and Drug Administration does not approve the use of breast implants prior to age 18 years, and the American Society for Plastic Surgery recommends that aesthetic breast surgery should be reserved for patients who are physically and emotionally mature and who are not seeking surgery to meet peer or parent expectations.

The adolescent who requests augmentation and her parent(s) should be counseled about the timing of the procedure as well as the risks, restrictions, recovery time, and potential impact of the surgery on the sensitivity of future mammography screening. It is also important to note, however, that there is no evidence that breast implants increase the risk of breast cancer or difficulty with breastfeeding.

MAJOR POINTS

- Breast cancer is exceedingly rare in adolescents.
- Breast self-examination is not recommended for most adolescents. It is recommended for adolescents with past or current malignancy at other sites, adolescents who had chest radiation 10 or more years earlier, and adolescent 18–21 years of age with a maternal history of the BRCA 1 or 2 gene.
- Observation and noninvasive testing are indicated for most adolescent breast complaints.
- Breast pain (mastalgia) in most patients is hormonally related, benign, and self-limited.
- Fibroadenomas are the most common solid breast lesions in adolescents. They are benign, often regress spontaneously, and do not require removal unless disfiguring or enlarging.
- Galactorrhea can be secondary to a variety of medications or, rarely, pituitary adenomas.
- Breast surgery before the completion of puberty should be avoided in females due to the potential for iatrogenic damage to the developing breast tissue.
- Breast cancer prevention may include physical exercise and avoidance of obesity, tobacco, and alcohol use.

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CHAPTER 22

Menstrual Disorders

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INTRODUCTION

Menstrual problems affect at least 75% of females at some time during the adolescent years. Although oligomenorrhea or amenorrhea, abnormal uterine bleeding, dysmenorrhea, and premenstrual syndrome are common throughout reproductive life, the predominant causes of these problems change with maturation. This chapter begins with a review of the normal menstrual cycle during adolescence, followed by discussions of the epidemiology, pathophysiology, evaluation, and management of each of these clinical issues in adolescent-aged patients.

NORMAL MENSTRUAL CYCLE

The median ages of menarche in the United States are 12.4 years across all races/ethnicities, 12.1 years for black females, 12.3 years for Hispanic females, and 12.6 years for white females. Menarche typically occurs 2 to 3 years after thelarche (i.e., breast budding), at a Tanner Stage of 4 for breast development. Girls with earlier thelarche tend to have a longer interval to menarche than girls with later thelarche. By age 15 years, however, 98% of girls in the United States achieve menarche.

The interval from menarche to the second episode of menstrual bleeding varies widely across individuals. By 1 year following menarche, 90% of girls have menstrual cycles ranging from 21–45 days and menstrual flow ranging from 2–7 days. With maturation, the proportion of cycles that are ovulatory increases and cycle duration shortens. By the third year after menarche, 60–80% of cycles are of 21–34 days duration. The individual's normal cycle length is established around the sixth gynecological year. Quantifying menstrual blood loss based on an adolescent's history is difficult and inexact. The number of pads or tampons used per day and the frequency of pad/tampon changes depend on the adolescent's familiarity or comfort with menstrual hygiene products, types and brands of products used, and personal fastidiousness. Most adolescents report three to six changes daily, although external constraints such as school rules and limited time between classes may make menstrual hygiene more problematic for adolescents than adults. Menstrual flow requiring changes of menstrual products every 1 or 2 hours is considered excessive, particularly when associated with flow of more than 7 days duration.

AMENORRHEA

Primary amenorrhea is defined as the absence of menarche by that age at which it is achieved by 95–98% of the population. Because 95% of girls in the United States reach menarche by age 14.5 years and 98% by age 15 years, a conservative and commonly used cut-point for defining primary amenorrhea is 15 years. The absence of breast development or pubic hair by age 13 years in girls signals a likely delay in menarche and should trigger an evaluation of pubertal delay (Chapter 10) well before the evaluation of primary amenorrhea.

In the adolescent who has achieved menarche, secondary amenorrhea is defined as the absence of menses for at least three consecutive cycles or for 6 months if regular cycles have not been established.

Pathophysiology

Many organizational systems have been proposed to help categorize the causes of primary and secondary amenorrhea. The system utilized below identifies the cause as originating in the hypothalamus, pituitary, ovary, or outflow tract (Box 22-1).

Hypothalamic causes of amenorrhea result in abnormal secretion of gonadotropin-releasing hormone (GnRH) which, in turn, affects pituitary secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and ovarian secretion of estrogen and progesterone. The associated menstrual cycle abnormalities range from mild luteal phase defects to severe hypoestrogenemia. Hypothalamic amenorrhea is much more likely to reflect functional suppression of GnRH secretion than a structural defect in the anatomy of the hypothalamus.

Functional hypothalamic amenorrhea may be caused by weight loss, strenuous exercise, acute or chronic illness, and emotional upset. All of these conditions, whether physical or emotional, produce physiological stress with increases in hypothalamic secretion of corticotropin-releasing hormone (CRH), which in turn increases corticotropin (ACTH) secretion by the anterior pituitary and corticosteroids by the adrenal gland. CRH also suppresses GnRH secretion, perhaps through an increase in central nervous system levels of dopamine or endogenous opioids. As a result of the GnRH suppression, pituitary secretion of LH decreases and ovulation ceases.

Ovulation and normal menstrual function generally reflect a positive energy balance between intake and expenditure and an energy reserve in the form of body fat. When depleted energy reserves threaten the basic metabolic processes required for survival, anovulation protects the female from the added energy burden of pregnancy. Studies of athletes have shown there is a significant correlation between strenuous exercise and disruption of the menstrual cycle. Up to two-thirds of runners have been found to have anovulation or short luteal phase cycles. Exercise has also been associated with a decrease in thyroxine and increases in growth hormone (GH), testosterone, ACTH, adrenal steroids, endorphins, and melatonin. Evidence suggests that the negative energy balance of excessive exercise may be due to an increase in insulin-like growth factor binding protein-1 (IGFBP-1) and a decrease in insulin-like growth factor (IGF) activity, which contribute to suppression of GnRH.

Body fat is a more important determinant of ovulation than body weight, with 22% the estimated minimum required to maintain regular ovulatory cycles in most adults. The average 18% body fat at menarche may contribute to the higher proportion of anovulatory cycles during the early gynecological years than thereafter. The mechanism underlying the association between body fat and ovulation appears to be leptin, which is produced in body fat and signals the brain that there are adequate

Box 22-1 Differential Diagnosis of Amenorrhea

Hypothalamic Causes

- GnRH deficiency
- Chronic/systemic illness
- Stress
- Excessive exercise
- Malnutrition, low body fat
- Tumor
- Thyroid disease

Pituitary Causes

- Absence of LH, FSH
- Destruction of pituitary gland
- Tumor

Ovarian Causes

- Gonadal dysgenesis
- Destruction of ovarian tissue
- Polycystic ovary syndrome
- Ovarian tumor

Outflow Tract Anomalies

- Imperforate hymen
- Transverse vaginal septum
- Agenesis of uterus, vagina

Other Causes

- Pregnancy
- Hormonal contraception
- Congenital adrenal hyperplasia
- Adrenal tumor

energy stores. With weight loss and a decrease in body fat, there is a fall in leptin levels leading to suppression of gonadotropin secretion. Chronic suppression of the hypothalamic–pituitary axis, as in patients with anorexia nervosa or persistent, excessive exercise, is associated with severe hypoestrogenemia. In addition to anovulation, the very low estrogen levels result in an atrophic endometrium and a complete absence of breakthrough bleeding. Bone mineralization peaks during adolescence and slows or halts in the absence of estrogen. The resulting plateau in bone density may place the young woman at lifelong risk of osteoporosis and fracture.

Structural hypothalamic amenorrhea most commonly is due to Kallman syndrome or congenital GnRH deficiency (Chapter 10). Other causes include hypothalamic tumors, irradiation of the central nervous system, and hypothyroidism. The menstrual abnormalities associated with hypothyroidism are due to increased hypothalamic secretion of thyroid-releasing hormone (TRH), increased prolactin, and negative feedback on GnRH.

Pituitary causes of amenorrhea include tumors, infarction, surgery, radiation, cysts, tuberculosis, sarcoidosis, replacement by fatty tissue, and rare inherited deficiencies of LH and FSH. Pituitary adenomas account for up to one-third of cases of secondary amenorrhea and, of these, half are prolactin-secreting (i.e., prolactinoma). Large prolactinomas can produce visual field cuts and headache. Most, however, are small microadenomas that present as galactorrhea and/or amenorrhea without a mass effect. Other, less common pituitary tumors are craniopharyngiomas, meningiomas, gliomas, chordomas, and metastases from other sites.

Tumors, infiltrative processes, and cysts of the pituitary or nearby tissue can decrease FSH and LH secretion by destruction of pituitary tissue and/or compression of the pituitary stalk with decreased delivery of GnRH from the hypothalamus to the pituitary. Compression can also disrupt dopaminergic regulation, resulting in hyperprolactinemia and feedback inhibition of GnRH secretion. In some cases, hyperprolactinemia presents as galactorrhea with relatively normal menses, whereas in others it presents as amenorrhea. Pituitary tumors associated with Cushing disease, hyperthyroidism, and acromegaly can cause amenorrhea but do so within a spectrum of other signs and symptoms.

Sheehan syndrome, or pituitary apoplexy, is a rare postpartum complication in which hemorrhagic shock causes infarction and necrosis of the pituitary gland, with subsequent deficiencies of one or more pituitary hormones.

Ovarian causes of amenorrhea present as hypergonadotropic hypogonadism (Chapter 10) and include gonadal dysgenesis or agenesis, premature ovarian failure, and resistant ovaries. Gonadal dysgenesis and premature ovarian failure account for 30–40% and 10–28% of primary amenorrhea, respectively. Gonadal dysgenesis, or Turner syndrome (Chapter 10), presents in its pure, 45,X form in 60% of cases and as genetic mosaicism in 40% of cases. Most patients with Turner syndrome have nonfunctioning ovarian streaks, pubertal delay, and primary amenorrhea. Although unusual, some patients with mosaic Turner syndrome produce sufficient estrogen to support pubertal development and menses. Rarely, a patient with mosaic Turner syndrome can become pregnant. However, even in those patients who do have functioning ovarian tissue, most experience premature menopause with accelerated follicular atresia.

Premature ovarian failure, defined as menopause before age 40 years, affects 1% of women. It presents with primary or secondary amenorrhea and elevated serum levels of LH and FSH due to hypoestrogenemia and the lack of negative feedback on the hypothalamic–pituitary axis. Although most cases are idiopathic, known causes of premature ovarian failure include radiation to the pelvis, chemotherapy, infection, trauma, and autoimmune disease. Ovarian failure is less likely in younger than in older women who are exposed to radiation or chemotherapy, perhaps because of younger and more numerous oocytes. Alkylating chemotherapeutic agents are particularly toxic to the ovary, and the use of multiple agents increases the chances for ovarian failure. Autoimmune diseases such as thyroiditis, adrenal insufficiency, and hypoparathyroidism have been associated with ovarian antibodies and lymphocytic infiltration into developing follicles. In galactosemia, metabolites of galactose impair germ cell migration to the genital ridge, resulting in premature ovarian failure. Finally, patients who are Fragile X carriers are at risk for premature ovarian failure.

It is important to recognize that elevated gonadotropins may not represent ovarian failure. Pituitary adenomas that secrete FSH and LH typically do not present with amenorrhea but, rather, with headaches and visual disturbances related to tumor growth. Patients with resistant ovaries have mutations of the gonadotropin receptor, resulting in present but unresponsive ovarian follicles and elevated serum gonadotropins. Late-onset congenital adrenal hyperplasia due to deficiency of 17-hydroxylase is manifested as amenorrhea and elevated gonadotropins in the presence of ovarian follicles (Chapter 23).

Outflow tract anomalies fall into four categories: agenesis/hypoplasia, abnormal canalization, duplication of structures, and the presence of a septum within the uterine cavity or vaginal canal. Most isolated abnormalities of the Müllerian duct and urogenital sinus are polygenic, but single gene mutations have been identified for a few rare syndromes.

The clinical severity of outflow tract anomalies varies widely. A study of fertile women having laparoscopic

bilateral tubal ligation performed for contraception revealed that 3% had previously unrecognized Müllerian tract anomalies. At the other extreme is Müllerian agenesis, or Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, which occurs in approximately 1 per 5000 female births. MRKH syndrome is the congenital absence of the proximal vagina and, in 90% of cases, the cervix and uterus. Those cases in which a normal or rudimentary uterus is present typically have functioning endometrium with obstruction to flow due to the abnormal vaginal canal.

Imperforate hymen is probably the most common obstructive anomaly of the female reproductive tract. Familial occurrences of imperforate hymen have been reported, but most cases are isolated events. The adolescent patient with an imperforate hymen may be asymptomatic before the accumulation of concealed menstrual flow or may present with recurrent bouts of cyclical abdominal pelvic pain. A bluish, bulging hymen and a vagina distended with blood may be found on genital inspection and recto-abdominal palpation. In some cases, the vagina may be extremely large, and the condition may result in back pain, pain with defecation, nausea and vomiting, and/or difficulty with urination. In extreme cases, hydronephrosis due to mechanical obstruction of the ureters from the grossly enlarged vagina can occur.

Transverse vaginal septa are believed to arise from a failure in fusion and/or canalization of the urogenital sinus and Müllerian ducts. Approximately 46% of vaginal septa occur in the upper vagina, 40% in the middle vagina, and 14% in the lower vagina. On speculum examination, the vagina is a short, blind pouch. The septa are usually less than 1 cm thick and may extend completely or partially from one vaginal sidewall to the other. Although transverse vaginal septa often have small central or eccentric perforations, hematocolpos remains a common presenting finding. Rarely, pyohematocolpos may be caused by ascending infection through the small perforation.

Androgen insensitivity syndrome typically presents as primary amenorrhea in an adolescent who is phenotypically female and genetically male (46X,Y). Testes are present but do not descend completely and are at increased risk for malignancy. Müllerian-inhibiting substance is produced, which prevents the development of the female internal reproductive structures, including the upper vagina, cervix, and uterus. Testosterone is also produced but there is end-organ insensitivity to its effects with abnormal negative feedback and high estrogen levels due to peripheral conversion of the testosterone. Breast development is normal, pubic and axillary hair is scant, the vagina is short, and the cervix and uterus are absent. Complete androgen insensitivity is usually diagnosed during puberty when a well-developed young woman presents with amenorrhea.

Hyperandrogenism as a cause of amenorrhea or oligomenorrhea is discussed in Chapter 23. Conditions associated with hyperandrogenism include polycystic ovary syndrome (PCOS), ovarian or adrenal tumors that produce androgens, congenital adrenal hyperplasia, and Cushing disease. PCOS is the most common endocrine disorder in women of reproductive age and accounts for more than 90% of adolescent hyperandrogenism. Late-onset congenital adrenal hyperplasia (CAH), or 21-hydroxylase deficiency, is an autosomal recessive disorder that typically presents during adolescence as amenorrhea or oligomenorrhea, hirsutism, and often virilization. Androgen-producing tumors are rare in adolescents but should remain in the differential diagnosis, especially in cases of amenorrhea associated with the rapid onset of hirsutism or virilization.

Evaluation

The evaluation of an adolescent with amenorrhea begins with a thorough developmental and sexual history. The history should identify the ages of thelarche (i.e., onset of breast development), pubarche (i.e., onset of pubic hair development), and menarche; menstrual pattern; timing of first and last sexual intercourse; height and weight progression along established growth curves; eating and exercise patterns; weight fluctuations; signs of hyperandrogenism; galactorrhea; pelvic pain; known genitourinary anomalies; and history of chronic illness.

The physical examination should include the stages of breast and pubic hair development; the determination of body mass index (BMI) from the height and weight; skin examination for acne and hirsutism; ophthalmological examination; thyroid palpation; breast examination for galactorrhea; abdominal examination for masses; and pelvic examination for hymenal patency (i.e., insertion of a moist cotton swab into the vagina and/or bimanual examination); mucosal estrogenization; clitoral size; and outflow tract anatomy. A well-estrogenized mucosa should appear pink and moist, as compared with the red, thin mucosa of hypoestrogenemia.

Patients who cannot tolerate bimanual examination or recto-vaginal examination and those in whom the examinations are inconclusive should have pelvic ultrasonography performed to identify developmental anomalies and/or genital tract obstruction. Ultrasound also allows measurement of the endometrial stripe, which is an index of estrogen stimulation of the endometrium, and identification of ovarian cysts or masses (Chapter 23). Ultrasound can be performed by transabdominal, transvaginal, and/or transperineal approaches. The latter can be helpful in young adolescents who cannot tolerate the transvaginal study. Magnetic resonance

imaging (MRI) of the pelvis and/or abdomen is an excellent modality for further defining the presence of a vaginal septum, uterine remnant, streak gonads, and renal anomalies. MRI of the sella with and without contrast is the preferred modality for evaluating a suspected prolactinoma.

Nearly all adolescents with primary or secondary amenorrhea warrant a qualitative test for human chorionic gonadotropin (HCG) to exclude pregnancy, even if sexual activity is denied, and measurement of serum prolactin and TSH levels. Signs of hyperandrogenism on physical examination should be explored with measurement of serum free and total testosterone, dehydroepiandrosterone-sulfate (DHEAS), FSH, LH, and perhaps 17-hydroxyprogesterone (Chapter 23). Adolescents with suspected but undiagnosed systemic illness should have a complete blood count, erythrocyte sedimentation rate, serum electrolytes, glucose, blood urea nitrogen (BUN), creatinine, liver function tests, total protein, albumen, and TSH.

Serum FSH and LH levels will help differentiate hyperfrom hypogonadotropic hypogonadism (Chapter 10). Elevated levels in a patient with primary amenorrhea and no history of radiation, chemotherapy, or autoimmune disease suggest gonadal dysgenesis and should trigger chromosomal analysis. If chromosomes are normal, serum levels of anti-ovarian antibodies should be measured. Low levels of FSH and LH in a patient with primary or secondary amenorrhea indicate hypogonadotropic hypogonadism due to decreased function at the hypothalamic or pituitary level. If there is no evidence of underlying systemic illness or other endocrine disorder, evaluation for Kallman syndrome should be pursued by formal olfactory testing, genetic and endocrine consultation, and head MRI.

As noted in Chapter 10, the assessment of pituitary function in an adolescent with primary amenorrhea in the setting of delayed puberty can be particularly difficult. Low or normal levels of serum GH and its mediators, IGF-1 and IGFBP-3, may reflect GH deficiency, malnutrition, low body weight, or constitutional delay of puberty. In adolescents with severe hypogonadotropic hypogonadism, GnRH stimulation testing by an endocrinologist can help determine whether anterior pituitary function is appropriate for the level of pubertal development.

Management

The management of primary or secondary amenorrhea depends on the adolescent's physical and psychosocial maturation as well as the underlying pathology. The major decisions are about hormonal therapy in patients with hypothalamic, pituitary, and ovarian causes, and about surgery in patients with outflow tract anomalies.

Hormonal therapy is indicated for all adolescents with ovarian failure. Those with primary amenorrhea who are pre-pubertal or in early puberty should be managed with low-dose estrogen replacement to stimulate maturation, followed by maintenance estrogen and progesterone, usually in the form of combination oral contraceptive pills (OCPs) containing 20–30 mcg estradiol or equivalent. Patients with secondary amenorrhea due to ovarian failure do not require titration of the estrogen dose and can begin maintenance therapy with low-dose OCPs.

Adolescents with primary or secondary amenorrhea due to hypothalamic suppression can be challenged with oral progesterone 10 mg daily for 5 days. Withdrawal bleeding in response to the progesterone challenge indicates an intact outflow tract that has been primed by estrogen. The adolescent with persistent amenorrhea who responds to the challenge should repeat the 5-day course every 3 months to prevent chronic endometrial hyperplasia, which is a risk factor for endometrial cancer. The adolescent who does not respond to the challenge either has insufficient estrogen to induce a proliferative endometrium or has an outflow tract abnormality.

The most common dilemma in the management of adolescents with amenorrhea is the use of hormone replacement therapy (HRT) in those with functional suppression of GnRH secretion. Although some studies suggest that bone density in adolescent athletes with hypothalamic amenorrhea may be protected by HRT with combined estrogen-progestin OCPs, current evidence does not support its use in adolescents with amenorrhea due to anorexia nervosa. Management should instead focus on weight gain and the maintenance of sufficient body fat to support menses (Chapter 35).

Patients with amenorrhea due to medication-induced hyperprolactinemia usually can be managed conservatively, with continuation of the responsible medication if it is considered important for overall physical and psychosocial health. Serum prolactin levels < 100 ng/ml can be monitored every 3 to 6 months, whereas those over 100 ng/dl generally warrant further evaluation with either head MRI or discontinuation of the medication responsible for the increase. Levels of 100–200 ng/dl in patients who are not on medications associated with hyperprolactinemia usually indicate pituitary microadenomas that do not require treatment unless breast discomfort develops or the patient wishes to conceive. In these cases, the usual treatment is a dopamine agonist such as bromocriptine. Levels > 200 ng/dl are associated with pituitary adenomas that are likely to produce other symptoms, such as headache or visual field cuts. Surgery, often with adjunctive radiation therapy, is indicated for these patients. AU7

Surgery is indicated to correct imperforate hymen, transverse vaginal septum, and some cases of Müllerian aplasia. The correction of imperforate hymen can be

performed at any age but is often delayed until early puberty when the estrogen effect on the mucosa facilitates a good repair. Puncture of an imperforate hymen without definitive repair can result in bacterial infection of an inadequately drained fluid collection and should be avoided. The level and thickness of a transverse vaginal septum should be determined by MRI prior to surgery to help plan the procedure.

The treatment of Müllerian aplasia begins with patient and family counseling about the cause and consequences of the anomaly. First and foremost is reassurance about female gender, both genetically and phenotypically. Although nonsurgical and surgical options exist for creating a vaginal canal, cervical and uterine dysgenesis is incompatible with successful pregnancy. In general, all techniques to establish a vagina should be delayed until mid to late adolescence when the patient can share in the decision about whether, when, and how to proceed. The nonsurgical method is considered first-line therapy and involves the use of vaginal dilators to apply progressive pressure against the vaginal dimple with gradual invagination of the mucosa. Recent studies demonstrate that 85–90% of patients achieve a functional vagina with this method. For those patients in whom dilators are unsuccessful, surgery can be considered. However, the patient and family must understand that most surgical interventions require the postoperative utilization of dilators.

ABNORMAL UTERINE BLEEDING

Abnormal uterine bleeding refers to the prolonged, acyclical, or heavy flow of blood and/or tissue from the endometrial cavity. Although most vaginal bleeding is of uterine origin, other causes should be considered, such as cervicovaginal trauma or mass (Box 22-2). When there is no identifiable structural, infectious, or hemostatic cause, the term dysfunctional uterine bleeding (DUB) applies. During early adolescence, most abnormal uterine bleeding meets the definition of DUB and reflects the irregular endometrial sloughing that accompanies anovulatory cycles.

Abnormal uterine bleeding typically is described in terms of its duration, quantity, and the interval between bleeding episodes. Menorrhagia refers to bleeding that lasts > 7 days or is > 80 ml in quantity. Menometrorrhagia is heavy, prolonged bleeding that occurs at irregular intervals. Polymenorrhea occurs at regular but short intervals of < 21 days.

Epidemiology

Most abnormal uterine bleeding during adolescence is DUB associated with anovulatory cycles. Less common causes include pregnancy, hormonal contraception, pelvic inflammatory disease (PID), bleeding disorders, hypo- or hyperthyroidism, PCOS, trauma, and congenital anomalies of the outflow tract. Unlike adults, endometrial cancer is an extremely rare cause of abnormal uterine bleeding in adolescents. A study of girls presenting with menorrhagia at menarche revealed that 45% had systemic bleeding dyscrasias. Platelet function disorders, including von Willebrand disease, were particularly common and probably are under-recognized in young adolescents with menorrhagia. Although von Willebrand disease is considered the most common inherited bleeding abnormality among females, with an overall prevalence of 1.3% in a heterogeneous population of U.S. children and adolescents, several studies suggest that other platelet function disorders may be responsible for many cases of unexplained menorrhagia. There is some evidence that

Box 22-2 Differential Diagnosis of Abnormal Uterine Bleeding

Outflow Tract

- Trauma
- Foreign body
- Tumor
- Cervical polyp
- Uterine myoma
- Intrauterine device
- Uterine carcinoma

Ovarian Causes

- Tumor
- Cyst

Anovulation

- Pituitary abnormalities
- Hypothalamic abnormalities
- Immaturity of the hypothalamic–pituitary axis
- Androgen excess
- Thyroid disease

Hematological Conditions

- Thrombocytopenia
- Clotting disorders
- Platelet disorders
- Anticoagulant medications

Pregnancy

- Ectopic
- Molar
- Miscarriage

Infection

- Sexually transmitted infections
- Pelvic inflammatory disease

Hormonal Contraception

menorrhagia associated with platelet dysfunction is more common in black than white females.

Pathophysiology

Anovulatory DUB in most adolescents is due to delayed maturation of the normal negative feedback mechanisms along the hypothalamic–pituitary–ovarian axis. The gradual rise in estrogen does not suppress FSH secretion, resulting in ongoing estrogen secretion by the ovaries and endometrial proliferation in response to the estrogen. In the absence of progesterone, which normally is increased in the luteal phase of the cycle, the thickening endometrium becomes increasingly unstable and disorganized shedding begins. Although immaturity accounts for most DUB during the first 1–2 years following menarche, it is unlikely beyond this point. Other causes of anovulation, such as PCOS, should always be considered if the DUB persists.

Pregnancy is always in the differential diagnosis of abnormal uterine bleeding, and a qualitative urine pregnancy test should be performed in nearly all patients. Consultation with an obstetrician is recommended for any pregnant patient who is bleeding and is essential if the bleeding is associated with abdominal pain or hemodynamic instability. The differential diagnosis includes threatened or spontaneous abortion, ectopic pregnancy, PID, and gestational trophoblastic disease.

von Willebrand disease is highly variable in severity and age at diagnosis. In many cases, menorrhagia at menarche is the first manifestation. Normally, platelets adhere to damaged blood vessels in a process mediated by the binding of von Willebrand factor (vWF) to a glycoprotein complex on the platelet membrane. In von Willebrand disease, underproduction or dysfunction of the vWF component of the Factor VIII molecule is associated with abnormal platelet adhesion at sites of vascular injury, reduced Factor VIII levels, and/or qualitative defects in Factor VIII activity. Patients with von Willebrand disease tend to have predominantly quantitative (Types I and III) or qualitative (Type II) defects of vWF, with Type I accounting for 70% of cases.

Evaluation

The evaluation of an adolescent with abnormal uterine bleeding should begin with characterization of the bleeding pattern. Specific information should include age at menarche; cycle length (i.e., day 1 of bleeding to day 1 of next bleeding episode), duration of bleeding; and quantity of bleeding (i.e., number of saturated tampons or sanitary napkins per 24 hours). Other information on history should include age at onset of sexual activity, history of sexually transmitted infections (STIs), condom use, new sexual partners within the past 3 months, contraception, past history of nonvaginal bleeding or bruising, family history of bleeding disorders, and current medications.

The physical examination should focus, first and foremost, on establishing hemodynamic stability through the evaluation of supine, sitting, and standing blood pressure and heart rate. Mucous membranes and skin should be examined for pallor, petechiae, ecchymoses, hirsutism, acne, and acanthosis nigricans. Lymphadenopathy and hepatosplenomegaly should be noted, and a new flow murmur on cardiac examination might suggest anemia. External genitalia should be examined for clitoromegaly, congenital anomalies of the introitus, and evidence of trauma. If DUB is likely and the patient is not sexually active, speculum examination is usually unnecessary. In other cases, however, it should be performed to inspect the cervix and vaginal canal and to collect samples for STI testing.

Pelvic ultrasonography is often performed to delineate anatomy when a structural anomaly is suspected, to assess the thickness of the endometrial stripe, to determine whether a pregnancy is intrauterine, or to determine whether hematocolpos or a uterine clot is present. Even when DUB has been heavy and prolonged, a thickened endometrial stripe is usually visualized. A uterine clot suggests that distention of the uterine cavity is interfering with myometrial contraction and hemostasis.

If the cause of abnormal bleeding remains uncertain, laboratory testing should include pregnancy testing (i.e., qualitative urine human chorionic gonadotropin [HCG]); STI testing of sexually active patients; measurement of serum TSH level and often serum androgen levels; CBC with platelet count; and prothrombin time and partial thromboplastin time. For patients in whom von Willebrand disease is suspected, the following laboratory studies should be ordered: Factor VIII activity, vWF antigen level, ristocetin cofactor activity, and multimeric analysis. The Platelet Function Analyzer (PFA-100), which is now available in many institutions, screens for acquired platelet disorders (e.g., aspirin-induced), von Willebrand disease, and some of the more complex inherited causes of platelet dysfunction. Tests of platelet aggregation represent the next level of evaluation but are laborious, costly, and not readily available in many institutions. In addition, interpretation of the results can be difficult because they are affected by hemolysis, lipemia, thrombocytopenia, and certain medications.

Management

When there is an identifiable cause for abnormal uterine bleeding, such as PID, that problem obviously should be treated. The more difficult management decisions pertain to DUB and patients with bleeding dyscrasias. In these situations, hemodynamic status and hemoglobin level

Box 22-3 Management of Dysfunctional Uterine Bleeding (DUB)

Mild: Hemodynamic Stability and Hemoglobin > 11 g/dl

- Menstrual calendar.
- Iron supplementation.
- Consider combined OCP.
- Re-evaluate in 1–3 months.

Moderate: Hemodynamic Stability and Hemoglobin > 9 g/dl

- Menstrual calendar.
- Iron supplementation.
- Combined OCP containing ≥ 30 mcg ethinyl estradiol, one tablet every 6 hours until bleeding stops or up to 4 days, followed by taper to one tablet every 8 hours for 2–3 days, one tablet every 12 hours for 2 days, one tablet (i.e., active hormone tablet in packet, not placebo-week tablet) daily for 2–3 weeks. Then discontinue pills for 1 week to allow withdrawal bleed, followed by OCP cycles for 3–6 months.
- Re-evaluate in 1–3 months.

Severe: Hemodynamic Instability and Hemoglobin < 9 g/dl

- Hospitalization for intravenous fluids and/or transfusion.
- Iron supplementation.
- Combined OCP, as noted above. If bleeding does not slow significantly with two doses, add the following to the oral contraceptive regimen: conjugated estrogen 25 mg intravenously every 4–6 hours until bleeding stops or up to 4 doses.
- Dilatation and curettage if bleeding persists.
- Combined OCP cycles for 3–6 months.

often dictate treatment (Box 22-3). It is very important to note that the management of abnormal uterine bleeding in adolescents is quite different than in older adults. Unlike adults in whom persistent or uncontrolled uterine bleeding commonly leads to dilatation and curettage (D&C), this is rarely required in adolescents and should be considered only when the options, discussed later, fail.

The stable adolescent with mild DUB and a normal hemoglobin level can be observed without treatment. The patient should record bleeding on a menstrual calendar, call immediately if flow increases or new symptoms develop, and schedule a follow-up visit within 1–3 months if bleeding stops or remains mild and intermittent. Hormonal therapy with a combined estrogen-progestin OCP can be initiated in those adolescents who are troubled by the bleeding, even if scant. In most cases, mild anovulatory DUB stops with the OCP and regular withdrawal bleeding during the placebo week of the pill cycle is established. After 3–6 months of regular menses on the pill, a trial without it can be considered.

The stable adolescent with mild-moderate anemia (i.e., hemoglobin level > 9.0 g/dl) should be managed with combined estrogen-progestin therapy for at least 3–6 months, as outlined in Box 22-3. Emergent care is essential for the unstable patient, and prompt inpatient care is recommended for the patient with a hemoglobin level < 9.0 g/dl who continues to have heavy bleeding. Of note, the initial hemoglobin and hematocrit values may be falsely elevated in an unstable patient and may decrease significantly with fluid resuscitation. Patients requiring the combined OCP several times daily for acute control of bleeding often benefit from the simultaneous administration of an anti-emetic to control the nausea associated with high-dose estrogen. Once the oral contraceptive is reduced to the maintenance dose of one pill daily, oral iron replacement therapy (i.e., 60 mg elemental iron orally three times daily) should be started for all patients with anemia and continued for at least 8 weeks.

Hormonal therapy for an adolescent with DUB usually consists of estrogen and progestin, administered as a monophasic combined OCP. Estrogen facilitates hemostasis and endometrial healing. Progestin halts endometrial proliferation and stabilizes the endometrial lining. Once the bleeding has stopped, the oral contraceptive should be continued as one pill daily until there is significant improvement in the hemoglobin level or for a minimum of 3 weeks to allow endometrial repair. At that point, the pill is stopped for 1 week and a withdrawal bleed occurs. The patient should be warned that this withdrawal bleed is likely to be heavy but painless and limited in duration, secondary to the endometrial proliferation induced by the high-dose estrogen during the initial phase of treatment. The oral contraceptive should then be cycled for 3–6 months according to the usual pill pack instructions to allow the endometrium to heal completely. Extended hormone replacement for up to 3 months prior to a withdrawal week is an option but is more likely to be associated with unpredictable breakthrough bleeding due to the prolonged endometrial stimulation and proliferation.

Norethindrone acetate or medroxyprogesterone acetate are progestin-only alternatives that can be used for the control of bleeding in patients who cannot tolerate estrogen or for whom it is contraindicated. Acutely, the progestin may be required in higher dosage and should be administered orally or intramuscularly. Once the bleeding stops, the progestin should be continued as a daily pill, a long-acting intramuscular injection (i.e., depot medroxyprogesterone acetate), or a progestin-containing intrauterine device (IUD).

Intravenous estrogen is available for patients who cannot tolerate or continue to bleed on the OCP. Of note, progestin should be administered with the estrogen to stabilize the endometrial lining. Conjugated estrogen in a

dose of 25 mg intravenously every 4–6 hours is administered for a maximum of four doses. When the bleeding is controlled, the estrogen and progestin should be continued as the OCP as noted previously and in Box 22-3. Rarely, transfusion of packed red blood cells is required for patients with severe anemia that has developed quickly. Most adolescents in whom the anemia has developed gradually, even if severe, are hemodynamically stable and do not require transfusion.

Other treatment modalities can be utilized as adjuncts to hormonal therapy for the acute management of severe or prolonged DUB, such as methergine or misoprostol, which stimulate uterine contraction. Antifibrinolytic therapy aids in preventing dissolution of clot and is commercially available in the United States as Amicar (aminocaproic acid). In patients with von Willebrand disease, an infusion of vWF-rich Factor VIII (i.e., Humate P) may be necessary acutely. These patients may also benefit from long-term use of the combined OCP therapy because the estrogen component of the pill increases vWF and Factor VIII levels.

Adolescents with von Willebrand disease or other causes of platelet dysfunction and those with the hemophilia gene who experience recurrent menorrhagia despite hormonal therapy may benefit from desmopressin (DDAVP) administered as a highly concentrated nasal spray (Stimate). DDAVP is a synthetic analog of antidiuretic hormone that increases vWF and Factor VIII levels, as well as platelet adhesion to vessel walls. The usual dose of Stimate is one puff in each nostril for the first 1–3 days of menses, and weights should be monitored daily because of the antidiuretic effect. Oral antifibrinolytic therapy may be considered for those patients who do not respond to Stimate. However, frequent, high dosing is typically required for oral antifibinolytic medications, with associated gastrointestinal side effects and low patient adherence to the regimen.

PRIMARY DYSMENORRHEA

Definitions

Dysmenorrhea: Painful menstruation.

Primary dysmenorrhea: Painful menstruation with no apparent pelvic pathology. This chapter focuses on primary dysmenorrhea.

Secondary dysmenorrhea: Painful menstruation caused by pelvic pathology, such as endometriosis, outflow tract obstruction, or PID. Chapter 23 discusses secondary dysmenorrhea.

Epidemiology

Dysmenorrhea is the most common cause of missed school and work time by females, estimated at more than 140 million lost hours per year. Dysmenorrhea of varying severity accompanies 20–90% of adolescent menstrual cycles. The prevalence of primary dysmenorrhea increases with adolescent gynecological age (i.e., time since menarche) due to its association with ovulatory cycles (see following discussion), peaks at age 17 years, and decreases with parity. Severe dysmenorrhea that significantly interferes with function 1–3 days per month affects 5–42% of adolescents and is more likely be primary than secondary in origin.

Pathophysiology

Primary dysmenorrhea is caused by hypercontraction of the myometrium, tissue ischemia, and hypersensitivity of pain nerve terminals in the uterine cavity. The underlying mechanism involves the endometrial production and secretion of prostaglandin F_2 alpha ($PGF_2\alpha$) and prostaglandin E_2 (PGE_2) during menses. $PGF_2\alpha$ is primarily responsible for the symptoms of dysmenorrhea, producing the uterine contractions and ischemia as well as mediating pain sensation. Endometrial levels of $PGF_2\alpha$ and PGE_2 are higher in the secretory than proliferative phase of the menstrual cycle, supporting the association of primary dysmenorrhea with ovulatory cycles; are highest in the first two days of flow, explaining why dysmenorrhea is more severe in the beginning than end of menses; and are higher in women with than without dysmenorrhea. Although serum levels of $PGF_2\alpha$ and PGE_2 are not increased during menstruation, studies have demonstrated that intravenous infusion of $PGF_2\alpha$ induces systemic symptoms similar to those that are associated with primary dysmenorrhea (e.g., headache, nausea, vomiting, backache, diarrhea, dizziness, and fatigue). The causative role of prostaglandins is further supported by consistent evidence demonstrating the effectiveness of prostaglandin synthetase inhibitors (i.e., NSAIDs) in the treatment of primary dysmenorrhea.

Evaluation

Key questions to ask the adolescent with dysmenorrhea include the following: Did the pain begin with menarche? Was the pain as severe when it began as it is now? Does the pain occur only during menstruation? Menstrual duration, flow, and interval should be reviewed, along with changes in cycle pattern over time. The effect of dysmenorrhea on the adolescent's function should be discussed in detail, including missed school and decreased social involvement. Those adolescents who have tried NSAIDs without success should be asked when they begin the medication. NSAIDs are most effective when begun with or shortly before the onset of pain because their primary mechanism of action is to decrease endometrial production of prostaglandins.

The history should also include questions about sexual activity, STIs, and sexual risk behaviors (e.g., number of lifetime partners, new partner within the past 3 months, non-use of condoms). A thorough review of systems is important because of the many non-gynecological conditions that can cause pelvic pain (Box 22-4). The psychosocial history should include questions about stress, substance abuse, and cigarette smoking, which has been specifically associated with dysmenorrhea.

Pelvic examination generally can be deferred in the adolescent with probable primary dysmenorrhea who denies history of sexual intercourse. The insertion of a moistened cotton swab into the vaginal canal can help rule out a hymenal abnormality or vaginal septum, and recto-abdominal examination can help identify a mass when bimanual vaginal examination is difficult. Laboratory testing is unnecessary in the adolescent with probable primary dysmenorrhea. If the history or physical examination suggests that the dysmenorrhea is secondary to organic pathology, the specific condition that is suspected should guide testing (Chapter 23).

Management

First- and second-line therapies for primary dysmenorrhea are NSAIDs and OCPs, respectively. Clinicians should explain that primary dysmenorrhea is normal but uncomfortable and that the symptoms can be controlled. Many studies have demonstrated that adolescents typically know little about effective treatment options for dysmenorrhea, and even those who use NSAIDs typically do not begin them before the onset of pain.

Box 22-4 Non-Gynecological Causes of Pelvic Pain

- Gastrointestinal disorders
- Inflammatory bowel disease
- Irritable bowel syndrome
- Constipation
- Lactose intolerance
- Musculoskeletal pain
- Inflammatory process
- Trauma
- Tumor
- Cystitis
- Ureteral obstruction
- Calculi
- Psychogenic disorders
- History of abuse

NSAIDs are divided into several groups, including salicylic acids, acetic acids, propionic acids, fenamates, benzenesulfonamides, furanones, and oxicams. Those that are best-studied and most widely used for the treatment of dysmenorrhea are the propionic acids (e.g., ibuprofen, naproxen) and fenamates (e.g., mefenamic acid). Mefenamic acid may be advantageous in some clinical situations because it competes with prostaglandins for binding sites, thus antagonizing prostaglandin action as well as inhibiting prostaglandin synthesis. The typical dosing patterns of commonly used NSAIDS are shown in Table 22-1.

NSAIDs should be started either with the onset of pain if it precedes menses or with the first sign of menstruation. There is no proven advantage to starting prior to the onset of menses in an individual whose pain begins after the onset of bleeding. NSAIDs typically are needed for only 1–3 days and are associated with minimal side effects when used in the recommended doses. Each formulation should be tried for two or three menstrual cycles, and a 6-month trial with at least two different formulations is recommended before deciding that NSAIDs are ineffective.

Hormonal therapy can be added to NSAIDs for patients with ongoing discomfort or can be used alone for patients who do not tolerate NSAIDs or derive no benefit from them. OCPs have been shown to decrease symptoms in more than 90% of patients with primary dysmenorrhea. The mechanisms of action include the inhibition of ovulation and the development of an atrophic endometrium, with resultant decreases in prostaglandins and menstrual flow. The patient should be counseled that maximal effect may be delayed for several cycles. If dysmenorrhea persists on the 28-day cycle of the usual OCP pack, the patient can skip the placebo pills and take only the hormone-containing pills for up to 3 months before allowing 7 days without hormones for a withdrawal bleed. Progestin-only methods, such as injectable depot medroxyprogesterone acetate (Depo-Provera) and the levonorgestrel-releasing intrauterine system (Mirena), also are effective for the treatment of dysmenorrhea.

Table 22-1 NSAID Regimens for Dysmenorrhea

NSAID	First Dose (mg)	Subsequent Dose (mg)
Ibuprofen	400–600	400 every 4–6 hours *or* 600 every 6 hours
Naproxen	500	250 every 6–8 hours
Naproxen sodium	550	275 every 6–8 hours *or* 550 every 12 hours
Mefenamic acid	500	250 every 6 hours

Some studies suggest that oral supplementation with vitamin B_1, magnesium, and vitamin E may be helpful in the management of dysmenorrhea. GnRH agonists may be needed for the control of dysmenorrhea secondary to endometriosis but rarely are indicated for primary dysmenorrhea.

PREMENSTRUAL SYNDROME

Definitions

Premenstrual dysphoric disorder (PMDD) is defined by the *Diagnostic and Statistical Manual of Mental Health Disorders*, 4th edition (DSM-IV-TR) according to the criteria noted in Box 22-5. The symptoms of PMDD are more severe than those of PMS and predominantly affect mood.

Premenstrual syndrome (PMS) a constellation of predictable physical, cognitive, affective, and behavioral symptoms that occur cyclically, beginning with ovulation, continuing during the luteal phase of the menstrual cycle, and quickly resolving with menstruation. To date, there is no universally accepted definition or set of diagnostic criteria for PMS.

Epidemiology

An estimated 70–90% of women experience some premenstrual symptoms. The 3–8% of these women who describe the symptoms as severe enough to affect quality of life probably represents the subgroup with PMDD. More than 200 symptoms have been described in the literature, the most common of which are listed in Box 22-6. At least one premenstrual symptom is reported by 50–100% of adolescents, and 14–89% of adolescents describe their symptoms as moderate to severe. There is a higher concordance of PMS among monozygotic than dizygotic twins, and a maternal history of PMS increases the likelihood of its development. The prevalence of PMS increases with advancing age beyond 30 years.

Pathophysiology

PMS probably represents an interaction between sex steroids and central neurotransmitters. There is some evidence supporting reduced serotonergic function in the luteal phase of the menstrual cycle and alteration in the response of the gamma aminobutyric acid (GABA) receptor complex. Although serotonergic dysregulation is the most plausible theory, variable response to selective serotonin reuptake inhibitors (SSRIs) implies the involvement of other factors. Estrogen, progesterone, and testosterone levels are normal, but women with PMS/PMDD may be more vulnerable to the normal cyclical fluctuations in serum levels of these hormones. Current evidence does not support associations of PMS with prolactin, growth hormone, thyroid hormone, adrenal hormones, luteinizing hormone (LH), follicle-stimulating hormone (FSH), antidiuretic hormone, insulin, zinc, vitamin A, vitamin E, thiamine, magnesium, or pyridoxine.

Box 22-5 DSM-IV-TR Criteria for the Diagnosis of PMDD

I. In most menstrual cycles in the past year at least five of these symptoms (including at least one of the symptoms in category A) were present for most of the time 1 week before menses, began to remit within a few days after the onset of the follicular phase (menses), and were absent in the week after menses.

A. Principal Symptoms
1. Markedly depressed mood, feelings of hopelessness or self-deprecating thoughts
2. Marked anxiety, tension
3. Marked affective lability (i.e., feeling suddenly sad or tearful)
4. Persistent and marked anger or irritability or increased interpersonal conflicts

B. Other Symptoms
1. Decreased interest in usual activities such as friends and hobbies
2. Subjective sense of difficulty in concentrating
3. Lethargy, easy fatigability, or marked lack of energy
4. Marked change in appetite, overeating, or specific food cravings
5. Hypersomnia or insomnia
6. A subjective sense of being overwhelmed or out of control
7. Other physical symptoms (e.g., breast tenderness, bloating, weight gain, headache, joint or muscle pain)

II. The symptoms markedly interfere with work, school, usual activities, or relationships with others.

III. Symptoms are not merely an exacerbation of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may be superimposed on any of these disorders).

Criteria I, II, and III are confirmed by prospective daily ratings for at least two consecutive symptomatic menstrual cycles. Adapted from: American Psychiatric Association. Diagnosis and Statistical Manual of Mental Disorders, 4th edition. DSM-IV-Text Revision. DSM-IV-TR. Washington, D.C. American Psychiatric Association, 2000.

Evaluation

There are no universally accepted findings on physical examination or laboratory evaluation that establish a diagnosis of PMS or PMDD. Important findings on history are as

Box 22-6 Symptoms Associated with PMS and PMDD

Emotional Symptoms

- Irritability
- Depression
- Fatigue or lethargy
- Anger/argumentative
- Insomnia or hypersomnia
- Mood lability
- Anxiety
- Poor concentration
- Confusion
- Tearfulness
- Social withdrawal

Physical Symptoms

- Headaches
- Swelling: legs or breasts; breast tenderness
- Increased appetite
- Food cravings
- Weight gain
- Sense of abdominal bloating
- Fatigue
- Muscle and joint aches and pain

Box 22-7 Approach to the Treatment of PMS and PMDD

Step 1a: Mild-moderate symptoms:

- Complex carbohydrates, aerobic exercise, calcium supplementation, and possibly magnesium or chasteberry fruit.

Step1b: Physical symptoms predominate:

- Spironolactone, oral contraceptive, Depo-Provera, NSAIDs.

Step 2: Mood symptoms predominate:

- SSRI or an anxiolytic medication.

Step 3: No response to Steps 1 or 2:

- Gynecological consultation about GnRH agonists.

Adapted from: American College of Obstetricans and Gynecologists: *Premenstrual syndrome. ACOG Practice Bulletin #15.* Washington, D.C., American College of Obstetricians and Gynecologists, April, 2000; and Johnson SR: Premenstrual syndrome, premenstrual dysphoric disorder, and beyond: A clinical primer for practitioners. Obstet Gynecol 2004;104:845–859.

follows: (1) symptoms occur in the luteal phase and resolve within a few days of menses; (2) symptoms recur over at least three menstrual cycles and cannot be explained by other physical or psychological problems; and (3) symptoms are severe enough to disrupt normal activities. PMS and PMDD can be exacerbated by and/or exacerbate (i.e., menstrual magnification) co-existing psychiatric or medical conditions such as seizures, migraine headaches, irritable bowel syndrome, asthma, and allergies.

Management

A stepwise approach to the management of PMS and PMDD is outlined in Box 22-7. For adults with severe symptoms, SSRIs are considered first-line therapy. Placebo-controlled studies have demonstrated improvements in both physical symptoms and mood with fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and venlafaxine. Unlike depression, the symptoms of PMS and PMDD typically improve within 24–28 hours of initiating therapy. Furthermore, the medications appear to be equally effective when used either continuously or only during the luteal phase (i.e., the 14 days following ovulation). Low-dose therapy is usually sufficient, and intermittent use has not been associated with symptoms of SSRI withdrawal. It is important to note that fluoxetine is the only SSRI approved for use in adolescents < 18 years of age. Studies suggest more variable effectiveness with the continuous or intermittent use of alprazolam, which affects the GABA receptor complex; clomipramine, which is a nonselective serotonin receptor agonist; and buspirone, which is a partial serotonin receptor agonist.

Studies exploring the use of OCPs for PMS or PMDD have yielded inconsistent results. A double-blind, placebo-controlled study of an oral contraceptive containing drospirenone and ethinyl estradiol 30 mcg in women with PMDD demonstrated improvement in a few physical symptoms. Another study of a newer formulation containing drospirenone and ethinyl estradiol (20 mcg) daily for 24 days and nonactive pills for 4 days (24/4 regimen) rather than the usual 21/7, showed improvement in both mood and physical symptoms. Generally, OCPs can be considered if the symptoms are primarily physical.

Other regimens to suppress ovulation can also be considered, such as continuous use of oral contraceptives for 3 months and the injectable depot medroxyprogesterone acetate (Depo-Provera). GnRH has been shown to be effective in adult women for the treatment of PMS and PMDD but is associated with severe hypoestrogenemia and increased risk of osteoporosis. GnRH with add-back estrogen-progestin therapy can be considered in adults when other modalities have failed but is rarely indicated for adolescents with PMS or PMDD. Spironolactone may help reduce premenstrual breast tenderness, bloating, or weight gain from fluid retention in some patients. Similarly, NSAIDs may help control some physical symptoms. Evidence

remains limited regarding the use of mineral supplementation, herbal preparations, and dietary manipulation.

One of the most promising interventions is calcium (1200 mg/day) in the form of calcium carbonate, which has been reported to reduce physical and emotional symptoms in a well-designed, multicenter study. A prospective case-control study, nested in the Nurses' Health Study II, demonstrated that the risk of developing PMS was reduced among women with high intake of calcium and vitamin D. Magnesium supplementation (200 to 400 mg/day) has been noted in some studies to reduce negative mood and water retention, but the mechanism of action is not understood and data are limited.

Placebo-controlled trials have demonstrated the possible effectiveness of chasteberry; ginko leaf extract for breast tenderness, fluid retention, and mood; and carbohydrates for the control of food craving and mood. The mechanism of action for the latter may involve an increase in tryptophan, which is a precursor to serotonin. Evidence is limited regarding the effectiveness of pyridoxine (vitamin B_6) and vitamin E.

MAJOR POINTS

- All patients with amenorrhea should be evaluated to determine pubertal staging and the presence of normal genital anatomy.
- During adolescence, eating disorders and excessive exercise are common causes of secondary amenorrhea.
- PCOS should be considered in the differential diagnoses of both amenorrhea and abnormal uterine bleeding.
- Anovulation is the most common cause of abnormal uterine bleeding in adolescents.
- Inherited bleeding disorders should always be considered in adolescents with heavy or prolonged uterine bleeding that began with menarche.
- Endometrial prostaglandins are responsible for the uterine contractions, tissue ischemia, and stimulation of endometrial pain nerve terminals of primary dysmenorrhea.
- Adolescents with dysmenorrhea who do not respond to medical therapy should be evaluated for endometriosis or outflow tract anomalies.
- Most menstruating adolescents have at least one premenstrual symptom.
- The diagnoses PMS and PMDD depend on recurrence over at least three cycles with adverse effects on school, work, and social function.

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CHAPTER 23

Polycystic Ovary Syndrome

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INTRODUCTION

Polycystic ovary syndrome (PCOS) may be the most common endocrine disorder in women of reproductive age, occurring in 4–6% of adolescents and 4–12% of adult women. In 1935, Stein and Leventhal first reported the association of polycystic ovaries with amenorrhea, hirsutism, and obesity. PCOS is now recognized as a syndrome characterized by ovarian dysfunction, increased androgen production, and disordered gonadotropin secretion. These abnormalities may cause anovulatory infertility, menstrual dysfunction, hirsutism, and acne. PCOS also is associated with metabolic abnormalities, including insulin resistance and hyperinsulinemia. Women with PCOS are at increased risk for Type 2 diabetes mellitus, dyslipidemia, and cardiovascular disease.

Recent research has shown that childhood conditions such as low birth weight and premature adrenarche are risk factors for PCOS. The manifestations of PCOS begin to appear with the onset of puberty and may adversely affect body image and self-esteem. Early diagnosis and treatment can help control the physical manifestations during adolescence and decrease clinical sequelae in adulthood.

DEFINITIONS

Acanthosis nigricans: Velvety, hyperpigmented, verrucous skin associated with insulin resistance.

Gonadotropins: Luteinizing hormone (LH) and follicle stimulating hormone (FSH), secreted by the anterior pituitary.

Hirsutism: An increased quantity and distribution of coarse, pigmented hair in females.

Idiopathic hirsutism: Hirsutism without hyperandrogenemia, menstrual irregularity, or an identifiable cause.

Late-onset congenital adrenal hyperplasia (CAH): 21-hydroxylase deficiency, resulting in elevated level of serum 17α-hydroxyprogesterone.

Metabolic syndrome: Definition in children and adolescents: waist circumference > 90th percentile; blood pressure > 90th percentile; fasting plasma glucose > 110 mg/dl; serum triglycerides > 110/ml; serum HDL cholesterol > 40 mg/dl.

Polycystic ovaries: 12 or more follicles in each ovary, each > 2–9 mm, or ovarian volume > 10 ml.

Premature adrenarche: The development of pubic hair in girls younger than 8 years and boys younger than 9 years due to adrenal hyperandrogenism.

Pubarche: Onset of pubic hair growth.

Thelarche: Onset of breast development.

Virilization: A manifestation of hyperandrogenemia; signs include acne, clitoromegaly, voice deepening, increased muscle mass, and frontal balding.

PATHOPHYSIOLOGY

The pathogenesis of PCOS is not well defined. However, research has shown that gonadotropin, ovarian steroid, adrenal steroid, metabolic, and genetic abnormalities all appear to be involved.

Gonadotropin Abnormalities

PCOS is characterized by a relative increase in the secretion of luteinizing hormone (LH) and a relative decrease in the secretion of follicle-stimulating hormone (FSH). Approximately 55–75% of women with PCOS have an elevated LH:FSH ratio (> 2.5:1), and administration of gonadotropin-releasing hormone (GnRH) evokes an exaggerated LH response. Women with PCOS may have increased LH pulse frequency, increased LH amplitude, and abnormal diurnal rhythm of LH secretion. The mechanism underlying LH hypersecretion may reflect impaired hypothalamic sensitivity to feedback inhibition from ovarian steroids such as estradiol, progesterone, and androgens. FSH secretion is similar to that of women in the early follicular phase of the menstrual cycle. High LH levels (which stimulate theca-interstitial cell secretion of androgens) and relatively low FSH levels (which prevent efficient aromatization) may lead to excess androgen production by the ovary.

Ovarian and Adrenal Steroid Abnormalities

Intrinsic defects in ovarian steroidogenesis, particularly dysregulation of ovarian androgen secretion, play a central role in the pathogenesis of PCOS. Thecal cells isolated from polycystic ovary follicles secrete increased amounts of androstenedione, 17α-hydroxyprogesterone, and progesterone, both basally and in response to LH. Ovarian androgen biosynthesis occurs primarily in the thecal-interstitial cells, and the excessive androgen production in women with PCOS appears to be caused by increased activity in the thecal cell steroid production pathway. Recent studies suggest that hyperandrogenemia in women with PCOS is the result of several defects in thecal cell steroidogenesis, rather than a molecular or genetic defect affecting a single steroidogenic enzyme. For example, the function of the thecal enzyme cytochrome P450c17 (CYP17) is dysregulated in women with PCOS. This enzyme has 17α-hydroxylase and 17,20-lyase activity. The latter enzyme is the rate-limiting step in androgen formation. Thecal cells from women with PCOS demonstrate elevated gene expression and activity of 17α-hydroxylase. Granulosa cells also exhibit some dysregulation of steroidogenesis and may contribute to hyperandrogenism. Hyperinsulinemia, which is commonly found in women with PCOS, may exacerbate steroidogenic dysregulation. Intrinsic defects in ovarian steroidogenesis are thought to contribute to impaired folliculogenesis, which is a key feature of PCOS.

The earliest abnormalities in women with PCOS are an increased number of early-growing follicles, arrested development of these follicles at a diameter of 4–8 mm, and impairment in the selection of a dominant follicle. Excessive intraovarian androgens appear to interfere with selection of a dominant ovarian follicle and thus with ovulation. In addition, granulosa cells produce inhibins, which regulate follicular steroidogenesis. Inhibin A and B concentrations are reduced in the follicular fluid of women with PCOS, suggesting that inhibin deficiency may play a role in the abnormal follicular maturation noted in women with PCOS.

Although the ovary is the principal source of excess androgen secretion, 50–60% of women with PCOS also have elevated levels of adrenal androgens. Increased 17, 20-hydroxlyase activity and adrenal androgen hyperresponsiveness to ACTH are thought to be two major abnormalities leading to adrenal androgen excess in PCOS, and both may be promoted by elevated ovarian androgens.

Metabolic Abnormalities

Many women with PCOS have hyperinsulinemia on the basis of insulin resistance and compensatory insulin secretion by the β-cells of the pancreas. Obesity is common in women with PCOS, and these women tend to have lower insulin sensitivity and higher insulin levels than obese women in the general population. A number of studies, although not all, have demonstrated that nonobese women with PCOS are more likely to have hyperinsulinemia than nonobese women without PCOS.

Several defects in the pathways that mediate insulin action and signaling are likely to be responsible for insulin resistance in women with PCOS. One of these appears to be a postbinding defect in insulin-mediated signal transduction, mediated in some women by abnormal serine phosphorylation of the insulin receptor. Approximately 50% of women with PCOS had increased serine phosphorylation of the insulin receptor, which decreases protein tyrosine kinase activity. Studies have shown that a factor extrinsic to the receptor, possibly serine kinase, is responsible for serine phosphorylation. Because serine phosphorylation modulates the activity of P450c17 (an enzyme that regulates the synthesis of sex steroids), a genetic defect involving serine protein kinase may cause both insulin resistance and excessive androgen production.

Insulin may increase ovarian androgen production directly through the stimulation of steroidogenesis in granulosa or thecal cells, as well as indirectly through the stimulation of LH secretion or the inhibition of hepatic production of insulin-like growth factor 1 binding protein (IGFBP-1).

Finally, insulin may increase bioavailable androgens by inhibiting liver synthesis and secretion of sex hormone-binding globulin (SHBG). Studies have also demonstrated that insulin may increase adrenal androgen production.

Genetics

Familial clustering of PCOS has been well documented, suggesting that genetic abnormalities are likely to play a role in its pathogenesis. The concordance rate for PCOS is 74% among monozygotic twins, 60% among dizygotic twins, and 22% among sisters. Candidate PCOS genes include those involved in ovarian steroidogenesis (CYP11a, CYP17, and CYP21), steroid hormone function (androgen receptor gene, sex hormone binding globulin gene), gonadotropin function (LH gene, LH receptor gene, follistatin gene), insulin secretion and action (variable number tandem repeats or VNTR, insulin receptor gene, insulin receptor substrate protein genes, calpain 10 gene), adipose tissue metabolism (leptin gene, leptin receptor gene, peroxime proliferators-activated receptor-gamma gene), and chronic inflammation (plasminogen activator inhibitor-1). Although many gene mutations and polymorphisms have been identified in women with PCOS, studies have not identified a specific gene or genes that appear to play a principal role in PCOS pathogenesis or to have obvious clinical significance. The clinical and biochemical variability of PCOS may be explained by genetic heterogeneity and/or the interaction of environmental factors, such as those related to obesity and diet, with a small number of genes, such as those involved in androgen production and insulin secretion or action.

Environmental Factors

Central obesity and diets high in saturated fats appear to be independent environmental risk factors for PCOS. Postulated mechanisms include the increased production of free fatty acids that affect insulin clearance, cell uptake of glucose, and glycogen synthesis; and adipocyte secretion of tumor necrosis factor α (TNFα), which may play a role in the pathogenesis of insulin resistance in women with PCOS.

Developmental Hypotheses

Nobels and Dewailley noted in the early 1990s that there is a striking resemblance between the endocrine characteristics of puberty and PCOS. They pointed out that both conditions are characterized by insulin resistance, hyperpulsatile gonadotropin secretion, hyperactive ovarian and adrenal androgen synthesis, and decreased levels of IGFBP-1 and SHBG. They proposed that PCOS may be thought of as an exaggerated transition to puberty and that increasing insulin levels and IGF-1 activity during puberty may predispose susceptible adolescents to developing PCOS.

Abbott et al. have hypothesized, based on animal models and human studies, that the clinical and biochemical features of PCOS are a consequence of genetically determined hypersecretion of androgens by the ovary during or before puberty. They suggest that hyperandrogenism then results in "programming" of the hypothalamic–pituitary axis to secrete excess LH and promotes abdominal adiposity that predisposes to insulin resistance. Finally, they propose that the severity of hyperinsulinemia and insulin resistance is influenced by genetic factors, such as polymorphism in the insulin gene regulatory region, as well as environmental factors such as obesity.

A diagram summarizing the hypothesized relationships between hyperinsulinemia and hyperandrogenemia and their role in the pathogenesis of PCOS is shown in Figure 23-1. The figure illustrates the importance of both genetic and environmental factors in the pathogenesis of PCOS.

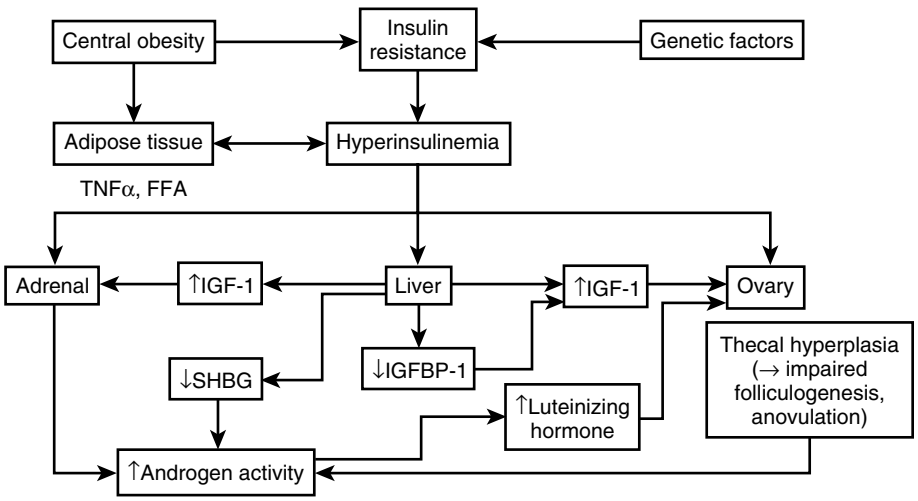

Figure 23-1 Hypothesized pathogenesis of PCOS.
Created by author.

Clinical Manifestations

The clinical manifestations of PCOS typically begin to appear with the onset of puberty. However, girls younger than 8 years with pubic hair and elevated adrenal androgens (i.e., premature adrenarche) appear to be at subsequent risk for excess androgen production by both the adrenals and ovaries and insulin resistance. Premature adrenarche therefore may represent the earliest PCOS phenotype.

Adolescents with PCOS typically present with symptoms and physical findings related to hyperandrogenism, anovulation, and insulin resistance. Clinical sequelae that are more commonly seen during adulthood include Type 2 diabetes mellitus, the metabolic syndrome, and cardiovascular disease.

Hyperandrogenism in patients with PCOS commonly presents with hirsutism and acne. Hirsutism is defined as the presence of excess terminal hair in females. Terminal hair (in contrast to vellus or lanugo hair) is coarse, pigmented, and > 0.5 cm long. Deciding whether the quantity or pattern of terminal hair is excessive can be highly subjective and is aided by the use of the Ferriman-Gallwey system, depicted in Table 23-1 and Figure 23-2. Acne, as discussed in Chapter 15, is caused by excess sebum production and the proliferation of keratinocytes, both of which are stimulated by androgens. Signs of virilization, such as clitoromegaly, frontal balding, deepening of the voice, and increased muscle mass, are uncommon in PCOS and should prompt evaluation for other causes of hyperandrogenism (see Evaluation, later).

Anovulation can present as oligomenorrhea, amenorrhea, dysfunctional uterine bleeding, or infertility (Chapter 22). Although anovulatory cycles during the 2 years following menarche are commonly attributed to physiological immaturity of the hypothalamic–pituitary–ovarian axis, a study comparing postmenarcheal adolescents with regular vs. irregular menses revealed higher androgen and LH level in the latter, consistent with early PCOS. In adult women with secondary amenorrhea or oligomenorrhea, PCOS accounts for 30–40% and 85–90% of cases, respectively, and is a frequent cause of infertility.

Insulin resistance and compensatory hyperinsulinemia begin early in the course of PCOS, particularly in obese adolescents. Acanthosis nigricans is associated with insulin resistance but is neither a sensitive nor specific marker for it. Morphologically, skin fold areas (e.g., posterior neck, axillae, inframammary folds, and vulvae) appear velvety, hyperpigmented, and verrucous (Figure 23-3). Histologically, there is hyperkeratosis and epidermal papillomatosis. Central obesity, or a waist circumference in females > 88 cm, is highly correlated with insulin resistance. Studies have demonstrated a wide range in the prevalence of obesity among patients with PCOS, but recent data indicate that at least 50% of adult women with PCOS are obese. Furthermore, even nonobese women with PCOS appear to have higher total body fat than nonobese women without PCOS.

Glucose intolerance or Type 2 diabetes mellitus affects approximately 20–40% of obese young women with PCOS and is often associated with the metabolic syndrome (see Definitions, previously). Adolescents with PCOS are up to 4.5 times more likely to have metabolic syndrome than age-matched controls after adjusting for body mass index.

Table 23-1 The Ferriman-Gallwey System for Scoring Hirsutism

Site	Grade[1]	Definition
Upper lip	1	A few hairs at outer margin.
	2	A small moustache at outer margin.
	3	A moustache extending halfway from outer margin.
	4	A moustache extending to mid-line.
Chin	1	A few scattered hairs.
	2	Scattered hairs with small concentrations.
	3, 4	Complete cover, light and heavy.
Chest	1	Circumareolar hairs.
	2	With mid-line hair in addition.
	3	Fusion of these areas, with three-quarter cover.
	4	Complete cover.
Upper back	1	A few scattered hairs.
	2	Rather more, still scattered.
	3, 4	Complete cover, light and heavy.
Lower back	1	A sacral tuft of hair.
	2	With some lateral extension.
	3	Three-quarter cover.
	4	Complete cover.
Upper abdomen	1	A few mid-line hairs.
	2	Rather more, still mid-line.
	3, 4	Half and full cover.
Lower abdomen	1	A few mid-line hairs.
	2	A mid-line streak of hair.
	3	A mid-line band of hair.
	4	An inverted V-shaped growth.
Arm	1	Sparse growth affecting not more than a quarter of the limb surface.
	2	More than this; cover still incomplete.
	3, 4	Complete cover, light and heavy.
Forearm	1, 2, 3, 4	Complete cover of dorsal surface; 2 grades of light and 2 of heavy growth.
Thigh	1, 2, 3, 4	As for arm.
Leg	1, 2, 3, 4	As for arm.

[1]Grade 0 at all sites indicates absence of terminal hair; a total score of 8 or more indicates hirsutism.

From: Hatch R, Rosenfield RL, Kim MH, et al.: Hirsutism: Implications, etiology, and management. Am J Obstet Gynecol 1981;140:815–830. Adapted from Ferriman D, Gallwey JD: Clinical

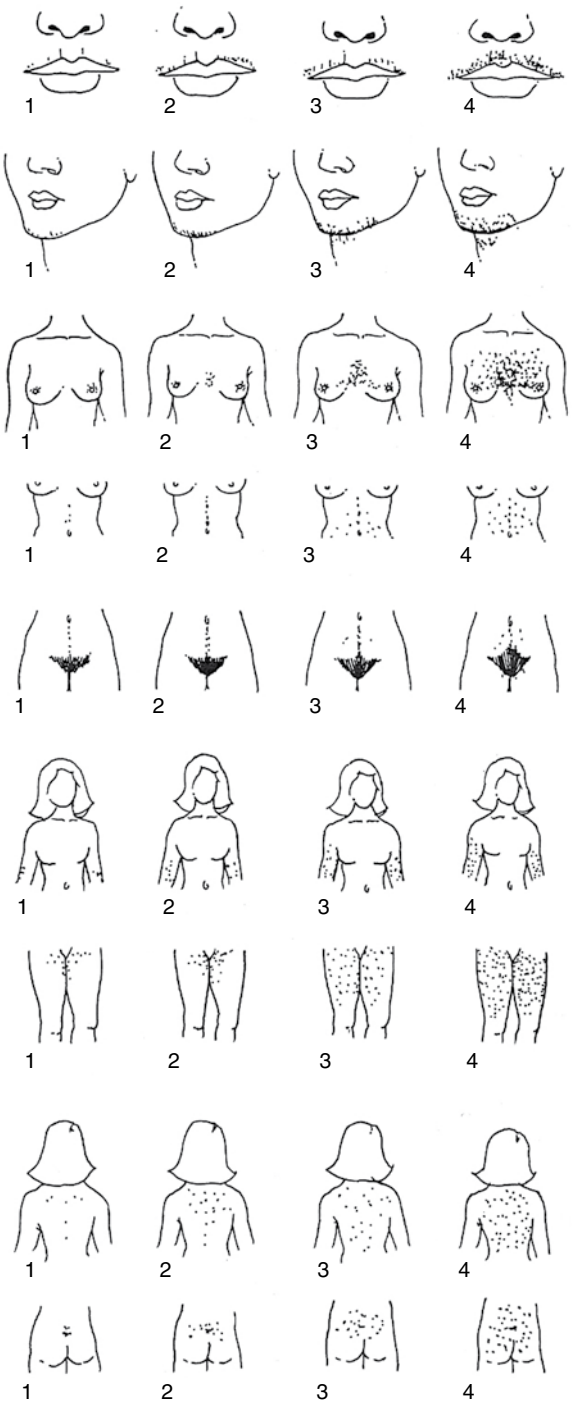

Figure 23-2 Ferriman-Gallwey system to evaluate for hirsutism. From: Hatch R, Rosenfield RL, Kim MH, et al.: Hirsutism: Implications, etiology, and management. Am J Obstet Gynecol 1981;140:815–830. Adapted from Ferriman D, Gallwey JD: Clinical assessment of body hair growth in women. J Clin Endocrinol Metab 1961;21:1440–1447.

A study of adult women with PCOS revealed that 43% met criteria for the metabolic syndrome. Participants with the metabolic syndrome and PCOS, compared with those with PCOS only, had higher free testosterone and lower SHBG levels.

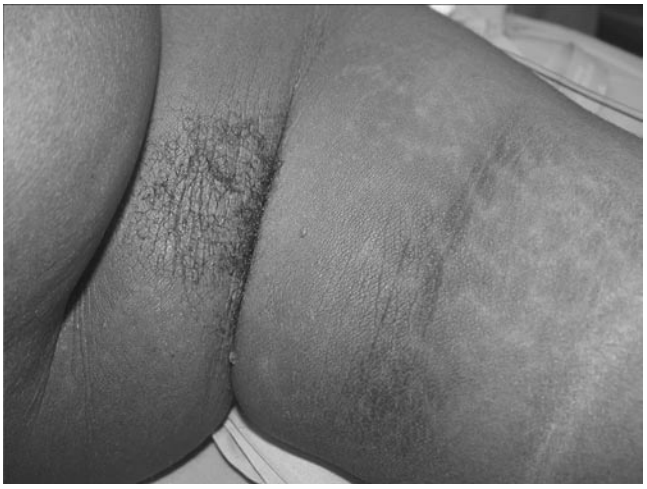

Figure 23-3 Axillary acanthosis nigricans. Photograph courtesy of Jill Huppert, M.D., M.P.H.

Clinical Sequelae

Cardiovascular disease is more prevalent in adult women with than without PCOS due to many of the manifestations discussed previously (i.e., obesity, central body fat distribution, Type 2 diabetes mellitus, and dyslipidemia). Women with PCOS are also at increased risk for hypertension and elevated levels of plasminogen activator inhibitor 1 (PAI-1), which inhibits fibrinolysis and has been associated with myocardial infarction. Although epidemiological data are limited, prospective studies have demonstrated a four-fold risk of hypertension and seven-fold risk of myocardial infarction in women who had undergone ovarian wedge resection for PCOS compared with control subjects without PCOS.

Infertility is a common presenting complaint of adult women with previously undiagnosed PCOS, and PCOS is the most common cause of anovulatory infertility. In addition to the difficulty with conception, women with PCOS are at increased risk for miscarriage, both after spontaneous and induced ovulation.

Endometrial cancer is associated with chronic anovulation, obesity, and hyperinsulinemia, all of which are features of PCOS. Studies have not demonstrated consistently that women with PCOS are at higher risk of breast or ovarian cancer.

Low self-esteem and poor body image during adolescence have been associated with the clinical manifestations of PCOS. Adolescents with PCOS also report lower health-related quality of life and more concerns about fertility than adolescents without PCOS.

Laboratory and Radiographic Findings

There is no one laboratory or radiographic study that is pathognomonic for PCOS. The most sensitive test for the

detection of hyperandrogenemia is the serum free testosterone level, but it is not specific for PCOS. A small proportion of patients with PCOS have mild to moderate elevations of serum dehydroepiandrosterone sulfate (DHEA-S), with normal levels of serum total and free testosterone. Other laboratory findings consistent with PCOS include elevated levels of serum LH and an LH:FSH ratio greater than 2.5:1. Serum concentrations of total and free estradiol are within the normal range for the early or mid follicular phase of the menstrual cycle. However, the pattern of estradiol secretion does not demonstrate the preluteal surge seen a normal ovulatory cycle.

Insulin resistance is manifested by an increase in the ratio of fasting insulin:glucose levels and by an abnormal oral glucose tolerance test. However, the cut-points that differentiate insulin resistance from normal and frank diabetes mellitus remain controversial due to physiological fluctuation in insulin levels and lack of a standardized insulin assay.

Polycystic ovaries (see Definitions, above) are seen more commonly on pelvic ultrasound in adults than adolescents with PCOS. However, the finding does not confirm PCOS and its absence does not exclude PCOS. Polycystic ovaries can also be seen in 21-hydroxylase deficiency, Cushing syndrome, androgen-secreting tumors, exogenous androgen use, insulin resistance, hyperprolactinemia, use of medications such as valproate, and in 25% of women with normal menstrual cycles.

DIAGNOSIS

Two sets of diagnostic criteria for PCOS are in common use (Table 23-2). The 1990 National Institutes of Health (NIH) criteria require oligo- or anovulation plus clinical and/or biochemical evidence of hyperandrogenism. The 2003 Rotterdam criteria require either both of these criteria or one of these criteria plus ultrasound evidence of polycystic ovaries. Both the NIH and Rotterdam criteria require the exclusion of other causes of hyperandrogenism, such as androgen-secreting tumors and congenital adrenal hyperplasia. As noted in Box 23-1, the Rotterdam Consensus Conference also produced criteria for the diagnosis of metabolic syndrome specifically in women with PCOS.

The major conditions that comprise the differential diagnosis of PCOS include those associated with increased ovarian or adrenal production of androgens. Testosterone excess alone is usually ovarian; DHEA and/or DHEA-S excess is adrenal; and androstenedione excess may be adrenal or ovarian. DHEA and DHEA-S do not have much androgenic activity but are converted first to androstenedione and then to testosterone, both of which do have androgenic activity. Young women with oligomenorrhea or secondary amenorrhea, accompanied by clinical signs of hyperandrogenemia, are likely to have PCOS. Nonclassic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency often is difficult to distinguish clinically from PCOS. Idiopathic hirsutism occurs in females with normal menses, normal androgen levels, and no identifiable cause for the hirsutism. Signs of virilization (see Definitions, discussed previously) or higher androgen levels than are typically seen in PCOS should prompt an evaluation for an androgen-secreting tumor. Cushing syndrome is a rare cause of hyperandrogenism and usually presents with clinical signs and symptoms that are not characteristic of PCOS, such as dorsal fat pad, telangiectasias, moon facies, and muscle atrophy.

Table 23-2 Diagnostic Criteria for PCOS

	NIH[1] Criteria	Rotterdam Criteria	
Oligo- or anovulation	+	±	
Clinical and/or biochemical signs of hyperandrogenism	+	±	2 of 3 required
Ultrasound evidence of polycystic ovaries	−	±	
Exclusion of other causes of hyperandrogenism	+	+	

+, required; −, not required; ±, required option.

[1]NIH, National Institutes of Health.

Adapted from: The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81(1):19–25.

Box 23-1 Diagnostic Criteria for the Metabolic Syndrome in Women with PCOS

Waist circumference	> 88 cm
Triglycerides	≥ 150 mg/dl
HDL-cholesterol	< 50 mg/dl
Blood pressure	≥ 130/≥ 85 mmHg
Oral glucose tolerance test	Fasting glucose 110–126 mg/dl and/or 2-hour glucose 140–199 mg/dl

Adapted from:The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81(1):19–25.

EVALUATION

The history of an adolescent with suspected PCOS should include the ages of menarche, pubarche, and thelarche; menstrual pattern; development of hirsutism and acne; and weight changes. Family history should be reviewed for first- and second-degree relatives with PCOS, menstrual irregularity, hirsutism, infertility, diabetes mellitus, hyperlipidemia, and cardiovascular disease.

Physical examination should include blood pressure, height, weight, calculation of body mass index, body habitus, and Tanner staging. Skin should be examined for acne, hirsutism, frontal balding, and acanthosis nigricans. If hirsutism is present, it is helpful to quantify it by the Ferriman-Gallwey system (Table 23-1 and Figure 23-2) so that response to treatment can be monitored. The thyroid should be examined because hypothyroidism may contribute to obesity, and hypo- or hyperthyroidism may cause menstrual irregularity (Chapter 22). Galactorrhea on breast examination would suggest hyperprolactinemia as a cause of amenorrhea. External genitalia should be examined for pattern of pubic hair growth and clitoral size. Signs of virilization should raise concern for an androgen-secreting tumor.

Box 23-2 outlines the laboratory evaluation for suspected PCOS (see Pathophysiology, previous discussion). A serum total testosterone level >150 ng/dl or a serum DHEA-S level >700 µg/d suggests an androgen-secreting tumor and warrants abdominal and pelvic imaging.

Box 23-2 Laboratory Evaluation for Suspected PCOS

Serum

- Testosterone: total and free
- Sex hormone-binding globulin (SHBG)
- Follicle-stimulating hormone (FSH)
- Luteinizing hormone (LH)
- Thyroid-stimulating hormone (TSH)
- Dehydroepiandrosterone sulfate (DHEA-S)
- 17-hydroxyprogesterone (if 21-hydroxolase deficiency is suspected)

Urine

- Pregnancy test
- Free cortisol or dexamethasone suppression test (if Cushing syndrome is suspected)

Radiological

- Pelvic ultrasound to evaluate for polycystic ovaries

Adapted from: The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81(1):19–25.

A diagnosis of 21-hydroxylase deficiency is excluded by early morning 17α-hydroxyprogesterone (17-OHP) serum levels < 200 ng/dl and confirmed by levels > 1000 ng/dl. Intermediate levels should be explored further by measuring serum 17-OHP 60 minutes after the parenteral administration of adrenocorticotropic hormone (ACTH) 0.25 mg. A defect in 21-hydroxylase activity decreases the conversion of 17-OHP to 11-deoxycortisol, resulting in increased levels of 17-OHP. Adult-onset 21-hydroxylase deficiency is one of the most common autosomal recessive diseases, occurring in 1–2% of the non-Jewish Caucasian population, and 4% of Ashkenazic Jews. It is controversial whether testing should be performed routinely in populations in which the frequency of CAH is low. Routine screening should probably be performed in populations at high risk for CAH.

In patients with clinical manifestations of Cushing syndrome, free cortisol should be measured with a 24-hour urine collection, or an overnight dexamethasone suppression test should be performed. Cushing syndrome is unlikely if the 24-hour urinary cortisol is < 50 µg (normal values may vary depending on the laboratory) or the morning serum cortisol level after dexamethasone is < 5 µg/d.

In adolescents with PCOS, testing for insulin resistance and hyperlipidemia should be considered, although their clinical utility is not well established, as noted previously. Tests used to screen for insulin resistance include fasting insulin and glucose levels and a 2-hour oral glucose tolerance test. Insulin resistance is likely in an adolescent if the fasting levels of glucose and insulin yield a glucose: insulin ratio < 7.

The standard use of pelvic ultrasonography to establish the diagnosis of PCOS remains controversial, although it is recommended by the Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. It can be particularly helpful in patients who do not meet NIH criteria for the diagnosis.

MANAGEMENT

The short-term goals in the management of PCOS are to improve hirsutism, acne (Chapter 15), and menstrual regularity (Chapter 22). Long-term goals include the prevention or management of obesity (Chapter 11), diabetes mellitus (Chapter 13), and cardiovascular disease (Chapters 12, 14).

Combined Estrogen/Progestin or Progestin-Only Therapy

A combination oral contraceptive pill (OCP) containing an estrogen and progestin is first-line therapy for most adolescents with PCOS. The OCP decreases LH secretion;

decreases ovarian and adrenal production of androgens; increases serum levels of SHBG; and inhibits 5α-reductase effects in the skin, leading to lower dihydrotestosterone. Reductions in androgen levels occur within the first month of therapy and do not appear to differ significantly by formulation. Minor, and usually transient, side effects include nausea, breast tenderness, headache, and irregular vaginal bleeding. Adolescents who begin the OCP should be evaluated regularly for side effects, response to treatment, adherence, and screening for sexually transmitted infections (STIs) if sexually active.

More serious side effects of the OCP include hypertension and venous thromboembolism (VTE). Although the absolute risk of VTE in adolescents is very low, those with a strong family history of VTE should be evaluated for an inherited thrombophilic disorder before beginning the OCP. This evaluation includes a thrombotic profile, including testing for Factor V Leiden mutation, in the affected family members and/or the adolescent.

Progestin-only therapy is an alternative to the OCP for adolescents with contraindications to estrogen use (e.g., active liver disease, systemic lupus erythematosus, migraine with aura, thrombophilic disorders). Options include depot medroxyprogesterone acetate (Depo-Provera) 150 mg intramuscularly every 90 days, or medroxyprogesterone acetate (Provera) 10 mg orally every day for 12–14 days monthly. Adverse effects include irregular bleeding and weight gain. In patients with PCOS, progestin-only therapy is not as effective as the OCP for the management of hirsutism, acne, or irregular menses.

Antiandrogens

Adolescents with hirsutism that does not improve with OCP may benefit from the addition of an antiandrogen. In the United States, spironolactone is the most commonly prescribed antiandrogen for the treatment of PCOS. It may be prescribed initially as 25 mg orally twice daily, then increased to a maximum of 100 mg twice daily. Spironolactone must be prescribed with an effective contraceptive agent in sexually active females because of its potential interference with sexual differentiation of the male fetus. Side effects include mild diuresis, rash, gastrointestinal symptoms, headache, menstrual irregularity, and hyperkalemia. Electrolytes and renal function should be checked periodically. Renal failure and hyperkalemia are contraindications to the use of spironolactone.

Cyproterone acetate is used outside the United States but has not been approved by the U.S. Food and Drug Administration (FDA). Flutamide has also been prescribed, but its association with hepatocellular toxicity limits its use.

Many patients will not experience complete resolution of hirsutism even with an antiandrogen. Waxing, bleaching, electrolysis, or laser hair removal may be used adjunctively. Eflornithine hydrochloride (Vaniqa) may be helpful, but few data are available in women with PCOS. It is available as a topical 13.9% cream and is applied as a thin layer to affected areas of the face twice daily.

Insulin-Sensitizing Agents

Insulin-sensitizing agents (e.g., metformin) are under active investigation for the treatment of PCOS and associated infertility. Although the FDA has not approved their use exclusively for PCOS, metformin is used commonly in the United States and elsewhere for this purpose. A recent survey of pediatric endocrinologists revealed that 30% consider metformin for all adolescents with PCOS and 68% consider it for obese adolescents with PCOS.

Metformin is an oral biguanide that interferes with hepatic gluconeogenesis; increases the number of insulin receptors; reduces serum insulin and androgen levels; and increases SHBG levels. Studies have demonstrated improvements in menstrual regularity, fertility, and lipid profiles in women with PCOS, regardless of the presence or absence of obesity and insulin resistance. In obese women, metformin plus the OCP appears to improve body mass index, waist-to-hip ratio, and insulin sensitivity. The literature on metformin use in adolescents is far more limited than that in adults, but the results are encouraging. Studies in preadolescent girls with precocious puberty suggest that insulin-sensitizing agents may prevent the progression to PCOS.

The most common side effects of metformin are nausea, vomiting, abdominal pain, and diarrhea. A rare but serious side effect is lactic acidosis, and its use is contraindicated in patients at increased risk for acidosis (e.g., renal insufficiency, congestive heart failure, dehydration). Therapy should be suspended temporarily in patients who are acutely ill or undergoing radiographic procedures involving the intravascular administration of iodinated contrast materials. Metformin is available in an oral tablet (500 mg, 850 mg, 1000 mg) and an extended-release oral tablet (500 mg, 750 mg, 1000 mg). Dosage ranges for PCOS have not been established, but the usual starting dose is 500–750 mg daily with weekly increases of 500 mg daily to a maximum of 2000 mg daily. Renal and hematological function should be assessed before initiation and annually thereafter.

Lifestyle Changes, Education, and Counseling

Weight reduction, through caloric restriction and exercise, should be a focus of management in obese adolescents with PCOS. Even moderate weight loss can significantly improve the hormonal and metabolic abnormalities

associated with PCOS. Referral to a dietician or a comprehensive weight management program may be helpful.

The complexity of PCOS often causes confusion for adolescents and parents. Office-based education, counseling about short- and long-term effects, written materials, and on-line resources should be reviewed frequently. It is especially important to refer adolescents who are struggling with self-esteem for supportive counseling.

Some adolescents with PCOS perceive themselves as infertile. Clinicians should reassure them that many women with PCOS are not infertile, that effective treatment is available for women with PCOS who have difficulty conceiving, and that it is important for them to use effective contraception if they do not desire pregnancy.

MAJOR POINTS

- PCOS is a common disorder that usually presents during adolescence and is characterized by hyperandrogenism, anovulation, and hyperinsulinemia.
- Clinicians must distinguish physiological anovulatory cycles from PCOS and differentiate PCOS from other causes of hyperandrogenism.
- Systemic medications that may be helpful in the management of PCOS include the OCP, spironolactone, and metformin.
- Weight management and exercise are essential in obese adolescents with PCOS, as weight loss may improve signs of hyperandrogenism and menstrual irregularity and may prevent the development of Type 2 diabetes and cardiovascular disease.
- Long-term, prospective studies are needed to identify those management strategies that can safely and effectively reduce the risk of infertility, diabetes, and cardiovascular disease in young women with PCOS.

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CHAPTER 24

Disorders of the Female Pelvis

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INTRODUCTION

Disorders of the female pelvis typically present with lower abdominal pain, a pelvic mass, or abnormal vaginal bleeding. Although the differential diagnoses for these presenting problems overlap in adolescents and adults, the leading causes change with advancing age. For example, pelvic pain is much more likely to be caused by pelvic inflammatory disease or adnexal torsion in an adolescent than an adult. An adnexal mass is much more likely to be caused by a uterine fibroid or gynecological malignancy in an adult than an adolescent. It therefore is important to understand the epidemiology of pelvic disorders and to collaborate with gynecological consultants on the evaluation and management of these problems in adolescents.

This chapter begins with an overview of acute and chronic pelvic pain. It then discusses adnexal torsion, functional ovarian cysts, endometriosis, congenital anomalies of the reproductive tract, and ovarian tumors.

DEFINITIONS

Adnexa: Region adjacent to the uterus that includes the ovary, fallopian tube, and associated structures.

Adnexal torsion: Excessive rotation of the infundibulopelvic ligament around its axis with impairment of flow through the ovarian artery and vein that supply the ovary and fallopian tube (Figure 24-1).

Chronic pelvic pain: In adults, noncyclical pain lasting at least 3 months or cyclical pain recurring over at least 6 months, either of which interferes with normal activities. In children, three or more bouts of pain severe enough to affect activities over at least 3 months.

Corpus luteum cyst: A collection of yellowish fluid within the ovary that forms when the corpus luteum does not involute after ovulation and continues to increase to a usual diameter of 3–8 cm.

Dermoid cyst: Mature, benign, cystic teratoma that can contain sebum, hair, and teeth.

Endometrioma: Benign growth of endometrial tissue outside the uterine cavity that is often described as a "chocolate cyst" on gross examination and may cause elevation of the serum CA 125 level.

Endometriosis: Condition in which endometrial glands and stroma are found outside the endometrial cavity of the uterus.

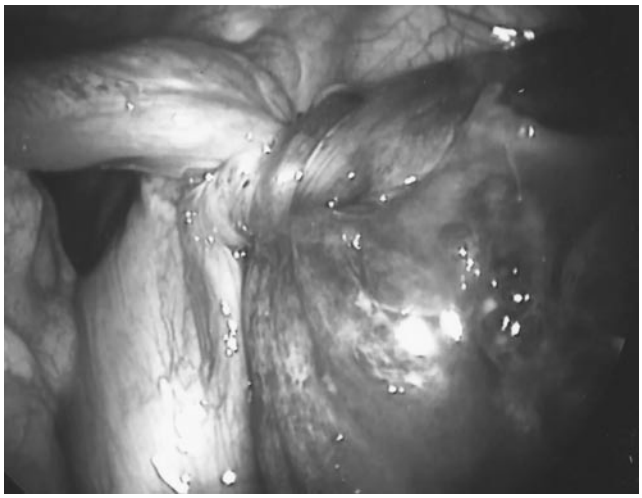

Figure 24-1 Laparoscopic view of torsed ovarian blood supply.

Follicular cyst: A thin-walled collection of fluid within the ovary that forms when the follicle does not rupture to release an ovum and continues to increase to a usual diameter of 3–8 cm.

Leiomyoma (fibroid): Benign growths arising from the uterine smooth muscle that are most likely to cause symptoms among women in their late 30s and 40s.

Müllerian ducts: Normally regress in the male fetus and form the fallopian tubes, uterus, and upper vagina in the female fetus.

Pelvic inflammatory disease (PID): Polymicrobial infection of the upper genital tract, usually beginning with *Neisseria gonorrhoea* or *Chlamydia trachomatis* and often involving additional organisms, such as anaerobic and facultative bacteria (Chapter 26).

Serous and mucinous cystadenomas: Benign ovarian tumors that range in diameter from 5–20 cm can be uni- or multilocular and tend to recur if not resected.

Teratoma: Immature to well-differentiated germ cell tissue that is normally foreign to the anatomical site in which it is found.

Wolffian ducts: Paired mesonephric ducts that normally regress in the female fetus and form the epididymis, vas deferens, seminal vesicles, and ejaculatory ducts in the male fetus.

LOWER ABDOMINAL PAIN

Pelvic and lower abdominal pain peaks in prevalence during adolescence and is three times more common in females than males. The differential diagnoses for acute and chronic, recurrent pain are shown in Boxes 24–1 and 24–2, respectively.

The evaluation of acute pelvic pain in a female of reproductive age must include pregnancy testing. Ectopic pregnancy, which typically presents with pain and bleeding, remains a leading cause of maternal mortality in the United States. If ectopic pregnancy is diagnosed or strongly suspected, emergency surgery is indicated. Clinical suspicion should always be high in a patient with pelvic pain, bleeding, positive urine or serum testing for beta-human chorionic gonadotropin (beta-HCG), and the absence of an intrauterine gestational sac on transvaginal ultrasonography. Other factors that support the diagnosis include history of prior ectopic pregnancy, PID, pelvic surgery, or intrauterine device; missed menstrual periods; symptoms of pregnancy; and fullness in the cul-de-sac or adnexa.

Chronic or recurrent abdominal pain affects up to 5% of adolescent females. The difficulty establishing a diagnosis often leads to anxiety and frustration for patients, families, and clinicians. Although the differential diagnosis is extensive and the evaluation can be lengthy, 95% of cases in one series had no identifiable organic pathology (i.e., functional pain). Factors associated with functional pain include environmental stress, absence of pain during sleep, variable location or description of the pain, family history of unexplained abdominal pain, and absence of weight loss.

Box 24-1 Differential Diagnosis of Acute Pelvic Pain in Adolescent Females

- Ectopic pregnancy
- Pelvic inflammatory disease
- Abortion
- Ruptured ovarian cyst
- Adnexal torsion
- Mittelschmerz
- Appendicitis
- Renal stone
- Urinary tract infection
- Obstructed viscus

Box 24-2 Differential Diagnosis of Chronic, Recurrent Pelvic Pain in Adolescent Females

- Functional pain
- Endometriosis
- Pelvic inflammatory disease
- Constipation
- Irritable bowel syndrome
- Lactose intolerance
- Inflammatory bowel disease
- Myofascial (i.e., abdominal wall) strain
- Obstructed viscus

The evaluation of an adolescent with acute or chronic pelvic pain should include a menstrual and sexual history; evaluation of growth and weight change; skin and mucosal examinations for rash or ulceration; joint examination for arthritis (e.g., inflammatory bowel disease); abdominal examination; rectal examination with testing for occult blood; and pelvic examination as tolerated. At a minimum, the patency of the reproductive outflow tract should be verified by inserting a cotton-swabbed applicator into the vagina. Whenever possible, a vaginal-abdominal or recto-abdominal examination should be performed to palpate the cervix, uterus, and adnexae. However, the pelvic examination should not be considered mandatory in the young, virginal adolescent. If the bimanual examination is inadequate or indeterminate, pelvic ultrasonography is indicated to help define the pelvic anatomy.

Laboratory evaluation should be guided by the findings on history and physical examination but generally should include urine testing for beta-HCG, complete blood cell count, erythrocyte sedimentation rate or serum C-reactive protein, and urinalysis.

ADNEXAL TORSION

Adnexal torsion occurs when the vasculature supplying the ovary and tube undergoes excessive rotation about its axis, producing a mechanical impairment to flow (Figure 24-1). Both the ovarian artery and vein are affected within the infundibulopelvic ligament. Venous flow is the first to be compromised due to the compressibility of the lower-pressure vessels. As venous congestion progresses, edema of the ovarian tissue stretches the ovarian capsule to capacity. The resulting high-pressure state within the ovary eventually compromises arterial flow, leading to ischemia, hemorrhage, and finally necrosis.

Epidemiology and Pathophysiology

Adnexal torsion is responsible for 3% of acute gynecological complaints. It is most likely to occur in adolescents and young adult women and is usually associated with underlying benign pathology such as cystic teratoma, tubal or follicular cyst, and serous or mucinous cystadenoma. Factors associated with torsion include excessively mobile mesovaria or fallopian tubes, congenitally long pelvic ligaments, tubal spasm, abrupt changes in intra-abdominal pressure, sudden changes in motion, and genetic predisposition.

Evaluation

The preoperative diagnosis of adnexal torsion is often difficult due to the overlap in symptoms and physical findings with other conditions. It therefore is imperative to maintain a high index of suspicion when evaluating adolescent females with acute-onset pelvic pain. Torsion usually presents with unilateral pain, more commonly on the right than left. Nausea and vomiting occur in 70–80% of patients with torsion, fever in 20%, and a palpable mass in 20–36%. Findings on pelvic ultrasound may include vascular engorgement and enlargement of the tube and/or ovary; stromal edema; and free fluid in the pelvis. However, because ultrasonography neither confirms nor excludes torsion, laparoscopy is indicated if the clinical suspicion of torsion is high.

Management

The management of adnexal torsion has become more conservative over the last decade. For many years, the standard treatment involved oophorectomy rather than untwisting or detorsing the involved reproductive structures. The rationale behind the previous recommendation of oophorectomy stemmed both from fears regarding the risk of malignancy associated with the torsed ovary and the risk of thrombus release into the systemic circulation after untwisting the ovarian vasculature. Ovarian malignancies have been reported in adult women with torsion but not in children or adolescents, and many case series have found no cases of thromboembolus release after detorsion.

In the past, torsed adnexae that appeared grossly necrotic were assumed to be damaged irreversibly. It now is recognized that clinical inspection does not reliably differentiate reversible ischemia from irreversible necrosis. The recommended procedure for adnexal torsion therefore is detorsion without removal of the involved structures.

FUNCTIONAL OVARIAN CYSTS

Epidemiology and Pathophysiology

Functional, or physiological, ovarian cysts are benign, encapsulated fluid collections within the ovary. The most common type is the follicular cyst, which typically ranges in diameter from 3–8 cm and resolves spontaneously in 4–8 weeks. Corpus luteum cysts (Figure 24-2) are similar in size but more likely to rupture than follicular cysts. Rupture of a corpus luteum cyst tends to occur late in the menstrual cycle and is associated with sexual intercourse, exercise, palpation, and abdominal trauma. Factors associated with functional ovarian cysts include smoking and underlying polycystic ovary syndrome (Chapter 23). Oral contraceptive pills (OCPs) and depot medroxyprogesterone acetate have been shown to decrease the likelihood of

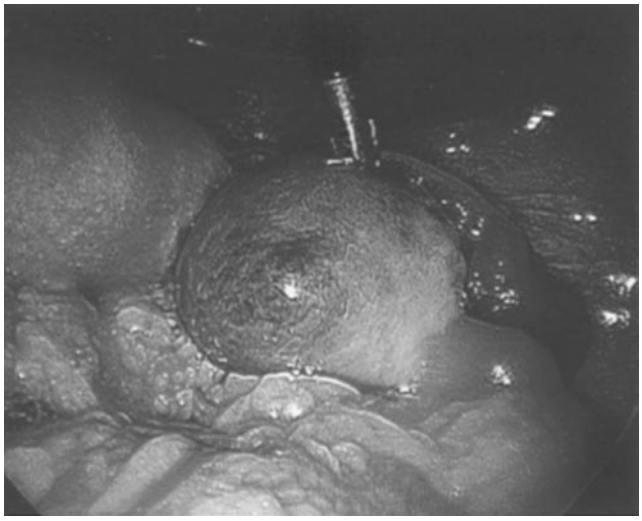

Figure 24-2 Laparoscopic view of a left ovarian corpus luteal cyst.

functional cyst formation but do not hasten regression of an existing cyst.

The likelihood that a functional cyst will regress decreases as its size increases. More than 80% of cysts 4 cm or less in diameter regress, compared with less than 30% of those 6–8 cm in diameter. Pain is also a function of cyst size. As the cyst diameter increases, stretch on the overlying ovarian cortex and capsule elicits pain. Rupture of the cyst into the peritoneal cavity can produce inflammation, peritonitis, and acute pain, particularly if there is associated hemoperitoneum.

It is important to differentiate functional ovarian cysts from normal follicles. The average follicle at the time of ovulation is painless, 2.5 cm in diameter, and readily visible on pelvic ultrasound. Interpreting the follicle as an abnormal mass or a likely source of pain can lead to unnecessary intervention and can delay other evaluation.

Evaluation and Management

The history should seek to identify the onset of the cyst relative to the menstrual cycle, the characteristics of the pain, and its effect on daily activities. Physical examination can help determine cyst size, but pelvic ultrasound usually is indicated for more accurate assessment of size and consistency. Indications for surgical intervention include cyst rupture with hemodynamic instability or severe, persistent pain; physical examination findings of persistent peritonitis; rapid increase in the diameter of a large cyst; and failure of a cyst to regress over several months' observation.

Most ovarian cysts during adolescence resolve spontaneously over the course of several menstrual cycles and can be monitored by serial pelvic examinations and/or pelvic ultrasounds. If pain is severe or torsion is suspected, diagnostic laparoscopy is the procedure of choice. Intraoperatively, the decision about whether to drain or resect a cystic structure can be difficult. A simple follicular cyst requires only drainage. A serous cystadenoma, which cannot be distinguished grossly from a follicular cyst, can recur and requires complete resection, with preservation of ovarian tissue. Hormonal suppression of new cyst formation with the OCP, contraceptive transdermal patch, or contraceptive vaginal ring is usually recommended for 3–6 months following drainage or resection.

ENDOMETRIOSIS

Endometriosis is a condition in which endometrial glands and stroma are found outside the uterine cavity. Severe or progressive dysmenorrhea is the presenting symptom in 64–94% of adolescents with endometriosis. Adults are more likely than adolescents to present with infertility and dyspareunia. Other common symptoms include nausea and vomiting during menses.

Epidemiology

Endometriosis has been reported in 19–73% of adolescents undergoing laparoscopy for chronic pelvic pain and in 50–70% of adolescents with pelvic pain that does not respond to estrogen-progestin therapy and nonsteroidal anti-inflammatory drugs (NSAIDs). Congenital anomalies occur in 5–6% of patients with endometriosis and include imperforate hymen, vaginal septum, hematocolpos, hematometra, and an obstructed uterine horn.

Pathophysiology

There are several hypotheses regarding the etiology of endometriosis. Sampson hypothesized that retrograde menses with peritoneal seeding of endometrial tissue explains the tendency for endometriosis to involve the dependent portions of the pelvis. The theory is also supported by the known association of endometriosis with Müllerian anomalies and outflow tract obstruction. Endometriosis appears to regress in patients with surgically corrected outflow tract obstruction, whereas it persists in those without structural anomalies. Meyer theorized that embryologically totipotential cells undergo metaplastic transformation into functioning endometrium. Halban's theory involves vascular or lymphatic spread due to a deficiency in cell-mediated immunity that inhibits adequate clearing of endometrial cells from aberrant locations.

Evaluation

The diagnosis of endometriosis depends on the gross visualization of endometrial implants within the pelvis or the microscopic finding of endometrial tissue on a peritoneal biopsy specimen. The diagnosis cannot be established by history, physical examination, or imaging studies. However, because NSAIDs and combined estrogen-progestin therapy constitute initial management for both primary dysmenorrhea (Chapter 22) and endometriosis, laparoscopy is reserved for those patients who have persistent pain after several months of treatment. The typical lesions of endometriosis in adolescents may differ from those in adults (Figure 24-3). It therefore is important that a gynecologist familiar with the surgical diagnosis and management of endometriosis in adolescents performs the laparoscopy. In addition to recognizing the lesions of endometriosis, the surgeon should be prepared to excise or ablate lesions that are contributing to pain and to biopsy peritoneal lesions that suggest endometriosis if the diagnosis cannot be established on gross examination.

Management

As noted above, the first-line treatment of adolescents with suspected or documented endometriosis involves the use of NSAIDs and combination estrogen-progestin therapy delivered as the combination OCP, transdermal patch, or vaginal ring. Most clinicians advocate the continuous use of OCPs to minimize the number of days with bleeding. A randomized control trial comparing a 28-day regimen with a 49-day regimen found that the total bleeding days were fewer with the 49-day regimen and that there was no significant difference in the number of days with spotting.

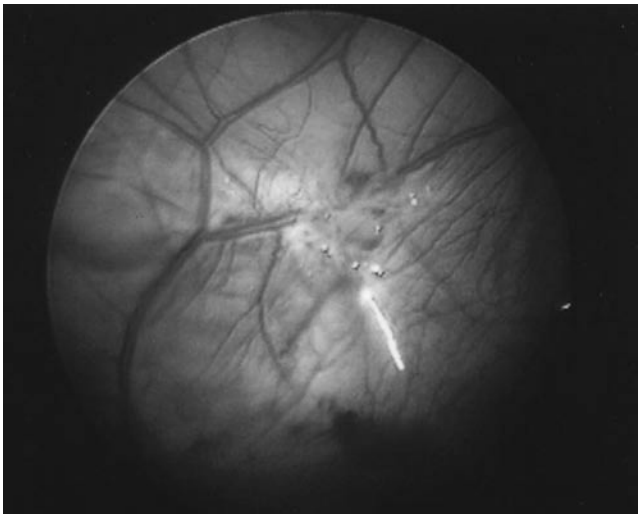

Figure 24-3 Intraoperative view of classic-appearing lesions of endometriosis in an adolescent.

Progestin-only protocols delivered orally as medroxyprogesterone or intramuscularly as depot medroxyprogesterone acetate have been used for the treatment of endometriosis, but studies suggest that these regimens are less effective in managing pain and less well-tolerated than combined estrogen-progestin regimens. In addition, depot medroxyprogesterone acetate continued beyond 2 years has been shown to decrease bone density.

If pain persists on combined estrogen-progestin therapy and NSAIDs, laparoscopy is indicated to establish the diagnosis and to surgically remove or destroy visible lesions of endometriosis. Following surgery, hormonal suppression should continue until pregnancy is desired to minimize disease progression, pain, adhesions, and infertility. Many patients with disease severe enough to warrant surgery require postoperative suppression with a gonadotropin-releasing hormone agonist (GnRH-a) to establish a hypoestrogenic state. Although these agents are highly effective in the treatment of endometriosis, their use in patients younger than 18 years is associated with a 5% loss in trabecular bone mineral density after 6 months of therapy. It therefore is recommended that adolescents attempt combination estrogen-progestin therapy again after 6 months of treatment with a GnRH-a. Those adolescents who are refractory to combination estrogen-progestin should be managed with a GnRH-a plus add-back hormonal therapy to preserve bone density. The add-back is usually administered orally as conjugated estrogen/medroxyprogesterone 0.625/2.5 mg daily.

Although surgery is effective in diminishing the pain of endometriosis, radical surgical procedures such as oophorectomy and hysterectomy should be avoided during adolescence because of the recurrent nature of the disease. In a double-blinded, randomized trial of adults with endometriosis, 63% of subjects managed with laser vaporization compared with 23% of control subjects reported significant pain relief at 6 months, and 90% of those in the treatment arm had continued pain relief at 1 year.

WOLFFIAN DUCT REMNANTS

Epidemiology and Pathophysiology

During normal embryonic development, the Wolffian or paired mesonephric ducts form the reproductive organs in males and degenerate in females. Remnants of the Wolffian duct system in females may be retained within the leaves of the broad ligament between the uterus, fallopian tube, and ovary. With puberty, these remnants may elongate and become distended with clear fluid secretions (Figure 24-4). Although the collections may reach sizes as large as 30 cm (Figure 24-5), they usually are painless because of their location outside the Müllerian and

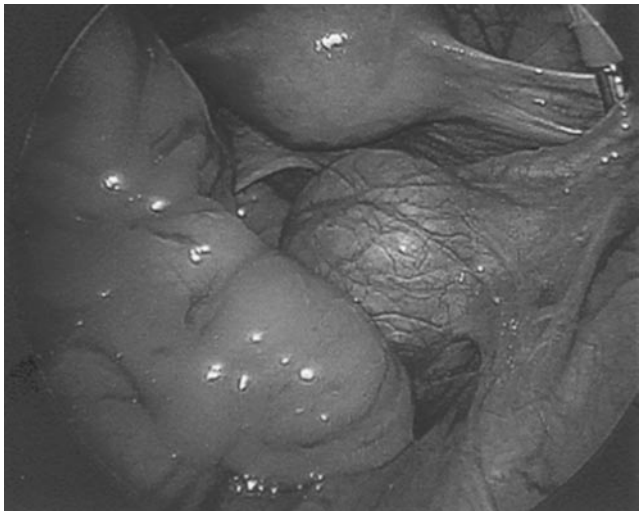

Figure 24-4 Laparoscopic view of a Wolffian duct cyst within the leaves of the right broad ligament.

ovarian structures. They may be discovered coincidentally, during evaluations of bloating or increasing abdominal girth, or through their association with adnexal torsion.

Evaluation and Management

Surgical intervention is the definitive treatment for distended Wolffian duct remnants. Pelvic ultrasonography should be performed preoperatively to determine whether the cystic structure is separate from the ovary.

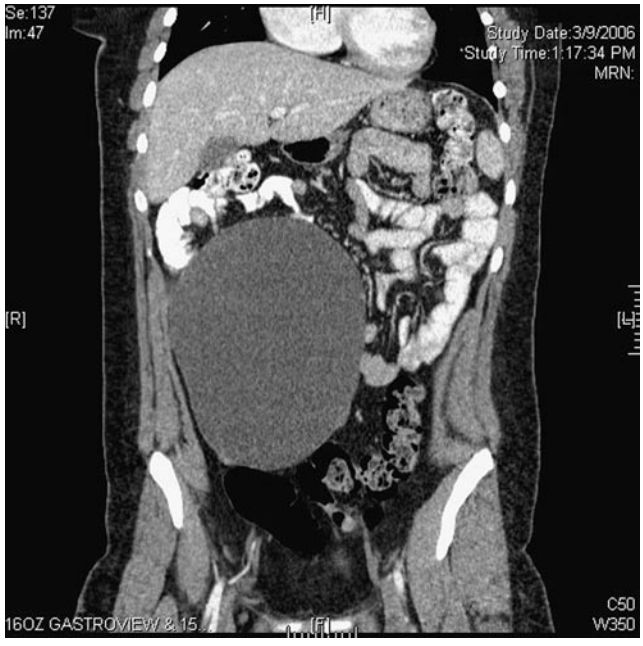

Figure 24-5 Radiographic view of a 15- to 18-cm Wolffian duct cyst.

Resecting the distended structures without damaging the functional Müllerian structures can be difficult because the fallopian tube may stretch and surround a cyst within the broad ligament. Open abdominal laparotomy has historically provided excellent visualization and circumferential palpation of the fallopian tube. Laparoscopy is less invasive but does not allow palpation and thus requires meticulous dissection to save normal reproductive structures. Additional surgical challenges may be involved if the cyst retains any communication with the functional urological system.

CONGENITAL ANOMALIES OF THE UTERUS, FALLOPIAN TUBES, AND VAGINA

Epidemiology and Pathophysiology

The fallopian tubes, uterus, and upper vagina develop from the Müllerian ducts, and the distal vagina develops from the urogenital sinus. The ovaries develop independently from both of these systems. Consequently, most women with congenital anomalies of the uterus, tubes, or vagina have normal ovarian anatomy and function. In contrast, because the development of the female reproductive tract and urinary tract are intertwined, women with anomalies of the genital tract often have anomalies of the urinary tract.

Developmental anomalies of the Müllerian system fall into three broad categories: agenesis, defects of lateral fusion, and defects of vertical fusion. Agenesis, or the Mayer-Rokitansky-Küster-Hauser syndrome, is congenital absence of the proximal vagina and cervix with variable development of the uterus. Lateral fusion defects reflect failed formation of a Müllerian duct, failed fusion of the two ducts, or failed absorption of the septum after fusion. Vertical fusion defects reflect failed fusion of the caudal Müllerian duct and urogenital sinus or abnormal canalization of the vagina following fusion.

The incidence of Müllerian anomalies is estimated to be 3%, but the true incidence is unknown because many are asymptomatic and subclinical. Patients with agenesis often present during adolescence with primary amenorrhea, whereas those with fusion defects may present during adolescence with abnormal bleeding, pelvic pain, or a mass associated with uterine or vaginal obstruction. In other cases, menses may be normal and the diagnosis may be delayed until infertility or obstetrical complications prompt evaluation.

Evaluation

Anomalies of the reproductive outflow tract should be suspected in adolescents with amenorrhea, oligomenorrhea,

or abnormal bleeding; cyclical pelvic pain with no or irregular bleeding; and dysmenorrhea that increases quickly in severity. In patients with obstructive anomalies, the uterine cavity and vagina may be distended by thickened, stimulated endometrium. Without a mechanism for drainage, the retained endometrial tissue causes increasing pain.

Pelvic examination, if tolerated by the adolescent, often provides evidence of an anomaly but rarely allows definitive diagnosis. Transabdominal and transvaginal ultrasonography helps define the anatomy further, but examination under anesthesia with hysterosalpingography and often laparoscopy is required in patients with complex anomalies. Consultation with a gynecologist who is familiar with congenital anomalies is essential for diagnosis, management, and patient counseling.

Renal ultrasound should be performed in all patients with congenital anomalies of the uterus and upper vagina because of the high rate of coincident renal anomalies. It is particularly important to determine the urogenital anatomy before attempting surgical correction of an obstructed reproductive tract to minimize the risk of injury to a misplaced or duplicated ureter.

Management

Nonobstructive anomalies of the Müllerian system, such as uterine agenesis, typically do not require surgical intervention. Depending on the anatomical structures involved and the severity, vaginal dilatation may be necessary to allow sexual intercourse. This can be performed at home by the patient when she is psychologically and emotionally ready.

Obstructive anomalies, particularly when there is functioning endometrium, require surgical intervention to relieve pain and allow appropriate flow of menstrual fluid. Hymenal and vaginal anomalies may be addressed by a vaginal approach. Obstruction caused by a relatively thin structure, imperforate hymen, thin vaginal septum, or lower vaginal atresia may all be treated by resection of the obstructing barrier and anastomosis of the upper vaginal mucosa either to the lower vaginal mucosa or the distal hymenal ring. If a thicker vaginal obstruction is present, a graft of skin or bowel segment may be necessary to bridge the upper and lower vaginal mucosal. The patient with a complex surgical repair may need to use a dilator for a short interval postoperatively.

OVARIAN TUMORS

Epidemiology and Pathophysiology

Ovarian tumors can be benign or malignant and can develop from germ cells, epithelial cells, or sex cord–stromal tissue. The most common benign ovarian neoplasms in adolescents are mature cystic teratomas and serous or mucinous cystadenomas (Figures 24–6 and 24–7). The most common malignant ovarian neoplasms in adolescents are germ cell tumors. However, less than 5% of ovarian malignancies occur in individuals under age 18 years, and only 1% of all malignancies in this age group are ovarian.

The most common germ cell tumor is the mature cystic teratoma, or dermoid cyst. It is a benign, multicystic mass that may include tissue of ectodermal, mesodermal, and endodermal origin, including teeth, hair, and skin. Although benign, the complications of benign teratomas include torsion in up to 16% of cases and, much less commonly, spontaneous rupture. The transition between the normal ovarian tissue and the teratoma,

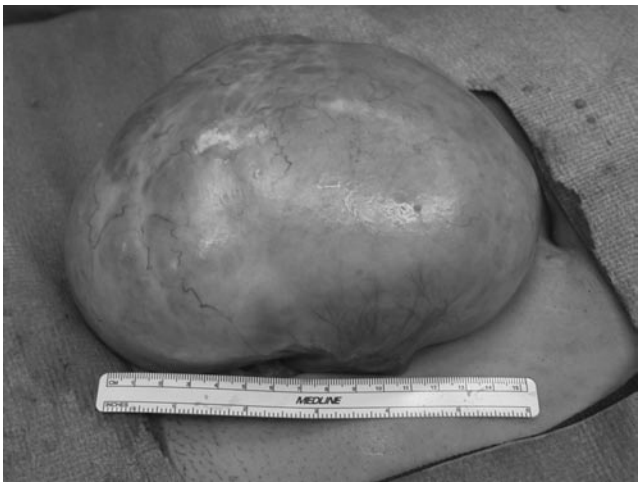

Figure 24-6 Intraoperative view of a left ovarian mass in a 15-year-old female.

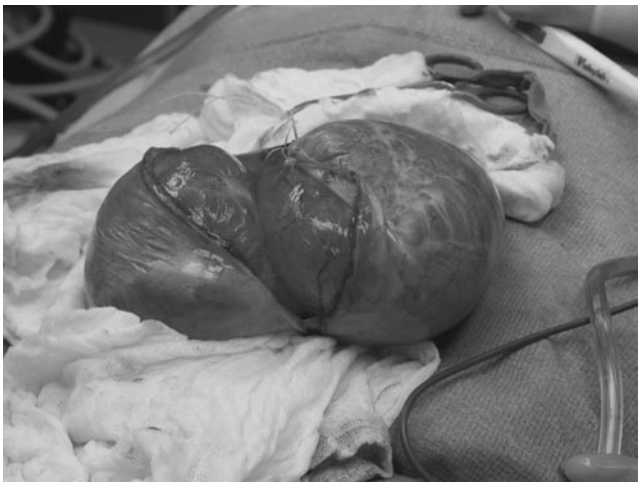

Figure 24-7 Intraoperative views during ovarian cystectomy. The ovarian cortex is open to allow dissection and removal of the mucin-containing cystadenomas.

termed Rokitansky's protuberance, can contain immature elements and therefore require careful histological examination. Immature teratomas are malignant ovarian tumors that contain disorganized tissue from all three germ cell layers. They comprise less than 1% of teratomas and are most likely to present during the first two decades of life. The most common malignant germ cell tumor is the dysgerminoma. It consists of primordial, sexually undifferentiated cells and is associated with gonadal dysgenesis and androgen insensitivity. Serum lactic dehydrogenase (LDH) levels and, less often, serum HCG levels are often elevated in patients with dysgerminomas (Table 24-1).

In adults, epithelial cell malignancies account for 6–11% of all adnexal masses and constitute the most common type of ovarian cancer. In adolescents, the most common epithelial cell tumors are benign serous or mucinous cystadenomas. They can reach large sizes and pose significant risk of torsion, as well as leakage into the peritoneal cavity. On histological examination, 7% of cystadenomas are borderline for malignancy and 4% are overtly malignant.

Sex cord–stromal tumors are uncommon in adolescents. For example, gonadoblastoma is a rare tumor composed of both sex cord and germ cell tissue. Most cases are in patients with gonadal dysgenesis and a Y chromosome or Y fragment, and 25–50% are associated with malignant dysgerminoma. Granulosa cell tumors are another rare type of sex cord–stromal tumor in adolescents. The juvenile subtype has a better prognosis than the adult subtype, with survival rates of 84–92%. Juvenile granulosa cell tumors secrete estrogen and may present as abnormal menstrual bleeding. Bilateral ovarian involvement is found in 5% of cases.

Table 24-1 Serum Tumor Markers

Human chorionic gonadotropin (HCG)	Dysgerminoma Mixed germ cell tumors Choriocarcinoma
Lactate dehydrogenase (LDH)	Dysgerminoma Mixed germ cell tumors
CA-125	Epithelial tumors Immature teratoma
Carcinoembryonic antigen (CEA)	Mucinous tumors Serous tumors
Alpha-fetoprotein (AFP)	Mixed germ cell tumors Immature teratoma Endodermal sinus tumors
Inhibin	Granulosa cell tumor
Müllerian-inhibiting substance	Granulosa cell tumor
Testosterone	Sertoli-Leydig cell tumor Leydig cell tumor
Estradiol	Adult granulosa cell tumor

Evaluation and Management

Pelvic ultrasound should be performed early in the evaluation of an adolescent with an adnexal mass. It helps delineate characteristics that may change the differential diagnosis and management plan, such as size, location, content (e.g., fluid or solid), and associated findings (e.g., ascites). Some ovarian neoplasms secrete protein tumor markers that facilitate diagnosis and provide a measure of the clinical response to treatment. The markers include alpha-fetoproten (AFP), lactate dehydrogenase (LDH), CA-125, human chorionic gonadotropin (HCG), carcinoembryonic antigen (CEA), inhibin, and Müllerian-inhibiting substance.

Surgery is directed at preservation of reproductive potential. Unless a malignancy is diagnosed at the time of the initial procedure, conservative surgery should be performed with excision of the lesion and ovarian reconstruction or a unilateral salpingo-oophorectomy. If malignancy is suspected or confirmed, adequate staging includes abdominal exploration, peritoneal washings, biopsies of suspicious areas, and periaortic and pelvic lymph node sampling. Minimally invasive surgery does have a role in the treatment of adolescents with pelvic masses but should only be performed if the surgeon is skilled at laparoscopy and if the procedure can be accomplished without spillage of malignant contents.

MAJOR POINTS

- The differential diagnosis for acute-onset pelvic pain in an adolescent female includes pelvic inflammatory disease, rupture of an ovarian cyst, ectopic pregnancy, and adnexal torsion.
- Adnexal torsion is a difficult diagnosis that requires a high index of suspicion and prompt surgical intervention. The treatment of choice is detorsion with preservation of ovarian tissue.
- First-line therapy for endometriosis is combined estrogen-progestin (e.g., OCPs) and NSAIDs. If pain persists, laparoscopy is indicated to confirm the diagnosis and to remove or ablate visible endometrial implants.
- Small, functional ovarian cysts may be managed conservatively without surgery if pain is controlled.
- Congenital anomalies of the female reproductive tract include Wolffian duct remnants, Müllerian duct agenesis, and fusion defects of the Müllerian system or urogenital sinus.
- Ovarian malignancies are rare during adolescence and are more likely to be of germ cell than epithelial cell origin.

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CHAPTER 25

Vaginitis, Urinary Tract Infection, and Vulvar Lesions

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INTRODUCTION

Vaginal and urinary symptoms are common complaints that produce significant physical and emotional discomfort for many adolescents. Patient embarrassment about the symptoms and clinician uncertainty about the evaluation can delay accurate diagnosis and treatment. Young adolescents may have difficulty describing the symptoms or may assume that the details on history are unnecessary for diagnosis. Others may worry that the symptoms imply or reveal sexual activity. For adolescents in whom the symptoms do reflect sexually transmitted infections, the delay or failure to treat imposes risk for both the patient and her sexual partners.

The goal of this chapter is to familiarize the reader with an evidence-based approach to the evaluation and management of urinary and vulvovaginal symptoms in adolescents. It is important to recognize that the chief complaint does not localize the pathology. In other words, urinary symptoms may reflect genital pathology and vice versa.

DEFINITIONS

Bacterial vaginosis: Vaginal discharge characterized by bacteria-coated epithelial cells and few white blood cells on wet mount.

Leukorrhea: Vaginal discharge with abundant epithelial cells.

Pyelonephritis: UTI (see below) with involvement of the upper tract.

Pyuria: > 10 leukocytes per microliter on an unspun midstream urine collection or > 10 leukocytes per high-powered field on a spun sample.

Urethritis: Inflammation of the urethra.

Urinary tract infection (UTI): Urinary symptoms, pyuria, and culture of a midstream, clean-catch urine specimen demonstrating > 10^2/ml to > 10^5/ml colony-forming units (CFU)/ml of a uropathogen. Studies and clinical guidelines vary in their choice of cut-point for a positive culture.

Urine leukocyte esterase: Screening test that detects pyuria with a sensitivity of 75–96% and specificity of 94–98%.

Urine nitrite: Screening that detects 10^5 CFU/ml with fair sensitivity and specificity.

Uropathogens: Bacteria that cause UTI, such as *Escherichia coli, Staphylococcus saprophyticus, Proteus mirabilis, Klebseilla* species, and enterococci.

Vaginitis: Vaginal inflammation, usually with vaginal discharge, itching, and irritation.

Vulva: External female genitalia, including the mons pubis, labia majora, labia minora, clitoris, vestibule of the vagina, bulb of the vestibule, and Bartholin's glands.

Wet mount: The microscopic evaluation of vaginal secretions collected by swab and suspended in 0.5–1 ml normal saline.

VAGINITIS

Vaginal secretions provide lubrication as well as local immune factors to protect against infection. The predominant endogenous bacteria, lactobacilli, produce lactic acid and hydrogen peroxide that maintains the low pH (2.5–4.5) of the vaginal canal. The usual flora also includes *Gardnerella vaginalis*; beta-hemolytic *Streptococci; Mycoplasma hominis, Ureaplasma urealyticum*; and *Candida* species. Less common colonizers include *Proteus, Klebsiella*, and other enterococci.

The vaginal flora is affected by endogenous and exogenous hormones, race, sexual behavior, contraceptive method, and douching. The proportion of anaerobic bacteria increases premenstrually. Baseline pH and the prevalence of bacterial vaginosis (BV), *M. hominis*, and group B streptococcus are higher in African-American than Caucasian or Mexican-American women. New and multiple sexual partners are associated with BV, and oral sex is associated with both BV and *Candida*. Consistent condom use, oral contraceptives, and frequent douching are associated with BV. Although most studies attempt to control for confounding variables, more research is needed to elucidate independent risk factors for BV.

Many adolescents have a normal, physiological vaginal discharge that is white, odorless, of small to moderate volume, and characterized by abundant epithelial cells (i.e., leukorrhea). The discharge may begin during the year prior to menarche and may continue throughout reproductive life. Physiological leukorrhea is a normal finding requiring only reassurance. In contrast, vulvovaginal itching, burning, pain, or redness are abnormal and warrant evaluation.

Vaginal discharge accompanied by symptoms is usually caused by candidiasis, BV, or trichomoniasis (Box 25-1). Other causes include *Neisseria gonorrhea* (NG), *Chlamydia trachomatis* (CT), retained foreign body (e.g., tampon), desquamative vaginitis secondary to overgrowth of aerobic bacteria, fistulae associated with inflammatory bowel disease or pelvic surgery, and vulvar contact dermatitis.

Box 25-1 Causes of Vaginal Discharge

- Candidiasis
- Trichomoniasis
- Bacterial vaginosis
- *Neisseria gonorrhea*
- *Chlamydia trachomatis*
- Foreign body
- Desquamative (aerobic) vaginitis
- Fistula

Candidiasis

Epidemiology: Vulvovaginal candidiasis is highly prevalent during adolescence and adulthood, with 50% of adult women reporting at least one lifetime episode and 25% reporting an episode before age 25 years. The prevalence of colonization in asymptomatic females is < 5% before menarche and 20% by late adolescence. *Candida* is detected by culture in 29–75% of women with vaginal discharge, and 5–58% with positive cultures for *Candida* report symptoms. The most common species is *Candida albicans*, identified in 80–90% of cultures, with *C. glabrata* occurring in 10–20%. Other *Candida* species have been reported in increasing numbers in the last few years, perhaps due to improved detection or to the use of therapies that preferentially eradicate *C. albicans*.

Pathophysiology: *Candida* species are considered to be part of the normal flora of the vagina. The change from asymptomatic colonization to vulvovaginal candidiasis reflects the loss of local immunity with a resulting increase in the quantity of *Candida* and a host inflammatory response. Factors that may precipitate a shift from colonization to infection include estrogen status, the presence of glycogen, and the loss of protective bacterial flora.

Candida prefers a nutrient-rich environment, and growth is enhanced by factors that increase the glycogen content of epithelial cells. Impaired glucose tolerance and high estrogen states, such as those created by pregnancy and the use of oral contraceptives, are known risk factors for candidiasis. Antibiotic use also is a risk factor for candidiasis, presumably due to the alteration of normal vaginal protective factors. Receptive oral sex appears to be the only sexual behavior that increases the risk of candidiasis.

Evaluation: The symptoms most consistently associated with candidiasis are vulvovaginal itching or burning, followed by erythema. The classic curdy, white discharge is seen in about 50% of women with candidiasis, and discharge alone is not strongly predictive of candidiasis. The gold standard for diagnosis is culture on selective media (Table 25-1), but the diagnosis is usually made clinically by microscopic examination of the wet prep with a drop of potassium hydroxide (KOH) added to the slide. Visualization of pseudohyphae and budding yeast forms is 22–50% sensitive for candidiasis (Figure 25-1). Unamplified RNA testing (Affirm VPIII, Becton Dickinson, Sparks, MD) is slightly more sensitive than wet mount and does not require microscopy but is more costly and complex to perform.

Management: Candidiasis is considered a self-limited disease for which symptomatic treatment is sufficient. However, recent evidence suggests that the inflammatory changes associated with candidiasis may increase a woman's susceptibility to infections such as human immunodeficiency virus (HIV).

Table 25-1 Diagnostic Test Characteristics for Candidiasis, Trichomoniasis, and Bacterial Vaginosis

	Test	Sensitivity (%)	Specificity (%)
Candidiasis	Wet mount	22–50	100
	RNA	?	?
	Culture	Gold Standard	
Trichomoniasis	In-pouch Tv culture	85	100
	Wet mount	36–70	99–100
	Rapid antigen (OSOM)	90	100
	RNA (Affirm VPIII)	90	99
	Conventional Pap smear	36–55	90
	Liquid-based Pap smear	61–96	99
	PCR[1]	84–98	94–99
Bacterial Vaginosis	Amsel criteria	77	58
	Nugent gram stain	89	90
	RNA (Affirm VPIII)	?	?
	Sialidase (BVBlue)	88	95
	pH and amines (FemExam)	71	72
	PCR[1]	84–98	94–99

[1]PCR, polymerase chain reaction.

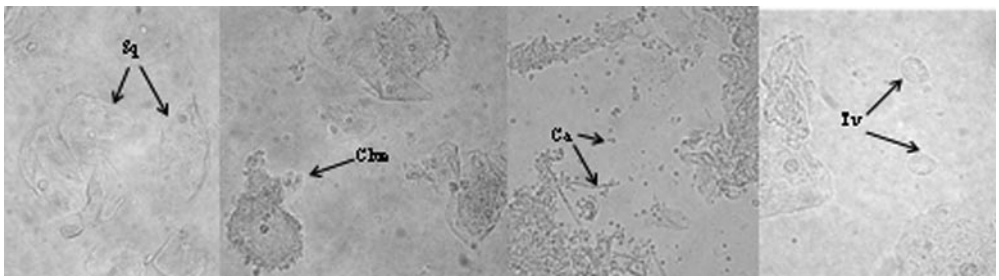

Figure 25-1 Example of wet mounts showing normal squamous cells (Sq), clue cells (Clue), *Candida* (Ca), and trichomonads (Tv).

About 5–10% of women suffer from recurrent vulvovaginal candidiasis, defined as four or more symptomatic episodes per year. These women may benefit from culture documentation of both infection and cure to identify the responsible *Candida* species and to distinguish between relapse and reinfection. Although most have no identifiable risk factors, they may warrant an evaluation for precipitating factors such as diabetes or immune compromise.

The goal of treatment is to alleviate symptoms and reduce the burden of *Candida* colonies. Topical antifungal agents, such as miconozole and clotrimazole, are safe and effective. A short, 1–3 day course produces a clinical cure and negative culture in 80–90% of patients. Even if the predominant symptoms are vulvar, intravaginal treatment is necessary to address the source of the *Candida*. All of the currently available preparations are equally effective; thus the choice will be guided by cost and availability. Oral fluconazole is effective at producing a cure and may be more acceptable to adolescents who have no experience using intravaginal items such as tampons. However, symptoms may persist longer following oral than intravaginal therapy.

Regardless of therapy, patients should be counseled that symptoms usually diminish in 24–72 hours and resolve within 6–8 days. Alternative therapies without proven efficacy for prevention or cure include cotton underwear, loose-fitting clothing, topical or oral lactobacillus, and yogurt.

Women with recurrent candidiasis may benefit from longer courses (7–14 days) of topical antifungal medications or repeated doses of oral fluconazole to cure each episode. They may also require weekly or monthly doses for suppressive therapy. Flucytosine and boric acid vaginal capsules have both been used successfully in some recalcitrant cases.

Trichomoniasis

Epidemiology: Trichomoniasis is caused by a parasitic protozoa, *Trichomonas vaginalis* (Tv). Prevalence in adolescents ranges from 5–17%. In the only population-based study to date, the prevalence of Tv is higher than NG, similar to CT, higher in African-American than Caucasian women, and higher in the southeast than other regions of the

United States. Tv is present in 12–30% of women with vaginal symptoms and is associated with sexual risk behaviors such as multiple partners and lack of condom use. Unlike CT and NG, young age is not an important risk factor for Tv. Although the majority of sexually transmitted infections (STIs) occur in asymptomatic women, Tv and NG are more strongly associated with genitourinary symptoms than CT. Thus, if the reason for STI testing is genitourinary symptoms, a careful assessment for Tv and NG is warranted.

Pathophysiology: Tv has four anterior flagella and an undulating membrane that provide propulsion and give the organism a jerky appearance on the wet mount. The free-swimming oval parasite takes on an amoeboid form when it attaches to the vaginal epithelial cells. Adherence is required to maintain infection and is promoted by the presence of iron and higher pH (which makes menses a favorable environment). Adhesion is disrupted by imidazole drugs such as metronidazole. After adhering, Tv releases proteases and glycoproteins that cause epithelial disruption. It induces an intense inflammatory response involving cytokines, IgG and IgA antibodies, neutrophil defensins, reduction of lactobacilli, and an increase in pH.

Clinically, the host response to infection corresponds to the findings of discharge, bleeding, and worsening of symptoms at menses. These mechanisms also explain the increased susceptibility of those infected with Tv to other pathogens, most notably HIV and human papillomavirus (HPV). Finally, unlike CT and NG, Tv does not require endocervical cells for survival and therefore can produce a symptomatic infection in women without a cervix. Untreated, Tv has been estimated to persist for up to 5 years in women and is highly transmissible between partners. Fomite transmission has been speculated but never proven conclusively.

Evaluation: The classic description of Tv infection is a characteristic frothy green discharge and punctate hemorrhage of the cervix (strawberry cervix). However, approximately 50% of women with Tv are asymptomatic, and the classic strawberry cervix is seen in less than 2% of infected subjects. In the population study, 98% of those with Tv denied symptoms in the last 30 days.

The most common method of diagnosis is wet-mount identification of *motile* trichomonads (Figure 25-1). Diagnosis can also be made using cytological characteristics on the Papanicolau smear. Both the wet mount and Pap smear are less sensitive than culture, although specificity is high. Liquid-based cytology, such as ThinPrep (Cytec Corp, Boxborough, MA), seems to have improved sensitivity. Culture is the diagnostic gold standard, but it is not widely available and requires up to 4 days in a microbiology laboratory for final reading. A comparison of the diagnostic methods is shown in Table 25-1.

Management: Historically, Tv has been viewed as a nuisance infection associated with sexual risk behaviors. Recent studies, however, have linked Tv infection to pelvic inflammatory disease (PID), the acquisition of HIV, and shedding of HIV.

Tv can be treated with an oral regimen of either metronidazole or tinidazole. Single-dose therapy is associated with better compliance and fewer side effects than multiday therapy, and tinidazole has fewer gastrointestinal side effects than metronidazole. Topical preparations may reduce symptoms but do not eradicate the infection. Partner treatment is recommended, and the patient should be advised to abstain from intercourse until both the patient and partner have completed therapy. As for all STIs, condom use should be encouraged to prevent reinfection.

Studies suggest that 5–9% of Tv isolates demonstrate some resistance to metronidazole. Clinically, treatment failure due to nonadherence or reinfection from an untreated partner are more common than resistance. Patients with suspected resistance can be treated with longer courses of metronidazole or a trial of tinidazole.

Bacterial Vaginosis

Epidemiology: BV refers to a nonspecific vaginitis first described by Gardner in 1955. BV was attributed to *Haemophilus vaginalis* (renamed *Gardnerella vaginalis*) until the 1980s, when the single-bacterium theory was discarded and the syndrome was redefined according to its four clinical characteristics, now termed Amsel Criteria (Box 25-2). Nugent Criteria for gram stain diagnosis of BV (Table 25-2) are used less commonly than Amsel Criteria. The term "bacterial vaginosis" reflects the bacteria-coated epithelial cells (i.e., clue cells) on wet mount that provide a clue to the diagnosis, coupled with the relative lack of white blood cells on wet mount compared with the causes of vaginitis discussed previously (Box 25-1).

The prevalence of BV is 12–18% in asymptomatic adolescent females who have not had sexual intercourse and 28–32% in those who have had intercourse. The rates are similar in adolescent and adult females and are higher in African-American than Caucasian females. Risk factors for BV include sexual intercourse, oral sex, smoking, and douching.

Pathophysiology: The pathophysiology of BV is complex and still incompletely understood. It is best

Box 25-2 Amsel Criteria for the Diagnosis of Bacterial Vaginosis (3 of 4 Required)

- Homogeneous thin, gray vaginal discharge
- pH > 4.5
- > 20% clue cells on wet mount
- "Whiff": fishy odor after application of potassium hydroxide (KOH)

Table 25-2 Nugent Gram Stain Criteria for Bacterial Vaginosis[1]

Score	Lactobacilli	*Gardnerella/ Bacteroides*	Curved Gram Variable Rods
0	4+	0	0
1	3+	1+	1+ or 2+
2	2+	2+	3+ or 4+
3	1+	3+	
4	0	4+	

[1]Score determined by the quantity seen in an oil immersion field. Total score: 0–3, negative; 4–6, intermediate; 7–10, bacterial vaginosis (BV).

described as a shift in the normal vaginal flora characterized by a decrease in lactobacillus species and an increase in anaerobic bacteria such as *Gardnerella vaginalis* and *Bacteroides* spp. These changes result in an elevated pH, the production of malodorous amines, and a possible increase in local cytokines. No single causative agent has been identified, and recent attention has turned to the molecular identification of species that cannot be cultivated in the laboratory.

Evaluation: At least three large studies in adult females and one study in adolescents found little correlation between a diagnosis of BV and vaginal symptoms. Factors that have been associated with BV include race, sexual behavior, douching, and smoking.

Table 25-1 compares various diagnostic methods for BV. Amsel Criteria are subjective, depend upon clinician experience, and require microscopy. Some have advocated using the combination of pH > 4.5 plus either clue cells or an amine odor to increase specificity without significant loss of sensitivity. Nugent Criteria are based on a gram stain of vaginal fluid and are considered the gold standard for diagnosis (Table 25-2). However, they are time-intensive and rarely used in clinical settings. Several objective, point-of-care tests have been developed, but the associations between these test results and clinical outcome remain unclear.

Management: Associations have been reported between BV and adverse outcomes, including premature birth, PID, and postoperative infections. There is good evidence that women with BV who are treated with metronidazole have fewer postoperative and postabortion infections. However, recent data using Nugent Criteria report no increased risk of PID in women with BV and no improvement in perinatal outcome with treatment of BV.

The Centers for Disease Control and Prevention (CDC) recommend treatment only for symptomatic BV and for asymptomatic women undergoing abortion or hysterectomy. Clinical relapses and treatment failures are common, making it important to limit diagnosis to those who are symptomatic and in whom other pathogens have been excluded. The goal of treatment is alleviation of symptoms, not cure, because BV represents a shift in normal flora. Accepted treatment regimens include intravaginal metronidazole or clindamycin and oral metronidazole. Intravaginal metronidazole appears to be the therapy that is least disruptive to other normal vaginal flora. Partner therapy is not recommended.

URINARY TRACT INFECTION

Urinary symptoms such as dysuria, urinary urgency, and urinary frequency are common reasons for health care visits among adolescent and young adult females. Although the symptoms often reflect an underlying urinary tract infection (UTI), it is important to recognize that STIs and vulvar lesions can present with urinary rather than vaginal symptoms (Box 25-3).

Epidemiology: Bacteriuria on urine culture is found in 5% of asymptomatic, nonpregnant adolescent females and in 24–57% of those with urinary symptoms. The former are defined as having asymptomatic bacteriuria, and the latter are defined as having UTI. In adult females, UTI is associated with sexual intercourse, new sexual partners, and the use of barrier contraceptives (e.g., diaphragm).

Pathophysiology: The most common urinary pathogens are bacteria that reside normally in the gastrointestinal tract. *Escherichia coli* is responsible for 60–90% of UTIs, enterococci for 10–30%, and *S. saprophyticus* for 5–10%. The transition from asymptomatic bacteriuria to UTI is mediated by local inflammation and is characterized by pyuria.

Evaluation

A positive urine culture is the gold standard for the diagnosis of UTI in a symptomatic patient with pyuria (i.e., >10 leukocytes per high-powered field). The definition of a positive urine culture varies across studies and clinical guidelines, from > 10^2 CFU/ml to > 10^5 CFU/ml. The presence of leukocyte esterase on dipstick testing of the urine indicates pyuria with a sensitivity of 75–96% and specificity of 94–98%. The presence of nitrite on dipstick testing indicates bacteriuria with a

Box 25-3 Conditions Associated with Urinary Symptoms

- Urinary tract infection: bacterial pathogen
- Sexually transmitted pathogen causing urethritis: Tv, NG, CT
- Vulvitis: candida, HSV
- Vulvar lesions
- Anatomical lesions: urethral diverticula, prolapse

fair sensitivity at high colony counts (i.e., 10^5 CFU/ml) but is relatively insensitive at lower colony counts.

Although history, pyuria, and dipstick testing are reasonably accurate for the diagnosis of UTI in adult populations, the accuracy diminishes when the prevalence of STIs increases, as in adolescent populations.

Women who experience one UTI are at increased risk for a second UTI and are at 4- to 12-fold risk for pyelonephritis (see Definitions, as discussed previously). The clinical manifestations of pyelonephritis include evidence of upper urinary tract involvement (e.g., fever, flank pain, and costovertebral angle tenderness), pyuria, and positive urine culture. Complications of pyelonephritis include sepsis, renal abscess, perinephric abscess, renal scarring, hypertension, and decreased renal function. Reflux nephropathy and recurrent pyelonephritis during early childhood may result in chronic scarring with the development of hypertension years later, during adolescence.

STIs must be considered in the evaluation of sexually active females with urinary symptoms. Tv and NG are more commonly associated with urinary symptoms than CT in both adolescent and adult women, although CT has been shown to cause sterile pyuria. Infections that cause vulvar lesions, such as herpes simplex virus (HSV), often are associated with dysuria (Chapter 28).

Other causes of urinary symptoms include urethral prolapse, urethral diverticulum, and nephrolithiasis. Urethral prolapse is associated with hypoestrogenization and is more common before than after menarche. Urethral diverticulum is more likely to cause urinary frequency and dribbling than dysuria. Stones can cause back, flank, abdominal, or pelvic pain; dysuria, urinary frequency; and hematuria.

Management

Asymptomatic bacteriuria progresses to clinical UTI within 1 week in 8–15% of females. In most females, however, asymptomatic bacteriuria is transient and requires no treatment. Pregnancy represents an important exception because of the association between asymptomatic bacteriuria and preterm delivery. Pregnant women therefore are screened and treated for asymptomatic bacteriuria.

Acute cystitis should be treated with a 3-day course of an oral antibiotic such as of trimethoprim, trimethoprim/sulfamethoxazole (TMP/SMX), or ciprofloxacin; or a 7-day course of nitrofurantoin. For patients who cannot tolerate these antibiotics, a 5-day course of amoxicillin-clavulanate can be prescribed. Single-dose treatment appears to be less effective than multiday regimens. Although the fluoroquinolones demonstrated the highest efficacy with the shortest treatment duration, their use for uncomplicated cystitis is discouraged because of the emergence of fluoroquinolone-resistant uropathogens. Nitrofurantoin is well tolerated and effective against most uropathogens when continued for a full 7-day course, but it is ineffective against many *Proteus, Enterobacter*, and *Klebsiella* species.

There is no evidence that increased hydration or cranberry juice are helpful in the treatment of acute cystitis, although there is evidence that cranberry juice may help prevent recurrent infections. Symptoms of acute infection usually resolve within 72 hours of antibiotic therapy. Phenazopyridine, a urinary analgesic, can be prescribed at a dose of 200 mg orally every 8 hours to control severe dysuria during the first 1–2 days of treatment.

VULVAR ABNORMALITIES

Developmental Variants

Concerns about the appearance of the external genitalia are common among adolescent females. In many cases, the concern reflects unfamiliarity with the normal developmental changes that occur during puberty (Figure 25-2). In addition to the growth of pubic hair, the labia minora elongate and become rugated and pigmented. Asymmetry or unilateral hypoplasia of the labia minora (Figure 25-3) rarely causes physical discomfort and generally requires no treatment other that reassurance that it is a variant of normal.

Variants of hymenal anatomy often are unrecognized until puberty, tampon use, or the initiation of sexual intercourse. The hymen remains imperforate until late in embryonic development, when normal canalization produces either a fimbriated or smooth opening (Figure 25-4). Imperforate hymen occurs in < 0.1% of females, but partial canalization with a resulting septate or cribiform hymen occurs in approximately 1% of females. Both of these conditions require surgical correction.

Vulvar Itching and Irritation

Vulvar itching and/or irritation (Table 25-3) can be caused by infectious agents or dermatoses. Infectious causes include candidiasis or trichomoniasis (see previous sections), genital herpes (Chapter 28), and genital warts (Chapter 27). *Candida* vulvitis produces significant erythema, edema hyperkeratosis or lichenification, and linear fissures or excoriations at the forchette (Figure 25-5). Psoriasis and eczema are common, noninfectious causes of chronic or recurrent vulvar itching. Lichen sclerosis is a noninfectious dermatosis affecting 1:1000 females and is less common in adolescents than in prepubertal and postmenopausal females. Lichen planus is an inflammatory condition of the skin, nails, and mucosal that typically appears as shiny, violaceous papules with white lines (i.e., Wickham striae). Vulvar involvement occurs in half of females with lichen planus, but it is much more common in adults than children or adolescents.

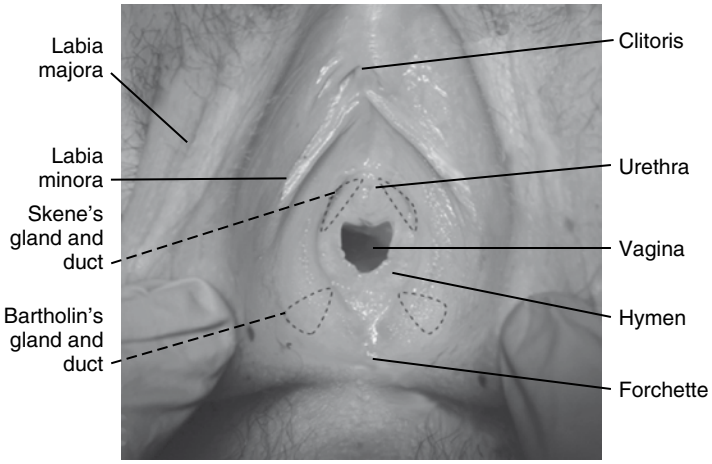

Figure 25-2 Normal vulvar anatomy in an adolescent with Tanner Stage 4 pubic hair and attenuated labia minora. Skene's and Bartholin's glands are not normally detectable; their anatomical locations are indicated with dotted lines for reference.

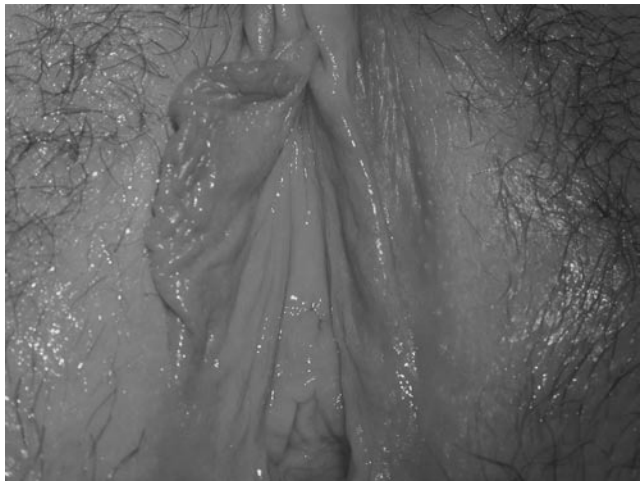

Figure 25-3 Normal labial asymmetry. Left labia minora is smaller and less rugated than the right.

Vulvar contact dermatitis can be caused by soaps, bubble bath, shampoo, perfume, feminine hygiene products, barrier contraceptive products, topical medications, latex, dyes, and semen. Approximately 20% of cases are allergic responses to an environmental trigger, whereas 80% are skin or mucosal damage caused directly by the trigger.

Folliculitis (i.e., infection of the hair follicle) and pseudo-folliculits barbae can occur in any hair-bearing area, particularly if shaved. Folliculitis usually responds to warm compresses but may require incision and drainage or antibiotics. Shaving should be discontinued for at least 30 days in pseudo-folliculitis barbae and preferably discontinued. Some patients have improved with topical antibiotics, retinoids, and laser therapy.

Hidradenitis suppurotiva is a chronic inflammatory skin condition affecting 1–4% of the population. Hair follicles and apocrine glands in androgen-sensitive skin manifest chronic obstruction and inflammation but, unlike acne vulgaris, there is no increase in sebum production (Figure 25-6). It is more common in postpubertal females and can occur in the axillae as well as the groin and vulva.

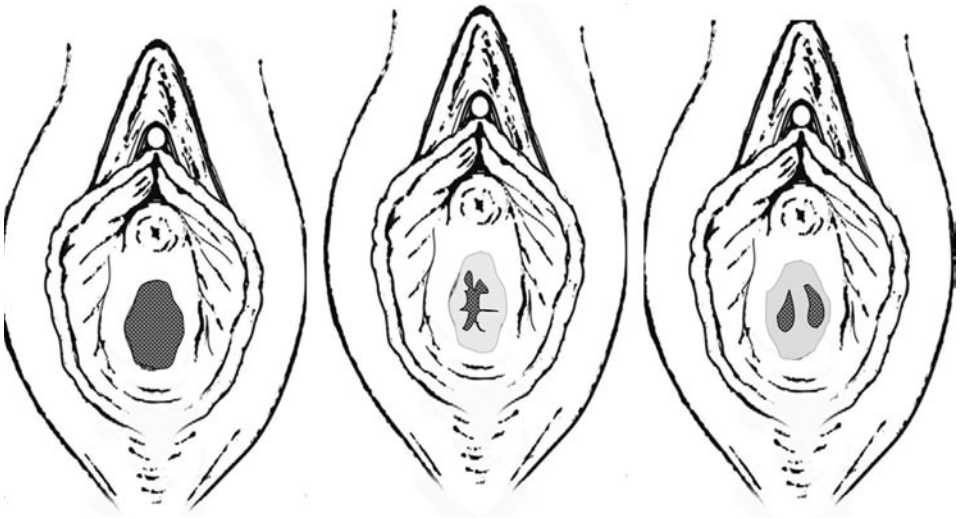

Figure 25-4 Normal hymen anatomy and variants. The fimbriated hymen has ruffled folded edges that may obscure the opening. The circumferential hymen is smooth and can form a complete or partial circle. The septate hymen has a longitudinal band of varying thickness. The examiner can use a cotton-tipped applicator moistened with anesthetic gel or can apply gentle downward traction on the labia majora to improve visualization.

Table 25-3 Causes of Vulvar Symptoms

Predominant Symptom	Etiological Category	Etiology
Itching and pain	Infectious	Vaginitis
		HSV
		HPV
		Folliculitis/furuncles (boils)
		Bartholin's abscess
		Clitoral abscess
	Noninfectious	Contact dermatitis
		Psoriasis
		Eczema
		Lichen sclerosis
		Lichen planus
		Fox-Fordyce disease
		Hidradenitis suppurativa
		Aphthous ulcers
		Behçet's disease
		Crohn's disease
Raised or palpable lesions	Infectious	HPV
		Molluscum contagiosum
	Noninfectious	Acrochordon (skin tags)
		Sebaceous glands
		Epidermal inclusion cysts
		Fox-Fordyce disease
		Hidradenitis suppurative
		Lipoma
		Syringoma
		Vaginal masses
Pigmented lesions	Noninfectious	Melanosis
		Acanthosis nigricans
		Nevus
		Sebhorreic keratosis
		Melanoma
		Vascular malformation

HSV, herpes simplex virus; HPV, human papillomavirus.

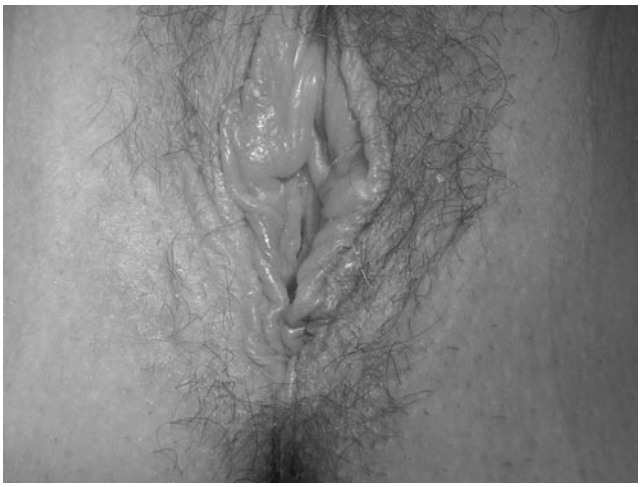

Figure 25-5 Lichenification of vulvar skin seen with chronic candidiasis.

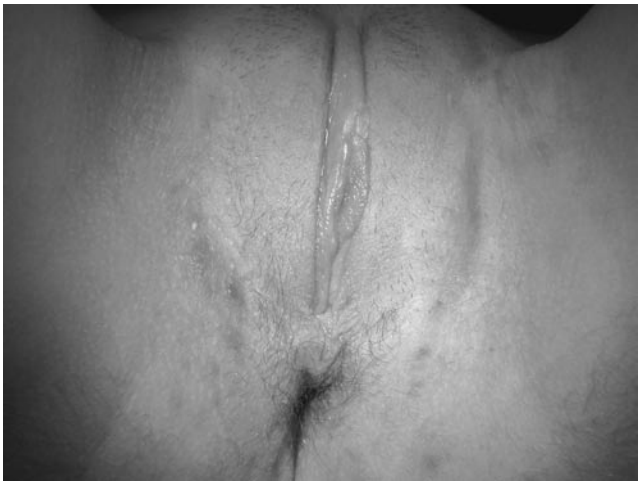

Figure 25-6 Pustular lesions, scarring, and hyperpigmentation in a female with hidradentitis suppurativa.

Patients present with erythema, itching, pain, and cystic nodules that initially are difficult to distinguish from folliculitis. The cysts may progress to boils that may rupture and lead to scarring, hyperpigmentation, or draining sinus tracts. Acute therapy includes warm compresses, incision and drainage, and oral antibiotics. Preventive therapy with demonstrated efficacy includes isotretinoin, topical and oral antibiotics, and oral contraceptive pills. Extensive disease may require surgery, and some believe that surgical resection is the treatment of choice.

Fox-Fordyce disease is a rare condition that results from the obstruction of apocrine glands without inflammation. It is most common in African-American adult women and presents as small, intensely pruritic, flesh-colored papules in the axillae and groin. Treatment suggestions are based on case reports and include topical antipruritic medications, topical antibiotics, oral contraceptive pills, and isotretinoin.

Vulvar Lesions

Vulvar masses and lesions may represent STIs, aphthous ulcers, or local manifestations of systemic diseases such as Crohn's disease or Behçet's disease. Aphthous ulcers of the vulva are usually large and shallow with a raised border and overlying exudate (Figure 25-7). Although several infectious etiologies have been proposed (e.g., Epstein-Barr virus, cytomegalovirus, and paratyphoid fever), the largest series in adolescents failed to identify infectious etiologies. Empirical treatments include topical anesthetics or steroids.

"Complex aphthosis" is the term used to describe patients without Behçet's disease who have recurrent, severe oral and genital ulcerations without other systemic manifestations. Behçet's disease has an unknown etiology and is rare in the United States and in children. The criteria for diagnosis of Behçet's disease include recur-

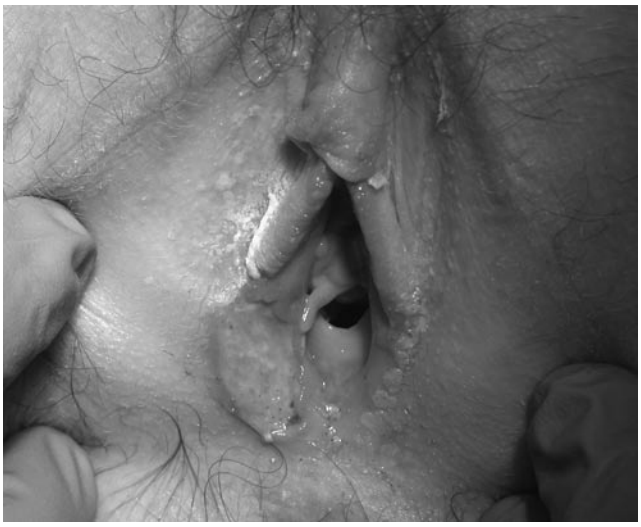

Figure 25-7 Large, shallow aphthous ulcer with raised pink edges and an overlying thin exudate on the ulcer. Other material seen in the labial folds represents residual from prior topical agents and inadequate hygiene.

rent oral ulceration plus at least two of the following: recurrent genital ulceration, uveitis, or skin lesions such as erythema nodosum. Ulcers are deep, painful, and heal with scarring. Patients may also develop arthritis, gastrointestinal lesions, vasculitis, and central nervous system involvement. The vulvar manifestations of Crohn's disease are characterized as "knife-cut" ulcers, usually located in the inguinal and interlabial folds. The ulcers may predate gastrointestinal symptoms and may be difficult to distinguish from hidradenitis suppurativa (Figure 25-8).

Acrochordons are more commonly called skin tags; they range in size from a few millimeters to more than 2 cm and can occur in any area of the body. Prevalence is unknown, but there appears to be a familial tendency. Molluscum contagiosum is caused by a poxvirus and transmitted through direct skin-to-skin contact, autoinoculation, or sexual contact. It is common in young children and adolescents. One seroprevalence study estimated that 23% of the adolescent population has been exposed. The infection presents as small, dome-shaped papules with central umbilication. Infection is usually self-limited except in immunocompromised patients. Diagnosis of these three entities is made clinically and confirmed with biopsy. The goal of treatment is to restore normal anatomy. Treatment options include excision, laser, and chemo-ablation. Both genital warts and molluscum respond to topical imiquimod.

Figure 25-8 Fistula track with smooth edges on the vulva in a patient with Crohn's disease. Patient was referred for possible Bartholin's abscess. Multiple perianal fistulas were also present.

Obstructed sebaceous glands and epidermal inclusion cysts present as small, firm, yellow, subcutaneous nodules that often appear following vaginal delivery. Syringoma is a rare, benign skin tumor that presents as a flesh-colored nodule on the labia minora or the eyelids, often associated with itching. Finally, a vaginal mass at the introitus can be mistaken as a vulvar lesion. Examples include urethral diverticula, endocervical polyps, and Gartner's duct remnants.

The most common pigmented lesions of the vulva in adolescents are vitilgo, melanosis (freckles), and acanthosis nigricans (Chapter 24). Although vulvar melanoma is rare in adolescents, there are case reports in adolescents with lichen sclerosis.

MAJOR POINTS

- Physiological leukorrhea is a white, odorless, nonpruritic, nonpainful discharge that typically begins shortly before menarche and may continue throughout reproductive life.
- Vaginal discharge accompanied by itching, pain, or odor is usually caused by candidiasis, bacterial vaginosis (BV), or trichomoniasis (Table 25-1). Other causes include NG, CT, foreign body, desquamation, fistulae, and contact dermatitis.
- Vaginal candidiasis responds to a 1–3 day course of a topical antifungal agent, such as miconozole and clotrimazole, in 80–90% of patients.
- Trichomoniasis can be treated with oral metronidazole or tinidazole in single-dose or multiday therapy. Topical preparations may reduce symptoms but do not eradicate the infection.
- BV in nonpregnant females should be treated if symptomatic with intravaginal metronidazole or clindamycin or oral metronidazole.
- Asymptomatic bacteriuria in nonpregnant females is usually transient and does not require treatment.
- Uncomplicated acute UTI should be treated with trimethoprim, trimethoprim/sulfamethoxazole (TMP/SMX), or nitrofurantoin. STIs should always be considered as a possible cause of urinary symptoms in sexually active adolescents.

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CHAPTER 26

Gonorrhea, Chlamydia, and Pelvic Inflammatory Disease

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INTRODUCTION

Adolescents and young adults aged 15–24 years account for half of the 19 million sexually transmitted infections (STIs) that occur yearly in the United States. Factors contributing to the high STI rate among U.S. youth include developmental characteristics such as cervical ectopy, sexual risk behaviors, and inadequate screening of asymptomatic patients. Factors that appear to protect adolescents from STIs include parental involvement, perceived parental disapproval of adolescent sexual activity, and academic achievement.

In addition to the risk of STI acquisition, delayed diagnosis and treatment of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in adolescents results in high rates of pelvic inflammatory disease (PID) and late sequelae such as infertility. This chapter reviews the epidemiology and pathogenesis of disease associated with these two organisms. The clinical presentations, evaluation, and management of adolescents with gonorrhea, chlamydia, and PID are discussed, with an emphasis on early recognition, treatment, and secondary prevention.

DEFINITIONS

Cervical ectopy or ectropion: Junction of the squamous and columnar epithelium that normally recedes proximally with maturation, from the ectocervix to the endocervical canal.

Cervicitis: Cervical inflammation due to infection, with resulting cervical erythema, friability, and/or discharge.

Endometritis: Inflammation of the lining of the uterus, usually due to an STI.

Fitz-Hugh-Curtis syndrome: Perihepatic inflammation (i.e., perihepatitis) that may occur as a complication of PID.

Pelvic inflammatory disease (PID): Polymicrobial infection of the upper female genital tract generally due to ascent of organisms from cervical infection with gonorrhea or chlamydia.

Salpingitis: Inflammation of the fallopian tubes, usually due to an STI.

Tubo-ovarian abscess (TOA): A complication of PID that results from collected fluid and bacteria in the fallopian tube with possible extension to the ovary.

GONORRHEA

Epidemiology

According to the 2005 STD Surveillance Report of the Centers for Disease Control and Prevention (CDC), the gonorrhea rates per 100,000 individuals were 625 for females aged 15–19 years, 261 for males 15–19 years,

581 for females 20–24 years, and 437 for males 20–24 years. Among incarcerated youth younger than 18 years, the prevalence rates were 6 per 100 females and 1 per 100 males. Direct medical costs in 2000 of gonococcal infection in individuals aged 15–24 years were an estimated $77 million.

The high rate of coinfection with *N. gonorrhoeae* and *C. trachomatis* has prompted recommendations to treat empirically for both organisms if test results for one are positive and results for the other are unknown or unavailable. In a study of 5877 high school students aged 14–20 years who were tested for both gonorrhea and chlamydia, 43% of those with gonorrhea also had chlamydia and 11% with chlamydia also had gonorrhea. In a study of incarcerated youth, 54% of females and 51% of males with gonorrhea also had chlamydia.

Risk factors for gonorrhea include young age, new or multiple sexual partners, minority race/ethnicity, substance use, and past gonorrhea. The likelihood of male-to-female transmission after one episode of sexual intercourse is 50–75% and may increase to more than 90% with repeated exposure. There are many strains of *N. gonorrhoeae*, and the predominant strains differ across regions of the United States. Approximately 20% of strains in the United States are resistant to penicillin and/or tetracycline. Resistance to fluoroquinolone antibiotics was first detected in the United States in 1991 and has continued to increase over time. In 2005, nearly 10% of all isolates received by the CDC were quinolone resistant, leading to recommendations to discontinued use of these antibiotic for gonorrhea treatment.

Pathophysiology

N. gonorrhoeae adheres to mucosal columnar epithelial cells, activates endocytosis, and replicates in both anaerobic and aerobic settings. Most strains of *N. gonorrhoeae* are killed by complement activation in the serum. Those that are resistant to host defenses appear to be more likely to cause epididymitis, PID, and intravascular dissemination.

An estimated 90% of males with gonorrhea develop symptoms. The average incubation time is 8 days, with a range of 2–14 days. The most common presenting complaints are a purulent or mucopurulent urethral discharge and/or dysuria. Epididymitis, presenting as testicular pain and swelling, is more commonly due to chlamydia than gonorrhea. Anorectal gonorrhea occurs in males who have anoreceptive intercourse and, compared to urethral or pharyngeal gonorrhea, is associated with a three-fold risk of human immunodeficiency virus (HIV) infection. Pharyngeal infection with *N. gonorrhoeae* occurs in less than 10% of adult men who are heterosexual and in 10–25% of adult men who are homosexual or bisexual. Although it can cause pharyngitis and/or lymphadenitis, many oropharyngeal infections are asymptomatic.

In females, gonorrhea most commonly infects the cervix. Of the 50% of infected women who develop symptoms, the usual presenting complaints are vaginal discharge and/or pruritis. Less commonly, gonorrhea in females presents as dysuria secondary to urethritis. Anorectal gonorrhea in females may represent inoculation from vaginal secretions and is asymptomatic in 97% of cases. As in males, pharyngeal gonorrhea in females is usually asymptomatic. Infections of Bartholin's or Skene's glands with *N. gonorrhoeae* are nearly always symptomatic and usually are accompanied by cervical infection. PID associated with gonococcal infection is discussed later.

Dissemination of *N. gonorrhoeae* via the bloodstream is three times more likely to occur in females than males, perhaps because of the higher rates of asymptomatic and untreated infections in females. Other factors associated with disseminated gonococcal infection (DGI) include menstruation, pregnancy, complement deficiencies, and systemic lupus erythematosus. DGI tends to present as either a triad of tenosynovitis, polyarthralgias, and characteristic skin lesions or as purulent arthritis. The skin lesions typically are painless; limited in number; located on the distal extremities; vary from macules to pustules to necrotizing ulcers; and may disappear within a few days, even without antibiotic treatment. In contrast, the joint symptoms usually are persistent and severe until antibiotics are begun, at which point resolution is dramatic (see Management, later).

Evaluation

Laboratory methods for the identification of *N. gonorrhoeae* include Gram stain, culture, and DNA assays (see Box 26-1). The choice of test depends on patient gender, specimen site, transport conditions, and population prevalence. Table 26-1 summarizes the sensitivities and specificities of the various tests in adolescent females and males. Gram stain is sensitive and specific for the detection of *N. gonorrhoeae* in specimens collected from the male

Box 26-1 Clinical Evidence of Gonorrhea

Suggestive

- Mucopurulent endocervical or urethral discharge *and*
- Exposure to sexual partner with *N. gonorrhoeae*

Diagnostic

- Gram stain of male urethra *or*
- Culture of male urethra, endocervix, pharynx, or rectum
- Nucleic acid amplification test (NAAT) of male urethra, endocervix, or urine
- Nucleic acid hybridization of male urethra or endocervix

Table 26-1 Sensitivities and Specificities of Laboratory Tests for *Neisseria gonorrhoeae* in Female and Male Adolescents

	Sensitivity (%)	Specificity (%)
Females		
Endocervical culture	70–93	100
Endocervical NAAT[1]	95–99	99
Urine NAAT	56–91	99
Males		
Urethral gram stain	81–94	94–97
Urethral culture	72–95	99
Urethral NAAT	96	99
Urine NAAT	90	99

[1]NAAT, nucleic acid amplification test.

urethra but is unreliable for specimens from other sites because of the presence of nonpathogenic gram-negative diplococci. Culture on Thayer-Martin medium remains the gold standard for diagnosis but requires specimens obtained by swab (e.g., endocervix, urethra, pharynx, or rectum); prompt inoculation into an appropriate medium; and incubation in a controlled environment. An important advantage of culture is the ability to assess the strain and antibiotic sensitivities of the organism. Nucleic acid amplification tests (NAATs) replicate the DNA or RNA sequences of *N. gonorrhoeae*. Its advantages include high sensitivity and specificity in male urethral, male urine and female endocervical specimens, and rapid results. Disadvantages are expense, lower sensitivity and specificity in female urine than in endocervical specimens, possibly lower sensitivity of urine in asymptomatic males, and lack of antibiotic sensitivity data.

Table 26-2 Screening Tests for Gonorrhea and Chlamydia

	Females	Males
Gonorrhea	Endocervical culture	Urethral culture
	Endocervical NAAT[1] or nucleic acid hybridization	Urethral NAAT or nucleic acid hybridization
	Urine NAAT	Urine NAAT
Chlamydia	Endocervical NAAT	Urethral NAAT
	Urine NAAT	Urine NAAT
	Endocervical non-NAAT test	Urethral non-NAAT test
	Endocervical culture	Urethral culture

[1]NAAT, nucleic acid amplification test.

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Sexually active adolescents who are asymptomatic, including females who identify themselves as homosexual, should be screened every 6–12 months for gonorrhea (Table 26-2) and tested if symptoms develop in the interim. Noninvasive screening of asymptomatic males and females and testing of males with symptoms of urethritis can be performed by urine NAAT. However, CDC recommendations for testing preferences include culture of the urethra in a male as the first choice, followed by NAAT of the urethra or urine. In females, the first choice is culture of the endocervix followed by NAAT or nonamplified nucleic acid hybridization testing of the endocervix. Urine NAAT is acceptable when pelvic examination is not possible. However, females with symptoms of upper or lower genital tract infection should have a pelvic examination to obtain an endocervical specimen. Symptoms suggesting pharyngeal or anorectal gonorrhea warrant site-specific culture because NAATs are not approved for these sites.

Management

CDC recommendations are shown for the treatment of cervical, urethral, and anorectal gonorrhea in Box 26-2, oropharyngeal gonorrhea in Box 26-3, and disseminated gonorrhea in Box 26-4. Due to the increasing prevalence of quinolone resistance, as of April 2007, the CDC no longer recommends fluoroquinolones for GC treatment anywhere in the United States. For pharyngeal infections, recommended treatment is with ceftriaxone, due to

Box 26-2 CDC Recommendations for the Treatment of Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum

First-Line

- Cefixime 400 mg orally in a single dose *or*
- Ceftriaxone 125 mg IM in a single dose

PLUS

- If chlamydia is not ruled out, azithromycin 1 g orally in a single dose *or*
- Doxycycline 100 mg orally twice a day for 7 days

Alternative

- Spectinomycin[1] 2 g IM in a single dose *or*
- Ceftizoxime 500 mg IM in a single dose *or*
- Cefoxitin 2 g IM with probenecid 1 g *or*
- Cefotaxime 500 mg IM in a single dose

PLUS

- If chlamydia is not ruled out, azithromycin 1 g orally in a single dose *or*
- Doxycycline 100 mg orally twice a day for 7 days

[1]Spectinomycin is not currently available in the United States.

Box 26-3 CDC Recommendations for the Treatment of Uncomplicated Gonococcal Infections of the Pharynx

- Ceftriaxone 125 mg IM in a single dose
  PLUS
- If chlamydia is not ruled out, azithromycin 1 g orally in a single dose *or*
- Doxycycline 100 mg orally twice a day for 7 days

Box 26-4 CDC Recommendations for the Treatment of Disseminated Gonococcal Infections

First-Line

- Ceftriaxone 1 g IM or IV every 24 hours

Alternative

- Cefotaxime 1 g IV every 8 hours *or*
- Ceftizoxime 1 g IV every 8 hours *or*
- Ciprofloxacin 400 mg IV every 12 hours *or*
- Ofloxacin 400 mg IV every 12 hours *or*
- Levofloxacin 250 mg IV daily *or*
- Spectinomycin[1] 2 g IM every 12 hours

} To be continued for 24–48 hours after improvement begins, followed by one of the subsequent regimens below

Subsequent

- Cefixime 400 mg orally twice daily *or*
- Cefpodoxime 400 mg orally twice daily

} To be completed at least one week of antimicrobial therapy

[1]Spectinomycin is not currently available in the United States.

difficulty with microbial eradication with other regimens. For management of patients with penicillan or cephalosporin allergies, please consult the CDC website (*www.edc.gov/STD/treatment*).

Patients should be advised to abstain from sexual activity for 7 days after treatment and encouraged to use condoms thereafter. Sexual partners from the preceding 60 days need referral to medical care for evaluation and treatment. No test of cure is required following treatment with any of the recommended regimens. Nonculture laboratory tests for *N. gonorrhoeae*, such as NAAT, may be falsely positive in adequately treated individuals for up to 3 weeks after treatment due to shedding of nonviable organisms.

CHLAMYDIA

Epidemiology

In 2000, the 1.5 million cases of *Chlamydia trachomatis* among U.S. individuals aged 15–24 years accounted for $248 million in direct medical costs. The estimated prevalence rates of chlamydia in 2000 among adolescents younger than age 20 years were 4–8% for males and 10–11% for females. In 2003, the prevalence of chlamydia among incarcerated males and females younger than age 18 years was 5% and 16%, respectively. Of those with chlamydia, 13% of males and 18% of females were coinfected with gonorrhea. The rate of transmission from asymptomatic males to female sexual partners is approximately 65%. Risk factors for acquisition of chlamydia are similar to those for gonorrhea, with young age accounting for the highest proportion of risk.

Pathophysiology

C. trachomatis is an obligate intracellular gram-negative bacterium. Small forms of the organism, called elementary bodies, penetrate columnar epithelial cells of the urethra, endocervix, rectum, pharynx, and conjunctiva. The elementary bodies transform within the cell into reticulate bodies, which then reorganize into new elementary bodies. When the cell ruptures 2–3 days later, these new elementary bodies infect other cells, thus perpetuating the infection. The long replication cycle explains why longer courses of antibiotics are required for chlamydia than gonorrhea. The intracellular transformation of the organism probably contributes to the short-lived immunity to infection and the high rates of reinfection.

An estimated 40% of males with nongonococcal urethritis (NGU) are asymptomatic, and chlamydia probably accounts for up to a third of NGU cases. When symptoms develop, the incubation period of 5–10 days is somewhat longer than that of gonorrhea and the dysuria and discharge tend to be milder. *C. trachomatis* can cause other syndromes in males, including proctitis, epididymitis, prostatitis, and Reiter syndrome (i.e., conjunctivitis, urethritis, and arthritis).

More than 50% of females with chlamydia are asymptomatic. When symptoms develop, the most common are vaginal discharge, lower abdominal pain, and/or dysuria. Chlamydia can infect the Bartholin's glands (with or without coexistent gonococcal infection), endometrium, fallopian tubes, and perihepatic region. Reiter syndrome occurs in females, although much less commonly than in males.

Lymphogranuloma venereum (LGV) is a disease caused by three types of *C. trachomatis* and is rarely seen in developed countries. The usual presenting manifestation is tender inguinal or femoral lymphadenopathy, often preceded by a transient genital ulcer. The diagnosis is confirmed by complement fixation > 1:64.

Evaluation

Multiple testing methods exist for the diagnosis of chlamydia. Compared with the limited sensitivity of chlamydia culture (50–85%), NAAT has demonstrated a consistently high sensitivity of 97% for endocervical samples. The CDC recommends annual chlamydia screening (Table 26-2) for all sexually active females aged 25 years and younger with NAAT of endocervical specimens (preferred) or urine specimens (alternative). Nonamplified nucleic acid hybridization testing, enzyme immunoassays, and direct fluorescent antibody testing of endocervical samples have lower sensitivities of 70–85%. For chlamydia testing of males, the CDC recommends NAAT of urethral swabs or urine as first choice, with a urethral non-NAAT test or culture as alternatives.

Management

CDC recommendations for the treatment of chlamydia are summarized in Box 26-5. Single-dose azithromycin, although more costly than doxycycline, is more cost-effective due to improved compliance and directly observed therapy. Patients should be advised to abstain from sexual activity for 7 days and encouraged to use condoms thereafter. Sexual partners during the 60 days preceding treatment require evaluation and treatment. Test of cure is not necessary following singe-dose azithromycin or the 7-day course of doxycycline because of their high efficacy but might be considered following use of an alternative regimen.

Box 26-5 CDC Recommendations for the Treatment of Chlamydia

First-Line

- Azithromycin 1 g orally in a single dose *or*
- Doxycycline 100 mg orally twice daily for 7 days

Alternate

- Erythromycin base 500 mg orally 4 times daily for 7 days *or*
- Erythromycin ethylsuccinate 800 mg orally 4 times daily for 7 days *or*
- Ofloxacin 300 mg orally 2 times daily for 7 days *or*
- Levofloxacin 500 mg once daily for 7 days

Nonculture tests for chlamydia can be falsely positive up to 3 weeks after appropriate treatment due to shedding of nonviable bacteria. When repeat testing following treatment is positive, however, the most likely explanation is reinfection. A survey of adolescents recently treated for chlamydia revealed that 25% had not notified sexual partners of the need for treatment.

PELVIC INFLAMMATORY DISEASE

Pelvic inflammatory disease (PID) is a polymicrobial infection of the upper genital tract that involves the endometrium, parametrium, fallopian tubes (i.e., salpingitis), and ovaries. Although more than half of cases begin with chlamydial or gonococcal cervicitis, the pathogenesis of PID depends on the ascension of multiple organisms from the vagina, through the inflamed cervix, and into the normally sterile environment of the upper genital tract.

Epidemiology

PID represents a spectrum of disease with a wide range of severity and sequelae. An estimated 60% of PID cases are subclinical, 36% are mild to moderate in severity, and 4% require hospitalization. The likelihood of PID is inversely related to adolescent age, with a dramatic decline in risk by young adulthood. A study of females attending an urban teen clinic over an 18-month period revealed that 10% were diagnosed with PID. Furthermore, 47% of those diagnosed with PID had more than one episode prior to or during the study follow-up period. Given the high risk of adverse sequelae following untreated PID, the CDC relaxed its diagnostic guidelines between 1998 and 2002. A study comparing the rates of PID among sexually active females admitted to a juvenile detention center before and after the CDC change revealed an increase from 5% to 9%, suggesting that more subjects met criteria for diagnosis under the new guidelines.

PID is more likely to develop during menses, following instrumentation of the upper genital tract, and with insertion of an intrauterine device. Oral contraceptive use appears to protect against the development of PID by as much as seven-fold, perhaps by increasing the viscosity of the cervical mucous or decreasing the myometrial contractility that propels organisms upward.

Pathophysiology

An analysis of PID cases compiled from 20 studies conducted worldwide revealed evidence of cervical infection with *C. trachomatis* in 29% of cases and *N. gonorrheoae* in 26%. Laparoscopic studies demonstrate that *Bacteriodes* and other anaerobes are the most

common organisms isolated from the upper genital tract of women with PID, regardless of the presence or absence of cervical gonorrhea or chlamydia. Other organisms implicated in the pathogenesis of PID include *Escherichia coli* and other gram-negative rods, *Gardnerella vaginalis, Mycoplasma hominis*, and *Ureaplasma urealyticum*.

The pathogenesis of acute PID begins with inflammatory disruption of the cervical barrier, facilitating ascension of vaginal microorganisms into the normally sterile environment of the endometrium. The spread from the vagina to the uterus is most likely to occur during menstruation when the cervical os is open and the mucus plug is absent. It is also hypothesized that menstrual blood promotes bacterial growth and that the myometrial contractions of dysmenorrhea propel bacteria from the uterus into the fallopian tubes. As a result of the infection, plasma cells infiltrate the endometrium and inflammation decreases tubal motility, resulting in hydrosalpinx (i.e., fluid-filled tube) formation. If treatment and resolution of the upper tract infection are delayed, the hydrosalpinx becomes pyosalpinx and infected contents spill from the fimbriated end of the tube into the peritoneal cavity.

At this point, an abscess may organize between the tube and ovary or within the tube (i.e., tubo-ovarian abscess). Studies of adolescents with PID indicate that although 15–20% have tubo-ovarian abscesses (TOAs) on ultrasound, less than 30% of those with TOAs have palpable adnexal masses on bimanual examination. Once microorganisms have spilled into the peritoneum, infected material may track along the paracolic gutter and cause an inflammatory response of the hepatic capsule and diaphragm. The resulting perihepatitis, or Fitz-Hugh-Curtis syndrome, typically presents as right upper quadrant and/or subscapular pain, associated with pelvic pain. Liver function studies usually are normal or demonstrate only mild elevations of the transaminases.

Long-term sequelae of PID include pelvic scarring and adhesions, ectopic pregnancy, infertility, and chronic pelvic pain. The likelihood of infertility increases from 8% after one episode of PID to 43% following three or more episodes. Prompt antibiotic therapy that provides broad coverage, as noted in following discussions, appears to decrease the risk of complications and sequelae.

Evaluation

The CDC guidelines for the diagnosis of PID (Box 26-6) encourage clinicians to err on the side of overdiagnosis rather than to risk missing the diagnosis or delaying treatment. Clinical diagnoses of PID have a positive predictive value (PPV) of 65–90% when compared with laparoscopy. The PPV tends to be highest among sexually active adolescents and other populations with high rates of gonorrhea or chlamydia. Because the initiation of antibiotics for PID is unlikely to interfere with the management of other causes of pelvic pain (Box 26-7), the CDC recommends that a finding of either uterine/adnexal tenderness or cervical motion tenderness is sufficient for a diagnosis of PID in a female who is at risk for STIs and who does not have another identifiable cause for her symptoms. The additional criteria noted in Box 26-6 support, but are not required for, a diagnosis of PID. The most conclusive evidence of PID comes from endometrial biopsy, pelvic imaging, or laparoscopy. These findings include endometritis on histopathology, tubal thickening or fluid on ultrasound or magnetic resonance imaging (MRI), and infection on

Box 26-6 CDC Criteria for the Diagnosis of PID

Minimum (i.e., at least one of the following)

- Uterine/adnexal tenderness
- Cervical motion tenderness

Supportive (i.e., not required for diagnosis)

- Oral temperature > 38.3° C (> 101° F)
- Abnormal cervical or vaginal mucopurulent discharge
- White blood cells on saline microscopy of vaginal secretions
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*

Box 26-7 Differential Diagnosis of PID

Gynecological

- Ectopic pregnancy
- Ovarian torsion
- Ovarian cyst or mass
- Endometriosis
- Dysmenorrhea

Gastrointestinal

- Appendicitis
- Appendiceal abscess
- Gastroenteritis
- Constipation
- Diverticulitis
- Irritable bowel syndrome
- Inflammatory bowel disease
- Cholelithiasis or cholecystitis (symptoms similar to perihepatitis)

Renal

- Stone
- Urinary tract infection

laparoscopy. However, as noted previously, the diagnosis and treatment of PID does not depend on these findings. Furthermore, endometrial biopsy is rarely indicated in the adolescent because of the near-zero risk of endometrial cancer. Pelvic ultrasound, particularly if done both transabdominally and transvaginally, can help establish the diagnosis of PID and identify a TOA. However, ultrasound is primarily used to exclude other pelvic pathology rather than confirm the clinical diagnosis of PID. Laparoscopy is rarely indicated for the adolescent with suspected acute PID but may be helpful in the evaluation of an adolescent with chronic pelvic pain (Chapter 24).

Management

Empirical antibiotic therapy for PID should provide broad coverage against *N. gonorrhoeae, C. trachomatis*, gram-negative bacteria, anaerobes, and streptococci, regardless of microbiology test results. Indications for hospitalization according to CDC treatment guidelines include potential surgical emergency, pregnancy, unresponsiveness or inability to tolerate outpatient therapy, and TOA (Box 26-8). Of note, the CDC no longer recommends hospitalization for adolescents with PID unless they meet one or more of these indications. Although at least 24 hours of inpatient therapy and observation are generally recommended for patients with TOA, regardless of age, there is no firm evidence documenting its superiority to outpatient care for patients who are able to adhere to prescribed antibiotics and close follow-up.

A randomized trial of inpatient parenteral vs. outpatient oral antibiotics for mild to moderate PID without TOA in adolescents and adults revealed no significant differences in the rates of symptom resolution, TOA formation, recurrence, ectopic pregnancy, infertility, or chronic pelvic pain over 35 months of follow-up.

CDC recommendations for parenteral and oral antibiotic regimens are summarized in Boxes 26-9 and 26-10. Due to increased resistance, fluoroquinolones are no longer recommended as part of PID treatment regimens. However, if the patient has a low risk of GC infection and the community prevalance of resistant GC is low, quinolones may be considered if GC culture and antibiotic sensitivities are obtained prior to initiation of therapy. Quinolones should not be used if non-culture GC testing is used or if antibiotic susceptibility testing is not available. If antibiotics are begun intravenously (IV), they can be discontinued 24 hours after clinical improvement and the total 14-day course can be completed with either oral doxycycline or oral clindamycin alone. Clindamycin is preferred over doxycycline for the patient with a TOA because of its anaerobic coverage. Although doxycycline can be administered IV, oral is preferred whenever possible because of the venous inflammation and pain associated with the infusion. All CDC treatment recommendations are subject to change, depending on the prevalent organisms in the population and their patterns of antibiotic sensitivity. It therefore is important to check the CDC website periodically for updates (*http://www.cdc.gov/std*).

Follow-up examination within 3 days of beginning antibiotics is essential for all patients with PID. If signs and symptoms have not improved considerably by that time, hospitalization is recommended for IV therapy and/or additional evaluation. Male sexual partners who had contact with patients with PID within 60 days of diagnosis should be treated for urethral gonorrhea and chlamydia,

Box 26-8 CDC Indications for the Hospitalization of Patients with Suspected PID

- Possible surgical emergency (e.g., appendicitis)
- Pregnancy
- Unresponsiveness to oral antibiotics
- Inability to adhere to or tolerate outpatient therapy
- Severe illness (e.g., vomiting, high fever, intractable pain)
- Tubo-ovarian abscess

Box 26-9 CDC Recommendations for the Intravenous (IV) Treatment of PID

First-Line Regimens

A. Cefotetan 2 g IV every 12 hours *or* cefoxitin 2 g IV every 6 hours *plus* doxycycline 100 mg orally (or IV) every 12 hours (avoid IV doxycycline if possible)
B. Clindamycin 900 mg IV every 8 hours *plus* gentamicin 2 mg/kg load followed by 1.5 mg/kg every 8 hours

Alternative Regimens

C. Ampicillin/sulbactam 3 g IV every 6 hours *plus* doxycycline 100 mg orally (or IV) every 12 hours

Box 26-10 CDC Recommendations for the Oral or Intramuscular (IM) Treatment of PID

Ceftriaxone 250 mg IM one dose *or* cefoxitin 2 g IM one dose with probenecid 1 g orally *or* other parenteral third-generation cephalosporin *and* doxycycline 100 mg orally twice daily for 14 days with or without metronidazole 500 mg orally twice daily for 14 days

MAJOR POINTS

- Gonorrhea and chlamydia infections are often asymptomatic.
- Routine screening of all at-risk adolescents is recommended at least yearly.
- Consider gonorrhea or chlamydia infection in females who present with urinary symptoms.
- PID is a clinical diagnosis that should be considered in any sexually active female with uterine/adnexal tenderness and/or cervical motion tenderness.
- Early, broad-spectrum antibiotic therapy for PID decreases the likelihood of long-term complications.
- Early and appropriate antibiotic therapy is necessary to prevent the long-term consequences of PID.
- Diagnostic and treatment guidelines are compiled by the CDC for all STIs and are available online at *http://www.cdc.gov*. The web site should be checked frequently for updates.

regardless of the presence or absence of symptoms or the results of microbiology testing.

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CHAPTER 27

Human Papillomavirus and Cervical Dysplasia

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INTRODUCTION

Human papillomavirus (HPV) is one of the most common sexually transmitted infections (STIs) worldwide. Although usually sub-clinical, HPV infection may cause abnormal Papanicolaou (Pap) tests, genital condylomata (warts), cervical dysplasia, and cervical cancer. Of the 100 HPV types that have been identified, approximately 40 of these infect the genital tract. These are classified as high-risk types, which may cause abnormal Pap tests and anogenital cancers, and low-risk types, which may cause genital warts. New information about the natural history of HPV infection in adolescent and young adult women and new technologies for Pap and HPV testing have led to revised recommendations for cervical cancer screening and prevention. Prophylactic HPV vaccines may become a highly effective strategy for prevention of HPV infection and HPV-related disease.

DEFINITIONS

HPV: Human papillomavirus is a DNA virus of the Papillomaviridae family that preferentially infects epithelial cells.

Cutaneous HPV: Types of HPV that cause plantar and common skin warts.

Mucosal HPV: High-risk and low-risk types of HPV that infect the epithelium of the anogenital and aerodigestive tracts.

Low-risk HPV: Types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, and 81 may cause abnormal Pap tests, genital warts (i.e., genital condylomata), and recurrent respiratory papillomatosis.

High-risk HPV: Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 may cause cervical, other anogenital, oral, esophageal, head, and neck cancers. Type 16 causes 40–60% and type 18 causes 10–20% of cervical cancer.

Recurrent respiratory papillomatosis (RRP): Rare complication of maternal-neonatal HPV transmission that may cause upper airway obstruction in infants and young children.

Papanicolaou (Pap) test: Evaluates exfoliated cervical epithelial cells as a screening test for cervical cancer and yields a cytological diagnosis.

Cervical ectopy: Normal extension of the endocervical columnar epithelium onto the ectocervix, commonly seen in adolescents. The transformation zone, where columnar cells are replaced by squamous epithelial cells, is particularly prone to HPV infection.

Squamous metaplasia: Process in which columnar epithelial cells mature into squamous epithelium.

Cervical dysplasia: Histological diagnosis of cervical intraepithelial neoplasia (CIN) made on cervical biopsy that ranges in severity from mild (CIN 1) to moderate (CIN 2) to severe (CIN 3, or carcinoma in situ).

PATHOPHYSIOLOGY

Transmission of anogenital HPV occurs primarily through sexual intercourse when there is a break in the integrity of the skin or mucosal surface. Adolescents may be at higher risk than adult women for HPV infection because of cervical ectopy and squamous metaplasia (see previous), which facilitate HPV replication and protein expression. Hormonal factors, such as pregnancy, may increase the risk of HPV infection by maintaining the transformation zone of the ectocervix and may influence disease progression by modulating the host immune response to infection. Vertical transmission from infected mothers to neonates and transmission through casual, nonsexual contact can occur, but the rates are thought to be low.

Figure 27-1 summarizes the classification system for HPV. More than 95% of genital warts and RRP contain HPV types 6 and/or 11. Almost all cervical cancers contain at least one high-risk HPV type, and approximately 70% contain types 16, 18, or both. Of note, terminology differs for the cytological diagnosis made on Pap test and the histological diagnosis made on cervical biopsy. The terminology for the cytological diagnosis is based on the 2001 Bethesda system (Table 27-1).

Although cervical HPV infection and abnormal Pap tests are common, progression to cervical cancer is rare. There are two main reasons for this. First, effective Pap screening and treatment of CIN prevents progression from precancerous lesions to cervical cancer. Second, in most women with high-risk HPV, host immune responses appear to prevent the active viral replication required for persistent infection, which is a prerequisite for the development of high-grade squamous intraepithelial lesion (HSIL), CIN 2, CIN 3, and cervical cancer. The median incubation period from initial HPV infection to carcinoma in situ is estimated to be 7 to 12 years.

Most HPV infections in adolescent and young adult women are subclinical and resolve spontaneously. Prospective studies of adolescent females following infection demonstrate spontaneous clearing of low-risk HPV types in 90% of subjects at a median of 170 days, and of high-risk HPV types in 75% at a median of 226 days. The 10% of subjects with persistent high-risk HPV were 14 times more likely to develop HSIL than those who cleared the infection. The average time from infection to development of HSIL was 20 months. The high rate of spontaneous resolution of the infection, the long lag time between infection and dysplasia, and the widespread use of the Pap test explain why the incidence rates of cervical cancer in the United States are only 1.3/100,000 at ages 20–24 years and 0 at ages 15–19 years.

The natural history of genital warts is unpredictable. They usually appear 2–3 months after infection, but viral latency within the cell can delay their appearance for years. Most resolve spontaneously over months to years, but their duration, size, and number are highly variable.

EPIDEMIOLOGY

An estimated 20 million individuals in the United States are infected with sexually transmitted HPV, and 6 million new infections occur each year. Initial visits to physicians' offices for genital warts rose from 56,000 in 1966 to 264,000 in 2003, and U.S. health care costs associated with HPV-related disease now exceed $6 billion dollars annually. HPV prevalence is highest among sexually active adolescent and young adult women (51–82%) and then declines over the third to sixth decades of life. Among U.S.

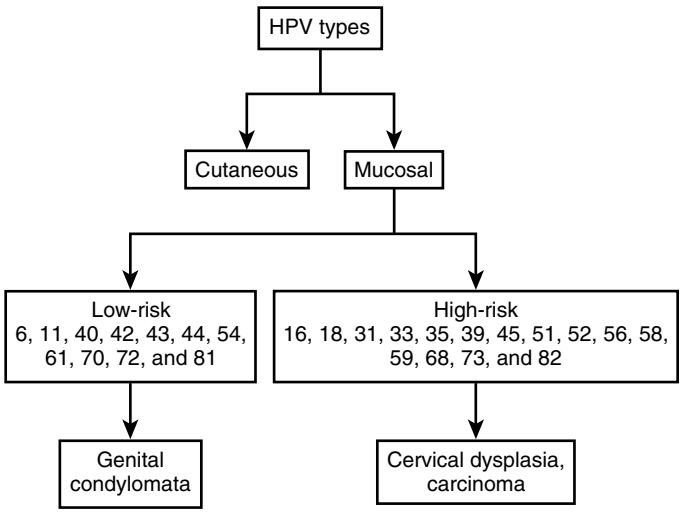

Figure 27-1 Classification of HPV types.
Adapted from: Munoz N Bosch FX, de Sanjose S, et al.: Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003;348:518–527.

Table 27-1 Classification of Cervical Cytology Results by the Bethesda System[a]

Category	Classification
I. Specimen adequacy	A. Satisfactory for evaluation B. Unsatisfactory for evaluation
II. General categorization	A. Negative for intraepithelial lesion or malignancy B. Epithelial cell abnormality
III. Interpretation/Result	A. Negative for intraepithelial lesion or malignancy (including infectious organisms and reactive cellular changes associated with inflammation) B. Epithelial cell abnormalities 1. Squamous cell a. Atypical squamous cells (ASC)[b] of undetermined significance (ASC-US) cannot exclude high-grade squamous intraepithelial lesion (ASC-H) b. Low-grade squamous intraepithelial lesion (LSIL). Includes HPV, mild dysplasia, and CIN[c] 1 c. High-grade squamous intraepithelial lesion (HSIL). Includes moderate and severe dysplasia, CIS[d], CIN 2, CIN 3 d. Squamous cell carcinoma 2. Glandular cell a. Atypical glandular cells (AGC) b. Atypical glandular cells, favor neoplastic c. Endocervical adenocarcinoma in situ (AIS)

[a]Revised 2001.
[b]In the revised Bethesda System, the category previously termed ASCUS (atypical squamous cells of undetermined significance) is subdivided into ASC-US and ASC-H.
[c]Cervical intraepithelial neoplasia.
[d]Carcinoma in situ.
Adapted from: Solomon D, Davey D, Kurman R et al.:The 2001 Bethesda System:Terminology for reporting results of cervical cytology. JAMA 2002;287:2114–2119.

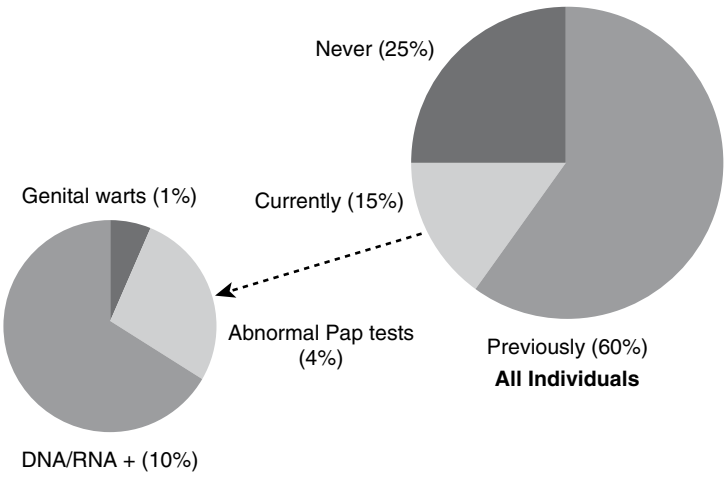

Figure 27–2 Prevalence of genital HPV infection in U.S. population aged 15–49 years.
Adapted from: Koutsky L: Epidemiology of genital human papillomavirus infection. Am J Med 1997;102:3–8.

males and females age 15–49 years, 60% were previously infected with HPV, 15% are currently infected, and 25% are uninfected. Of the 15% currently infected, 10% have subclinical infection as evidenced by HPV DNA or RNA positivity. Another 1% have genital warts, and 4% have abnormal cervical cytology (Figure 27-2).

Risk factors for HPV infection and the progression of HPV-related disease are noted in Boxes 27-1 and 27-2, respectively. Although condom use may not protect against HPV infection, consistent use promotes viral clearance and decreases the likelihood of HPV-related disease. HIV infection and organ transplantation with resulting T-cell deficiency, T-cell dysfunction, and altered cytokine expression are important risk factors for HPV infection and the development of HPV-related disease.

Prevalence trends by age for HPV-related abnormal Pap tests depend on the specific cytological result. The trend for low-grade squamous intraepithelial lesion (LSIL)

Box 27-1 Risk Factors for HPV Infection

- Young age at first intercourse
- Older partner age
- Increased numbers of partners and partners' partners
- Sexual abuse
- Herpes simplex virus 2 (HSV-2) infection
- Cigarette smoking
- Immunosuppression

Box 27-2 Risk Factors for the Development of HPV-Related Disease

- Immunosuppression
- No or inconsistent condom use
- Deficiency of micronutrients (e.g., folate)
- Hormonal contraception
- Pregnancy and parity
- HSV-2 and/or chlamydia infection
- Cigarette smoking
- Viral factors (e.g., HPV genotype, viral load)

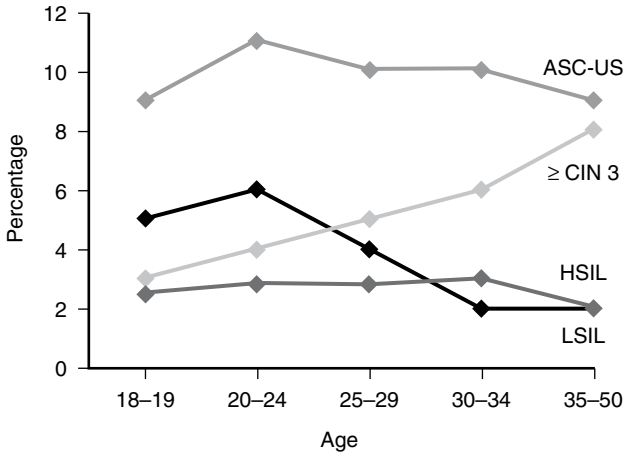

Figure 27–3 Cervical cytology by age.
Adapted from: Kulasingam SL, Hughes JP, Kiviat NB, et al.: Evaluation of human papillomavirus testing in primary screening for cervical abnormalities: Comparison of sensitivity, specificity, and frequency of referral. JAMA 2002; 288:1749–1757.

is similar to that for HPV infection, with a decline in the third decade (Figure 27-3). Trends for HSIL and ASC-US remain relatively stable with age, whereas the prevalence of cervical carcinoma increases with age from the early 20s to 50s. Despite a dramatic decline in the incidence of cervical cancer over the past 50 years due to widespread Pap screening and treatment of precancerous lesions, cervical cancer is still the fourth most commonly diagnosed cancer among women in more developed regions of the world and the second most commonly diagnosed cancer among women in less developed countries.

EVALUATION

The evaluation of an adolescent with known or suspected HPV infection begins with a history and physical examination. The history should explore risk factors for HPV acquisition, transmission, and disease development. The evaluation of a patient with anogenital warts and recommendations for cervical cancer screening during adolescence are discussed later.

Anogenital Warts

HPV-related anogenital warts may appear as cauliflower-shaped growths (i.e., condylomata acuminata); smooth, raised papules; thick keratoses resembling common skin warts; and/or small, flat-topped lesions (Box 27-3 and Figure 27-4). In women, they may occur on the vulva, vagina, cervix, perineum, and perianal areas. In men, they may occur on the inner surface of the prepuce, frenulum, penile shaft, glans, scotum, and anus. Genital warts are usually asymptomatic but occasionally cause pruritus, burning, pain, bleeding, or vaginal discharge.

The differential diagnosis of genital warts includes micropapillomatosis labialis, pearly penile papules, seborrheic keratosis, condyloma latum (i.e., secondary syphilis), molluscum contagiosum, and granuloma inguinale. Micropapillomatosis labialis involves the labia majora and consists of small papular projections, each with its own separate base, which differentiates it from condylomata acuminata. Pearly penile papules occur on the corona and are considered a normal finding. Seborrheic keratoses are wartlike, pigmented, benign, and usually asymp-

Box 27-3 HPV-Related Anogenital Warts

Condylomata acuminate:	Cauliflower-shaped growths with finger-like projections
Papular:	1–4 mm, smooth, well-circumscribed
Keratotic:	Thick; resemble a common skin wart
Flat-topped papules:	Small; difficult to detect

Figure 27-4 Genital warts (photograph).
Published previously in: Kahn JA, Hillard PA: Human papillomavirus and cervical cytology in adolescents. Adolesc Med Clin 2004;15:301–321.

tomatic. The mucocutaneous lesions of secondary syphilis may be difficult to distinguish from genital warts without laboratory testing. Molluscum contagiosum is a benign, self-limited eruption of multiple small, umbilicated, cutaneous papules. Granuloma inguinale is caused by sexual acquisition of *Calymmatobacterium granulomatis* and is diagnosed by the microscopic finding of Donovan bodies on tissue smear or biopsy. Lastly, vulvar intraepithelial neoplasia or cancer can be confused with genital warts. Biopsy of genital warts is usually not necessary unless the diagnosis is unclear or there is substantial hyperpigmentation, ulceration, or suspicion of cancer.

Cervical Cancer Screening

Since the 1927 introduction of the Pap test, mortality from cervical cancer has decreased 70%. The major limitation of the Pap test is its false-negative rate due to errors in sampling and interpretation. Liquid-based cytological screening, such as ThinPrep 2000 (Cytyc Corporation, Marlborough, MA) and SurePath (TriPath Imaging, Burlington, NC), initially were thought to decrease the false-negative rate, but a recent meta-analysis revealed no improvement over conventional Pap tests. Consequently, the American Cancer Society (ACS) and the American College of Obstetricians and Gynecologists (ACOG) endorse both the traditional Pap and liquid-based testing. If the traditional Pap test is used for screening, it should be performed yearly. If liquid-based cytological testing is used, it may be performed every 2 years if noncompliance with follow-up is not a concern. Cervicography, or high-resolution photography of the cervix after application of acetic acid, is designed to enhance the diagnosis of severe dysplasia but is costly and of low predictive value in adolescents.

Evidence of the causal association between HPV infection, cervical dysplasia, and cervical cancer has led to the increasing use of HPV DNA testing as an adjunct to the Pap test. In women with ASC-US, HPV DNA testing is more sensitive than repeat Pap testing for the detection of high-grade cervical dysplasia (83% vs. 67%). DNA testing is not helpful in women with LSIL because 80% are positive for high-risk HPV types. Given these results, high-risk HPV DNA testing is now commonly used as an adjunct to Pap testing to determine which women with ASC-US should undergo colposcopy. Hybrid Capture II (Digene, Gaithersburg, MD) is a hybridization/signal-amplification test that detects 13 high-risk HPV types and is commercially available in the United States.

HPV DNA testing may offer a strategy for primary screening in parts of the world where pelvic examination for Pap testing is not feasible. Self-collected vaginal swabs yield test results similar to those of clinician-collected samples in both adults and adolescents. However, studies in the United States suggest that adults and adolescents differ in their preferences for self- vs. clinician-testing. Adult women prefer self-testing, whereas adolescents prefer clinician-testing and express concern about their ability to self-collect correctly.

The ACS has issued special guidelines for cervical cancer screening in adolescents. The guidelines were developed in response to data demonstrating a difference in the natural history of HPV in adolescent and adult women. Although HPV infection is very common in sexually active adolescents, LSIL in adolescents usually regresses spontaneously and the development of cervical cancer during adolescence is extremely rare. The traditional initiation of Pap screening at the onset of sexual activity therefore might lead to unnecessary procedures to evaluate abnormal results. The revised ACS guidelines recommend the initiation of Pap screening 3 years after sexual initiation or by 21 years of age, followed by annual screening if the conventional Pap smear is used and testing every 2 years if the liquid-based Pap smear is used. ACOG guidelines also note that clinicians should consider the likelihood of sexual abuse, sexual risk behaviors, and adherence to follow-up in deciding when to initiate screening.

In adolescents newly diagnosed with human immunodeficiency virus (HIV) infection, the ACS recommends Pap testing twice in the year after diagnosis and, if negative, annually thereafter. If sexual abuse involving vaginal intercourse has occurred, a clinician accustomed to examining abused children and adolescents should initiate screening when the patient's emotional and physical comfort allow the speculum examination. Regardless of an adolescent's need for Pap testing, the ACS and ACOG emphasize the importance of providing routine STI screening, contraceptive counseling, and other preventive health care services.

MANAGEMENT

Genital Warts

Spontaneous resolution of genital warts occurs in 40% of cases, and there is no evidence that treatment diminishes viral transmission. HPV-related genital warts are benign lesions, do *not* progress to malignancy, and should not be treated or removed in an effort to prevent cancer if the diagnosis is certain. However, if the diagnosis is uncertain and the lesion raises concern about vulvar intraepithelial neoplasia or squamous cell carcinoma, excisional biopsy is essential. This is particularly important in patients who are at increased risk for mucocutaneous malignancies, such as those with immunosuppression and HIV infection.

Many patients with genital warts request treatment for cosmetic reasons or, less commonly, because of pain or itching associated with the lesions. After education about the natural history of genital warts and the transmission of HPV, patient- or clinician-applied treatment (but not both simultaneously) can be prescribed (Tables 27-2 and 27-3). Of note, topical 5-flourouracil cream, interferon, and podophyllin 10–25% resin are no longer recommended for the treatment of genital warts.

There are two options for the home-based, patient-applied treatment of genital warts. One, not both, of the following options should be prescribed at any given time:

- Podofilox 0.5% solution or gel is applied to genital warts twice daily for 3 days, followed by 4 days of no therapy. The total treated surface area should not exceed 10 cm^2, and a maximum of 0.5 ml should be applied daily. Podofilox should not be used in the vagina or anus and is contraindicated in pregnancy.
- Imiquimod 5% cream is applied to genital warts 3 nights weekly for up to 16 weeks. Patients should be instructed to wash off the cream with soap and water the morning after application. There is no surface area limitation to its use. Imiquimod has not been evaluated for use in the vagina or anus, and its safety profile during pregnancy is unknown.

There are three options for the office-based treatment of genital warts by a clinician. Only one of the three options is indicated at any given time:

- Trichloroacetic acid 80–90% is applied to anogenital warts of the skin or mucosal surfaces of the vagina, cervix, penis, periurethra, perineum, and anus.

Table 27-2 Patient-Applied Treatment of Genital Warts

Patient-Applied	Clearance Rates (%)	Recurrence Rates (%)	Advantages	Disadvantages
Podofilox 0.5% solution or gel	45–88	4–38	May be applied at home. Easy to apply.	Possible toxic systemic effects. Not useful for cervical or mucosal lesions. Erosion, burning, pain, itching.
Imiquimod 5% cream	27–54	13–19	May be applied at home. Can be applied to new warts as they appear.	Takes up to 16 weeks to treat. Local erythema, erosion, burning, pain, and itching.

Table 27-3 Provider-Applied Treatment of Genital Warts

Provider-Applied	Clearance Rates (%)	Recurrence Rates (%)	Advantages	Disadvantages
Trichloroacetic acid or bichloroacetic acid 80–90%	50–80	35	Inexpensive. Easy to apply. Safe in pregnancy.	Pain on application. Destroys normal tissue if over-applied.
Cryotherapy	27–88	21–40	Well-tolerated. Useful for most warts. Safe in pregnancy. Minimal scarring.	Pain, necrosis, blistering. Over-application leads to complications. Under-application leads to poor results.
Surgical removal	35–72	19–29	Useful for extensive disease. Safe in pregnancy.	Expensive. Requires hospital setting and expertise. Scarring. Risk of bleeding.

- Cryotherapy is indicated for the treatment of genital warts of the external genitalia and cervix but should be avoided in the vagina or anus because of possible fistula or scar formation. Nitric oxide is applied to warts of the external genitalia, and nitrous oxide is applied to warts of the cervix.
- Surgical removal or laser therapy is indicated for genital warts that are large, multifocal, or unresponsive to other therapies.

Abnormal Pap Tests

Interpretation of the Pap test begins with an adequate cytological sample. A Pap test that reveals no endocervical cells should be repeated. If the Pap test reveals inflammation, the patient should be evaluated for sexually transmitted or other infections (e.g., vaginal candidiasis) and the Pap test should be repeated 2–3 months after appropriate treatment.

The management of abnormal Pap tests has changed considerably since the availability of HPV DNA testing. Guidelines of the American Society for Colposcopy and Cervical Pathology (ASCCP), ACS, and ACOG for the management of immunocompetent patients with ASC-US, ASC-H, LSIL, and HSIL are summarized in the following discussion. Immunosuppressed or HIV-infected patients with these lesions should always be referred for prompt colposcopy.

ASC-US: Recommendations for the management of adolescents with ASC-US on Pap testing have changed along with our understanding of the natural history of HPV infection in this age group. Given the likelihood of spontaneous resolution of high-risk HPV during adolescence, ACOG suggests that adolescents with ASC-US, even if positive for high-risk HPV types, may be followed with either repeat Pap testing at 6 and 12 months or a single HPV test at 12 months. Until late 2007, ASCCP recommended reflex HPV DNA testing for patients with ASC-US and colposcopy if the testing revealed high-risk HPV types. Revised recommendations, expected shortly, are expected to call for annual Pap testing without HPV testing and referral to colposcopy only if the Pap test is persistently abnormal for 24 months.

ASC-H: Immediate colposcopy is recommended for adults and adolescents with Pap test results of atypical squamous cells in which HSIL cannot be excluded.

LSIL: ASCCP and ACOG recommendations for the management of LSIL depend on patient age. For adults, colposcopy is recommended. For adolescents, revised recommendations are expected to follow the same path as that described above for ASC-US: annual Pap testing without HPV testing and referral to colposcopy only if the Pap test is persistently abnormal for 24 months.

HSIL: Immediate colposcopy is recommended for adults and adolescents with HSIL.

Colposcopy

Colposcopy allows magnified examination of the cervix and lower genital tract for the detection and biopsy of epithelial lesions that are potentially dysplastic or malignant. It is particularly important to visualize the junction between the squamous epithelium of the ectocervix and the columnar epithelium of the endocervix. Adolescents should be encouraged to inform parents when colposcopy is recommended, and a preprocedure visit should allow adequate time for patient education, STI testing, and treatment of positive results.

The treatment of CIN 2 or CIN 3 diagnosed on colposcopically directed biopsy depends on patient age, lesion size, and lesion distribution. ACOG guidelines state that adolescents with CIN 2 who adhere to follow-up visits can be followed with observation alone. Ablative or excisional therapy is indicated for adolescents with CIN 2 who cannot adhere to follow-up, all adolescents with CIN 3, and all adults with CIN 2 or CIN 3. Ablative procedures include cryotherapy and carbon dioxide laser. Excisional procedures include cold knife conization and loop electrosurgical excision procedure (LEEP).

Patient Education

Although HPV infection is extremely common, the risk of acquiring HPV and developing HPV-related diseases can be decreased by practicing safe sexual behaviors and obtaining regular Pap screening. Health care providers must educate adolescents about HPV infection, its transmission, its sequelae, and prevention strategies. Adolescents should understand that HPV infection is acquired through sexual contact, not necessarily penetrative sexual intercourse. Clinicians should encourage adolescents to postpone sexual initiation, limit their number of sexual partners, use condoms consistently, and avoid tobacco use. In addition, providers should provide clear recommendations for Pap screening.

HPV VACCINES

Prophylactic HPV vaccines designed to prevent HPV acquisition may provide a strategy for primary prevention. Two types of vaccine have been developed. One is a bivalent vaccine designed to protect women against infection caused by Types 16 and 18 and is predicted to

prevent 70% of cervical cancer in vaccinated females. The other is a quadrivalent vaccine that includes Types 6 and 11, as well as Types 16 and 18. It therefore could prevent most genital warts and RRP, as well as most cervical cancer.

Both the bivalent and quadrivalent vaccines are comprised of capsid proteins from each of the component HPV types. These proteins can self-assemble into virus-like particles that induce a neutralizing antibody response. The vaccines do not contain any viral DNA and therefore cannot cause HPV infection or HPV-related diseases. Clinical trials have demonstrated that both vaccines have few side effects, are well tolerated, and are highly effective in preventing HPV infection and HPV-related CIN. However, counseling patients about safe sexual behaviors and regular Pap screening remains important, because vaccines are not 100% protective against either HPV infection or the development of cervical cancer.

MAJOR POINTS

- In adolescence, HPV prevalence is high and infection occurs rapidly after sexual initiation.
- Infection may be asymptomatic or transient, or lead to adverse sequelae.
- HPV types 6 and 11 are the most common types associated with the development of external lesions such as genital warts.
- HPV types 16 and 18 are the most common types associated with the development of abnormal cervical cytology and cervical cancer.
- Adolescents should be screened for abnormal cervical cytology approximately 3 years after first sexual intercourse or by the age of 21 years, whichever occurs first.
- HPV infection and LSIL have high rates of regression in the adolescent population.
- Persistent infection with high-risk HPV types may lead to cervical cancer.
- Adolescents should be educated about HPV infection, prevention, and potential sequelae.
- HPV vaccination is likely to provide significant but incomplete protection against HPV infection and HPV-related disease.
- The Centers for Disease Control and Prevention *(http://www.cdc.gov)* and the American Society for Colposcopy and Cervical Pathology *(http://www.asccp.org)* maintain up-to-date web sites on the evaluation and management of HPV-related disease.

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CHAPTER 28

Genital Ulcer Disease: Herpes Simplex Virus, Syphilis, and Chancroid

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INTRODUCTION

Genital ulcer disease (GUD) is a general term that usually refers to lesions caused by specific sexually transmitted infections (STIs). Although GUD is common throughout the world, the specific causes vary widely by geographic region. Genital herpes, syphilis, and chancroid lead the differential diagnosis, but conditions unrelated to STIs should also be considered, such as trauma, Stevens-Johnson syndrome, Beçhet syndrome, Crohn disease, carcinoma, and bacterial infection. In 25% of cases, no etiology is identified. When the cause is unknown or diagnostic testing is unavailable, the World Health Organization (WHO) recommends the use of epidemiologic data to guide presumptive treatment for the most prevalent organism(s) in the geographic region.

Risk factors for GUD include male gender, lack of circumcision, sexual risk behaviors, and infection with human immunodeficiency virus (HIV). The discrepancy by gender may reflect the higher rates of hidden, asymptomatic, and undiagnosed GUD in women than men due to anatomy, access to care, and social stigma. The association of GUD with HIV warrants HIV testing at presentation and, if negative, at 3–6 months.

This chapter focuses on the three leading causes of GUD in the United States: genital herpes, syphilis, and chancroid.

GENITAL HERPES

Epidemiology

Genital herpes is caused by herpes simplex virus (HSV) Type 1 (HSV-1) and Type 2 (HSV-2). The most common cause of the first symptomatic episode of genital herpes among adults is HSV-2 in the United States and HSV-1 in the United Kingdom. An estimated 45 million people in the United States have genital infections with HSV-1 and/or HSV-2. Annual visits to physician offices in the United States for first episodes of genital herpes have increased 14-fold in 40 years, from less than 19,000 to more than 269,000 (Figure 28-1).

HSV-1 and HSV-2 both can infect the oral and/or genital areas. HSV-1 can be transmitted through sexual or nonsexual contact and is the most common cause of oral herpes. HSV-2 is almost always transmitted through sexual contact, regardless of site, and accounts for at least 70% of genital herpes in the United States. Among individuals aged 12–25 years, seropositivity rates are 30–70% for HSV-1 antibody and 10–30% for HSV-2 antibody.

HSV-1 seropositivity increases from 44% in individuals aged 12–19 years to 56% in those aged 20–29 years to 90% in those aged 60–69 years. Factors associated with HSV-1 seropositivity include female gender, Hispanic ethnicity, black race, poverty, crowded living conditions, and HSV-2 seropositivity. Genital infection with HSV-1 is

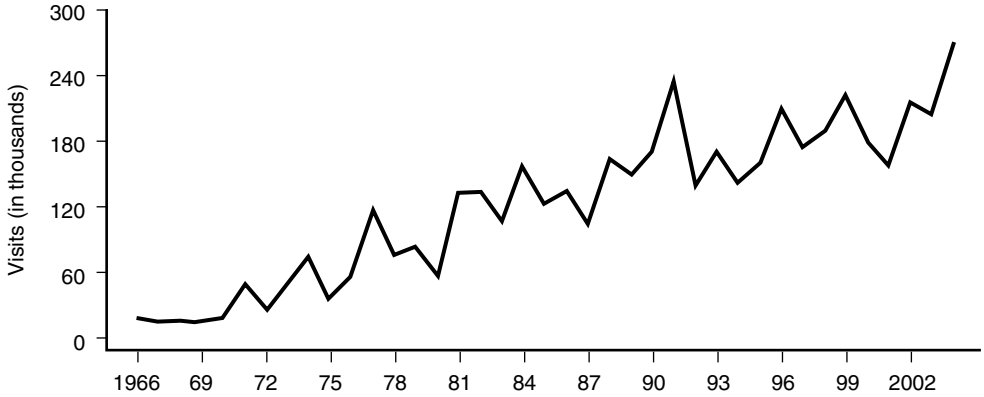

Figure 28-1 Initial visits to physicians' offices for genital herpes, United States, 1966–2004. From: Centers for Disease Control and Prevention: *Sexually Transmitted Disease Surveillance, 2004*. Atlanta, GA, U.S. Department of Health and Human Services, September, 2005, Figure 39.

associated with receptive oral sex, and the proportion of genital herpes cases caused by HSV-1 appears to be increasing over time. Oral HSV-1 infection appears to protect against genital HSV-1 infection and to attenuate the symptoms of genital HSV-2 infection.

In contrast to the significant rates of HSV-1 seropositivity among prepubertal children, HSV-2 seropositivity is unusual until adolescence. The prevalence of HSV-2 seropositivity then increases quickly, from 6% among individuals aged 12–19 years to 17% among those aged 20–29 years. Unlike the continued increase in HSV-1 with age, HSV-2 seropositivity reaches a plateau of 24–28% by age 30 years. Factors associated with HSV-2 seropositivity include female gender, Hispanic ethnicity, black race, low socioeconomic status, increased number of lifetime sexual partners, history of other STIs, and cocaine use. HSV-2 transmission is more efficient from male to female than the reverse. Among couples who are discordant for infection, the rate of transmission is approximately 12% per year. Viral shedding and transmission can occur at any time but are most common during symptomatic outbreaks. Although only 10% of seropositive individuals report past symptoms, studies suggest that recall increases significantly following patient education about the clinical manifestation of genital herpes.

Pathophysiology

Acquisition of HSV is thought to require direct contact of the mucosa or broken skin with infected secretions. In the active state, the virus replicates in the epidermis and dermis, causing local inflammation and cellular destruction. The virus can spread through the lymphatic system to regional lymph nodes, travel along peripheral axons to sensory nerve root ganglia, and replicate within neural tissue. Local inoculation can also spread the virus beyond the primary site of infection. In the case of HSV-1, the virus can travel along neurons to the brain, causing encephalitis. Immunocompetent hosts with intact immune systems usually can control the infection and the lesions heal.

After the initial infection, HSV resides in a latent phase within the nerve root ganglion until there is a stimulus for reactivation, such as ultraviolet light, local trauma, fever, or immunosuppression. Reactivation severity correlates with the quantity of replicating virus and the immunologic status of the host. Although humeral immunity plays a role in containing HSV infection, cell-mediated immunity appears to be the most important mechanism.

Genital HSV infections are categorized according to the presence or absence of pre-existing, type-specific, serum antibodies. Primary infection occurs in the absence of antibodies to either HSV-1 or HSV-2. Non-primary infection occurs in the absence of antibodies to the current HSV type and the presence of antibodies to the other HSV type (e.g., first HSV-2 infection in an individual with pre-existing antibodies to HSV-1). Recurrent infection (i.e., reactivation) occurs in the presence of antibodies to the current HSV type.

Primary genital herpes is characterized by painful skin and/or mucosal lesions accompanied by systemic symptoms (e.g., fever, headache, mylagias, and malaise) in 40% of males and 70% of females. The lesions begin as papules and develop into clustered pustules or vesicles on an erythematous base. The pain begins within several days of appearance, as the lesions become ulcers with serous drainage. Up to 95% of males and 99% of females with primary genital HSV infection have these painful lesions, which persist with viral shedding for a mean of 11 days in males and 12 days in females. Mucosal re-epithelialization and nonmucosal crusting begins 4–15 days after appearance of the lesions, with complete healing within 17 days in males and 20 days in females. Systemic symptoms tend

to be most severe during the first week of illness but can persist with regional lymphadenopathy for up to 3 weeks.

Other symptoms that can accompany primary HSV infection include dysuria, urinary urgency, and urethral discharge in males. Superinfection of ulcerated lesions can occur in females, and proctitis with rectal pain, bloody or mucoid discharge, tenesmus, and constipation can occur in males and females. HSV is the most common cause of nongonococcal proctitis in males. In contrast to gonococcal proctitis, HSV proctitis often presents as a sacral neuropathy with urinary retention, constipation, and perineal dysesthesia. Proctitis may be found in women and heterosexual men who deny anal intercourse and can be associated with perianal lesions.

Extragential manifestations of primary genital herpes include pharyngitis, other skin lesions, and central nervous system (CNS) complications. Pharyngitis, which is associated with oral–genital exposure, can manifest as mild erythema to diffuse ulceration with cervical lymphadenopathy and may be associated with tender cervical nodes. Skin lesions can occur in nongenital locations such as the buttock, groin, thigh, and finger and are usually spread by autoinoculation. CNS complications include aseptic meningitis, transverse myelitis, sacral radiculopathy, and encephalitis. The stiff neck, headache, and photophobia of aseptic meningitis usually begin 3–12 days after the onset of genital lesions and resolve within 1 week. Encephalitis is more likely to be associated with HSV-1 than HSV-2 infection.

HSV does not usually disseminate in immunocompetent patients, but maternal genital herpes at the time of vaginal delivery does pose a significant risk to the infant. Patients with severe atopic dermatitis and other generalized skin disorders are also at risk of dissemination.

Recurrent genital herpes outbreaks are usually shorter, milder, and more localized than the primary outbreak. Prodromal symptoms are common and include pain in the buttocks or legs for hours to days before the appearance of the skin lesions, which tend to be unilateral. Viral shedding lasts approximately 4 days, crusting begins within 4–5 days, and re-epithelialization is completed within 6–10 days. Recurrences tend to be more severe in females than males. The vaginal ulcerations of recurrent HSV may be confused with trauma or vaginitis because of their often linear appearance.

Recurrences affect 60–90% of individuals within 1–2 years of the primary HSV-2 outbreak, with a median of five recurrences in males and four in females during this time period. Those with longer primary episodes tend to have more recurrences, possibly because more ganglionic cells are infected. Viral shedding occurs in up to one-half of subclinical HSV reactivation episodes, with the highest rates of these episodes in the 6 months following primary infection. Asymptomatic shedding can come from small lesions of the cervix, vulva, urethra, penis, and anus. Over time, the duration of subclinical shedding decreases.

Immunocompromise and pregnancy are associated with more severe clinical outbreaks. Immunocompromised patients have clinical infections that persist for longer periods of time, are slower to respond to antiviral therapy, and are associated with prolonged shedding of virus.The major concern with HSV infection during pregnancy is transmission to the neonate during delivery. The risk of transmission is 50% for primary HSV-2 without prior HSV-1, 20% for primary HSV-2 with prior HSV-1, and < 1% for recurrent HSV-2, as maternal HSV-2 antibodies appear to protect the infant.

Evaluation

HSV culture is currently considered the gold standard for confirmation of suspected genital herpes. Its sensitivity depends on the type of lesion from which the specimen is collected. HSV culture is 90–94% sensitive for new vesicular lesions, 70% for ulcers, and 20–30% for crusted lesions. Most culture results are available in 1–4 days, and the viral type can be determined utilizing immunofluorescent techniques. Because a negative culture does not rule out HSV infection, repeat cultures should be performed during subsequent episodes to increase detection rates.

HSV is part of a promising polymerase chain reaction (PCR) multiplex test that is not yet commercially available for clinical use. The test uses a specimen collected from a lesion and detects syphilis and chancroid as well as HSV. HSV antigen can also be detected by direct immunofluorescence and immunoperoxidase staining, but their sensitivities are lower at 70–90%. Cytologic examination with Tzanck preparation for multinucleated giant cells and Pap smear are not considered reliable.

Serologic testing is not routinely used to confirm genital herpes because seroconversion in primary infection can take up to 3 weeks and recurrent infection may not produce a rise in titer. Newer serologic assays, which are glycoprotein G (gG)-based type-specific have specificities of greater than 96% and sensitivities of 80–98%. Despite these improvements, these serologic tests, which are based in enzyme-linked immunosorbent assay (ELISA) and immunoblot assays, should be utilized cautiously because they can give both false-negative and false-positive results. Serologic tests are most useful for diagnosing unrecognized infection and to confirm a clinical diagnosis in the face of a negative culture. Although finding HSV-2 usually indicates an STI, these tests do not help distinguish modes of transmission for HSV-1 infection. There are also suggestions in the literature that screening pregnant women may identify individuals who are seronegative in the face of a seropositive partner. This would help determine the risk for acquisition

and transmission to the neonate and allow better counseling on prevention.

Management

All patients with genital herpes should be advised to inform sexual partners and to avoid sexual contact during the prodromal and active phases of infection. Asymptomatic shedding does occur, and it is important for partners to understand the ongoing risk of transmission.

Systemic antiviral therapy with acyclovir, valacyclovir, or famciclovir is recommended for primary and recurrent genital herpes, although the dosing schedules vary (Table 28-1). HSV-infected cells selectively phosphorylate these antiviral medications, which are incorporated into the DNA of the virus and lead to chain termination. Treatment of an acute episode decreases symptom duration, symptom severity, viral shedding, and new lesion formation. It should be started when active lesions are present and preferably within 1 week of lesion onset in primary infection and within 1 day of lesion onset in recurrent infection. Symptomatic improvement usually begins within 48 hours, but the medication does not decrease the likelihood of recurrence once it is discontinued.

Suppressive therapy can reduce recurrent episodes by 70–80% and is recommended for individuals with six or more recurrences yearly. Valacyclovir at a higher dose (i.e., 1 g daily) may be needed for individuals with 10 or more recurrences per year. Because recurrences tend to decrease in frequency over time regardless of treatment, a trial off suppressive therapy should be considered at 1 year. Patients should understand that suppressive therapy does not eliminate viral shedding and that transmission to sexual partners may still occur.

Resistant strains of HSV have been identified in immunocompromised patients following prolonged or frequent antiviral therapy. In these cases, foscarnet may be given intravenously until there is clinical resolution.

Acyclovir is recommended by the Centers for Disease Control and Prevention (CDC) for pregnant women with primary genital herpes, a severe recurrence, and frequent recurrences. Obstetrical management guidelines call for cesarean section when active lesions or prodromal symptoms are present at the time of delivery. Although there have been studies evaluating the use of antivirals late in the third trimester and through delivery, there is no universal recommendation for their use in patients with recurrent episodes.

New HSV research developments include the use of topical microbicides to prevent HSV transmission and a prophylactic vaccine.

Table 28-1 CDC Treatment Guidelines for Genital Herpes Simplex Virus

	One of the Following Regimens	
	Drug	**Dose**
First clinical episode	Acyclovir	400 mg orally three times a day × 7–10 days
	Acyclovir	200 mg orally five times a day × 7–10 days
	Famciclovir	250 mg orally three times a day × 7–10 days
	Valacyclovir	1 g orally twice a day × 7–10 days
Episodic therapy for recurrent episodes	Acyclovir	400 mg orally three times a day × 5 days
	Acyclovir	800 mg orally twice a day × 5 days
	Acyclovir	800 mg orally three times a day × 2 days
	Famciclovir	125 mg orally twice a day × 5 days
	Famciclovir	1 g orally twice a day × 1 day
	Valacyclovir	500 mg orally twice a day for 3 days
	Valacyclovir	1 g orally once a day × 5 days
Suppressive therapy for recurrent episodes	Acyclovir	400 mg orally twice a day
	Famciclovir	250 mg orally twice a day
	Valacyclovir	500 mg orally once a day
	Valacyclovir	1 g orally once a day for 10 or more recurrences per year

From: Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines 2006. MMWR 2006;55(RR-11).

SYPHILIS

Epidemiology

In 1999, the CDC launched a National Plan to Eliminate Syphilis from the U.S. The rates of primary and secondary syphilis had been declining since the early 1990s, and the 2.1 cases per 100,000 population in the year 2000 was the lowest rate recorded in 60 years. Between 1992 and 2004, racial discrepancy in the rates of syphilis declined from a black:white ratio of 63:1 to 5.6:1; rates in the southern states decreased from 22.9 to 3.6 per 100,000; and the rates of primary and secondary syphilis among women, as well as congenital syphilis, declined significantly.

Between 2003 and 2004, latent syphilis declined 5–7%, rates in women did not change, and rates of both primary and secondary syphilis among men increased (Figure 28-2). Currently, the highest rates of syphilis are in women aged 20–24 years and men aged 35–39 years. In the year 2004, 41% of all U.S. cases of primary and secondary syphilis were among blacks, 48% of cases were in the southern states, and 21% of all U.S. counties accounted

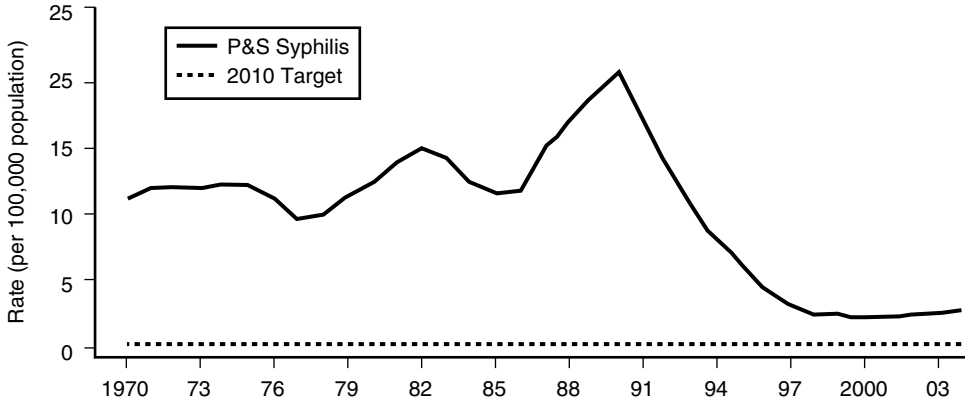

Figure 28-2 Trends in rates of primary and secondary syphilis in the United States, 1970–2004. From: Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance, 2004*. Atlanta, GA, U.S. Department of Health and Human Services, September, 2005, Figure 26.

for 100% of cases. Among individuals aged 15–19 and 20–24 years, the rates of syphilis were 1.7 and 5.0 per 100,000 population, respectively.

Syphilis is six times more common in men who have sex with men (MSM) compared with men who only have sex with women. Contributing factors include nonuse of condoms, anonymous partners, HIV infection, and methamphetamine use. Oral–genital sex was the only sexual contact reported by one-fifth of men who were newly infected with syphilis.

Pathophysiology

Treponema pallidum enters through breaks in the skin, attaching to and multiplying within host cells at the site of inoculation. Lymphatic and circulatory dissemination occurs within hours of infection and, even in this primary stage of infection, there is evidence of meningeal involvement. The primary, secondary, latent, and tertiary stages of syphilis are described below.

Primary syphilis is characterized by a chancre at the site of inoculation that appears 9–90 days (average 3 weeks) after exposure and resolves within several weeks without treatment. It begins as a papule that evolves into a sharply demarcated, indurated ulcer. Although usually painless and firm-based, it can be tender and purulent, particularly when coinfected with HSV or *Hemophilus ducreyi.* Nonsuppurative, painless, firm, bilateral inguinal lymphadenopathy may accompany the ulcer. The chancre is usually located on the coronal sulcus, glans, prepuce, or penile shaft in men and the labia or vagina in women. However, it can appear wherever abraded skin is exposed to infected secretions.

Secondary syphilis develops within a few weeks to months of the primary lesion and is characterized by circulating immune complex; a diffuse, nonpruritic, maculopapular rash involving the face, trunk, genitalia, palms, soles, and mucous membranes; headache; sore throat; fever; myalgias; malaise; and generalized lymphadenopathy. Less common manifestations include alopecia, arthritis, bursitis, osteitis, gastritis, hepatitis, meningitis, cranial nerve palsies, glomerulonephritis, iritis, uveitis, and retinitis. Secondary syphilis can also involve the formation of grayish skin masses with mucoid secretions that contain spirochetes, usually found on genitalia or the mouth. The lesions resolve in 2–10 weeks without treatment but in 25% of cases relapse within 1 year.

Latent syphilis can persist indefinitely. It is associated with seropositivity but no clinical manifestations of disease. Early latent syphilis is defined as less than 1 year and late latent syphilis as more than 1 year since infection.

Tertiary syphilis refers to diverse clinical manifestations, one or more of which appear in 25–40% of untreated individuals one to 30 years after initial infection. The most common tertiary presentations are gummatous syphilis, cardiovascular syphilis, and late neurosyphilis. Gummas are granulomatous, hypersensitivity reactions to the spirochete that begin as nodules and can progress to ulceration, atrophic scar formation, and fatal tissue destruction. Skin and bones are the most common sites of gumma formation, but nearly any organ can be involved. Cardiovascular syphilis includes obliterative end-arteritis and aortitis, which can lead to aortic aneurysm and aortic valve insufficiency. Tertiary neurosyphilis involves parenchymatous disease of the brain and spinal cord 15–20 years primary infection, with progressive mental illness, dementia, paresis, and tabes dorsalis. It is important to recognize that other CNS manifestations of syphilis may appear in the primary and secondary stages of disease. For example, asymptomatic meningitis (i.e., CSF abnormalities) can occur with primary infection and usually resolves spontaneously.

Neurosyphilis is a particular concern in HIV-infected individuals who appear to clear CSF abnormalities more slowly and are at risk for treatment failure and relapse. It is hypothesized that HIV impairs the immunologic clearance of the organism and that an intact immune system is needed, along with antibiotics, to eradicate the organism from the CNS.

Evaluation

T. pallidum can be identified by darkfield examination of lesion exudate or lymph node aspirate, direct fluorescent antibody testing of biopsy specimens, and PCR. However, darkfield examination is time-intensive and requires training and experience; biopsy generally is not clinically necessary; and PCR for *T. pallidum* is not commercially available. Most diagnoses of syphilis therefore are established by a combination of nontreponemal and treponemal serologic tests.

The nontreponemal tests are performed as the initial screen and include the Venereal Disease Research Laboratory (VDRL) and Rapid Plasma Reagin (RPR). The results are reported as quantitative antibody titers, which generally reflect disease activity. Titers are lower in primary than secondary syphilis and usually become undetectable following treatment. Some treated individuals, however, continue to have a low titer (referred to as a "serofast reaction"). The false-positive rate of 1–2% is associated with intravenous drug use, hepatitis, pregnancy, connective tissue disease, mononucleosis, other spirochetal infections, and malignancy. False-negative results occur when the test is performed too early in the course of the illness or when a blocking antibody prevents an accurate reading. Patients who are HIV-infected usually have accurate serologic test results.

Because of the possibility of a false positive, the nontreponemal test is followed-up and confirmed with a treponemal test. The commonly used tests include the fluorescent treponemal antibody absorbed (FTA-ABS) and the microhemaglutination assay (MHA-TP). The diagnosis of syphilis can be made when a positive nontreponemal test is confirmed by a treponemal test. It is important to note that treponemal tests are not always positive and in fact are negative in 10% of cases of primary syphilis. The treponemal test is almost always positive in the secondary stage of this illness. Once positive, treponemal tests usually stay positive for life and are indicative of past or present infection. However, some individuals do revert to a negative treponemal test when treated early in the course of the disease.

If a patient is presenting in the latent stage, it is important to determine whether it is early latent or late latent disease because therapy is different for each. If the timing of the history of a chancre or rash is not clear, it is better to err on the side of classifying the illness as late latent disease.

Patients with neurosyphilis have CSF abnormalities including elevated protein, mild leukocytosis of > 5 white blood cells (WBCs)/mm^3, and/or a reactive VDRL-CSF. A positive VDRL-CSF confirms the diagnosis of neurosyphilis, but up to 70% of individuals with neurosyphilis have a negative VDRL-CSF. In addition, patients with HIV infection may have mild CSF pleocytosis on the basis of HIV, which confounds the diagnosis of neurosyphilis. False-positive VDRL-CSF can occur with blood contamination of the CSF. Some authors recommend a CSF FTA-ABS, which is less specific but more sensitive than the VDRL-CSF. A negative CSF FTA-ABS is believed to effectively exclude the diagnosis of neurosyphilis.

Lumbar puncture (LP) for CSF evaluation should be performed in any patient with syphilis who has evidence of neurologic, ophthalmologic, cardiovascular, or gummatous disease, regardless of past treatment history. LP should be performed in any HIV-infected patient with untreated syphilis of unknown duration or in the late latent stage, regardless of clinical manifestations. LP is not recommended in HIV-negative patients with primary and secondary syphilis since prompt treatment has been shown to prevent future neurologic disease.

Management

CDC treatment recommendations for syphilis depend on the stage of illness (Table 28-2). If the stage is unknown, the guidelines for late latent syphilis should be applied. The Jarisch-Herxheimer reaction can occur within 24 hours of treatment; is characterized by headache, myalgia, and fever; is more common in early than later stages of syphilis; and is associated with premature labor and fetal distress.

The drug of choice for the treatment of syphilis is penicillin G. Skin testing and desensitization are recommended for patients with penicillin allergy. Doxycycline and tetracycline are alternatives, but their use is limited by multiple doses daily, a 14-day course for primary and secondary infections, and a 28-day course for latent infections. Although some studies have demonstrated the efficacy for azithromycin administered as a single 2-g dose to patients with early and early latent syphilis, there have been reports of macrolide-resistant strains and treatment failures in Seattle, Baltimore, San Francisco, and Ireland. Ceftriaxone is listed as an alternative in the CDC guidelines for all stages, but optimal dosing and duration are not well defined. All patients who are treated for syphilis should be screened for HIV at baseline and, if negative, at 3 months.

A four-fold decrease in the titer of the same nontreponemal test should be demonstrated to document the adequacy of treatment. Titers should be obtained at baseline, 6, and 12 months for primary and secondary syphilis; and at baseline, 6, 12, and 24 months for latent syphilis. If

Table 28-2 CDC Treatment Guidelines for Syphilis

	One of the Following Regimens	
	Drug	**Dose**
Primary and secondary syphilis	Benzathine penicillin G	2.4 million units IM × one dose
Early latent syphilis	Benzathine penicillin G	2.4 million units IM x one dose
Late latent syphilis	Benzathine penicillin G	2.4 million units IM × 3 doses each 1 week apart
Tertiary syphilis	Benzathine penicillin G	2.4 million units IM × 3 doses each 1 week apart
Neurosyphilis	Aqueous crystalline penicillin G	3–4 million units IV every 4 hours or by continuous infusion × 10–14 days, total daily dose of 18–24 million units
	Procaine penicillin *plus* Probenicid	2.4 million units IM once a day × 10–14 days 500 mg orally four times a day × 10–14 days

From: Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines 2006. MMWR 2006;55(RR-11).

the titer does not fall at least four-fold or if signs and symptoms recur after treatment, HIV testing should be repeated. HIV-infected patients with syphilis should have titers repeated at 3-month intervals to assure the adequacy of treatment. Follow-up of neurosyphilis involves examination of the CSF every 6 months until the cell count normalizes. Retreatment of neurosyphilis should be considered if the cell count in the CSF does not decrease in 6 months or normalize in 2 years.

CHANCROID

Epidemiology

The WHO estimates that there are 6 million cases of chancroid worldwide and that up to one-half of all cases of GUD in Asia, Africa, and the Caribbean are due to chancroid. However, diagnostic testing for *H. ducreyi* is unavailable in many resource-poor countries, and access to testing is limited even in countries such as the United States.

As shown in Figure 28-3, reported cases of chancroid in the United States have fallen dramatically over the past two decades. During the mid-1990s, HSV and syphilis were found in GUD cases from 10 U.S. cities participating in a surveillance study, whereas chancroid was found in cases from only two cities. By 2004, no state reported more than four cases of chancroid and, of the 30 total cases nationwide, 20 were in men.

Pathophysiology

H. ducreyi infects the skin or mucosa through microabrasions during sexual intercourse. Only some strains of the organism are virulent, and those strains are resistant to both cell-mediated and complement-mediated host responses. Polymorphonuclear lymphocytes and macrophages infiltrate the epidermis and dermis in response to the infection, forming a papule within 3–10 days. The papule progresses to a pustule more commonly in males than females, and the pustule progresses to an ulcer within 2–3 days. The typical ulcer of chancroid is painful, well circumscribed, and nonindurated. It has ragged, undermined edges; a friable, granulomatous base; and a yellow or gray purulent exudate. One ulcer is seen in half of males with chancroid, whereas several discrete lesions are common in females. "Kissing ulcers" can occur from autoinoculation. Without treatment, the ulcers can last weeks to months and are susceptible to superinfection by other bacteria.

Ulcers in males are commonly located on the prepuce, frenulum, and coronal sulcus, although they can be found on the glans, meatus, and penile shaft. Edema of the prepuce and phimosis are potential complications, and cases of acute purulent urethritis have been also been reported. In females, lesions are most commonly seen on the labia majora, posterior fourchette, labia minora, periurethral area, and clitoris. There can also be vaginal, cervical, and

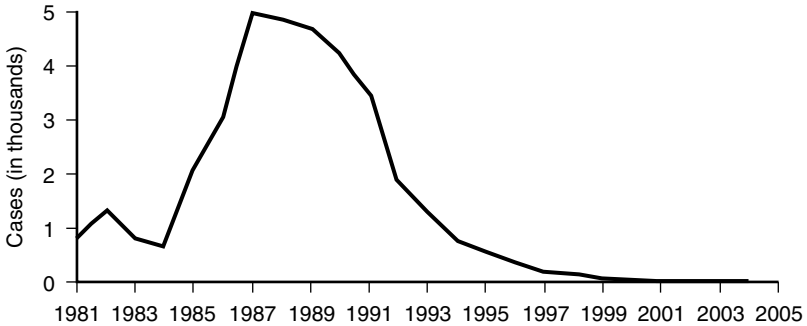

Figure 28-3 Reported cases of chancroid, United States, 1981–2004.
From: Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance, 2004*. Atlanta, GA, U.S. Department of Health and Human Services, September, 2005, Figure 38.

perianal ulcers. Because of the location of lesions in women, the presenting complaint may be dysuria, painful defecation, dyspareunia, or vaginal discharge.

Tender regional lymphadenitis follows the ulcer stage in up to 50% of individuals. This represents an inflammatory response without a significant numbers of organisms. The lymphadenopathy is usually unilateral, matted, and erythematous. Nodes that fill with thick viscous pus constitute a bubo, which can rupture spontaneously and/or form an inguinal abscess, large ulcer, or draining sinus. Surgical drainage is indicated if the bubo is large and intact.

H. ducreyi does not appear to disseminate or become invasive even in immunocompromised individuals. However, immunocompromise is associated with prolonged incubation and more severe regional disease.

Evaluation

The diagnosis of chancroid is made by demonstrating *H. ducreyi* and excluding other causes of GUD, which in the United States means primarily HSV and syphilis. Microscopic examination of a gram-stained preparation of material from an ulcer or bubo may reveal *H. ducreyi*, but the sensitivity and specificity are low because of the many other microbes that colonize the lesion. Culture of *H. ducreyi* from a calcium alginate or cotton swab of the ulcer base carries a sensitivity of 65–70% when one medium is used and 80–90% when two are used. Ideally, the specimen should be cultured on collection because transport media are generally unavailable. Alternatively, the swab can be stored at 4 °C.

PCR is the most sensitive test for *H. ducreyi*, at 90%, but it is not available for commercial use. Serologic tests such as enzyme immunoassay, dot immunobinding, agglutination, complement fixation, and fluorescent antibody assay do not differentiate current from past infections and therefore are of limited use for immediate diagnosis. Rapid diagnostic testing of swab material, using indirect immunofluorescence of monoclonal antibodies directed against outer membrane proteins, appears to be more sensitive than culture and may prove particularly useful in resource-poor countries.

Management

Presumptive treatment for clinically suspected chancroid should be initiated if specific laboratory testing is unavailable and syphilis and HSV are excluded. CDC-recommended treatment options are outlined in Table 28-3 and include azithromycin, ceftriaxone, ciprofloxacin, or erythromycin. Ciprofloxacin cannot be used in pregnancy, and resistance to ciprofloxacin and erythromycin has been reported worldwide. Treatment failures with ceftriaxone have also been reported in Africa.

Table 28-3 CDC Treatment Guidelines for Chancroid

One of the Following Regimens	
Drug	**Dose**
Azithromycin	1 g orally × one dose
Ceftriaxone	250 mg IM × one dose
Ciprofloxacin	500 mg orally two times a day × 3 days
Erythromycin	500 mg orally three time a day × 7 days

From: Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines 2006. MMWR 2006;55(RR-11).

Lack of circumcision and HIV infection are associated with poorer response to treatment. Patients who are HIV-infected should be closely monitored and may need longer courses of therapy with ciprofloxacin or erythromycin. All patients should be tested for HIV at the time of diagnosis and retested for syphilis and HIV in 3 months if the initial tests are negative.

Symptomatic improvement usually occurs in 3 days, with objective improvement in 7 days, complete ulcer healing in 2 weeks, and resolution of lymphadenopathy in 3 weeks. Buboes may require incision and drainage, and larger ulcers may require more than 2 weeks of therapy for complete healing. Treatment failure should raise questions about the diagnosis as well as prompt repeat HIV testing.

MAJOR POINTS

- HSV is the most common cause of GUD in the United States.
- GUD is associated with increased susceptibility to and increased transmission of HIV, and all patients with GUD should undergo HIV testing.
- Immunocompromised patients are more likely to present with complications of GUD, may have a prolonged clinical course, and may require longer therapeutic regimens.
- Muliplex PCR is the most sensitive testing method for HSV, syphilis, and chancroid but is not yet available for commercial use.
- Condoms decrease, but do not completely prevent, the transmission of organisms responsible for GUD.

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CHAPTER 29

Human Immunodeficiency Virus

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INTRODUCTION

The human immunodeficiency virus (HIV) was identified in 1983, 2 years after the first five cases of the acquired immunodeficiency syndrome (AIDS) were reported by the Centers for Disease Control and Prevention (CDC). The ensuing years witnessed rapid advances in the prevention and management of HIV/AIDS and dramatic shifts in its epidemiology. In developed countries, the availability of effective antiretroviral therapy reduced perinatal transmission to 1–3%; prolonged survival; increased resistance to 15% of circulating strains; and introduced a set of common side effects called body-fat abnormalities. In developing countries, however, less than 20% of those needing antiretroviral therapy receive it and interventions to reduce behavioral risk have had limited impact. As a result, the developing world accounts for 95% of AIDS-related deaths and new HIV infections.

In the United States, the face of the HIV/AIDS epidemic has changed dramatically. Adolescents and young adults less than 25 years of age now account for half the new HIV infections reported annually to the CDC and for most perinatally acquired infections. As a result, strategies to prevent new infection and manage the long-term effects of past infection have focused increasingly on the second and third decades of life.

The objectives of this chapter are to review the epidemiology, pathophysiology, evaluation, and management of HIV/AIDS in youth who acquire the infection perinatally or behaviorally. Although many clinicians who care for adolescents will refer HIV-infected patients, all should be knowledgeable about preventive counseling, postexposure prophylaxis, HIV screening, the acute seroconversion syndrome, and when to begin therapy.

DEFINITIONS

Acquired immunodeficiency syndrome (AIDS): The advanced stages of HIV infection defined by the CDC as a CD4 T-cell count < 200 per cubic millimeter (mm^3) and opportunistic infections that include but are not limited to *Pneumocystis carinii* pneumonia (PCP), toxoplasmosis, tuberculosis, wasting syndrome, fungal infections, and malignancies.

Acute HIV seroconversion syndrome, primary HIV infection, or acute retroviral syndrome: Transient symptoms associated with the rapid viral replication and pronounced immune response that follows initial infection.

Behavioral transmission: HIV infection acquired through sexual contact or parenteral drug use.

Human immunodeficiency virus (HIV): The retrovirus that causes AIDS by infecting helper T cells of the immune system. HIV-1 is the most common serotype in the United States and worldwide.

HIV-risk behaviors: Young men who have sex with men (YMSM), unprotected sexual intercourse, sexual contact with an HIV-infected partner, and injecting drug use.

Opportunistic infections: *Pneumocystis carinii* pneumonia, toxoplasma, *Mycobacterium avium*, and other infections associated with low CD4 cell counts (< 200) in individuals infected with HIV.

Opt-out screening: Patients are notified that HIV testing will be performed and they can decline the test. Unless the patient does not agree to testing, consent is assumed.

Partner notification: The term "partner" refers to a sexual contact or an individual who has shared injection equipment with an HIV-infected patient. Partner notification can be accomplished by the patient, health care provider, or health department.

Postexposure prophylaxis: Secondary prevention of infection after exposure to HIV such as through sexual contact, injecting drug use, bites, contact with wounds, or needlestick injuries outside the delivery of health care. It consists of a 28-day course of antiretroviral therapy.

EPIDEMIOLOGY

According to the CDC, the risk of HIV infection in the United States remains high for young men who have sex with men (YMSM) and young women who have sex with men (YWSM). The peak ages for new infection (i.e., 13–24 years) and AIDS (i.e., 25–34 years) are consistent with the average 10-year lag noted in studies of natural history. Perinatally acquired HIV declined sharply in the United States following the 1995 introduction of routine, voluntary HIV screening during pregnancy and the treatment of infected mothers during labor and delivery. Still, in 2005, 68 cases of AIDS were reported in children younger than 13 years. The prevalence of perinatally acquired infection is now highest among older adolescents and young adults who were born during the late 1980s. Many of these youth have been exposed to multiple medications and have developed resistance mutations that require increasingly complex treatment regimens. They often have lost parents to AIDS, lack family support, face social stigma, and experience developmental and cognitive delays secondary to the virus.

HIV/AIDS in the United States disproportionately affects young women and minorities. African-Americans comprise 15% of U.S. youth and two-thirds of youth with new infections. Females account for 36% of new infections among those aged 13–19 years, 28% among those aged 20–24 years, and 25% among those aged 25 years and older. The efficiency of transmission is higher from males to females than the reverse, perhaps reflecting the susceptibility of cervical columnar cells to inflammation and infection.

In 2005, approximately 47% of high school students in the United States were sexually active, with 6% initiating sex before age 13 years and 14% reporting four or more lifetime sexual partners. Although nearly 88% of youth report school-based education about HIV/AIDS prevention, less than 65% of sexually active youth report condom use at last sexual intercourse. Behavioral risk factors for HIV infection during adolescence include early sexual debut, increased numbers of partners, alcohol and/or drug use prior to sexual activity, and injection drug use. Youth who are gay, bisexual, or transgender; runaway or homeless; in foster care; mentally ill; or sexually abused are particularly vulnerable to HIV infection.

PATHOPHYSIOLOGY

Understanding HIV infection and the mechanisms by which antiretroviral medications work begins with an understanding of the HIV life cycle and the host response to acute HIV infection.

HIV Life Cycle

Fusion and entry: Through a complex set of interactions among the virus, host cell receptors, and chemokines, the virus attaches to the CD4 receptor on the host lymphocyte and enters the cell. Elucidation of the attachment and entry process has led to the development of new compounds to block this binding process.

Reverse transcription: Once the virus is in the host cell, its reverse transcriptase copies the viral RNA into viral DNA, which is then incorporated into the host chromosome. Nucleoside reverse transcriptase inhibitors (NRTIs) compete with native nucleosides for incorporation into the DNA chain and, once incorporated, cause chain termination. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) bind to the reverse transcriptase and induce a conformational change that renders the enzyme inactive.

Integration and translation: Viral DNA that has been incorporated into the host chromosomes can remain latent in some T cells for years while its expression in other cells leads to the formation of viral proteins and subsequently viral particles. The pool of latently infected cells that are not affected by antiretroviral therapy and pose a major barrier to the cure of HIV infection.

Viral protein formation: Once the viral proteins are synthesized, the enzyme protease is involved in the formation of functional viral components. Protease inhibitors (PIs), which comprise another class of antiretroviral medications, interfere with protease function.

Assembly: The viral components are assembled into new viral particles which then bud through the cell surface and go on to infect other cells. Unless interrupted by antiretroviral therapy, billions of new virions are produced daily and the host immune system is rapidly overwhelmed.

Acute HIV Infection

HIV penetrates mucosal surfaces and disseminates via the bloodstream. Lymphocytes are the first cells infected, with subsequent involvement of the regional lymph nodes. Viremia is detectable 4–11 days following infection, and signs and symptoms correlate with viral load. The emergence of HLA-restricted CD8 cells that are cytotoxic to HIV, as well as rising levels of HIV-specific antibody, are associated with declines in both plasma viremia and clinical manifestations. This lag in the antibody level explains why traditional HIV tests can be negative during the acute, symptomatic phase of infection.

EVALUATION

HIV Testing

In 2006, the CDC revised its recommendations regarding HIV testing in health care settings (see Box 29-1). The goals of the revised recommendations are to increase HIV screening, to detect HIV infection earlier, to link individuals with previously undiagnosed infection to services, and to continue the downward trend in the rate of perinatal transmission. The CDC recommends "opt-out screening" in which all patients in health care settings are notified that HIV testing will be performed unless the patient actively declines testing. Furthermore, the CDC recommends that written consent for HIV should be part of the general consent for medical care rather than a separate process of consent. The guidelines call for annual screening of all patients who are considered high-risk for HIV infection and screening in the third-trimester for pregnant women in areas with high rates of infection among pregnant women.

It is important to note that the CDC recommendations in Box 29-1 do not apply to non-health care settings and do not preclude the need to follow local laws regarding HIV consent and testing. Issues of consent, confidentiality, and anonymity for HIV testing vary by state, health care facility, and laboratory. All test sites should respect patient privacy, but not all test sites offer anonymity. The patient and health care provider should understand the legal and ethical parameters prior to testing, particularly when the patient is a minor.

All U.S. states require laboratories and/or providers to report HIV infection and AIDS. In most jurisdictions, statutes protect the reports from subpoena. Local and state health departments provide information about the reporting process for HIV/AIDS and the requirements for other sexually transmitted infections (STIs).

Standard and rapid screening tests for HIV detect antibody in blood or saliva through enzyme-linked immunosorbent assay (ELISA), with a false-positive rate of 2%. If the initial ELISA screen is positive (i.e., reactive), confirmatory testing by Western Blot (WB) is performed to identify the specific HIV antibodies. This combined, two-step ELISA/WB strategy is extremely accurate. Sexually active teens should be screened routinely for HIV, just as they are for other STIs, and those requiring interval STI testing or treatment should be retested for HIV.

Box 29-1 CDC Recommendations Regarding HIV Testing

- HIV testing should be voluntary.
- HIV screening should be performed routinely in all patients aged 13–64 in all health care settings unless prevalence rates of HIV are less than 0.1%.
- Opt-out screening is recommended.
- Consent for routine care should incorporate consent for HIV testing.
- Prevention counseling should not be required as part of HIV screening programs.
- Counseling about HIV prevention should accompany notification of HIV infection.
- HIV testing should be encouraged for patients who seek STI evaluation or treatment.
- Patients with TB should be screened for HIV.
- High-risk patients should be screened annually.
- HIV rapid testing should be offered by clinical sites with high no-return rates.
- A positive HIV-antibody test must be confirmed by a positive Western blot or immunofluorescent antibody test.
- Nucleic acid testing should be performed if the acute retroviral syndrome is suspected.
- All pregnant women should be screened for HIV in early pregnancy. This should be repeated in the third trimester in areas where there are high rates of HIV in pregnant women.
- Pregnant women who have not been screened and those with risk behaviors following negative tests should have HIV rapid testing performed during labor.

Acute HIV Infection

Acute HIV infection should always be considered for the sexually active adolescent who presents with a mononucleosis-type syndrome. Typical symptoms include fever,

fatigue, lymphadenopathy, pharyngitis, rash, and myalgias. Less common symptoms include diarrhea, headache, nausea/vomiting, night sweats, hepatosplenomegaly, weight loss, thrush, oral ulcers, genital ulcers, and neurologic symptoms. The latter may present as aseptic meningitis, peripheral neuropathy, facial palsy, Guillain-Barré syndrome, brachial neuritis, cognitive impairment, and/or psychosis. Laboratory abnormalities can include thrombocytopenia (most common), leukopenia, abnormal liver function tests, and occasionally a depressed CD4 T-cell count.

The vast majority of febrile illnesses during adolescence do not represent acute HIV infection. However, given the high incidence of new HIV infections during adolescence relative to other age groups, an adolescent with a mononucleosis-type syndrome and a history of HIV-risk behavior should be tested for both baseline HIV antibody and plasma viremia. The antibody test may be nonreactive for up to 3 months following infection and is performed to determine whether the patient had been infected previously. Nucleic acid tests for viremia may be negative for up to 30 days following infection, depending on the viral load (i.e., HIV RNA copies/ml). Because false positives are also common, HIV RNA >50,000 copies/ml is necessary to diagnose acute HIV seroconversion in a patient with a negative antibody test.

Newly Diagnosed HIV Infection

The evaluation of patients new to HIV care should include a thorough medical and social history, physical examination, and baseline laboratory tests. The history should explore symptoms of infection, underlying medical conditions (e.g., pregnancy, malignancy, immunosuppression), pressing social needs (e.g., housing), ongoing risk behaviors, and ability to adhere to medications and follow-up.

In 2006, the U.S. Department of Health and Human Services (DHHS) issued revised guidelines for the baseline laboratory evaluation of adolescent and adult patients with HIV infection who are new to care (see Box 29-2). Recognizing the prevalence of drug-resistant HIV strains, the guidelines call for genotypic resistance testing before treatment in all patients with HIV RNA >1,000 copies/ml and encourage the consideration of resistance testing in all patients who are new to care, regardless of viral load or treatment plan. The DHHS Panel emphasizes that recommendations pertaining to HIV care change frequently and encourages health care providers to check the AIDSinfo web site frequently (http://AIDSinfo.nih.gov).

Potential Exposure to HIV

Exposure to HIV during adolescence can occur through sexual contact, the sharing of drug-use equipment, or contact with blood and/or genital secretions. In some cases the contact is known to be infected with HIV, but in most cases the HIV status of the contact is unknown. Adolescents who are within 72 hours of known or high-risk exposure should be offered prophylaxis with a 28-day course of combination antiretroviral therapy. Prior to initiating the therapy, the following laboratory studies should be performed: CBC, liver function studies, HIV antibody testing, RPR, and hepatitis B and C serologies. A full history should be obtained to avoid the use of medications that interact with antiretroviral therapy.

Box 29-2 Baseline Laboratory Evaluation for Patients New to HIV Care

- Confirmation that HIV antibody test is positive
- CD4 T cell count
- Plasma HIV RNA measurement of viral load
- Genotypic resistance testing if HIV RNA > 1,000 copies/ml. Consider resistance testing in all patients new to care.
- Complete blood count
- Serum electrolytes, blood urea nitrogen, creatinine, liver function studies, and lipid panel
- Urinalysis
- Tuberculin skin test, unless there is a known history of prior tuberculosis or positive skin test
- *Toxoplasma gondii* IgG level
- Hepatitis A, B, and C serologies
- Rapid plasma reagin (RPR)
- Testing for *Chlamydia trachomatis* and *Neisseria gonorrhea*
- Papanicolaou testing in females

Adapted From: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services. October 10, 2006; 1–113. Available at *http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentsGL.pdf*.

MANAGEMENT

Acute HIV Infection

The management of acute HIV infection is controversial. Some experts argue that early antiretroviral therapy may limit viral dissemination, enhance HIV-specific immune responses, and decrease symptoms associated with acute seroconversion. However, the evidence supporting these theories is inconclusive. The 2006 DHHS guidelines therefore state that antiretroviral therapy should be optional for adolescents and adults with acute HIV infection or seroconversion within the previous six months. If the decision is to treat, genotypic resistance testing should be performed to help construct the treatment regimen. Patients diagnosed with acute seroconversion syndrome should be counseled immediately about their high infectivity and the importance of safer sex practices.

Health Maintenance for HIV-Infected Youth

Current health care guidelines call for the quarterly monitoring of HIV-specific parameters and at least annual monitoring of general health issues. The HIV-specific parameters include CD4 T-cell count, measurement of HIV RNA, and an assessment of adherence to antiretroviral therapy (if applicable). General health issues include an assessment of psychosocial issues such as health insurance, housing, substance use, domestic violence, and sexual behaviors.

HIV-infected individuals should see a nutritionist at least yearly and a dentist every 6 months. Individuals with CD4 T-cell counts <50 cells/mm^3 are at risk for cytomegalovirus (CMV) retinitis and should be examined by an ophthalmologist annually. Hepatitis B immunization is indicated for all seronegative individuals. Hepatitis A immunization is indicated for seronegative individuals who are at increased risk of exposure (e.g., men who have sex with men, [MSM]). The inactivated trivalent influenza vaccine is indicated annually, and the 23-valent polysaccharide pneumococcal vaccine is indicated every 5 years for all HIV-infected individuals.

Studies exploring models of health care delivery for HIV-infected youth demonstrated higher rates of follow-up in programs that incorporate the following: multidisciplinary staff attuned to adolescent development; provision of or referral for the treatment of substance use and other mental health disorders; peer support groups; transportation to visits; reminder calls; and adaptation of medication regimens to individual lifestyles.

Antiretroviral Therapy

Adult guidelines for antiretroviral therapy and prophylaxis against opportunistic infections generally are followed for adolescents infected perinatally and behaviorally (Table 29-1). Pediatric doses should be used for those adolescents with sex maturity ratings (i.e., Tanner stages) of 1 to 2; adult doses should be used for those with sex maturity ratings of 3 to 5. At no point in the transition from pediatric to adult dosing should the pediatric dose exceed the maximum recommended adult dose.

Providers who prescribe medications for the management of HIV/AIDS must follow the literature closely for updates in therapeutic guidelines. Regardless of guidelines, however, a patient's emotional readiness to begin treatment must always be considered, given the complexity of the regimens, the side effects, and the association of drug resistance with nonadherence. Many studies have now documented the association between patient outcome and clinician expertise in HIV care. The 2006 DHHS guidelines therefore recommend that HIV primary care should be delivered by a clinician who actively manages at least 20 HIV-infected patients.

Table 29-1 Recommendations for the Initiation of Antiretroviral Therapy in Patients with HIV Infection

Patient Indicators	Antiretroviral Therapy
AIDS-defining diagnosis	Initiate
Severe HIV-related symptoms	Initiate
Pregnancy	Initiate
CD4 count < 200 cells/mm^3	Initiate
CD4 count 200–350 cells/mm^3	Usually initiate
CD4 count > 350, cells/mm^3, HIV RNA < 100,000 copies/ml	May initiate
CD4 count > 350, asymptomatic	Defer

Adapted From: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services. October 10, 2006; 1–113. Available at *http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentsGL.pdf.*

Table 29-2 categorizes the antiretroviral medications by drug class (i.e., NRTIs, NNRTIs, and PIs) and summarizes the toxicities common to all medications within a class and those specific for a given medication. Table 29-3

Table 29-2 Antiretroviral Medications and Associated Toxicity

Drugs by Class	Toxicity
NRTIs	Lactic acidosis, hepatotoxicity, hepatic steatosis, myopathy, lipoatrophy
Zidovudine (AZT)	Marrow suppression
Stavudine (D4T)	Pancreatitis
Emtricitabine (FTC)	
Didanosine (DDI)	Pancreatitis
Abacavir (ABC)	Hypersensitivity
Zalcitabine (DDC)	
Tenofovir (TDF)	Nephrotoxicity
NNRTIs	
Delaviridine	
Efavirenz	Transient central nervous system effects
Nevirapine	Stevens-Johnson syndrome, toxic epidermal necrosis, hepatotoxicity
PIs	Insulin resistance, hyperlipidemia, hepatotoxicity
Atazanavir	Indirect hyperbilirubinemia, QTc prolongation
Fosamprenavir	Sulfa rash
Indinavir	Nephrotoxity
Lopinavir	Gastrointestinal
Nelfinavir	
Ritonavir	Interacts with many other drugs
Saquinavir	

NNRTI, Non-nucleoside reverse transcriptase inhibitor; NRTI, Nucleoside reverse transcriptase inhibitor; PI, Protease inhibitor.

Table 29-3 Antiretroviral Regimens for Initial Therapy

	NNRTI		PI		Dual-NRTI
Preferred	efavirenz	**or**	atazanavir + ritonavir; or fosamprenavir + ritonavir; or co-formulated lopinavir/ritonavir	**plus**	co-formulated tenofovir/emtricitabine; or co-formulated zidovudine/lamivudine
Alternative	nevirapine	**or**	atazanavir; or fosamprenavir; or fosamprenavir + ritonavir; or co-formulated lopinavir/ritonavir	**plus**	co-formulated abacavir/lamivudine; or didanosine + (emtricitabine or lamivudine)

NNRTI, Non-nucleoside reverse transcriptase inhibitor; PI, Protease inhibitor; NRTI, Nucleoside reverse transcriptase inhibitor.
Adapted From: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services. October 10, 2006; 1–113. Available at *http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentsGL.pdf.*

summarizes the components of antiretroviral therapy regimens recommended by the 2006 DHHS Panel for initial treatment. The Panel categorizes each component as preferred or alternative to preferred. A regimen should include one NNRTI plus two NRTIs or one PI (single or ritinovir-boosted) plus two NRTIs. Combinations to *avoid* are zidovudine + stavudine because of their antagonistic effects, and stavudine + didanosine because of the high risk of lactic acidosis, hepatotoxicity, myopathy, and lipoatrophy.

Failure to respond, toxicity, and intolerance are indications for a change in regimen. Treatment failure is defined as HIV RNA > 400 copies/ml at 24 weeks or > 50 copies/ml at 48 weeks; an increase in CD4 T-cell count of < 50 cells/mm^3 at 1 year; or the development of HIV-related disease at 3 months. Poor adherence is not an indication for a change in regimen because of the risk of developing drug resistance, unless it is believed that the new regimen will simplify administration enough to alter adherence. Before changing the regimen, resistance testing of the new regimen should be performed to ensure responsiveness to at least one of its component medications.

Opportunistic Infections

Table 29-4 addresses when to institute prophylaxis for opportunistic infections. The most common opportunistic infections in adolescents with HIV are invasive bacterial infections (e.g., sinusitis, pneumonia, bacteremia); *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia (PCP); *Herpes zoster*; esophageal candidiasis; and disseminated *Mycobacterium avium* complex (MAC).

Bacterial Infections: Local resistance patterns to infectious agents, as well as recent prophylaxis or treatment, should be considered when treating bacterial infections. Severe immunocompromise (CD4 T-cell count < 200 cells/mm^3) requires broad-spectrum antibiotics that cover both resistant and nonresistant organisms. Invasive bacterial disease in an HIV-infected patient generally is treated with a broad-spectrum cephalosporin (e.g., ceftriaxone, cefotaxime, or cefuroxime) until an organism is identified. Fever and an indwelling catheter are indications for coverage of both gram-negative and gram-positive organisms, such as with ceftazidime to cover pseudomonas and vancomycin to cover methicillin-resistant *Staphylococcus aureus.*

PCP: Suspicion of PCP should prompt presumptive treatment with trimethoprim/sulfamethoxazole (TMP/SMX) in the patient without known sulfa hypersensitivity. Treatment should not await confirmation of the diagnosis because clinical deterioration may be rapid, and culture for *P. jiroveci* of infected secretions collected by bronchoscopic bronchoalveolar lavage remain positive for at least 72 hours after the start of antibiotics. The starting dose for PCP is TMP 15–20 mg/kg body weight/day and SMX 75–100 mg/kg/day administered intravenously in three to four divided doses. Once the patient has stabilized, the TMP/SMX can be administered orally to complete a 21-day course. Adverse reactions to TMP/SMX are common in HIV-infected adults and can include Stevens-Johnson syndrome, hematologic abnormalities, and gastrointestinal complaints. Patients with mild skin rashes (*not* Stevens-Johnson) can be rechallenged with TMP/SMX.

Patients with documented or suspected PCP who cannot tolerate TMP/SMX can be treated with pentamidine 4 mg/kg/day, given intravenously over 60–90 minutes until clinical improvement, followed by oral administration to complete a 7- to 10-day course. However, pentamidine should be used cautiously in the setting of renal insufficiency or other nephrotoxic medications. When pentamidine cannot be used, alternative regimens include oral atovaquone (750 mg twice daily);

Table 29-4 Prophylaxis against Opportunistic Infections

Infection	Medication	When to Initiate Prophylaxis	When to Stop Prophylaxis
Pneumocystis jiroveci (formerly *Pneumocystis carinii*)	TMP/SMX (DS daily, SS daily, DS QOD) Dapsone 100 mg daily Pentimadine (aerosolized) 300 mg monthly Atovoquone 1500 mg daily	CD4 T-cell count < 200 (or CD4 T-cell % < 14)	CD4 T-cell count > 200 for > 3 months
Toxoplasma gondii	TMP/SMX (DS daily or SS daily) Dapsone 50 mg daily *plus* Pyrimethamine 50 mg weekly *plus* Leucovorin 25 mg weekly Atovaquone with or without Pyrimethamine	CD4 T-cell count < 100 and positive serology to toxoplasma	CD4 T-cell count > 200 for > 3 months CD4 T-cell count > 200 for > 6 months if patient with history of toxoplasmosis and has undergone treatment
Mycobacterium avium complex	Azithromycin 1200 mg weekly Clarithromycin 500 mg BID	CD4 T-cell count < 50	CD4 T-cell count > 100 for > 3 months CD4 T-cell count > 100 for 6 months with a history of disseminated MAC *after* 12 months of therapy *and* asymptomatic
Mycobacterium tuberculosis	INH 300 mg daily for 9 months	+ PPD > 5 mm in HIV patient (must rule out active disease with CXR)	

BID, twice daily; CXR, Chest X-ray; DS, double-strength; INH, isoniazid; MAC, *Mycobacterium avium* complex; PPD, purified protein derivative; QOD, every other day; SS, single-strength; TMP/SMX, Trimethoprim/sulfamethoxazole.

clindamycin and primaquine (contraindicated in patients with glucose-6-phosphate-dehydrogenase deficiency); trimetrexate glucuronate with leucovorin (folinic acid); or dapsone/trimethoprim.

Moderate or severe PCP, defined as an alveolar-arterial gradient >35 mmHg or a partial pressure of arterial oxygen < 70 mmHg, benefit from corticosteroids begun within 72 hours of the suspected or confirmed diagnosis. Clinical studies vary in their corticosteroid doses, but most have included tapers that last the duration of antibiotic treatment.

Candidiasis: Uncomplicated orpharyngeal candidiasis usually can be treated topically with clotrimazole troches 10 mg orally four to five times daily for 14 days or nystatin suspension four times daily for 14 days. Severe oropharyngeal candidiasis in an HIV-infected patient warrants the consideration of an oral azole instead of topical therapy. Fluconazole given once daily for 7–14 days is generally well tolerated and effective. Alternatives include itraconazole solution, which is better absorbed than the capsular form, and ketoconazole, which is limited in its effectiveness by poor absorption. Prior to the initiation of an azole, liver function studies should be checked and other medications (e.g., antiretrovirals) that utilize the cytochrome P-450 pathway should be noted and monitored.

Varicella-zoster Virus (VZV): The VZV can manifest as chickenpox on primary infection and as herpes zoster syndrome or "shingles" on reactivation of latent VZV infection within the sensory dorsal root ganglia. HIV-infected patients are susceptible to clinically severe primary varicella and subsequent herpes zoster, particularly as the CD4 T-cell count falls below 200 cells/mm^3. HIV-infected patients with primary varicella and a primary or recurrent bout of herpes zoster should be treated with acyclovir intravenously or orally, depending on the severity of illness. Of note, the dose of acyclovir requires adjustment in patients with abnormal renal function.

Nonoccupational Postexposure Prophylaxis (NPEP): The CDC recommends that NPEP be offered to any individual who presents within 72 hours of exposure to a known HIV-infected contact when that exposure is through the vagina, rectum, eye, mouth, other mucous membrane, or nonintact skin and to the contact's blood, semen, vaginal secretions, rectal secretions, breast milk, or any body fluid that has visible blood. The caveat is that this should be an isolated exposure. This means that NPEP is not indicated for the individual who regularly has unprotected sex with an HIV-infected partner. It would be indicated, however, following

condom breakage for the couple who regularly has protected sex.

A case-by-case decision about NPEP should be made when the contact's HIV status is unknown. Generally, risk is considered negligible if the contact's secretions were not visibly contaminated with blood. Even when risk is considered substantial, NPEP is not indicated beyond 72 hours of exposure.

Current guidelines recommend NPEP with a three-drug, NNRTI-based or PI-based regimen. The preferred NNRTI regimens are (efavirenz) + (lamivudine or emtricitabine) + (zidovudine or tenofovir). The preferred PI-based regimens are (lopinavir/ritonavir) + (lamivudine or emtricitabine) + (zidovudine). Regardless of the regimen, the baseline laboratory evaluation described above should be performed, along with counseling about medication side effects and signs of seroconversion. Patients should be evaluated for side effects at 48–72 hours after beginning treatment; for toxicity at 2 weeks; and for HIV testing at 6 weeks, 3 months, and 6 months.

Secondary Prevention: Education about the secondary prevention of HIV is essential for all HIV-infected individuals, as well as those with suspected acute seroconversion or who are on NPEP. The counseling should include the importance of and strategies for partner disclosure. Some individuals who are reluctant to tell partners alone are able to disclose in the presence of clinicians. Others may rely on anonymous partner notification systems through local departments of health. Issues of patient safety (e.g., domestic violence or partner retaliation) should always be considered prior to disclosure. It is important to review state laws about provider responsibilities with regard to partner notification.

OUTCOME

Outcome data for HIV-infected adolescents are available through a federally funded project entitled Reaching for Excellence in Adolescent Care and Health (REACH). The project was a study of disease progression in individuals infected at ages 12–18 years, primarily through sexual contact. Analysis of the REACH data suggests that infection during adolescence compared with adulthood may be associated with better response to therapy and longer survival. Potential explanations for the findings include the higher thymic reserve of adolescents compared with adults and the lower rates of fat and muscle wasting. However, the relatively short duration of the REACH follow-up and its inherent limitations (e.g., timing of infection) leave many questions unanswered and emphasize the importance of ongoing clinical research with HIV-infected adolescents.

MAJOR POINTS

- Adolescents represent half of new HIV infections in the United States. The risk of infection is particularly high for minority adolescents and young men who have sex with men (YMSM).
- Routine HIV testing and education are critical components of primary and preventive care for adolescent-aged patients.
- The acute HIV seroconversion syndrome is commonly missed and should be included in the differential diagnosis of any adolescent presenting with a mononucleosis-like syndrome and a history of HIV-risk behavior.
- Adolescents who are within 72 hours of known or high-risk exposure should be offered prophylaxis with a 28-day course of combination antiretroviral therapy.
- The treatment of HIV infection and opportunistic infections in adolescents with sex maturity ratings (i.e., Tanner stages) of 3 and greater is the same as that for adults. Dosage adjustments should be made for adolescents with sex maturity ratings of 1 to 2.
- Appropriate adolescent HIV care utilizes a multidisciplinary care team addressing psychosocial and medical needs and discussing future transition to adult care. Although adherence might not be achieved, engagement in care should be the goal as it sets the groundwork for future care.

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CHAPTER 30

Contraception

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INTRODUCTION

Contraception is essential for the vast majority of sexually active adolescent females who do not wish to become pregnant. Although adolescent pregnancy remains more prevalent in the United States than other developed countries, the availability of several novel contraceptive delivery systems in the United States accounts for 50–75% of the decline noted in the last 10–15 years. The common factor shared by these transdermal, vaginal, intrauterine, intramuscular, and subcutaneous systems is a longer duration of action compared with the oral contraceptive pill, making successful use more likely. Although condom use probably has had a lesser impact on adolescent pregnancy than the more efficacious hormonal methods, the percentage of sexually active high school students reporting condom use at last intercourse increased 37% over 12 years, reaching 63% in 2003 and remaining stable at that level in 2005.

Clinicians must be prepared to counsel adolescents about both the advantages of sexual abstinence and the risks of unprotected sexual intercourse. For those adolescents who are or plan to become sexually active, the provision of confidential and comprehensive reproductive health care is essential. This chapter reviews the trends and rates of adolescent sexual activity, pregnancy, and contraceptive use. The mechanisms, contraindications, benefits, risks, and side effects of the specific contraceptive methods available to U.S. adolescents are then discussed. Of note, Tables 30-2 and 30-3 at the end of this chapter provide important information about specific contraceptive methods. Referring to these tables will be helpful as you read through the definitions below.

DEFINITIONS

Barrier contraception: Blocks sperm transport. Methods such as condoms and diaphragms often are used in conjunction with spermicides.

Emergency contraception: Reduces the risk of pregnancy by at least 75% if initiated within 72 hours after unprotected intercourse. There are no medical contraindications to its use except that it is ineffective if taken during an established pregnancy.

Estrogens such as ethinyl estradiol are produced synthetically and used with progestins to enhance the contraceptive effect and regulate bleeding. Methods include combination oral contraceptive pills, transdermal patches, and the vaginal ring.

Hormonal contraception: Contains estrogens and progestins or progestins alone. Delivery systems for the hormone(s) include oral contraceptive pills, transdermal patches, vaginal rings, intramuscular injections, intrauterine devices, and subcutaneous implants.

Menstrual molimina: Uncomfortable symptoms associated with menses that suggest ovulatory cycles (e.g., dysmenorrhea, breast tenderness, bloating, or mood changes).

Permanent contraception: Irreversible or permanent male or female sterilization. This option is rarely indicated for adolescents, and clinicians with experience and expertise in its use during adolescence should always be involved in the discussions and decisions.

Progestins or ***progestogens*** are produced synthetically and can be used for contraception either alone or with estrogens. Progestin-only methods (e.g., depot medroxyprogesterone acetate, progestin-only pills, and the progestin intrauterine system) prevent pregnancy by suppressing ovulation and altering the endometrium, cervical mucus, and sperm transport.

Reversible contraception: Includes hormonal and barrier methods that can be discontinued to allow subsequent pregnancy.

Spermicides: Topical formulations that kill sperm. Intravaginal formulations are available as a gel, foam, cream, film, suppository, or tablet. Many condoms also are manufactured with spermicides.

EPIDEMIOLOGY

Pregnancy affects one-third of U.S. females by age 20 years, despite a dramatic decline in the rate of teen pregnancy over the last 50 years (Figure 30-1). Most adolescent pregnancies are unintended and abortion rates remain high, at 744 per 1000 live births for adolescents age < 15 years and 400 per 1000 for those age 15–19 years. Adolescent pregnancy rates in the United States are two to three times the rates in Canada and Europe and eight times the rates in the Netherlands and Japan, despite similar rates of sexual activity (Figure 30-2). Explanations for the lower rates in these countries compared with the United States include better contraceptive counseling, access, services, and utilization. Healthy People 2010, a government initiative that provides a blueprint of U.S. health priorities, calls for contraceptive use by 100% of teens who are at risk for unintended pregnancy and the delivery of reproductive health education that includes contraception to 90% of all adolescents by age 18 years.

The 2002 National Survey of Family Growth (NSFG) indicated that 77% of adolescents had received such education and that 98% of those who reported sexual activity had previously used some method of contraception (Figure 30-3). Condoms are the most frequently used method, reported by 94% at some time in the past, 66% at first intercourse, and by 54% at last intercourse (Figures 30-3 to 30-5). Conversely, more than half of

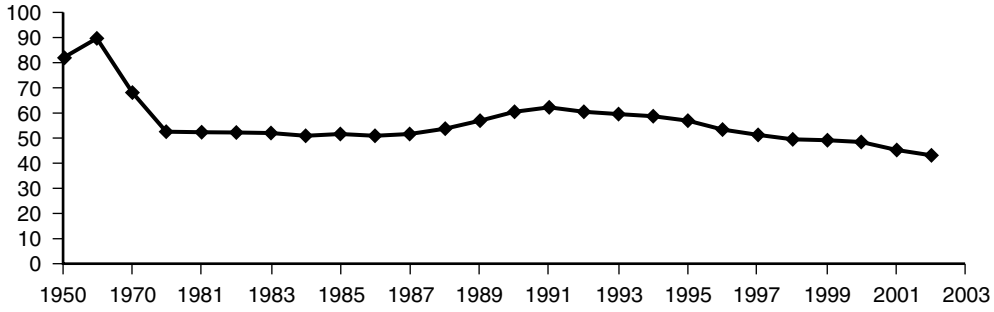

Figure 30-1 Adolescent pregnancy rates.
National Center for Health Statistics: *Health, United States, 2004, with Chartbook on Trends in the Health of Americans*. Hyattsville, MD, National Center for Health Statistics, 2004, p. 43–44.

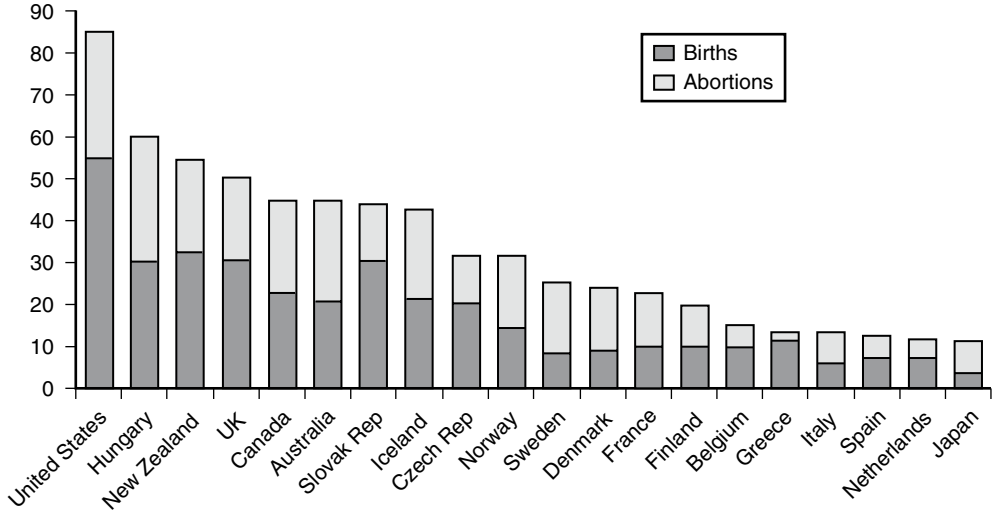

Figure 30-2 International birth and abortion rates.
Data plotted from: UNICEF Innocenti Research Center: Teenage Births in Rich Nations, Innocenti Report Card 3. Florence, Italy, UNICEF IRC, pp 32.

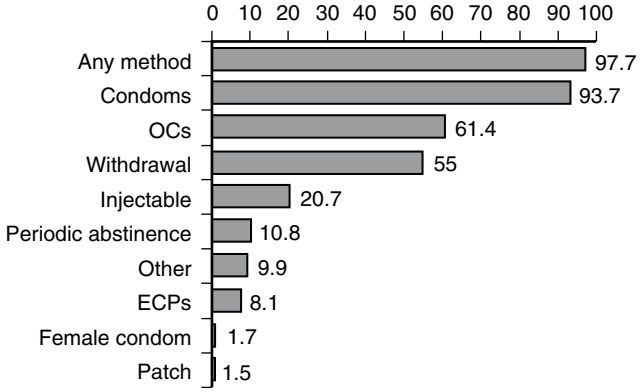

Figure 30-3 Ever use of contraception by sexually active adolescents ages 15–19.
Data from National Survey of Family Growth. Abma JC, Martinez GM, Mosher WD, et al.:Teenagers in the United States: Sexual activity, contraceptive use, and child bearing, 2002. National Center for Health Statistics. Vital Health Stat 23(24), 2004.

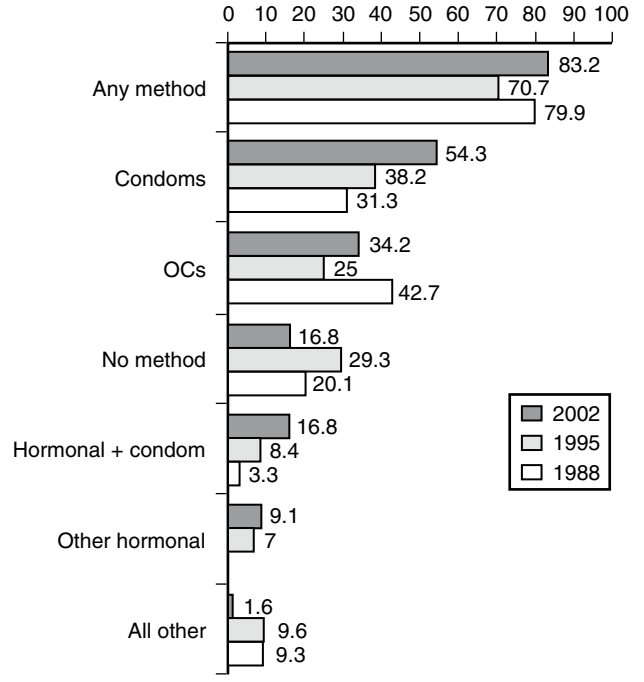

Figure 30-4 Contraception at last intercourse—trends.
Data from National Survey of Family Growth. Abma JC, Martinez GM, Mosher WD, et al.:Teenagers in the United States: Sexual activity, contraceptive use, and child bearing, 2002. National Center for Health Statistics. Vital Health Stat 23(24), 2004.

adolescents reported that they at some time had relied on withdrawal to protect against pregnancy. Information regarding the use of newer contraceptive options is only partially reflected in the 2002 NSFG data. For example, the contraceptive patch was approved by the U.S. Food and Drug Administration (FDA) in 2001 and had been used by only 1.5% of adolescents in 2002. Depot medroxyprogesterone acetate (DMPA or Depo-Provera) was approved for contraceptive use in 1992 and by 2002 had been used by 20% of sexually active adolescents.

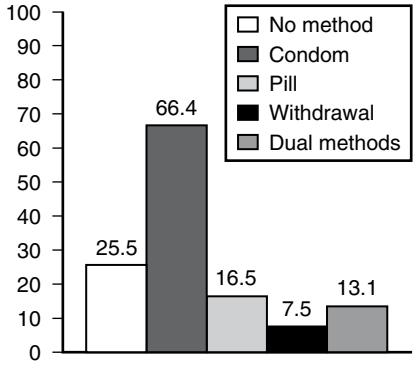

Figure 30-5 Contraception use at the time of first intercourse.
Data from National Survey of Family Growth. Abma JC, Martinez GM, Mosher WD, et al.:Teenagers in the United States: Sexual activity, contraceptive use, and child bearing, 2002. National Center for Health Statistics. Vital Health Stat 23(24), 2004.

Overall, the trends in contraceptive use demonstrate increases for the longer-acting methods that are easier to use. The next cycle of national surveys will provide information about methods such as the intravaginal ring and the levonorgestrel-containing intrauterine system (IUS, Mirena).

MECHANISMS OF ACTION

The primary mechanism of action of combination oral contraceptives is the inhibition of ovulation. The progestin component of oral contraceptives also thickens the cervical mucus and makes it more hostile to sperm. The endometrial thinning that occurs with the combination oral contraceptives results in lighter, shorter menstrual periods but probably does not contribute to the contraceptive effect. Oral contraceptives are not abortifacients. The progestin component of the combination pills prevents the luteinizing hormone (LH) surge that triggers ovulation. Estrogen suppresses follicle-stimulating hormone (FSH) and follicular development. Traditional cycles of oral contraceptives arbitrarily consist of 21 days of hormonally active pills (estrogen and progestin) followed by 7 days of placebo pills. Bleeding occurs during the placebo week due to the withdrawal of hormones supporting the endometrium.

Progestin-only contraceptives such as DMPA and progestin-only pills also inhibit ovulation, although not as efficiently as combination oral contraceptives. Other contraceptive effects of progestins include thickening of the cervical mucus, sufficient thinning of the endometrium to decrease the likelihood of implantation, and impaired motility of the fallopian tubes.

EVALUATION

The evaluation of an adolescent female who requests contraception should include a review of medical conditions, current medications, menstrual history, social history, and family history.

Medical Conditions

A publication of the World Health Organization (WHO) entitled *Medical Eligibility Criteria for Contraceptive Use* provides evidence-based ratings of the safety of specific contraceptive methods for women with various medical conditions (Box 30-1). Although specific hormonal methods may be relatively or absolutely contraindicated for women with certain medical conditions, pregnancy also poses significant risks for these women. The WHO therefore also lists those medical conditions that are associated with increased risk during pregnancy (Box 30-2), allowing a comparison of the contraceptive and pregnancy risks for a given condition. Most medical conditions that preclude the use of oral contraceptives (according to the WHO categorization) are uncommon in adolescents (Table 30-1). Migraine headache with aura, however, is not uncommon and is considered a condition that poses an unacceptable health risk for combination oral contraceptives.

By logical extension, the contraindications to oral contraceptive use also apply to other combination hormonal methods, such as the transdermal patch and intravaginal ring. Although patient package inserts for combination and progestin-only methods often use similar lists of medical conditions that preclude use, the WHO guidelines reflect both international consensus and well-performed recent studies.

Box 30-1 World Health Organization (WHO) Medical Eligibility Ratings for Contraceptive Use

1. A condition for which there is no restriction for the use of the contraceptive method
2. A condition for which the advantages of using the method generally outweigh the theoretical or proven risks
3. A condition for which the theoretical or proven risks usually outweigh the advantages of using the method
4. A condition that represents an unacceptable health risk if the contraceptive method is used

Box 30-2 Conditions That Expose a Woman to Increased Risk as a Result of Unintended Pregnancy

- Breast cancer
- Complicated valvular heart disease
- Diabetes: insulin-dependent; with nephropathy/retinopathy/neuropathy or other vascular disease; or of > 20 years' duration
- Endometrial or ovarian cancer
- High blood pressure (systolic > 160 mmHg or diastolic > 100 mmHg)
- HIV/AIDS
- Ischemic heart disease
- Malignant liver tumors (hepatoma)
- Schistosomiasis with fibrosis of the liver
- Severe (decompensated) cirrhosis
- Sickle cell disease
- Sexually transmitted infection (STI)
- Stroke
- Thrombogenic mutations
- Tuberculosis

From: *Medical Eligibility Criteria for Contraceptive Use*, 3rd ed. Geneva, World Health Organization, 2004.

Table 30-1 Medical Conditions Precluding Oral Contraceptive Use[a]

Medical Condition	WHO Category
Thrombophlebitis or thromboembolic disorder	4
Past history of deep vein thrombosis or thromboembolic disorders	4
Cerebrovascular or coronary artery disease	4
Valvular heart disease with thrombogenic complications	4
Uncontrolled hypertension	4
Diabetes with vascular involvement	3 / 4
Headaches with focal aura	4
Major surgery with prolonged immobilization	4
Breast cancer	4
Carcinoma of endometrium	1
Other known or suspected estrogen-dependent neoplasia	Not discussed
Undiagnosed abnormal genital bleeding	2
Cholestatic jaundice of pregnancy	2
Jaundice with prior pill use	3
Acute or chronic hepatocellular disease with abnormal liver function, hepatic adenomas, or hepatic carcinomas	4
Known or suspected pregnancy	Not applicable
Hypersensitivity to any component of the product	Not discussed

[a]As listed in pill package inserts.

Excerpted from: Hatcher RA, Nelson AL: Combined hormonal contraceptive methods. In: Hatcher RA, Trussell J, Stewart FH, et al. (eds): *Contraceptive Technology*. New York, Ardent Media, 2004, p. 412, with permission.

Current Medications

Drugs that may decrease the effectiveness of combination hormonal contraceptives are listed in Box 30-3. There are anecdotal reports of decreased effectiveness in women using broad-spectrum antibiotics, but studies have demonstrated that the serum levels of contraceptive hormones in subjects on antibiotics are well within the therapeutic range. Consequently, backup methods of contraception are not routinely recommended when antibiotics are prescribed for women on combination hormonal contraception.

Menstrual History

Adolescents with a menstrual history of marked irregularity and/or amenorrhea of > 90 days should be evaluated for underlying medical conditions that will be masked, and possibly treated, with hormonal therapy. The most common disorders among adolescents that require consideration are polycystic ovary syndrome (PCOS) and eating disorders. Pregnancy as a cause of menstrual irregularity, oligomenorrhea, or amenorrhea must always be considered, and a urine pregnancy test should always be performed.

Social and Sexual History

Confidentiality is particularly important when providing reproductive health services and contraception to adolescents. Whenever possible, policies regarding confidentiality should be discussed with the adolescent and parent on the first office visit. The challenge is to facilitate communication between the adolescent and parent or other supportive adults while simultaneously respecting the adolescent's right to privacy and providing a setting in which the adolescent is comfortable discussing sexual behavior.

The sexual history should include discussion of the age at first sexual intercourse; number of sexual partners; past and current condom use; past and current use of other contraceptive methods; history of sexually transmitted infections; and use of alcohol, tobacco, or illicit drugs. Substance use directly affects sexual history, both as an indicator of risk behavior and as a factor that decreases the likelihood of successful contraceptive use. Adolescent substance use is associated with unplanned sexual intercourse, inconsistent condom use, and multiple sexual partners.

Parents may be concerned that tobacco use in adolescents significantly increases cardiovascular risks and thus precludes combination hormonal contraceptive use. Although combination oral contraceptives should not be used by smokers older than 35 years, the baseline cardiovascular risks in adolescent smokers are quite low and pregnancy increases the risks markedly (Figure 30-6). Thus, encouraging adolescents to stop smoking is good clinical care, but withholding oral contraceptives from adolescent smokers increases cardiovascular risks by increasing the risk of pregnancy.

Box 30-3 Drugs That May Reduce Oral Contraceptive Effectiveness

- Antituberculous drugs
- Systemic antifungals
- Anticonvulsants
- Anti-HIV protease inhibitors
- Over-the-counter drugs
  - St. John's Wort

Family History

Family history is important when considering estrogen-containing hormonal contraception, particularly with regard to an inherited thrombophilia. History of venous thromboembolic disease without clear external cause (e.g., prolonged immobilization) in a first-degree relative should prompt evaluation. Adolescents and their mothers with a family history of breast cancer frequently ask about the risks of oral contraceptives. Among all women with a family history of breast cancer, oral contraceptives do not increase the risk of developing breast cancer, although women with known *BRCA1* mutation may have a slightly increased risk.

Physical Examination

Although careful history taking is important in adolescents who are seeking contraception, adolescents frequently are deterred from seeking care by the prospects of a gynecologic examination. The FDA has concluded that "physical examination may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician." Good clinical practice dictates measurement of blood pressure, height, and weight; calculation of body mass index (BMI); determination of Tanner stages; and breast examination. Adolescents frequently and incorrectly believe that oral contraceptives are associated with weight gain. Progestin-only methods, particularly DMPA, have been associated with weight gain in adolescents. Establishing the baseline weight and helping the adolescent who has completed growth maintain it, regardless of contraceptive method, is a part of routine care. Urine-based testing for sexually transmitted infections is indicated for all sexually active adolescents, but the absence of testing should not prohibit the provision of contraceptives. Pelvic examination should be dictated by clinical judgment, and cervical

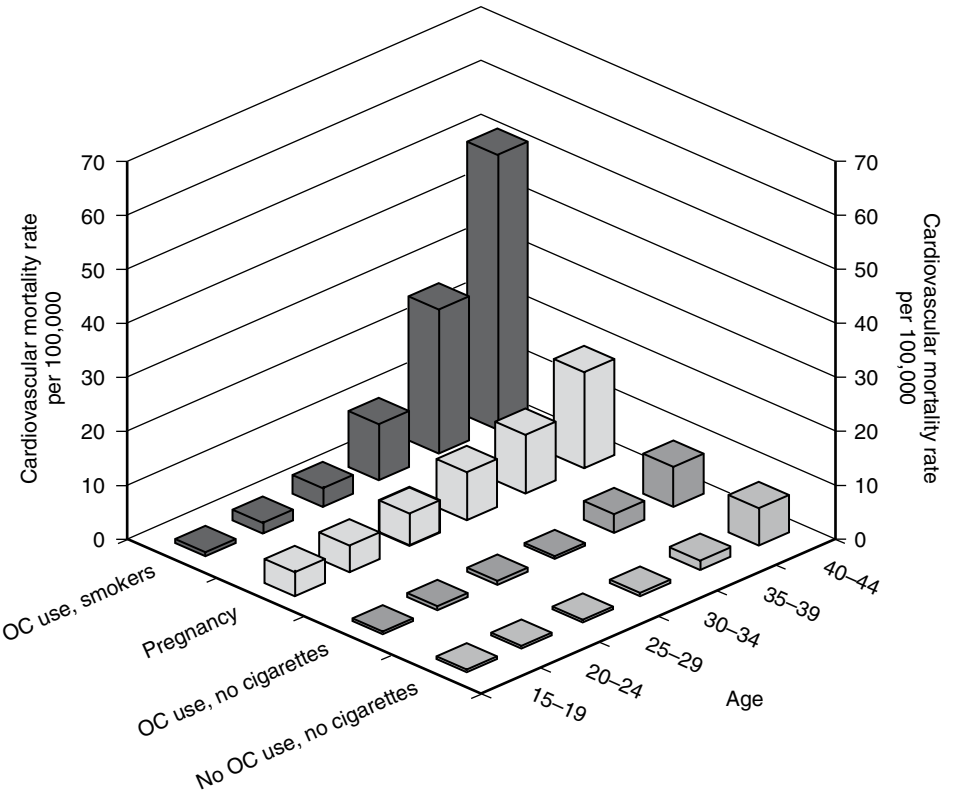

Figure 30-6 Estimated annual cardiovascular mortality rates associated with oral contraceptive (OC) use and smoking compared with pregnancy.
Data from Schwingl PJ, Ory HW, Visness CM: Estimates of the risk of cardiovascular death attributable to low-dose oral contraceptives in the United States. Am J Obstet Gynecol 1999;180 (1 Pt 1):241–249.

cytology testing should begin approximately 3 years after the initiation of vaginal intercourse. Pelvic examination should not delay or deter contraceptive services.

MANAGEMENT

Adolescents at risk for unintended pregnancy should be counseled about contraceptive options, regardless of the presenting complaint or reason for visit. This counseling can be challenging for the clinician and confusing for the patient. It includes the communication of a digestible amount of information; screening for medical contraindications or risks; dispelling of myths and misinformation; understanding of patient preferences; discussion about confidentiality; and parent or partner involvement if desired by the adolescent.

Once a specific method is chosen by the patient, the clinician should review its effectiveness, correct use, medically serious risks, and bothersome side effects. Younger adolescents are at higher risk for discontinuation, incorrect use, and inconsistent use of all methods. Additional time and effort expended by the clinician to help the adolescent use her chosen method correctly decreases the likelihood of a subsequent unintended pregnancy. Before leaving the office, the adolescent should understand when to initiate use of the method; its common side effects; serious side effects that should prompt immediate consultation and/or discontinuation; what to do if the method is forgotten or problems with use arise (including a phone number to call); when a follow-up visit is recommended; when to consider emergency contraception; and the importance of consistent and correct condom use.

For many adolescents, emergency contraception may become an important option. In addition to encouraging the selection and consistent use of a highly effective method, clinicians should counsel adolescents about the availability of emergency contraception by prescription. Emergency contraception has been judged to be safe and effective in preventing unintended pregnancies and abortions, even for young teens. Although political considerations have delayed over-the-counter availability, the advance provision of a prescription for emergency contraception should be considered for some adolescents seeking contraceptive services.

Table 30-2 Methods of Contraception

Method	Characteristics	Effectiveness	Duration of Use	Advantages and Indications	Disadvantages and Cautions	Medical Risks	Side Effects and Frequency	Warning Signs	Chief Mechanism of Action	Specific Counseling Principles
					HORMONAL METHODS					
Combination oral contraceptive pills (OCs)	• Combination estrogen and progestin pills • 21/7 formulation or extended cycle 84/7 or other (arbitrary regimen) • Monophasic or multiphasic formulations	• Perfect use: 0.3% • Typical use: 8%	Daily pill-taking; ovulation may be more likely with extension of hormone-free interval	• Decreased dysmenorrhea and cycle-related pain (mittelschmerz) • Decreased menstrual blood loss • Decreased menstrual molimina and menstrual mood changes—PMS • Regular menstrual cycles • Decreased functional ovarian cysts • Decreased acne and hirsutism (PCOS) • Potential benefit on menstrual-exacerbated medical conditions (asthma, seizures) with extended cycling • Menstrual suppression for girls with developmental delay, hematologic conditions, or other medical conditions	• Daily administration • Need for refills every 28 days • Need for storage and daily access	• No protection from STIs • Increased risk for venous thromboembolic phenomena • Small increased risk for elevated blood pressure (BP) • Possible increased risk for cervical dysplasia and carcinoma (no need to modify American Cancer Society guidelines for screening initiation)	• Breakthrough spotting and bleeding occur in 30–50% of users in the first month of use, typically with resolution by the 3rd to 4th month of use • All other effects infrequent (< 5% or no different from placebo): breast tenderness, nausea or vomiting, increase in headache frequency or severity, mood changes • No greater weight gain than placebo in controlled trials	• **A**bdominal pain • **C**hest pain • **H**eadaches • **E**ye problems • **S**evere leg pain	Inhibition of ovulation	• Start day: quick start, first-day start, Sunday start • Daily regimen: take at consistent time with routine activities (e.g., tooth brushing) or set alarm (cell phone) • What to do with missed pills • Possible side effects; irregular bleeding common in first 1–3 months • Chart menstrual bleeding

Continued

Table 30-2 Methods of Contraception—cont'd

Method	Characteristics	Effectiveness	Duration of Use	Advantages and Indications	Disadvantages and Cautions	Medical Risks	Side Effects and Frequency	Warning Signs	Chief Mechanism of Action	Specific Counseling Principles
Transdermal patch	Estrogen and progestin in adhesive layer of patch	As with OCs	Once-a-week dosing × 3 weeks, with 1 week no patch	• Weekly administration • Likely similar to OCs; data not as well-substantiated as with OCs	• Similar to OCs • Difficult to conceal • Local skin irritation, patch detachment	Similar to OCs	Similar to OCs beyond 3 months, with greater risk of breast tenderness, spotting, and dysmenorrhea in early cycles	As with OCs	As with OCs	• Irregular bleeding may occur in first few cycles • Chart menstrual bleeding • Start day as with OCs • What to do with dislodged patch, missed patch, and late patches • Where to apply the patch
Intravaginal ring	Flexible, transparent ring releasing estrogen and progestin	As with OCs	Ring kept in place for 21 days, then removed for 7 days	• Convenience of monthly administration • Better cycle control than OCs • Indications and benefits likely similar to OCs—data not as well-substantiated as with OCs	Similar to OCs	Similar to OCs	Vaginal discomfort or discharge, possible expulsion	As with OCs	As with OCs	• Insert not later than cycle day 5, with backup for first 7 days • Chart bleeding
Progestin-only pills (POPs)	Progestin-only daily pill with no hormone-free days	Slightly less than combination OCs	Daily pill administration with need for obsessive regularity	• No estrogen for women with medical contraindications • Potential for amenorrhea or less bleeding • Decreased dysmenorrhea and menstrual molimina • Daily use less confusing • May be appropriate during breastfeeding	• Menstrual cycle disturbances common • Need for obsessive regularity of pill-taking • Possible increased risk of depression • Less available to pharmacies	• See WHO precautions • Have not been shown to increase cardiovascular diseases or malignancy • Less likely than combination OCs to cause headaches, elevated BP, and other medical risks	Irregular bleeding or amenorrhea common	• Abdominal pain (ovarian cyst or ectopic) • Amenorrhea after previously regular cycles (possible pregnancy) • Repeated, severe headaches • ≥ 3 hours	• Ovulation inhibition by decreasing GnRH pulse frequency, and suppression of midcycle LH and FSH peaks • Thickens cervical mucus, preventing sperm penetration	• Consistent daily pill-taking every 24 hours • Menstrual bleeding irregular • Chart menstrual bleeding • Ovulation not consistently inhibited • Use backup × 48 hours if late pills,

								late, need for backup	• Endometrial atrophy	or consider emergency contraception
Depot medroxy-progesterone acetate (DMPA)	Progestin-only intramuscular injection	• Perfect use: 0.3% • Typical use: 3%	Intramuscular injection every 12 weeks	• Extremely effective long-term, reversible contraceptive • No estrogen for women with medical contraindications • Potential for amenorrhea or less bleeding • Decreased dysmenorrhea and menstrual molimina • May be appropriate during breastfeeding • Temporary effective contraception (awaiting sterilization, during Accutane use) • Culturally acceptable (injections may be preferred in some cultures) • Minimal drug interactions • Decreased frequency of seizures in women with seizure disorders • Fewer crises in women with sickle cell disease	• Delayed return of ovulation up to 9–10 months after last injection • Weight gain, 2–3 kg/year, cumulative • Not possible to discontinue immediately • Return visit every 11–13 weeks • No protection from STIs • Possible increased risk of depression • Bone density declines that may be only partially reversible; FDA "black box" warning suggesting use <2 years	• See WHO precautions • Have not been shown to increase cardiovascular diseases or malignancy • Less likely than combination OCs to cause headaches, elevated BP, and other medical risks	• Irregular bleeding or amenorrhea common • Chart menstrual bleeding • Amenorrhea 50% at 1 year; 80% at 2 years	• Repeated, very painful headaches • Heavy bleeding • Depression • Severe lower abdominal pain • Pus, prolonged pain, or bleeding at injection site	• Ovulation inhibition by decreasing GnRH pulse frequency, and suppression of mid-cycle LH and FSH peaks • Thickens cervical mucus, preventing sperm penetration • Endometrial atrophy	• Inevitability of menstrual changes • Chart menstrual bleeding • Increasing rates of amenorrhea over time (50% at 1 year) • Need for injection every 11–13 weeks • Weight gain likely • Use of emergency contraception if >13 weeks • Adequate calcium intake (1300 mg/d)

Continued

Table 30-2 Methods of Contraception—cont'd

Method	Characteristics	Effectiveness	Duration of Use	Advantages and Indications	Disadvantages and Cautions	Medical Risks	Side Effects and Frequency	Warning Signs	Chief Mechanism of Action	Specific Counseling Principles
Progestin implant (Implanon—anticipated availability in near future)	Single 4-cm-long implant releasing progestin over 3 years	Perfect use and typical user failure rates the same: 0 pregnancies/70,000 cycles	Effective for 3 years	• Extremely effective long-term, reversible contraceptive • High continuation rates • No estrogen for women with medical contraindications • Coitus-independent • Potential for amenorrhea or less bleeding • Decreased dysmenorrhea and menstrual molimina • May be appropriate during breastfeeding • Minimal drug interactions	• Menstrual cycle disturbances common • No protection against STIs • Insertion and removal difficulties (likely less than Norplant)	• See WHO precautions • Cardiovascular diseases or malignancy	• Irregular bleeding very common • Amenorrhea common	See DMPA and POPs	As with DMPA	• Not yet available • Chart menstrual bleeding
Levonorgestrel intrauterine system (LNG-IUS)	Intrauterine device with levonorgestrel progestin release	Rivaling sterilization; 0.1% in first year Typical use = Perfect use	Approved for 5 years; likely up to 7 years	• Extremely effective long-acting method • Convenient • Low risk of side effects • Cost-effective • Decreased menstrual blood loss by 90% • Amenorrhea in 20–50% of users at 1 year	• Irregular bleeding common in early months • Cramping and pain with insertion • Risk of expulsion 2–10% • Risk of perforation with insertion, <0.1%	• Nulliparity may increase risk of expulsion • Slight increased risk of uterine infection in first 3 weeks after insertion • Women at risk for acquiring STIs may not be optimal candidates	• Irregular bleeding common in first few weeks • Amenorrhea 20–50% at 1 year • Cramping and pain with insertion	• Excessive bleeding • Pelvic pain or cramping • Expulsion • Lengthening of string may herald expulsion • Signs of PID: no evidence to support necessity of removing IUD to treat	• Impaired sperm function and prevention of fertilization • Thickens cervical mucus • Inhibits sperm capacitation and survival • Endometrial atrophy • Not an abortifacient	• Insertion at any point in the cycle if not pregnant • Chart menstrual bleeding

Copper IUD	IUD with copper release	Rivaling sterilization; Perfect use: 0.6% Typical use: 0.8%	Approved for 10 years; likely up to 12 years	• Extremely effective long-acting method • Convenient • Low risk of side effects • Cost-effective	• Irregular bleeding common in early months • Cramping and pain with insertion • Heavier bleeding common • Increased cramping with menses • Risk of expulsion 2–10% • Risk of perforation with insertion < 0.1%	• Nulliparity may increase risk of expulsion • Slight increased risk of uterine infection in first 3 weeks after insertion • Women at risk for acquiring STIs may not be optimal candidates	• Irregular bleeding common in first few weeks • Cramping and pain with insertion • Increased bleeding and cramping	• Excessive bleeding • Pelvic pain or cramping and dysmenorrhea • Expulsion • Lengthening of string may herald expulsion • Signs of PID: no evidence to support necessity of removing IUD to treat	• Impaired sperm function and prevention of fertilization • Not an abortifacient	• Insertion at any point in the cycle if not pregnant • Chart menstrual bleeding
Emergency contraception—emergency contraceptive pills (ECPs)	Two regimens available: progestin-only and estrogen/progestin combination	• Progestin-only (levonorgestrel) reduces risk of pregnancy by 89% • Combination pills reduce risk of pregnancy by 75%	• Traditionally taken as 2 doses, 12 hours apart; also effective as single dose • Traditionally felt to be effective up to 72 hours after unprotected sex • Effective up to 120 hours • More effective if taken sooner	• If no contraception had been used • Male condom slipped, broke, or leaked • Female condom, diaphragm, or cervical cap torn, dislodged, or removed too soon • Too many missed pills: ○ • ≥ 2 missed pills in 1st week ○ • ≥ 5 pills in 2nd or 3rd week ○ • ≥ 2 days late restarting pack	• Combination pills: nausea 50%, vomiting 20% • Progestin-only pills: nausea/vomiting half as likely • Menstrual changes in subsequent cycle • Consider pregnancy if menses delayed >7 days	No evidence-based medical contraindications to emergency, other than pregnancy (when it is ineffective)	• Nausea and vomiting: see counseling • Delayed menses: see counseling	Exclude established pregnancy by history	• Depends on timing in cycle • Multiple sites of action, potentially affecting: - Follicle maturation, egg maturation, ovulation - Sperm migration and function - Fertilization	• Exclude already established pregnancy • Access use of contraception • Ensure that adolescent does not desire pregnancy • Discuss possible failure rate of ECPs • Discuss side effects: nausea/vomiting; consider prescribing anti-emetic

Continued

Table 30-2 Methods of Contraception—cont'd

Method	Characteristics	Effectiveness	Duration of Use	Advantages and Indications	Disadvantages and Cautions	Medical Risks	Side Effects and Frequency	Warning Signs	Chief Mechanism of Action	Specific Counseling Principles
				• Late for DMPA > 14 weeks • Late reinserting ring ≥ 2 days • *Coitus interruptus* practiced incorrectly • IUD expelled • Rape or sexual assault					- Zygote, morula, and blastocyst development and transport in tube and endometrial cavity - Development of receptive uterine lining - Maintenance of necessary hormone levels by the corpus luteum • Does not interrupt an established pregnancy—not an abortifacient	• Discuss choice of ongoing contraception and need to initiate new method • Discuss the lack of protection for future acts of unprotected intercourse • See clinician for exam if no period in 3 weeks
					BARRIER METHODS					
Condoms: Male	• Latex and nonlatex (polyurethane) as well as intestinal caecum ("natural skin") • Spermicidal lubricant as option; Nonoxynol-9 may increase risk of STI acquisition	• Perfect use: 2% • Typical use: 15%	Single use	• By decreasing risk of STIs, help to preserve fertility • Inexpensive • Available without exam, prescription, or fitting • Easy to use • Male participation • Portability	• Latex-allergic individuals should use polyurethane condoms • Individual concerns about decreased sensitivity • Disruption of spontaneity • Problems with erection	• Latex allergy • Nonoxynol-9 possibly associated with increased risk of STI acquisition	Infrequent	Observe correct technique "start to finish"	Barrier to semen passage	• Have condoms available • Store in cool place • Check expiration date • Discuss condom use with partner • Open carefully • Use "start to finish" before any contact

	• Decreased risk of STIs (including HIV) when used consistently and correctly			• Minimal side effects • Adolescents at risk for STIs should use in addition to hormonal methods	• Embarrassment with purchase or discussion • Coitus-dependent • Lack of male cooperation • Polyurethane condoms may be more likely to break than latex					• Unroll correctly • Water-based lubricants only, if required • Hold condom in place at the base before withdrawing penis • Check condom for damage • If condom breaks, falls off, leaks, or not used: emergency contraception • Do not reuse
Vaginal barriers: female condom, diaphragm, contraceptive sponge, cervical cap, Lea's Shield, FemCap	• Physical barriers used with spermicide • Varying designs	• Female Condom Perfect use: 5% Typical use: 21% • Diaphragm Perfect use: 6% Typical use: 16% • Sponge Perfect use: Parous 20% Nulliparous 9% Typical use: Parous 32% Nulliparous 16% • Cervical Cap Perfect use: Parous 26% Nulliparous 9%	• Single use for female condom, sponge • Multiple use for diaphragm, cap • Device-specific instructions for length of time inserted prior to intercourse, time left in place after intercourse, and need to reapply spermicide with second act of intercourse	• Medically safe • No systemic effects • Female-controlled method • Use when contraception is needed intermittently • STI protection likely	• Nonoxynol-9 may increase risk of STI acquisition • Increased risk for UTI, bacterial vaginosis, and vaginal candidiasis • Physical discomfort due to device • Physical discomfort due to spermicide • Latex allergy (diaphragm, cap) • TSS rare • Fitting issues • Difficulty removing (sponge)	• No systemic effects of spermicides • No risks with fetal spermicide exposure	• UTIs, vaginal infections not uncommon • Latex allergy, especially in health care workers	TSS warning signs: - Sudden high fever - Vomiting, diarrhea - Dizziness, faintness, weakness - Sore throat, aching muscles and joints - Rash (like a sunburn)	• Physical barrier to shield cervix from semen • When used with spermicide, killing sperm	• Combination of methods with condoms increases effectiveness (do not use male and female condoms together) • Correct and consistent use • No douching after intercourse • Avoid oil-based lubricants • Specific method fitting (diaphragm, cap) • Specific method instruction with insertion and removal • Specific method instruction with repeated intercourse

Continued

Table 30-2 Methods of Contraception—cont'd

Method	Characteristics	Effectiveness	Duration of Use	Advantages and Indications	Disadvantages and Cautions	Medical Risks	Side Effects and Frequency	Warning Signs	Chief Mechanism of Action	Specific Counseling Principles
		Typical use: Parous 32% Nulliparous 9%								• Have supplies and spermicide available • Cleaning and disinfecting reusable methods (diaphragm and cap) • Discuss emergency contraception
Spermicides	• Formulations include gel, foam, cream, film, suppository, or tablet • Chemicals that kill sperm in different doses and concentrations	• Perfect use: 18% • Typical use: 29% • Increased effectiveness with barrier method	Coitus-dependent with each act of intercourse	• Over-the-counter use • No medical encounter required • Female-controlled method • Can be used when intercourse is infrequent • Can be used as backup for hormonal methods	• Nonoxynol-9 may increase risk of STI acquisition • Allergy or sensitivity to spermicidal agents or ingredients in base • Inability to learn correct insertion technique may limit use • Possible risk of recurrent UTIs • Vaginal irritation • Waiting time for method to dissolve or disperse	• No systemic effects of spermicides • No risks with fetal spermicide exposure	Vaginal irritation	If used with vaginal barrier, watch for signs of TSS	• Kills sperm • Formulation helps disperse the spermicide • Surfactants destroy sperm cell membrane	• Combination of methods with condoms increases • Correct and consistent use • No douching after intercourse • Specific method instructions for use • Reuse with repeated intercourse • Have supplies available • Discuss emergency contraception

ECP, Emergency contraceptive pill; FDA, U.S. Food and Drug Administration; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HIV, human immunodeficiency virus; IUD, intrauterine device; LH, luteinizing hormone; OC, oral contraceptive; PCOS, polycystic ovary syndrome; PID, pelvic inflammatory disease; PMS, premenstrual syndrome; POP, progestin only pills; STI, sexually transmitted infection; TSS, toxic shock syndrome; UTI, urinary tract infection; WHO, World Health Organization.

Table 30-3 Contraceptive Effectiveness

Method	Percent of Women Experiencing an Unintended Pregnancy Within the First Year of Use: Typical Use	Percent of Women Experiencing an Unintended Pregnancy Within the First Year of Use: Perfect Use	Percent of Women Continuing Use at One Year
No method	85	85	
Spermicides	29	18	42
Withdrawal	27	4	43
Periodic abstinence	25		51
Calendar		9	
Ovulation method		3	
Sympto-thermal		2	
Postovulation		1	
Cap			
Parous women	32	26	46
Nulliparous women	16	9	57
Sponge			
Parous women	32	20	46
Nulliparous women	16	9	57
Diaphragm	16	6	57
Condom			
Female (Reality)	21	5	49
Male	15	2	53
Combined pill and minipill[a]	8	0.3	68
Evra patch[b]	8	0.3	68
NuvaRing[c]	8	0.3	68
Depo-Provera	.3	0.3	56
Lunelle[d]	3	0.05	56
IUD[e]			
ParaGard[f]	0.8	0.6	78
Mirena[g]	0.2	0.2	81
Norplant[b] and Norplant-2[i]	0.05	0.05	84
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.

Lactational Amenorrhea Method: LAM is a highly effective, *temporary* method of contraception.

[a] progestin only pill (POP)
[b] transdermal estrogen and progestin
[c] intravaginal ring releasing estrogen and progestin
[d] intramuscular progestin
[e] intrauterine device
[f] copper T
[g] levonorgestrel intrauterine system (LNG-IUS)
[h] subcutaneous 6-rod system releasing progestin
[i] subcutaneous 2-rod system releasing progestin

Excerpted from: Trussell, J: The essentials of contraception: Efficacy, safety, and personal considerations. In: Hatcher RA, Trussell J, Stewart FH, et al. (eds): *Contraceptive Technology*. New York,Ardent Media, 2004, p. 226, with permission.

MAJOR POINTS

- Unintended pregnancies among adolescents in the United States are common.
- Confidentiality is an essential aspect of contraceptive health care for adolescents.
- Successful use of contraception requires consistent, correct, and ongoing use.
- Hormonal contraceptives in general, and longer-acting methods in particular, provide effective contraception for adolescents.
- Most adolescents are healthy and have no contraindications to the use of hormonal contraception.
- Although use of specific hormonal methods may be relatively or absolutely contraindicated for patients with specific medical conditions, pregnancy also presents significant risks for these patients.
- Condoms should be encouraged for all adolescents, in addition to hormonal contraception.
- Advance provision of emergency contraception should be offered to all adolescents seeking contraception.

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MENTAL AND BEHAVIORAL PROBLEMS

PART IV

CHAPTER 31

Mental Retardation and Developmental Disabilities

THOMAS S. WEBB, MD, MSc

INTRODUCTION

Mental retardation (mental retardation) and/or developmental disabilities (developmental disability) affect an estimated 1.5–4% of individuals in the United States. Ongoing advances in fetal, neonatal, and pediatric care are contributing to steady increases in the numbers of infants, children, and adolescents with significant neurodevelopmental and genetic conditions. These trends have prompted a gradual change in sociocultural attitude such that increasing proportions of children and adolescents with neurodevelopmental disabilities live at home with their families, attend school with typically developing peers, and are incorporated into community life. Consequently, clinicians who care for adolescents can expect to see increasing numbers of patients with developmental disabilities. Pediatricians, family practice physicians, and adolescent medicine specialists commonly are asked to coordinate the health care provided by a multidisciplinary team and to facilitate access to educational and community services. This coordination requires an understanding of the spectrum of conditions that contribute to neurodevelopmental disabilities. The objectives of this chapter are to define the core concepts and conditions, review the epidemiology and pathophysiology of mental retardation and neurodevelopmental delay, and suggest approaches to evaluation and management.

DEFINITIONS

Adaptive behavior is defined by the American Association on Intellectual and Developmental Disabilities the "collection of conceptual, social, and practical skills that people have learned so they can function in their daily lives." Examples of conceptual skills include reading, writing, and money concepts. Social skills include developing interpersonal relationships, following instructions, and obeying laws. Practical skills are everyday activities such as bathing, toileting, dressing, preparing food, using the telephone, driving or using public transportation, shopping, paying bills, and working. Adaptive functioning can be assessed using standardized methods (i.e., the Vineland Adaptive Behavior Scales) to determine an age equivalence and standard score similar to IQ testing. The IQ and adaptive behavior scores can then be used to determine what levels of community supports would be beneficial to the individual.

Developmental disability is defined by the Developmental Disabilities Assistance and Bill of Rights Act of 2000, Public Law 106–402, according to the five criteria noted in Box 31-1. Not all individuals with developmental disabilities have mental retardation,

Box 31-1 Federal Definition of Developmental Disability (Public Law 106–402)

A condition that:

- Is attributable to a mental or physical impairment or both
- Is manifested before the age of 22 years
- Is likely to continue indefinitely
- Results in substantial functional limitations in three or more life areas
- Requires services, individualized support, or other forms of assistance

Box 31-2 Definition and Classification of Mental Retardation

Definition: Significant limitations of both intellectual function and adaptive behavior beginning at age < 18 years.

Classification by IQ:

- Borderline 70–79
- Mild 50–69
- Moderate 35–49
- Severe 20–34
- Profound < 20

nor do all individuals with mental retardation meet the criteria for the diagnosis of a developmental disability. A developmental disability can differentially impact motor, communication, and cognitive abilities, resulting in considerable heterogeneity across affected individuals. Thus, the adolescent with the communication impairments of autism has different issues and needs than the adolescent with the motor difficulties of cerebral palsy or the adolescent with the cognitive issues surrounding idiopathic mental retardation.

Intellectual function involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly, and learn from experience.

Intelligence quotient (IQ), determined by cognitive testing, is used to assess intellectual functioning and capacity. Most IQ tests have a standard error of five points. The cut-points between the levels of mental retardation therefore differ by five points across evaluators and publications. Some evaluators consider scores as high as 75 to reflect mild mental retardation. In addition, IQ testing depends not only on the individual's cognitive capacity but also on cultural and language background, emotional and physical health, and testing environment. Results therefore must be interpreted within the context of these factors to determine whether it is a valid measure. Repeated testing over time also helps to determine the accuracy and stability of the diagnosis.

Mental retardation is defined by the American Association on Intellectual and Developmental Disabilities as "a disability characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills" that originates before age 18 years. By most definitions, a score that is at least two standard deviations below the mean IQ of 100 is considered mental retardation. The levels of mental retardation are categorized by IQ range as borderline, mild, moderate, severe, and profound (Box 31-2).

Although the term mental retardation is frequently used in the health, education, and legal systems, there is a growing effort to use alternative language that carries less negative connotations. Cognitive disability and intellectual disability are preferred terms in the disability community. In Britain, mental retardation is frequently called learning disability, which is different than the typical U.S. definition of a specific problem in reading, writing, mathematics, or other single area of learning. For the purposes of this chapter, we use the traditional term mental retardation but encourage the use of cognitive or intellectual disability.

People-first language recognizes the person before the disability. The phrase "the patient with autism" is people-first, appropriate language. The phrase "the autistic patient" is considered inappropriate.

World Health Organization (WHO) definitions of impairment, disability, and handicap provide a standard terminology that supports a holistic approach to the care of individuals with developmental disabilities. For example, an adolescent with spina bifida has an impairment in the motor function of her legs, resulting in an ambulatory disability and a handicap when accessing buildings without ramps. The WHO International Classification of Function (Figure 31-1) provides a conceptual model of the interactions between health, impairment, disability, and environment leading to either participation or handicap.

EPIDEMIOLOGY

Prevalence estimates of mental retardation and developmental disability vary depending on the diagnostic criteria used and the populations studied. For example, criteria for the diagnosis of open spina bifida are present at birth, whereas some criteria for the diagnosis of cerebral palsy call for the persistence of clinical manifestations until at least age 2 years. Thus, birth-cohort data may reflect different prevalence rates for cerebral palsy than do early

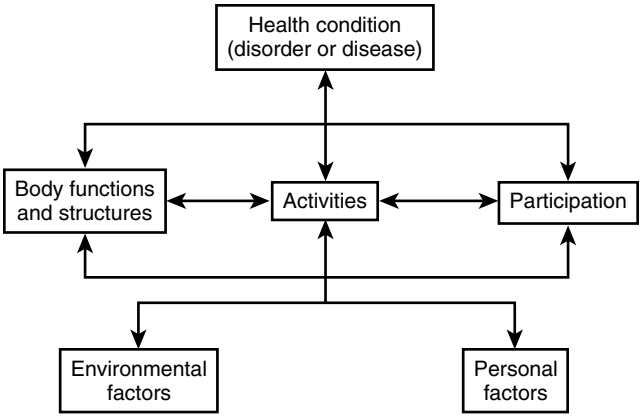

Figure 31-1 WHO international classification of function. Conceptual model of interactions leading to individual social participation or limitation/handicap.
From the World Health Organization: *International Classification of Functioning, Disability, and Health.* Geneva, World Health Organization, 2001, pp. 1–21. This figure has been reprinted with permission of the World Health Organization (WHO), and all rights are reserved by the Organization.

childhood data. Similarly, because autism spectrum disorders or mild mental retardation might not be recognized until school age, prevalence estimates for toddlers may be considerably lower than those for older children.

In addition to subject age, the site of subject recruitment (e.g., clinical setting, school) affects the estimate. Although most children live at home and in the general community, those with more profound disabilities may require institutional placement and would therefore be missed in community-based studies. Standard epidemiologic tools, such as birth registries, medical records, school system data, and community agency reports therefore provide varying estimations rather than a composite picture of prevalence and service need.

Using early intervention and school-based prevalence data, 4–17% of children qualify for the diagnosis of developmental disability. Preschool intervention and special-education services at the elementary school level can facilitate development so that some children do not meet the federal definition of developmental disability by adolescence. Using national surveys and more rigorous classification systems, the overall population prevalence rates are 7.8 per 1000 for mental retardation and 11.3 per 1000 for developmental disability. An estimated 1.4 per 1000 individuals with mental retardation reside in institutions.

Specific conditions other than mental retardation that are commonly associated with developmental disability include cerebral palsy (0.35%), autism (0.34%), and Down syndrome (0.12%). As definitions and case finding methods change, autism may become statistically more prevalent. Severe hearing loss (0.11%) and vision impairment (0.12%) are conditions with multiple possible etiologies that can be classified as developmental disability. Most of these estimates reflect population rather than birth prevalence, resulting in higher rates for conditions with longer survival.

PATHOPHYSIOLOGY

A developmental disability can be congenital or acquired. A congenital condition can result from a chromosomal abnormality, single gene defect, multifactorial condition, or environmental factors such as maternal malnutrition, alcohol or drug abuse, placental/intrauterine problems, trauma, or infections. There is a growing literature of potential environmental toxins associated with congenital abnormalities. Approximately 30–50% of mental retardation remains unexplained despite improvements in neuroimaging and genetic testing, although newer technologies such a functional magnetic resonance imaging and genetic microarray testing may provide advancements in the near future (Table 31-1).

EVALUATION

Adolescents with developmental disabilities benefit from periodic evaluation of physical, psychological, and behavioral health. This requires a review of school and adaptive function, prevocational progress, and community involvement. Physical evaluation of the adolescent with unexplained mental retardation should include a periodic assessment of dysmorphic features, preferably by a provider trained in the recognition of the physical phenotypes associated with genetic conditions. Between 5% and 20% of syndrome diagnoses are made through these serial evaluations because the recognizable physical features develop over time in the older child. An example is the postpubertal development of macro-orchidism in males with fragile X syndrome, café au lait spots in neurofibromatosis, and adenoma sebaceum in tuberous sclerosis.

Table 31-1 Causes of Mental Retardation and Percentage of Cases Attributable to Each Cause

Cause	%
Idiopathic	30–50
Chromosome abnormality	4–28
Genetic syndrome	7–21
Abnormality of central nervous system	7–17
Teratogenic	5–13
Environmental deprivation	3–12
Prematurity	2–10
Metabolic	1–5

Adapted from: Curry CJ, Stevenson RE, Aughton D, et al.: Evaluation of mental retardation: Recommendations of a consensus conference. Am J Med Genet 1997;72:468–477.

Genetic Testing

Due to advances in genetic testing, adolescents with unexplained mental retardation may benefit from repetition of analyses done prior to the mid-1990s. Both the American College of Medical Genetics and the American Academy of Neurology recommend that children with mental retardation have at least one evaluation that includes chromosomal analysis, fragile X DNA testing (FMR1 mutation), and possibly the Rett syndrome genetic test (MECP2 deletion) in females. There is no longer a recommendation that dysmorphic features need to be present to justify chromosomal analysis. However, dysmorphic features, family history of mental retardation, and severity of mental retardation are associated with higher rates of abnormal findings on chromosomal analysis and fragile X testing.

Recommendations regarding gender-specific genetic testing in individuals have changed as better analyses have revealed less discrepancy in rates between males and females. For example, it is now recommended that fragile X testing should be performed in both females and males with unexplained mental retardation because the prevalence of FMR1 mutations approximates 2–4% in both genders. Although there are no recommendations yet to test males for Rett syndrome, the MECP2 deletion/mutation does occur in males with more severe mental retardation. In females, Rett syndrome is the second most common genetic cause of mental retardation after Down syndrome, and testing is recommended for females with mental retardation accompanied by regression, seizures, autistic behaviors, or stereotypic hand movements such as hand-wringing (Box 31-3).

Box 31-3 Evaluation of Unexplained Mental Retardation

Physical examination

- Dysmorphic features
- Growth parameters

Genetic testing

- Chromosome analysis
- Fragile X DNA testing

Magnetic resonance imaging of brain

- Focal neurologic asymmetries
- Microcephaly
- Macrocephaly
- Moderate, severe, profound mental retardation
- Spasticity

Computed tomography of brain

- Cranial/skull abnormalities
- Central nervous system calcification syndromes

The utility of testing for specific gene deletion syndromes such as velocardiofacial, Prader-Willi, or Williams syndrome depends on the physical and behavioral phenotype. It is probably more cost-effective to refer to a clinical geneticist prior to requesting these more expensive diagnostic tests. Routine testing for metabolic disorders is very low-yield at any age. If it has not been performed in childhood, it probably should be considered only in those adolescents with significant growth failure; recurrent unexplained severe illnesses; progressive loss of psychomotor skills; unusual physical features such as coarse facies, cataracts, corneal clouding, developmental bone abnormalities, skin changes (i.e., ichthyosis), or unexplained deafness; or unusual laboratory abnormalities such as unexplained metabolic acidosis, hyperammonemia, or hyperuricemia.

Genetic abnormalities associated with mental retardation increasingly are detected by newer technologies such as subtelomeric rearrangement analysis and microarray testing. As expected, their yield increases when there is a family history of mental retardation, growth retardation, multiple dysmorphic features, and concurrent congenital abnormalities. The utility of this testing depends, in part, on the patient or family's desire to confirm cause. The testing is of particular importance for reproductive planning by the patient and/or first-degree relatives.

Neuroimaging

Neuroimaging is recommended in the younger child with global developmental delay. The likelihood of finding minor structural abnormalities increases up to three-fold in the presence of microcephaly, macrocephaly, abnormal cranial contour, focal neurological asymmetries, and more severe cognitive impairment. In general, magnetic resonance imaging of the brain is more sensitive than computed tomography for the detection of small harmatomas or subtle abnormalities in myelination or gray matter differentiation. Studies are ongoing regarding the utility of functional magnetic resonance imaging and positron emission tomography scanning in patients with mental retardation.

Multifactored Evaluation

Adolescents with developmental disabilities can have variable strengths and challenges in cognitive, academic, social, and perceptual motor skills. Multifactored evaluation can help determine the appropriate learning environment for the adolescent, including needed services and adaptations. A comprehensive evaluation of intelligence, functional/adaptive skills, language and communication skills (including reciprocal social abilities), and academic skills (reading, writing, spelling, and arithmetic) will elucidate most learning challenges. These evaluations can be requested through the school district under the Individuals with Disabilities Education Act (Box 31-4).

Box 31-4 Recommended Components of Multifactored Evaluation

- Cognitive/intelligence (IQ)
- Adaptive/behavior scales
- Academic (reading, writing, arithmetic, spelling)
- Receptive and expressive language
- Pragmatic/social skills
- Mental health assessment
- Vocational readiness assessment (ideal but not routine)

Learning and development are not static processes, and changes can occur for students already diagnosed with learning problems and currently receiving school services. Periodic reassessment by multifactored evaluation allows the adolescent, family, and school to adjust the learning program to these changing needs. Particular attention should be given to an adolescent who manifests deterioration in school performance or behavior. In addition to a reevaluation of the school's educational and behavioral plan, adolescents with developmental disabilities are at increased risk for the development of mental health disorders. Routine mental health screening should therefore be included in the periodic assessments. It is important for clinicians, teachers, and caregivers to remember that adolescents with more significant cognitive impairments may manifest their emotional disturbances through behaviors such as temper tantrums, self-injury, or physical aggression.

Social skills typically are learned informally through nonclassroom activities, sports, clubs, volunteering, and job opportunities. Adolescents with developmental disabilities may need more formalized social skills programs, as they often are excluded from these typical peer activities. The health care provider needs to ask specifically about the adolescent's involvement in activities that may facilitate vocational development, such as volunteerism and after-school or summer jobs, as well as participation in group activities such as Special Olympics, therapeutic recreation classes, or social skills development classes offered through speech therapists or other service providers.

MANAGEMENT

Medical Home

The adolescent medicine provider is uniquely qualified to be the centerpiece of an integrated system of care that addresses the primary, preventive, specialty, psychosocial, and financial needs of the patient with a developmental disability. The American Academy of Pediatrics (AAP), Healthy People 2010, the New Freedom Initiative, and the Institute of Medicine all recommend better care coordination for children and youth with special health care needs. The AAP endorses the concept of a medical home, which is an "accessible, continuous, comprehensive, family-centered, coordinated, compassionate, and culturally effective" practice that partners with the family to negotiate and coordinate services through the health care, educational, and community systems.

The medical home includes a coordinated plan of care across disciplines that incorporates the values and goals of the adolescent and family; a centralized, accessible, confidential record of pertinent medical information; linkages to family and community supports; the continuous education of all participants about the patient's condition and needs; and an ongoing needs assessment regarding school and social activities.

The longitudinal, comprehensive medical care of adolescents with developmental disabilities should include typical primary and preventive care as well as disability-specific monitoring and screening for the development of secondary conditions. For example, adolescents with spina bifida, just as those without, should receive preventive care according to the evidence-based recommendations discussed in Chapter 2. In addition, adolescents with spina bifida frequently require regular re-evaluation of pre-existing issues (e.g., neurogenic bladder and bowel, ventriculperitoneal shunt, scoliosis, mobility equipment) and screening for new, high-prevalence complications (e.g., obstructive sleep apnea, decubitus ulcers, kidney stones). In the medical home model, the primary care provider offers these preventive and screening services; facilitates the involvement of other health professionals; coordinates the delivery of care; and promotes communication with the patient, family, and health care team.

Box 31-5 lists, by organ system, conditions that are found more frequently or are more difficult to diagnose in patients with developmental disabilities. In addition, it is important to utilize the most appropriate growth charts for a given condition. Some diagnoses, such as cerebral palsy, Down syndrome, and Williams syndrome, have diagnosis-specific growth charts, which can be obtained from the respective advocacy agencies.

Some adolescents with developmental disabilities cannot easily provide medical histories. Others have significant anxiety about medical visits and may demonstrate challenging behaviors. Many of the examination techniques that help younger children, such as distraction, hand-over-hand palpation, warnings, and choices, can also help older patients. Physical restraint should be avoided whenever possible. Scheduling extra time for the office visit and delaying the physical examination until late in the visit will usually help.

Box 31-5 Common Conditions of Adolescents with Developmental Disabilities

Dermatological
- Pressure sores
- Xerosis

Endocrinological
- Early/delayed puberty
- Hypogonadism

Gastrointestinal
- Constipation
- Encopresis

Gastroesophageal reflux
- Rumination
- Swallowing difficulties

Genitourinary
- Enuresis
- Undescended testes

Mouth, Ears, Eyes
- Dental caries
- Gingivitis
- Hearing loss
- Vision problems

Neurological
- Sleep disorders
- Seizures

Orthopedic
- Dislocations
- Kyphoscoliosis
- Hypermobility
- Osteopenia
- Overuse syndromes

Psychiatric
- Attention Deficit/Hyperactivity Disorder
- Anxiety
- Depression
- Obsessive-compulsive disorder
- Oppositional defiant disorder

Pulmonary
- Aspiration
- Sleep apnea

Guidelines about the goals and tasks of the medical home are available from professional societies such as the AAP, the American Academy of Family Medicine, and the American Association of Medical Genetics, as well as from advocacy groups such as the Down Syndrome Association and the Spina Bifida Association. These guidelines outline both general recommendations for youth with special health care needs and screening and monitoring recommendations for youth with specific developmental disabilities.

Immunizations

With few exceptions, adolescents with developmental disabilities should receive all routine immunizations. Many individuals with developmental disabilities remain in group settings beyond the school years, and all of these settings should require evidence of immunization. Parents, and subsequently their mature children, therefore should be encouraged to maintain life-long records of up-to-date immunization.

Adaptive Equipment

The health care provider should routinely assess adaptive equipment such as orthotics, wheelchairs, canes, and crutches, and communication devices for fit, correct usage, working condition, and effectiveness. Occasionally, equipment is no longer needed. More often, potentially beneficial adaptations are discontinued by the adolescent. Taking the time to listen to the adolescent, to review the initial reasons for the equipment, and to consider a reassessment or update by the prescribing specialist can help maximize the adolescent's function and autonomy.

Adolescent Autonomy

Adolescents with developmental disabilities should be encouraged to assume increasing responsibility for their health care and activities of daily living. While adolescents and parents usually consider this an important and positive goal, the transition presents new challenges for families. Health providers can facilitate the transition by giving adolescents up-to-date lists of their medical problems, medications, allergies, equipment and vendors, and provider and pharmacy contact information.

All adolescents who are developmentally ready for time alone with their health providers should be offered that time at every health care visit. Parents can help adolescents prepare for visits during the transition phase by thinking through and writing down topics for discussion. Health providers should speak directly to adolescents rather than through parents and should seek adolescents' opinions regarding management decisions. Although final decisions may rest with legal guardians, adolescents find this shared decision making to be critical to their self-concept and willingness to participate in their care.

Adolescents who have difficulties with fine or gross motor function may struggle with aspects of self-care

such as bladder catheterization, personal hygiene, or medication adherence. Occupational and physical therapists can suggest small adaptations such as pictorial plus written instructions, strategically placed reminder signs, alarms on watches or cell phones, and checklists. Internet resources that help promote adolescent self-care are shown in (Box 31-6).

Psychosexual Counseling

Alterations in sensation, motor control, flexibility, and learning ability can affect sexual curiosity and exploration during puberty for adolescents with developmental disabilities. Low self-esteem or anxiety about sexual function lead some adolescents with developmental disabilities to resist psychosexual development, whereas sexual risk behaviors become a path by which others attempt to fit in with peers. Adolescents with cognitive and/or emotional issues can become both sexual victims and/or perpetrators due to difficulty understanding social cues and societal expectations. All adolescents benefit from developmentally appropriate counseling about sexuality and sexual behavior. For adolescents with developmental disabilities, this counseling can be incorporated into an interpretive interview in which the clinician teaches and the patient explains back to the clinician his or her understanding of the information. A teaching physical examination allows the clinician to explain developmental changes, such as occur in the breasts, genitalia, and skin, to the patient as the examination proceeds.

Health Insurance

Adolescents with developmental disabilities often have greater medical needs and costs than their typically developing peers. Private insurance policies vary in the coverage provided, and obtaining accurate information can be difficult. Some families may qualify for additional coverage through their state's Title V program, Medicaid, or the State Child Health Insurance Program (SCHIP). Some adolescents qualify for Supplemental Security Income (SSI), which can provide monthly payments to cover health care costs and access to Medicaid insurance. If a parent is retired, disabled, or deceased, the adolescent may qualify for Social Security Disability Insurance under that parent's policy. This program also provides monthly income payments as well as access to Medicare insurance after a 2-year waiting period.

Parental insurance plans often cover adult children up to the age of 21–25 years if the dependent remains in school. Some allow disabled, dependent children to remain on the parent's policy indefinitely with proper documentation. Parents should be encouraged to explore these options with their benefits office before the adolescent's 18th birthday. Although many state programs, such as Title V and SCHIP, end at age 18–21 years, for certain diagnoses a few states continue Title V resources through adulthood. Covered services such as medical equipment should be carefully reviewed and utilized before coverage is lost.

At age 18 years, the adolescent who has been receiving SSI must undergo a redetermination process using the more stringent adult criteria. However, SSI also has financial eligibility requirements, which would no longer include the parents' resources. The adolescents' own assets and income become the financial criteria. Therefore, families should be aware that most adults who receive SSI cannot have individual assets exceeding $1500. Programs are available to preserve money for specific purposes; for example the Plan to Achieve Self-Support (PASS) program allows individuals receiving SSI to save money for a vocational goal such as college or opening a business. The Impaired Related Work Expenses (IRWE) and Blind Impaired Work Expenses (BIWE) programs allow deductions for impairment-related supports and work adaptations. Families can also create Special Needs Trusts, which allow money to be set aside for the individual without jeopardizing government benefits. Because these programs have complicated regulations, families should be encouraged to seek the assistance of experienced financial planners and lawyers.

Box 31-6 Internet Resources for Adolescent Self-Care Readiness

- Adolescent Health Transition Project: *http://depts.washington.edu/healthtr/*
- American Academy of Pediatrics: *http://www.medicalhomeinfo.org/tools/youthstart.html*
- Health Care Transitions: *http://hctransition.ichp/edu/Health*
- Ready to Work (HRTW) National Center: *http://www.hrtw.org/index.html*

School

Most adolescents with developmental disabilities qualify for an Individualized Education Program (IEP) as a result of the Education for All Handicapped Children Act of 1975 and the Individuals with Disabilities Education Act (IDEA) of 1990, which was last amended in 2004. An IEP provides for free and appropriate public education in the least restrictive environment for all students with disabilities and includes special education; transportation; speech, audiological, psychological, physical, and occupational therapy; and recreational and medical services. Most states use the following diagnostic categories for IEP services: autism, deafness, deaf-blindness, emotional

disturbance, hearing impairment, learning disability, mental retardation, multiple disabilities, orthopedic impairment, other health impairment, speech or language impairment, traumatic brain injury, and visual impairment (Box 31-7).

Medical providers can assist with the IEP development by providing a list of accurate diagnoses; describing conditions that might affect school performance; outlining health-related services needed during the school day; and educating families about their right to attend a pre-IEP conference, to refuse to sign an IEP until they are satisfied with the proposed services, and to have a friend or other advocate attend the IEP meeting. Although health care providers are welcome at IEP meetings, most can provide useful input through written communication or by teleconference. Offering to review the completed IEP for appropriate health-related services is valuable to families and schools. Families should also be counseled that they can request a reevaluation of an IEP at any time, even before the routine annual review is due.

When adolescents reach age 16 years, the IEP should include an individualized transition plan. Transition plans should include postsecondary education programs, which could be college, vocational training programs, supported community employment, enclaves, sheltered workshops, volunteering experiences, or adult day habilitation programming, depending on the choices and abilities of the adolescent. In addition, the plan should address community living, recreation and leisure, relationships, transportation, and community integration based on the adolescent's preferences. The adolescent should be present and, when possible, direct the development of the transition plan. As part of this transition planning, adolescents should request participation by representatives from the state vocational rehabilitation services. Vocational counselors can assist adolescents with planning for college or vocational-technical education. Participation in the latter has been shown to help students with developmental disabilities stay in school longer, improve attendance, and maintain employment. Students with an IEP are entitled to school services until at least age 21 years, although these services need not be in the classroom and often include community-based, vocational-technical training.

Box 31-7 Diagnostic Categories for Individualized Education Program (IEP) Services

- Autism
- Deafness
- Deaf-blindness
- Emotional disturbance
- Hearing impairment
- Learning disability
- Mental retardation
- Multiple disabilities
- Orthopedic impairment
- Other health impairment
- Speech or language impairment
- Traumatic brain injury
- Visual impairment

Guardianship

Parents of an adolescents with developmental disabilities are often surprised to learn they are no longer the legal guardians once their children reaches the age of majority (age 18 years in most states). Adolescents then become responsible for their own medical decisions. Under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), health care providers must have written permission from the adult patient to discuss care with anyone other than the patient. There have been medical emergencies where parents were refused access to their adult children with developmental disabilities because they did not have guardianship.

Guardianship is a legal process through the probate courts that requires the individual to be declared incompetent in at least one important area, such as medical decision making or the management of financial issues. A statement of expert evaluation, completed by a physician or psychologist, provides supporting documentation that the adolescent is unable to make self-care decisions in areas such as health, safety, living arrangements, and/or finances. After an application is submitted by the family, a hearing is held before a judge or magistrate who makes the formal declaration. Guardianship can be limited to only certain areas, such as health care, thus protecting the right of self-determination in other aspects of the individual's life. Box 31-8 lists options for decision support that preserve self-determination.

Box 31-8 Options For Decision Support that Preserve Self-Determination

- **Power of Attorney for Health Care Decisions:** Similar to the process used by the general population in case their decision-making capacity is diminished
- **Circle of Support:** An informal group of volunteer advocates who ensure all the needs of the individual are met
- **Micro-board:** Similar to a circle of support, but the individual serves as chair of the group
- **Conservatorship:** The individual is deemed mentally competent but has a physical disability that impairs his or her ability to make decisions

However, these options may not carry the same legal recognition across different states.

OUTCOME

At least 80–85% of adolescents with developmental disabilities survive into adulthood. Through quality care coordination by the adolescent health provider and with the assistance of family, friends, teachers, and counselors, many can integrate into their communities and form adult relationships, including friendships, dating, and marriage. Adolescents with developmental disabilities have various levels of living options, including independent living similar to typically developing young adults; remaining in the family home; living autonomously with support services; or residing in a setting with greater daily assistance, such as a group home, intermediate care facility, or residential care (Table 31-2). The most appropriate setting depends on the abilities of the adolescent and the preferences of both the adolescent and family. Regardless of the choice, families should periodically review these options with the responsible community funding agency.

Finally, families should be encouraged to develop a lifelong plan for the adolescent's future that addresses issues such as future guardianship, financial planning, wills, and special needs trusts.

Table 31-2 Living Options for Adults with Mental Retardation/Developmental Disabilities

Independent	25–30% live independently; half of these adults live with a spouse.
Family home	60% live with family; half of these adults live with elderly parents.
Supported living	20% receive individualized support, choosing where they wish to live.
Group home	40% live with 1–6 residents, supervised partial-day to 24 hours daily.
Intermediate care	10–20% live in Medicaid-funded facilities mandated to provide active treatment services to enhance development, well-being, and quality of life in the least restrictive environment possible. Usually for nonambulatory adults who require significant assistance with activities of daily living.
Residential care or nursing home	10–20% live with 16 or more residents in larger settings that provide the highest level of continuous support. Usually for adults with significant behavioral challenges who are unsafe in less intensive care environments.

Adapted from: Bradock D, Emerson E, Felece D, et al.: Living circumstances of children and adults with mental retardation or developmental disabilities in the United States, Canada, England and Wales, and Australia. Ment Retard Dev Disabil Res Rev 2001;7:115–121.

MAJOR POINTS

- Mental retardation and/or developmental disabilities affect an estimated 1.5–4% of individuals in the United States.
- Mental retardation is diagnosed by standardized testing and is defined as a limitation of both intellectual and adaptive functions with onset before age 18 years.
- A developmental disability is categorized by federal law as a mental and/or physical impairment manifesting before age 22 years that is lifelong, causes limitation in three areas of life function, and requires services, supports, and/or other assistance.
- Health providers should use patient-first language when referring to individuals with a disability.
- Routine genetic testing and neuroimaging should be considered in an adolescent with unexplained mental retardation, especially if previous testing has not been done within the past 10 years and/or there is a family history consistent with an inheritable disorder.
- Adolescents benefit from a multifactored evaluation to assess strengths and weaknesses when developing an Individualized Education Program through the school system.
- Adolescents with developmental disabilities should be encouraged to discuss their diagnoses with their health care providers during an interpretive interview and teaching physical examination. They should also gradually assume responsibility for their own medical care, which can be facilitated by portable, personal medical records.
- Adolescents with developmental disabilities should have an individualized transition plan for school, health care, and future community services, beginning at age 16 years. This plan should address self-care and independent living skills, vocational planning, community integration, financial planning, and health insurance and medical resources for the future.

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CHAPTER 32

Attention-Deficit/ Hyperactivity Disorder in Adolescence

MARK L. WOLRAICH, MD

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common mental disorder of childhood. Although the manifestations of ADHD probably are present from birth, the diagnosis usually is not made until children are of elementary school age. Up to 65% of diagnosed children continue to manifest signs and symptoms of ADHD after puberty and, in many cases, the condition is first recognized in adolescence. Given the high prevalence of ADHD and its effects on behavior, clinicians who care for adolescents should be familiar with its presentation, evaluation, and management.

EPIDEMIOLOGY

The prevalence of ADHD in the U.S. elementary school population is approximately 9% among males and 3% among females. Boys are more likely than girls to have disruptive behavior associated with hyperactivity, whereas girls are twice as likely as boys to have inattention. The annual costs for office visits and injury-related visits are 62% and 130% higher, respectively, for a child with than without ADHD.

DIAGNOSIS

Diagnostic Criteria

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) defines ADHD as inattention and impulsivity/hyperactivity. As outlined in Table 32-1, nine behaviors characterize each of these two core dimensions. Inattention includes problems of executive function, such as disorganization and difficulty filtering out extraneous stimuli. Impulsivity/hyperactivity includes three impulsive and six hyperactive behaviors. A behavior is considered present if it is inappropriate for age, has been present for at least 6 months and causes some impairment in more than one setting (e.g., school and home). In addition, some of the symptoms need to begin before age 7 years, causes significant impairment, and is not the result of another mental disorder (Box 32-1). Some individuals manifest many of the behaviors but, because of compensatory strengths, have no significant dysfunction and therefore do not meet diagnostic criteria.

DSM-IV identifies three subtypes of ADHD, based on the symptoms that have predominated during the preceding 6 months. ADHD, Combined Type is diagnosed if six or more symptoms of inattention and six or more symptoms of impulsivity/hyperactivity have been present for at least 6 months. ADHD, Predominantly Inattentive Type is diagnosed for six or more symptoms of inattention but fewer than six symptoms of impulsivity/hyperactivity. ADHD, Predominantly Hyperactive-Impulsive Type is diagnosed for six or more symptoms of impulsivity/hyperactivity but fewer than six symptoms of inattention.

Table 32-1 Dimensions and Behaviors of ADHD

Dimension	Behaviors
Inattention	Careless mistakes Difficulty sustaining attention Seems not to listen Fails to finish tasks Difficulty organizing Avoids tasks requiring sustained attention Loses things Easily distracted Forgetful
Hyperactivity/Impulsivity	
Hyperactive Type Impulsive Type	Fidgeting Unable to stay seated Moving excessively (restless) Difficulty engaging in leisure activities quietly "On the go" Talking excessively Blurting answers before questions completed Difficulty awaiting turn Interrupting/intruding upon others

Box 32-1 DSM-IV Criteria for the Diagnosis of ADHD

Each behavior is defined as present if it meets the following criteria:

- Inappropriate for developmental age
- Onset before 7 years of age
- Present for at least 6 months
- Present in two or more settings (e.g., home, school, or work)
- Significant impairment in social, academic, or occupational functioning

The three subtypes of ADHD are defined as follows:

- Combined — ≥ six behaviors in each dimension are present
- Inattentive — ≥ six behaviors in this dimension are present
- Hyperactive/Impulsive — ≥ six behaviors in this dimension are present

American Psychiatric Association: *Diagnostic and Statistical Manual of Mental of Mental Disorders*, 4th ed. TR. Washington, D.C., American Psychiatric Association, 2000.

Many studies have shown that the most salient manifestations of ADHD during childhood change during adolescence. Hyperactivity often diminishes as academic problems surface or increase. The child who could manage elementary school work may begin to struggle with the increased organizational, classroom, and homework demands of middle and high school. As expectations increase, adult supervision typically decreases. Peer relationships assume greater importance, and difficulties with social interactions often escalate. Adolescents with ADHD manifest both emotional immaturity and more emotional lability than same-aged peers. They therefore tend to spend relatively more time with younger children or adults who tolerate their behavior.

Limitations of the Diagnostic Criteria

The DSM-IV diagnostic criteria for ADHD are less than perfect. First, the criteria do not include a developmental perspective. Second, they were derived primarily from research in children aged 6–13 years. Third, the manifestations are highly dependent on contextual factors, such as classroom structure and adult-to-child ratio. Fourth, the criteria do not specify whether the observers should be parents, teachers, or other adults. Fifth, there is no adjustment for interobserver variability in the definition of inappropriate behavior. For all of these reasons, families and schools frequently look to clinicians for help with assessing behavior and learning during childhood and adolescence.

ASSOCIATED CONDITIONS

A diagnosis of ADHD is associated with a two- to five-fold lifetime risk of at least one other psychiatric disorder. The most common associated conditions are listed in Table 32-2. The conditions are categorized as internalizing and externalizing mental health disorders, cognitive deficits, motor dysfunction, and medical conditions. Prospective studies of children with ADHD demonstrate an increased risk for the development of major depressive disorder and substance-related disorder during adolescence and young adulthood.

An estimated 15–25% of adults with substance-related disorder have ADHD, and rates of substance-use treatment and substance-related motor vehicle collision are higher among adults with than without ADHD. ADHD is also associated with increased rates and earlier initiation of cigarette smoking. Evidence does not support, however, an association between treatment of ADHD with stimulants and subsequent development of substance use. In fact, a meta-analysis of seven studies demonstrated that treatment of ADHD with stimulant medication decreased the likelihood of subsequent substance use, with a stronger protective effect during adolescence than adulthood. A new diagnosis of ADHD should not be made in individuals who are actively using alcohol or illicit drugs because of the associated cognitive impairments. It is generally best to reassess

Table 32-2 Conditions Associated with ADHD

Category	Condition
Externalizing Mental Health	Oppositional defiant disorder
	Conduct disorder
	Substance-related disorder
Internalizing Mental Health	Major depressive disorder
	Dysthymia
	Generalized anxiety disorder
	Post-traumatic stress disorder
	Obsessive-compulsive disorder
	Panic disorder
	Phobia
Cognitive	Communication disorder
	Learning disorder
Motor Skills	Developmental coordination disorder
	Tourette syndrome
	Chronic tic disorder
General Medical	Sleep disorder
	Thyroid disorder
	Medication-induced disorder

after a minimum 1-month period of abstinence from all psychoactive drugs.

Sleep disturbance unrelated to pharmacotherapy has been reported in both children and adolescents with ADHD, although the literature in adolescents is far more limited. In children, the associated disorders include dyssomnias (e.g., insomnia, excessive sleepiness, disordered sleep/wake cycles) and parasomnias (e.g., sleep-related walking, terror, rhythmic movement, paralysis) (see Chapter 17).

EVALUATION

Obtaining a thorough developmental, behavioral, and school history from the adolescent and parents is the first step in the evaluation of ADHD. Although adolescents may be better able to describe their current symptoms than younger children, they tend to under-report impairment on both interview and self-completed questionnaires. Parents and teachers may have difficulty providing detailed information. This is further complicated by the limitations of parent and teacher reports on adolescents. In elementary school, a child typically spends most of the day with one or two teachers who observe that child in multiple settings. In middle and high school, an adolescent interacts with five to seven teachers daily, each of whom sees 100–150 students daily. Consequently, inter-rater variability on teacher ratings for ADHD is high, and intra-rater reliability changes as the school year progresses, with lower reliability in the fall than spring semesters.

For these reasons, information should be collected by direct interview of adolescent and parents; self-administered questionnaires completed by adolescent, parents, and multiple teachers; and review of Individual Education Plans (IEPs) or 504 Plans, if available. For the adolescent, the Conners-Wells Adolescent Self-Report Scale is recommended. For the parents and teachers, the respective versions of the Vanderbilt Forms are recommended(*http://www.nichq.org/resources/toolkit/*). These survey instruments focus specifically on the diagnosis of ADHD, take only a few minutes to complete and interpret, and are widely available. Psychoeducational testing does not establish or refute the diagnosis but can help identify areas of cognitive strength and weakness. Neuropsychological testing generally is not indicated in the evaluation of ADHD.

Clinicians should explain to parents that school-aged children and adolescents who are having educational problems are entitled to some school-based evaluation. Parents should be encouraged to request, in writing, that the school complete a multidisciplinary evaluation. If the diagnosis of ADHD has been established, a report from the clinician to the school can help facilitate the process. The school evaluation typically includes the *Wechsler Individual Achievement Test*, 2nd Edition (WIAT-II) or the *Woodcock Johnson Achievement Tests*, 3rd Edition (WJ-III) and a test of cognitive ability, as measured by the intelligence quotient (IQ). Definitions of impairment vary by state and school district, but most incorporate in the definition a discrepancy among ability, achievement, and performance as measured by grades.

Adolescents with ADHD should be evaluated for co-occurring conditions through parent and patient interview and the administration of a broad-based rating scale, such as the Youth Self-Report or the Behavior Assessment System for Children. The clinician should talk with the adolescent about the use of tobacco, alcohol, marijuana, and other drugs; driving behavior for those with a driving license or permit; and sexual risk behaviors.

MANAGEMENT

The National Institute of Mental Health (NIMH) Multimodal Treatment Study of Children with ADHD demonstrated that the combined use of medication and behavior therapy was more effective in the treatment of ADHD than medication alone, behavior therapy alone, or usual care. The rates of normalized behavior at 14 months of treatment were 68% for combined therapy, 56% for medication alone, 34% for behavioral therapy alone, and 25% for usual care. The specific medications and behavioral interventions are described later.

Stimulant Medications

More than 300 studies involving 6000 subjects have demonstrated the short-term efficacy of stimulant medications for the treatment of ADHD in children, adolescents, and adults. Table 32-3 summarizes the available formulations of dextroamphetamine, methylphenidate, and mixed amphetamine salts. The formulations differ in duration of action but are similar in effectiveness and side effects. A 70% response rate is reported for the first stimulant prescribed, and systematic trials of other formulations boost the total response rate to 80–90%. Despite this high response rate, nonresponse does *not* exclude the diagnosis of ADHD.

Newer stimulant formulations have extended the duration of action, thus avoiding administration at school. Methylphenidate extended-release preparations that utilize microbead technology (i.e., Metadate CD, Ritalin LA, and Focalin XR) have an 8-hour duration of action, which is equivalent to twice-daily dosing of regular methylphenidate. OROS methylphenidate (i.e., Concerta) utilizes an osmotic pump system and has a 12-hour duration of action.

The stimulant medications reduce the core symptoms of inattention, hyperactivity, and impulsivity; improve academic productivity; and, in some patients, reduce oppositional and aggressive behaviors. Stimulants do not, however, improve either academic performance (i.e., in contrast to productivity) or cognitive ability. As noted previously, stimulants do not increase (and may actually decrease) the risk of substance use. Although methylphenidate, but not dextroamphetamine, is reported to lower the seizure threshold, both medications have been used to treat ADHD in patients with seizure disorders, with no apparent increase or difference in the rates of recurrent seizures.

Side effects of all stimulants include anorexia, abdominal discomfort, sleep disturbance, anxiety, headache, and rebound behavior. Overfocus, defined as listlessness or "zombie-like" behavior, usually responds to a decrease in dose. Recent studies refute early concerns that stimulants exacerbate tics. The usual course of tic disorders is one of waxing and waning severity, thus complicating assessment of a potential association with stimulant medication.

Of particular concern and controversy is the potential association of the stimulant drugs with sudden death. As of 2006, 17 cases of sudden death in individuals on amphetamines and eight cases in individuals on methylphenidate had been reported to the U.S. Food and Drug Administration (FDA). Twelve of the 17 in the amphetamine group and seven of the eight in the methylphenidate group were younger than age 18 years. Given that these data emerged in the context of 1.5 million prescriptions for stimulant medications, the number of reports to the FDA might not represent risk over and above that of the general pediatric population. It is clear that a better surveillance system is required to identify individuals who are at significantly increased risk. On the basis of these data, the Drug Safety and Advisory Committee recommended to the FDA that stimulant drugs include a black-box warning describing their cardiovascular risks. The FDA decided against the black-box warning but does urge physicians to identify cardiac conditions in patients being considered for treatment with stimulant medications and, if prescribed, to monitor their cardiac status closely.

Table 32-3 Dosing and Pharmacokinetic Information

Medication	Brand Name	Starting Dose	Dose Interval	Onset	Duration (hr)	Maximum Dose
Mixed salts of amphetamine	Adderall	2.5–5 mg	QD–BID	20–60 min	6	40 mg
	Adderall XR	5 mg	QD	20–60 min	12	
Dextroamphetamine	Dexedrine/ Dextrostat	2.5 mg	BID–TID	20–60 min	4–6	40 mg
	Dexedrine Spansule	5 mg	QD–BID	60+ min	6 +	40 mg
Lisdexamfetamine	Vyvanse	30 mg	QD	20–60 min	10–12	70 mg
Methylphenidate	Concerta	18 mg	QD	20–60 min	12	54 mg
	Daytrana Patch	10 mg	QD	20–60 min	11	30 mg
	Methylin	5 mg	BID–TID	20–60 min	3–5	60 mg
	Methylin ER	20 mg	QD–BID	1–3 hrs	2–6	60 mg
	Ritalin	5 mg	BID–TID	20–60 min	3–5	60 mg
	Ritalin SR	20 mg	QD–BID	1–3 hr	2–6	60 mg
	Ritalin LA	20 mg	QD	8 hr	8	60 mg
	Metadate CD	20 mg	QD	8 hr	6–8	60 mg
Dextromethylphenidate	Focalin	2.5 mg	BID–TID	20–60 min	3–5	20 mg/day
	Focalin XR 7	5 mg	QD	20–60 min	4.5–7	20 mg/day
Atomoxetine	Strattera	0.5 mg/kg	QD	2–6 wk	24	1.4 mg/kg/day

Managing the side effects of the stimulant medications rests largely on dose titration and administration timing. The usual pediatric approach to dosing (i.e., mg/kg) does not apply well to stimulants. An adult with mild ADHD may require a much lower dose than a young child with severe ADHD, and the dose required by an individual may change significantly over time. It is best to begin all patients at the lowest dose for the given formulation and to increase the dose gradually, up to the recommended maximum dose, until behavior is optimized and side effects are minimized. Patients with the inattentive subtype may get by with 6–8 hours of coverage during the school day, whereas those with the impulsive/hyperactive or combined subtypes may require 12 hours of coverage. Functional aspects to follow when adjusting medication include classroom disruption, time required to complete homework, peer and family relationships, and ability to participate in organized activities.

Second-Tier Medications

Atomoxetine (i.e., Strattera) is a nonstimulant, highly specific inhibitor of noradrenergic reuptake approved for the treatment of ADHD. It demonstrates no abuse liability and, unlike the stimulants, is unscheduled by the Drug Enforcement Administration. It should be initiated at approximately 0.5 mg/kg/day and increased to 1.2 mg/kg/day in 2 weeks. Adolescents who continue to manifest symptoms can be increased to a maximum of 1.4 mg/kg/day or 100 mg/day. Adverse effects include sedation, appetite suppression, nausea, vomiting, and headaches. Most are short-term and can be managed by changing the time of administration or splitting the total daily dose. Atomoxetine does not appear to interact with the stimulants, but there are no formal studies of combined therapy, Atomoxetine dosing should be reduced if co-administered with agents that inhibit the P450 microsomal enzyme system.

Third-Tier Medications

Bupropion is not approved for the treatment of ADHD or for use in children, but one randomized controlled trial has demonstrated its efficacy in the treatment of childhood ADHD. Tricyclic antidepressants are not approved for ADHD but are approved for other uses in children. Their use should be limited to those adolescents who have failed other medication trials.

Behavioral Therapy

Behavior therapy is most effective when directed toward parents, other caregivers, and teachers and when used in combination with pharmacotherapy for the child or adolescent. The adult therapy focuses on developing a structured environment in which the adolescent has clear rules and limits. Play therapy, cognitive therapy, and cognitive-behavioral therapy directed at the child or adolescent has not demonstrated effectiveness in improving the core symptoms of ADHD. Family therapy may be helpful, particularly on issues such as sibling relationships, but the evidence for its efficacy is weak.

School and Social Adaptation

School problems, such as poor test grades and missed or incomplete assignments, are the most common parental complaints of adolescents with ADHD. Interventions targeting these problems, such as tutoring and assistive note-taking, tend to be labor-intensive and inaccessible to many youth. A diagnosis of ADHD alone does not qualify a student for these services in public schools. However, many students with ADHD qualify under the "Other Health Impaired" category of the Individuals with Disabilities Education Act or under Section 504 of the Rehabilitation Act. Physicians may facilitate this process by educating parents about these services (*http://www.ideapractices.org/index*) and providing documentation of the diagnosis and impairment.

Social skills therapy alone has not been shown to be effective for adolescents with social impairment related to ADHD. Similarly, there are no reports of effective psychosocial interventions for the driving risks accompanying adolescent ADHD. Reasonable parental approaches are to limit the number of passengers and the driving times. Parents should be encouraged to discuss alcohol and drug use regularly with their teenager and to plan medication dosing so that the adolescent will have coverage during periods when they are likely to be driving.

Adherence

Adolescents with ADHD may have negative attitudes toward any treatment of ADHD, including medication, behavioral therapy, and school support. Studies indicate that adherence to pharmacotherapy diminishes after elementary school, even when symptoms persist, and that patients who did not begin medication during childhood are unlikely to begin it during adolescence. Important factors promoting adherence include self-concept, family stability, internal locus of control, motivation, simplified medication regimens, lack of side effects, and a positive physician–patient relationship. If adolescents prefer to forego medication at a given time, it may be helpful to concur and then develop a plan with adolescents that helps them achieve their goals through the use of tutors, behavioral interventions, organizational help, or other strategies that they believe will help. Reevaluation of this plan in 2–4 weeks will determine whether it is working and what needs to be changed. If the plan is unsuccessful, the adolescent may be more willing to consider other options.

Transition to Adulthood

Older adolescents and young adults with ADHD face important barriers to health care. An estimated 80% of health insurance policies impose specific limitations on ADHD care, more than 25% of policies exclude ADHD from coverage, and median out-of-pocket costs are two times higher for individuals with than without ADHD. Young people with ADHD are less likely to be full-time employees eligible for employer plans and less likely to be full-time students covered under parent plans. In addition to the financial barriers, college or full-time employment often coincides with a transition from pediatric to adult care. The planning and organization required to make this transition, coupled with the insurance barriers, results in inadequate care for many young people with ADHD.

In addition to the health care barriers, older adolescents with ADHD confront significant challenges as they transition from high school to college, work, or military. College admission tests (i.e., SAT and ACT) allow students with ADHD to apply for special accommodations, including extended time on testing, and many colleges have special admission and matriculation programs for students with ADHD. However, the military services require enlistees to pass the Armed Services Vocational Aptitude Battery (ASVAB) without accommodation. Causes for military rejection include a history of immaturity and impulsiveness, a chronic history of academic skill deficits that interfere with work or school after age 12, or the current use of medication to improve or maintain academic skills. Under certain circumstances, individual military services may grant waivers to individuals who do not meet the basic eligibility criteria. A waiver typically requires the demonstration of school or work success without the use of medication.

OUTCOME

Educational attainment and occupational outcome is lower for individuals with than without ADHD. Among individuals with ADHD, those with Predominantly Inattentive Type or Combined Type are less likely to graduate from college than those with Predominantly Hyperactive/Impulsive Type. However, those with Predominantly Hyperactive/Impulsive Type and Combined Type are at higher risk for oppositional defiant disorder, suicide attempts, and arrests then those with Predominantly Inattentive Type. At least one study indicates that appropriate treatment allows adolescents with ADHD to achieve at the same level as peers without ADHD.

MAJOR POINTS

- ADHD is a neurobiological condition that, in most cases, continues to manifest symptoms and dysfunction into adolescence.
- The prevalence and severity of comorbid conditions are higher in adolescents than younger children with ADHD.
- The mainstays of treatment for children and adolescents with ADHD are both stimulant medications and psychosocial intervention. There is no evidence that medication is less effective in adolescents or young adults with ADHD than it is in children with ADHD.
- Treatment of ADHD with psychostimulants does not increase, and may decrease, the risk of substance use.
- Managing the side effects of the stimulant medications rests largely on dose titration and administration timing. The side effect of greatest concern and controversy is the potential association with life-threatening arrhythmia. The most common side effects are decreased appetite, abdominal discomfort, sleep disturbance, anxiety, headache, and rebound behavior.
- Transition planning for health care, college, and/or work should begin by mid-adolescence for most individuals with ADHD.

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CHAPTER 33

Oppositional Defiant Disorder and Conduct Disorder

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INTRODUCTION

Oppositional defiant disorder (ODD) and conduct disorder (CD) are severe, disruptive behavior disorders that impair psychosocial function. Children with ODD are at increased risk of CD as adolescents, and adolescents with CD are at increased risk of antisocial personality disorder as adults. Some individuals progress beyond antisocial personality disorder to psychopathy, which is characterized by extreme coldness and callousness toward others.

DEFINITIONS

ODD is defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) as a pattern of negativistic, hostile, and defiant behavior with at least four of the eight manifestations shown in Box 33-1 that are present during the same 6-month period. The diagnostic criteria for ODD require that the manifestations are outside the developmentally normal range for age; cause impairment in social, academic, or occupational functioning; and are not due to a primary psychotic or mood disorder. If the individual meets criteria for CD, the diagnosis of ODD is automatically excluded. Although ODD is usually diagnosed during childhood or adolescence, it can be diagnosed during adulthood. Studies of the natural history and management of ODD are limited by its tendency to coexist with other psychiatric diagnoses.

CD is defined by DSM-IV as a pattern of behavior in which the rights of others or societal rules are violated in at least three of four areas within the past 12 months and at least one of the areas within the past 6 months (Box 33-2). Whereas ODD encompasses verbal aggression leading to dysfunction, CD typically involves physical aggression or theft. Childhood-onset CD, defined as fulfilling at least one criterion prior to age 10 years, carries a poorer prognosis than adolescent-onset CD.

Box 33-1 DSM-IV Criteria for the Diagnosis of Oppositional Defiant Disorder (ODD)

Four or more of the following are present during the same 6-month period:

- Often loses temper
- Often argues with adults
- Often actively defies or refuses to comply with adults' requests or rules
- Often deliberately annoys people
- Often blames others for his or her mistakes or misbehavior
- Is often touchy or easily annoyed by others
- Is often angry and resentful
- Is often spiteful or vindictive

American Psychiatric Association: *Diagnostic and Statistical Manual of Mental of Mental Disorders*, 4th ed. TR. Washington D.C.,American Psychiatric Association, 2000.

Box 33-2 DSM-IV Criteria for the Diagnosis of Conduct Disorder (CD)

A repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated, as manifested by the presence of behaviors in at least three of the following four areas within the past 12 months and at least one of the areas in the past 6 months:

1. Aggression to people and animals
   - Often bullies, threatens, or intimidates others
   - Often initiates physical fights
   - Has used a weapon that can cause serious physical harm to others
   - Has been physically cruel to people
   - Has stolen while confronting a victim
   - Has forced someone into sexual activity
2. Destruction of property
   - Has deliberately engaged in fire setting with the intention of causing serious damage
   - Has deliberately destroyed others' property (other than by fire setting)
3. Deceitfulness or theft
   - Has broken into someone else's house, building, or car
   - Often lies to obtain goods or favors or to avoid obligations (i.e.,"cons others")
   - Has stolen items of nontrivial value without confronting a victim
4. Serious violations of rules
   - Often stays out at night despite parental prohibitions, beginning before age 13 years
   - 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)
   - Is often truant from school, beginning before age 13 years

American Psychiatric Association: *Diagnostic and Statistical Manual of Mental of Mental Disorders*, 4th ed. TR. Washington D.C., American Psychiatric Association, 2000.

EPIDEMIOLOGY

Prevalence estimates for ODD among U.S. children and adolescents range from 0.1–28.6%. The wide variability in prevalence reflects, in part, changes in the diagnostic criteria between DSM-III and -IV. Onset is usually before age 8 years and is not later than early adolescence, with symptoms increasing gradually over months to years. Males are two to three times more likely to be affected than females, but the gender difference diminishes with advancing adolescent age. ODD affects 50% of children with attention-deficit/hyperactivity disorder (ADHD) and is most commonly seen in those with manifestations of both hyperactivity and impulsivity/inattention (Chapter 32).

The prevalence of ODD falls during adolescence as the prevalence of CD rises. An estimated 1.5–3.4% of older children and adolescents have CD. Up to 50% of children and adolescents seen in consultation by psychiatrists have behaviors consistent with CD. Males outnumber females at all ages, but the gender discrepancy decreases with age. Although males are more likely to behave aggressively and females are more likely to behave antisocially, there is crossover in behavior by gender. CD can begin at any age from preschool to late adolescence but usually appears in late childhood or early adolescence.

Like ODD, CD commonly coexists with ADHD. However, the prevalence of comorbidity is even higher with CD than ODD and, for those with comorbidity, impairment is more severe and prognosis is poorer. The overlapping symptoms of manic and disruptive behaviors have created controversy about whether bipolar disorder and CD can coexist. Evidence suggests the two conditions can coexist and that early phenotyping will strengthen studies of genetic linkage, natural history, and treatment.

Low socioeconomic status (SES) places children and adolescents at increased risk for both ODD and CD. Crowded living conditions and neighborhood crime have been implicated, but discordant or abusive family relationships probably account for most of the SES effect. ODD has been associated with difficult infant temperament; poor maternal–infant attachment; maternal depression; low maternal involvement; and family history of disruptive behavior, mood, and substance use disorders. Strong patterns of inheritance have been reported in twin studies of CD and behavioral genetic studies of antisocial behavior.

PATHOPHYSIOLOGY

Animal and human studies point to serotonin as a major mediating neurotransmitter in aggressive and antisocial behavior. Serotonin levels in the cerebrospinal fluid (CSF) are reported to be lower in aggressive and risk-taking monkeys compared with normal controls, as well as in aggressive, suicidal, and impulsive adult men compared with those without hostility or impulsivity. CSF levels of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin, were found to be lower in children with disruptive behavior disorders than in children with obsessive-compulsive disorder. Furthermore, the levels were inversely correlated with aggression and directly correlated with social competence at 2-year follow-up.

Testosterone has been implicated in the pathophysiology of postpubertal aggression. Low resting heart

rates have been correlated with increased risk of violent and antisocial behavior, suggesting involvement of the autonomic nervous system.

EVALUATION

There are no specific laboratory tests or requisite structured interviews to diagnose ODD or CD. Diagnosis is made by patient interview and reports about the patient's behavior from collateral informants such as parents and teachers.

The accurate diagnosis of ODD or CD depends on confirming that the characteristic behaviors cannot be explained solely by the associated comorbidities. The differential diagnosis is complex and may include ADHD, adult antisocial personality disorder, psychotic disorders, mood disorders, learning disorders, communication disorders, mental retardation, substance use disorders, sleep disorders, seizure, hyperthyroidism, lead toxicity, and metabolic disorders such as Wilson disease.

The history and physical examination should be used to guide decisions about laboratory testing, radiographic studies, psychoeducational testing, and speech or language evaluation. Laboratory tests to consider include a complete blood count, serum electrolytes, liver and thyroid function tests, urine drug screen, and serum lead level. There are no characteristic wave patterns of ODD or CD on electroencephalography, but the study is indicated if the history suggests a seizure disorder. Similarly, computed tomography (CT) or magnetic resonance imaging (MRI) of the head typically is read as normal in patients with ODD and CD, but is indicated if history or physical examination suggests an intracranial mass or lesion.

MANAGEMENT

Psychosocial intervention generally is recommended as first-line treatment for ODD and CD, with adjunctive pharmacotherapy for those with severe aggression and impulsivity. The available evidence suggests that parent-management training (PMT), problem-solving skills training (PSST), and multi-systemic therapy (MST), but not traditional individual or family therapy, may be effective. PMT, which focuses on improving the parent–child relationship and child-rearing at home, appears effective in the management of school-age children with CD. PSST is a cognitive-behavioral model aimed at improving parental understanding of negative interactions and parental skills in diminishing power struggles and strengthening parent–child fit. MST is a comprehensive, rigorous, home-based intervention delivered by trained therapists that addresses individual, family, and environmental variables. A randomized trial of serious juvenile offenders demonstrated that those receiving MST compared with usual treatment had fewer subsequent arrests, spent less time incarcerated, and demonstrated significant decreases in aggression.

There is limited research on specific pharmacotherapy for ODD or CD alone, although studies do suggest that antipsychotics, mood stabilizers, and stimulants may help control the behaviors in patients with co-occurring conditions. For example, methylphenidate and clonidine each appear to decrease oppositional defiant symptoms in patients with ADHD and ODD or CD, but there are no studies that have examined the use of either in patients with ODD alone. Isolated studies have demonstrated the effectiveness of methylphenidate for the treatment of CD without ADHD, valproic acid for the treatment of explosive outbursts and mood lability in ODD or CD, and risperidone for the long-term treatment of children with disruptive behavior disorders and subaverage intelligence.

Mood stabilizers and atypical antipsychotic medications appear to help control aggressive behaviors, juvenile delinquency, and behavioral disinhibition in adolescents with CD and comorbidities such as bipolar disorder. Unlike ODD, there have been several randomized, placebo-controlled trials for CD demonstrating the effectiveness of lithium, divalproex, risperidone, haloperidol, and molindone. A dose–response study of divalproex sodium in the treatment of male adolescents with CD revealed better impulse control and self-restraint in the high-dose than the low-dose group. A 10-week, randomized, double-blind, placebo-controlled study of risperidone in adolescents with CD demonstrated effectiveness in decreasing aggression. Another study of risperidone in children ages 5–12 years with disruptive behavior disorders and subaverage IQ scores of 36–84 demonstrated that it was both effective and well tolerated.

OUTCOME

In a prospective study of 177 preadolescent boys with ODD at baseline, 44% developed CD within 3 years. In a prospective study of boys with CD at baseline, diagnostic criteria for CD were met by half the boys within one year of follow-up and by 88% within four years of follow-up. In a prospective study of 79 boys with ODD at baseline, follow-up at two years revealed ODD and/or ADHD in 76% and, of these, one-quarter had additional diagnoses such as anxiety or mood disorders. In girls, ODD is a risk factor for subsequent depression, anxiety, and persistent ODD. In both boys and girls, physical fighting is a significant risk factor for progression from ODD to CD. For the majority of children with ADHD, ODD is likely to persist into adolescence, especially if there are negative parenting practices and maternal psychopathology.

Prognosis is poorer for children with comorbid ODD or CD compared with those with ODD or CD alone, given the higher rates of aggression and delinquency

during adolescence and violent offense in adulthood. One study suggests that increases in household income over time are associated with improved prognosis for children with ODD or CD.

In a study of 225 twins, childhood CD and hyperactivity both were strong predictors of antisocial personality disorder in adulthood. Importantly, a higher number of hyperactive and CD symptoms also were associated with poorer outcomes. In contrast, another study showed that CD with or without ADHD is a strong predictor of antisocial behaviors based on electrodermal responses and accelerated habituation. Other factors that predict chronic aggression include early onset, high levels of aggression at a young age, male gender, poor prosocial behavior, and negative life events.

MAJOR POINTS

- ODD often, but not always, progresses to CD.
- Research on pharmacological treatment for ODD has been quite limited.
- Psychosocial therapy such as parent-management training has been found to be effective for the treatment of ODD.
- Treating comorbid condition such as ADHD can often diminish oppositional and defiant symptoms.
- Conduct disorder is quite common among children and adolescents referred for psychiatric consultation.
- Early-onset CD (i.e., prior to age 10 years) carries a poor prognosis.
- Research suggests that intensive psychosocial therapy plus pharmacotherapy is effective for the management of CD.

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CHAPTER 34

Alcohol, Tobacco, and Drug Use

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INTRODUCTION

Despite a decade-long decline in the overall rates of substance use among U.S. adolescents, 21% of 8th-graders and 48% of 12th-graders in 2006 continued to report lifetime use of some illicit drug. The progress reflected by the declining use of tobacco, alcohol, marijuana, and most other illicit drugs was counterbalanced by plateaus in the use of prescription-type drugs (e.g., OxyContin, Vicodin, sedatives, amphetamines) and over-the-counter medications.

The literature on the epidemiology of adolescent substance use is extensive and methodologically strong. In comparison, outcome studies of prevention, early intervention, and treatment strategies are more limited in their scope and generalizability. This chapter reviews the rates and correlates of adolescent substance use, office-based tools for screening, and the evidence underlying approaches to prevention and treatment.

DEFINITIONS

Abuse: Repeated use of drugs to produce pleasure, alleviate stress, and/or alter reality.

Addict: Individual who cannot resist the use of drugs or alcohol for physiological or psychological reasons.

Addiction: Chronic, relapsing disease characterized by compulsive drug seeking, drug abuse, and long-lasting chemical changes in the brain.

Binge drinking: Consumption of five or more drinks at one time.

Dependence: An adaptive physiological state that occurs with regular drug use and results in a withdrawal syndrome when use is stopped.

Dual diagnosis: Coexisting substance use disorder and other mental health disorder.

Intoxication: Reversible, substance-specific syndrome caused by ingestion of or exposure to that substance.

Recovery: Process of reversing drug dependence and addiction.

Relapse: Resumption of drug use after a period of abstinence.

Tolerance: A condition in which higher or more frequent doses of a drug are required to produce the same effect as during initial use.

User: Individual who uses a substance to produce pleasure, alleviate stress, and/or alter reality.

Withdrawal: Symptoms that occur when a dependent individual stops using the drug or substance.

EPIDEMIOLOGY

Information about the rates of substance use among U.S. adolescents comes from three major surveys: Monitoring the Future (MTF), the Youth Risk Behavior Survey (YRBS), and the National Survey on Drug Use and Health (NSDUH), formerly known as National Household Survey on Drug Abuse. MTF is an annual, nationally representative, school-based survey of drug behaviors and attitudes conducted among 12th-grade students since 1975 and 8th- and 10th-grade students since 1991. YRBS

is a biennial, nationally representative, school-based survey of health-risk behaviors conducted among 9th- to 12th-grade students since 1991. NSDUH is a nationally representative, home-based survey of civilians 12 years of age and older residing in the United States. Unlike MTF and YRBS, NSDUH includes out-of-school youth and allows comparison of adolescent and adult rates.

Decades of survey research support the following general conclusions: drug use is common among adolescents; use peaks during the second and third decades of life for most substances; declining rates of perceived harm precede increasing rates of use; illicit drugs are relatively easy to very easy to obtain; and association with users increases the likelihood of use. The 2006 MTF survey demonstrated an all-time low in cigarette smoking among 8th-, 10th-, and 12th-graders; a 25% decline since 2001 in marijuana use over the past month, to 12.5%; and a continued downward trend in alcohol use. However, use of OxyContin among 8th-graders nearly doubled over the preceding 4 years and 4–7% of 8th- to 12th-grade students reported abuse of over-the-counter medications. The rates of binge drinking are higher among young adults aged 18–25 years than among adolescents, and full-time college students are more likely to report any drinking, binge drinking, and heavy drinking than their same-aged peers.

The specific drugs included in the 2006 MTF survey and the trends in their rates of use are shown in Box 34-1. Lifetime and annual use rates for tobacco, alcohol, and most illicit drugs continued the declines first observed in the mid-1990s, with the greatest declines over a 10-year period observed among the youngest (i.e., 8th-grade) students. On the other hand, the 1-year declines were small relative to preceding years and far lower among 8th- than 12th-grade students (0.5% vs. 2.1%). Furthermore, 30% of 12th-graders reported they had been drunk in the preceding month and 32% reported marijuana use within the preceding year. Of particular concern were the 4-year increase in OxyContin use and the plateaus in Vicodin and sedative use.

Boxes 34-2 and 34-3 summarize the risk and protective factors, respectively, associated with adolescent substance use. Taken together, these factors help guide individual risk assessment and provide targets for prevention and treatment strategies. Strong, consistent evidence supports the association of adolescent and biological parent use of alcohol; adolescent use of nicotine with in-utero exposure to maternal smoking; and adolescent use of most illicit substances with environmental exposure to family use, physical or sexual abuse, mental health disorders, and peer use or acceptance of use. Behavioral signs associated with adolescent substance use include

Box 34-1 Trends in Drug Use Identified in the 2006 Monitoring the Future (MTF) Survey

Decreasing Use	Stable Use	Increasing Use
Cigarettes	Inhalants	Ecstasy
Alcohol	LSD	OxyContin
Marijuana	Other hallucinogens	Vicodin
Methamphetamine	Powder cocaine	
Crack cocaine	Crystal methamphetamine	
	Heroin	
	Other narcotics	
	Tranquilizers	
	Sedatives	
	Ketamine, rohypnol, gamma-hydroxybutyrate (GHB)	
	Anabolic steroids	

Box 34-2 Risk Factors for Adolescent Substance Use

- Chaotic home environments
- Parental substance use and/or mental illness
- Ineffective parenting
- Lack of parent–child attachments and nurturing
- Inappropriately shy or aggressive behavior in the classroom
- School failure
- Poor social coping skills
- Affiliation with peers who display deviant behaviors
- Perceived approval of drug use by family, school, peers, coworkers, community

Box 34-3 Factors Protecting against Adolescent Substance Use

- Strong and positive family bonds
- Parental monitoring of adolescent's activities and peers
- Clear rules of conduct that are consistently enforced within the family
- Involvement of parents in the lives of their adolescent
- Success in school
- Strong bonds with school, religious group, or other social institution
- Adoption of conventional norms about drug use

irritability, social isolation, unexplained absences, and progressive alienation; decreased school performance, attendance, or behavior; and health-related symptoms such as change in weight, sleep, hygiene, or somatic well-being.

Substance use often coexists with other mental health disorders. A large study of more than 20,000 individuals revealed at least one serious comorbid mental health disorder in 37% of individuals with alcohol abuse and 53% of those with drug abuse. Among those with a mental health disorder, 29% had abused alcohol and/or drugs. The common use of drugs to self-medicate underlying mental health disorders highlights the importance of simultaneous treatment of substance use and comorbid conditions.

PATHOPHYSIOLOGY

All substances of abuse function as neurochemicals that alter brain chemistry on first and repeated use. For example, opiates, nicotine, cannabis, and phencyclidine bind to brain receptors and act as agonists or antagonists of endogenous neurochemical messengers; cocaine blocks dopamine reuptake; and amphetamines stimulate neurotransmitter release. The biological mechanisms underlying addiction involve the mediating effects of gene expression on the acute and long-term effects of substance use. The acute effects are believed to originate with dopamine in the mesolimbic and mesocortical systems that project from the ventral tegmental area to the nucleus accumbens and frontal cortex. The longer-term consequences and the maintenance of addiction appear to be mediated by the function of individual neurons and neural circuits within the frontal cortex, temporal lobes, and thalamus.

The study of medications to treat addiction has helped clarify its pathophysiology. For example, naltrexone is an opiate receptor antagonist that decreases the release of dopamine in the nucleus accumbens in response to alcohol anticipation or ingestion, thus diminishing the responsiveness to alcohol. Acamprosate is structurally related to gamma-aminobutyric acid (GABA); it antagonizes the effects of excitatory amino acids such as glutamate, and helps maintain abstinence from alcohol. Disulfiram (i.e., Antabuse) inhibits acetaldehyde dehydrogenase, an enzyme involved in the metabolism of alcohol. The resulting increase in serum acetaldehyde produces severe nausea, tachycardia, flushing, vertigo, and anxiety that begins within minutes of alcohol consumption and lasts for hours to days. Buprenorphine is an opiate receptor agonist that produces 40% of maximum opiate activity, blocks receptor binding by more potent opiates, and does not cause withdrawal if discontinued.

EVALUATION

Screening for the use of tobacco, alcohol, and other drugs should be included in the routine evaluation of every adolescent. The clinician should recognize risk factors, behaviors, and physical findings associated with use and should know the street names of common drugs of abuse (Table 34-1). Indirect, trigger questions (Box 34-4) are often less threatening and more conducive to dialogue than direct, "yes/no" questions. The questioning and discussion should take place with the adolescent alone, when the parent is out of the examining room. When the parent returns to the room, the clinician should note that the discussion took place and should encourage ongoing conversations at home about substance use and parental expectations.

Adolescents who deny use should be commended and engaged in a brief exploration of the health and social consequences of peer use. Adolescents who admit to use should be assessed further to determine the level of involvement (Table 34-2). A brief questionnaire, such as that outlined in Box 34-5, can help identify adolescents with problem use. Positive responses to at least two of the six questions in that instrument indicate use that is interfering with function and warrants intervention.

Understanding the adolescent's readiness for behavioral change (Table 34-3) can help guide referral for treatment. It is important to recognize, however, that an adolescent with problem use is unlikely to stop using or even agree to treatment based on one office visit or confrontation. The concept of "motivational interviewing" (Table 34-4) can help the clinician avoid confrontation that will close off future communication with the adolescent. Specific questions to guide the interview are summarized in Table 34-5.

The outcome of such an interview will help determine the next strategy. A young person who confidentially admits to experimenting and who recognizes the dangers inherent in use might benefit from establishing a "contract" to cut back and eventually cease using while continuing to see the clinician for ongoing counseling and assessment. Monitoring the patient's progress and periodic urine testing for drugs of abuse will play a role in this approach.

Deciding when to break confidentiality is one of the most challenging aspects of adolescent health care. It is a common dilemma when working with an adolescent who is using alcohol or drugs regularly. Emotional and physical dependence on the substance, as well as the high prevalence of comorbid mental health problems, may interfere with safe or even rational decision making on the part of the adolescent. Regular use with no desire to change places the adolescent at high risk for serious health consequences and usually warrants parental involvement.

Table 34-1 Common Drugs of Abuse

Drug	Street Names	Route	Intoxication Effects	Examination Findings
Alcohol	Beer, wine, distilled spirits, "Alcopops"	Ingestion	Decreased inhibition, euphoria	Slurred speech, alcohol odor, intoxication
Tobacco	Cigarettes, cigars, blacks, snuff, chew	Inhalation (smoked) Absorption	Reported calming effect	Stained fingers, teeth, clothing; tobacco odor
Marijuana	Weed, Blunt, Grass, Pot, Herb	Inhalation Ingestion	Euphoria, mental slowing, impaired memory	Cough, impaired memory and learning, anxiety/panic attacks, tachycardia
Benzodiadepines: Xanax Valium Ativan Librium	Candy, Downers, sleeping pills	Ingested Injection	Sedation	Drowsiness, loss of consciousness, respiratory depression, decreased gag reflex, slurred speech, withdrawal, dizziness
Rohypnol	Forget-Me Pill, Roofies, Rophies, R2, Roche, Mexican Valium	Ingestion	Amnesia, date rape	Memory loss, physical/ sexual assault, drowsiness, slurred speech
GHB (gamma-hydroxybutyrate)	Liquid Ecstasy, Grievous Bodily Harm	Ingestion	Decreased inhibition, euphoria, amnesia, date rape	Drowsiness, loss of consciousness, nausea/vomiting, respiratory depression, slurred speech
Ketamine	Cat Valium, K, Special K, Vitamin K	Ingestion Injection Inhalation (smoked)	Hallucinations	Hallucinations, altered perceptions, nausea, hypothermia
PCP (phencyclidine)	Angel Dust, Boat, Love Boat, Peace Pill	Injection Ingestion Inhalation (smoked)	Hallucinations	Hallucinations, altered perceptions, nausea, hypothermia
LSD (lysergic acid diethylamide)	Acid, Blotter, Microdot	Ingestion Absorption	Hallucinations	Hallucinations, altered perceptions, nausea, hyperthermia, tachycardia, hypertension, sleeplessness, numbness/weakness
Mescaline	Peyote, Buttons, Mesc, Cactus	Ingestion Inhalation (smoked)	Hallucinations	Hallucinations, altered perceptions, nausea, hyperthermia, tachycardia, hypertension, sleeplessness, numbness/weakness
Psilocybin	Magic Mushrooms, Shrooms	Ingestion	Hallucination	Hallucinations, altered perceptions, sleeplessness, nervousness, paranoia
Narcotics				
Codeine Hydrocodone	Vicodin Tylenol 3, T3s, Percs	Ingestion	Euphoria, decreased inhibition	Drowsiness, loss of consciousness, respiratory depression, decreased gag reflex, slurred speech, withdrawal, pinpoint pupils
Heroin	H, Horse, China White, Black Tar, Smack	Injection Inhalation (snorted or smoked)	Euphoria, decreased inhibition, avoidance of withdrawal	Drowsiness, loss of consciousness, respiratory depression, decreased gag reflex, slurred speech, withdrawal, pinpoint pupils, track marks, skin abscesses
Oxycodone	OxyContin, Oxy, O.C., Percocet, Killer	Ingestion Injection Inhalation (snorted)	Euphoria, decreased inhibition	Drowsiness, loss of consciousness, respiratory depression, decreased gag reflex, slurred speech, withdrawal, pinpoint pupils
Methamphetamine	Crystal Meth, Meth, Ice	Inhalation Ingestion	Mental stimulation, enhanced mood	Aggression, psychotic behavior, tachycardia, hypertension, arrythmias, weight loss, irritability

Amphetamine	Speed, Uppers, Hearts, Crosses, Black Beauties	Ingestion Injection Inhalation (smoked)	Mental stimulation, enhanced mood	Tachycardia, hypertension, arrythmias, weight loss, irritability
Cocaine	Coke, Crack, Rock, Blow	Inhalation (smoked or snorted) Ingestion	Mental stimulation, enhanced mood	Chest pain, myocardial infarction, hyperthermia, anxiety/panic attacks, dilated pupils
MDMA (3,4 methyl-enedioxymetham-phetamine)	Ecstasy, X, XTC, Adam, Eve	Ingestion	Tactile sensitivity, empathic feelings	Hyperthermia, bruxism, impaired memory, tachycardia, hypertension
Inhalants	Solvents, gasses, spray paint, Poppers, Whippets, Laughing Gas, Nitrites	Inhalation	Decreased inhibition, euphoria, warmth	Headache, nausea/vomiting, slurred speech, decreased coordination, brain damage, paint around nostrils and mouth

Box 34-4 Indirect Questions That Help Trigger Discussion of Substance Use

- Tell me about tobacco and drug use at your school.
- Do you know people who use?
- Do you have friends who use?
- Do you find yourself going to parties where people are drinking or using drugs?
- Has anyone ever offered you tobacco, alcohol, or other drugs?
- Have you ever tried tobacco, alcohol, or other drugs?
- Have you talked to your parents about tobacco, alcohol, or other drugs?
- Have you used any medications for any reason other than what it was intended for?

Box 34-5 CRAFFT Substance Abuse Screening Test

- Have you ever ridden in a **CAR** driven by someone (including yourself) who was "high" or had been using alcohol or drugs?
- Do you ever use alcohol or drugs to **RELAX**, feel better about yourself, or fit in?
- Do you ever use alcohol or drugs while you are by yourself? **ALONE**?
- Do you ever **FORGET** things you did while using alcohol or drugs?
- Do family or **FRIENDS** ever tell you that you should cut down on your drinking or drug use?
- Have you gotten into **TROUBLE** while you were using alcohol or drugs?

From: Knight JR, Sherritt L, Shrier LA, et al.: Validity of the CRAFFT Substance Abuse Screening Test among adolescent clinic patients. Arch Pediatr Adolesc Med 2002;156:607–614.

Table 34-2 Stages of Substance Use

Abstinence	No use
Experimentation	"Learning the mood swing," casual and intermittent use
Regular use	"Seeking the mood swing," associating with users, identifying sources, binges
Problem use	Experiencing negative consequences (e.g., social, family, school, legal problems)
Abuse	Continued use despite consequences, dependence, preoccupation with use
Dependence	Loss of control, essentially continuous use, withdrawal symptoms

Table 34-3 Stages of Change

Precontemplation	Limited recognition of the problem and no desire to change behavior
Contemplation	Recognition that behavior is creating problems and identification of need to change
Planning	Developing a plan to discontinue or taper use
Action	Taking the necessary action to change the use pattern or discontinue completely
Maintenance	Avoiding challenging situations and continuing nonuse behavior
Relapse	Part of the continuum, leading back to contemplation and planning stages

Table 34-4 Principles of Motivational Interviewing

Express empathy	Understand and accept
Develop discrepancy	Help the individual understand problems associated with the behavior
Avoid arguments	Increase awareness of the problem and the need to do something about it
Roll with resistance	Avoid opposing resistance or reluctance by offering new perspectives, strategies, and information
Support self-efficacy	Enhance the individual's belief that he or she can change

Table 34-5 FRAMES Interviewing Mnemonic

Feedback	"I think you really have more of a problem with alcohol use than you want to admit, and you are moving along a path that as an outsider I can see is dangerous."
Responsibility	"It seems to me that some of your family problems really are, in fact, related to your drinking, and you need to recognize that."
Advice	"I think you need to look at how alcohol is affecting your life and family, and I think you need to cut back."
Menu of choices	"I'm not saying you have to totally change your lifestyle. I'm just suggesting that going over to Sarah's house where there is always partying and drinking is part of the problem. Maybe you can find an alternative to that kind of partying."
Empathy	"I know making these changes won't be easy, but...."
Self-efficacy	"You can do this, and you need to because the situation is getting out of control."

Depending on the adolescent's attitude during the visit, the clinician may choose to talk with the parent(s) with the adolescent present or may discuss matters privately with the parents and arrange a follow-up visit for the family.

Parental involvement and laboratory drug screening are always warranted when substance use produces serious medical complications or when medical instability is thought to be secondary to substance use. Alcohol, inhalants, sedatives, tranquilizers, and narcotics in high dose can present with cardiorespiratory depression and coma. Stimulants, cocaine, and hallucinogens can cause tachyarrhythmias, hypertension, seizures, and hyperthermia. Alcohol withdrawal, which is uncommon in adolescents, can involve tremor, anxiety, irritability, and seizures within 12 hours of discontinuation; insomnia, sweating, hypertension, tachycardia, and fever within 24 hours; and delirium tremens (i.e., confusion, hallucinations, and delusions) at 2–5 days. Narcotic withdrawal presents with anxiety, agitation, mydriasis, yawning, hypertension, tachycardia, abdominal cramping, vomiting, and diarrhea. Chronic use of marijuana can cause gynecomastia, hypospermia, and amotivation. Chronic, prolonged use of inhalants can cause liver, kidney, and neurological toxicity. Chronic use of stimulants and phencyclidine can cause psychosis. The difficulty of establishing a diagnosis in some of these settings, the need for historical information, and the risk to life makes involvement of parents essential to evaluation and management.

MANAGEMENT

The first step in treatment is recognizing the problem and discussing it with the adolescent. This may begin outside the health care setting by a parent, other family member, friend, teacher, or coach. In many cases, clinical help is sought when attempts to discuss the problem with the adolescent elicit denial, anger, or resistance to intervention. In other cases, family and friends have recognized the problem but avoided discussing it with the adolescent. Regardless of the presenting issues or the adolescent's initial reaction, the clinician should maintain a caring attitude, avoid contention, and help parents adhere to consistent limits.

There are five general levels of care for adolescents who are using substances. Early intervention applies to casual, infrequent users who have experienced no, or minor, negative consequences of their use. Initial outpatient treatment typically involves individual and/or group counseling once or twice weekly. In more intensive outpatient treatment programs, the adolescent may spend half or full days at a treatment center in counseling and educational sessions. Residential programs require the adolescent to spend days and nights living in the treatment center. Medically managed, intensive inpatient treatment is designed for the patient with severe medical complications of acute, high-dose use or chemical dependency associated with chronic use and withdrawal.

The medical management of acute, high-dose effects of substance use typically falls into two general categories: supportive care for cardiorespiratory depression and control of sympathomimetic effects, usually with short-term use of benzodiazepines. Longer-term pharmacotherapy for the management of substance use is rarely indicated in adolescents and is beyond the scope of this chapter. In adults, pharmacotherapy has demonstrated effectiveness for the treatment of alcohol and opiate abuse. The U.S. Food and Drug Administration (FDA) has approved three drugs for the treatment of alcohol abuse in adults: naltrexone, acamprosate, and disulfiram. The treatment of opiate addiction in adults often involves maintenance therapy with buprenorphine, methadone, or naltrexone.

Once the acute effects of drug use are controlled, the importance of ongoing drug treatment must be discussed with the adolescent and family. The adolescent, and at

times the family, may resist ongoing treatment on the premise that the negative consequences just experienced will be sufficient to end future use. Unfortunately, recurrent use is more likely than abstinence. Ongoing treatment to prevent future use therefore should be considered the essential next step in the adolescent's management.

Treatment models fall into three broad categories. Family therapy, in which a strong alliance is built between the adolescent and therapist, has been shown to be effective for the treatment of adolescent substance abuse. Individual therapy, group therapy, residential programs, and other intensive strategies (e.g., wilderness programs) are more controversial. The Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Services Administration (SAMHSA) within the U.S. Department of Health and Human Services provides a substance abuse treatment facility locator (*http://www.findtreatment.samhsa.gov*) that links individuals to treatment options in their communities. The locator identifies more than 10,000 programs nationwide for outpatient, hospital inpatient, and residential treatment of adolescents and adults with alcohol and drug abuse.

MAJOR POINTS

- Approximately one-fifth of 8th-grade students and one-half of 12th-grade students in the United States have used an illicit drug at some time in their lives.
- Substance use disorders affect approximately one-third of individuals with other mental health disorders, and other mental health disorders affect more than one-third of individuals with alcoholism and more than one-half of those with drug abuse.
- Strong, consistent evidence supports the association of adolescent and biological parent use of alcohol; adolescent use of nicotine with in-utero exposure to maternal smoking; and adolescent use of most illicit substances with environmental exposure to family use, physical or sexual abuse, mental health disorders, and peer use or acceptance of use.
- Behavioral signs associated with adolescent substance use include irritability, social isolation, unexplained absences, and progressive alienation; decreased school performance, attendance, or behavior; and health-related symptoms such as change in weight, sleep, hygiene, or somatic well-being.
- Screening for the use of tobacco, alcohol, and other drugs should be included in the routine evaluation of every adolescent.
- Whenever possible, substance use treatment should involve the family.
- Drug addiction is a chronic disease. Treatment works and is cost-effective. However, relapse is common and should be considered part of the recovery process.

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CHAPTER 35

Eating Disorders

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INTRODUCTION

Eating disorders affect 5 to 10 million females and 1 million males in the United States. Regardless of specific diagnosis, age of onset, or duration of illness, all eating disorders can be fatal and most are associated with changes in affect, self-esteem, energy, judgment, concentration, and social function.

The mechanisms underlying eating disorders involve a complex interplay of genetic and environmental factors. This chapter reviews the epidemiology, pathophysiology, evaluation, and management of anorexia nervosa, bulimia nervosa, and common, nonspecific eating disorders of adolescence.

ANOREXIA NERVOSA

Definition

Anorexia nervosa refers to a condition in which a person purposely limits his or her food intake and refuses to maintain a weight within a healthy range for his or her height and age. Some teens may lose weight, whereas others may simply not gain weight at an appropriate rate for their pubertal state, resulting in a low body mass index (BMI). The *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition, Text Revision (DSM-IV-TR) criteria for anorexia nervosa and its two major subtypes (i.e., restrictive and binge eating/purging) are summarized in Box 35-1. Applying the DSM-IV criteria can be difficult in adolescents who are physically immature and/or unable to articulate their self-perceptions. Of note, a diagnosis of anorexia nervosa can be established with the first three criteria alone in males and in females with primary amenorrhea.

Box 35-1 Diagnostic Criteria for Anorexia Nervosa

- Inability to maintain body weight range within a minimally normal weight range for height and age.
- Intense fear of gaining weight or becoming fat, even though underweight.
- Distorted body image, undue influence of body image on self-esteem, or denial of the seriousness of the current low body weight.
- Amenorrhea in the postmenarcheal female.
- Restrictive subtype: the person has not regularly engaged in binge eating or purging behavior (weight is mainly controlled by reducing oral intake).
- Binge eating/purging subtype: patient regularly engages in binge eating and/or purging (e.g., self-induced vomiting, misuse of laxatives).

Adapted from: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. TR. (DSM-IV-TR). Washington, D.C., American Psychiatric Association, 2000.

Epidemiology

Anorexia nervosa is the third most common chronic illness of adolescent girls. The disease affects approximately 1% of females and 0.1% of males aged 10–25 years in the United States. Incidence rates over the past two decades have shown no dramatic changes and, despite concerns of increasing prevalence among children, data are scant in prepubertal populations. Adolescents with body dissatisfaction and subdiagnostic dieting behavior appear to be at particularly high risk for the development of anorexia nervosa. Mortality in patients with anorexia nervosa is high at 5% due to suicide and medical complications.

Pathophysiology

Recent twin studies demonstrate that 58–76% of the variance in anorexia nervosa is genetically explained. A susceptibility locus on chromosome 1 provides further support to a genetic key. What triggers a susceptible individual to develop a full-blown eating disorder remains unclear but appears to involve a complex interplay of social pressure, media influence, personality traits, and neurochemistry.

Evaluation

When evaluating a patient with weight loss and amenorrhea, the differential diagnosis must include central nervous system tumors, malignancy (e.g., leukemia, lymphoma), inflammatory bowel disease, and endocrinopathies including Addison's disease. These can generally be excluded by a thorough history and physical examination. Consultation with a psychiatrist is indicated if other mental health diagnoses cannot be excluded (e.g., major depressive disorder, obsessive-compulsive disorder, body dysmorphic disorder). Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) can present with sudden-onset anorexia nervosa and should always be considered in the atypical presentation or young preteen (Box 35-2).

Box 35-2 Differential Diagnosis of Anorexia Nervosa

- Central nervous system lesion
- Major depressive disorder
- Malignancy
- Obsessive-compulsive disorder
- Inflammatory bowel disease
- PANDAS: **P**ediatric **A**utoimmune **N**europsychiatric **D**isorders **A**ssociated with **S**treptococcal infection
- Endocrinopathy

Management

Most adolescents with anorexia nervosa respond as outpatients to interdisciplinary, team-based care delivered by a physician for medical supervision, a mental health therapist, and a registered dietician. Box 35-3 lists criteria for hospitalization, as recommended in a position paper of the Society for Adolescent Medicine. Whenever possible, adolescents requiring hospitalization should be admitted to a unit specializing in eating disorders.

In the medically stable patient, outpatient treatment should begin by halting further weight loss.This requires gradual, small increases in oral intake coupled with activity restriction tailored to the patient's willingness to eat, the severity of malnutrition, and the rapidity of recent weight loss. A food journal reviewed weekly by an experienced dietician can help identify problems such as substandard portion sizes and monotonous food choices.

At present, there is inadequate evidence to support the use of routine psychopharmacotherapy in adolescents with anorexia nervosa. Individual and family therapy are effective in adolescents, but no single modality has emerged as superior to others.

Refeeding syndrome: When a patient is ill enough to warrant hospitalization, one should monitor for signs of refeeding syndrome. Originally described as a complication of total parenteral nutrition, refeeding syndrome

Box 35-3 Criteria for Hospitalization

- Unstable vital signs:
  - Severe bradycardia (HR < 50 beats/min daytime; < 45 beats/min at night)
  - Hypothermia (temp < 96°F)
  - Hypotension (< 80/50 mm Hg)
  - Dramatic orthostatic changes (> 20 beats/min in pulse or > 10 mm HG in blood pressure)
- Electrolyte abnormalities
- Dehydration
- Cardiac arrhythmia
- Acute medical complication of malnutrition (e.g., syncope, seizure)
- Suicidal ideation, severe depression, or psychosis
- Uncontrollable binge/purge cycles
- Failure of an outpatient treatment program
- Comorbid diagnosis interfering with outpatient treatment (e.g., obsessive-compulsive disorder, substance abuse)
- Weight below 75% of ideal body weight

Golden NH, Katzman DK, Kreipe RE, et al.: Eating disorders in adolescents: Position paper of the Society for Adolescent Medicine. J Adolesc Health 2003;33:496–503.

has now been reported in patients who are re-fed both orally and by nasogastric tube. Key components of refeeding syndrome are hypokalemia, hypophosphatemia, and hypomagnesemia due to the intracellular shifts that occur with transition from a catabolic to anabolic state. Complications can include cardiac arrhythmia, fluid overload, congestive heart failure, respiratory depression, ataxia, confusion, rhabdomyolysis, and renal decompensation.To prevent refeeding syndrome, energy intake should begin at 1000 kcal/day or 500 calories above the established outpatient diet, whichever is higher. Intake should then be increased by 250–300 kcal/day until the goal intake is achieved. Basic serum electrolytes, glucose, phosphorus, magnesium, and calcium should be monitored daily for several days, especially in patients with chronic starvation and critically low body weight.

Cardiovascular complications: Resting bradycardia and autonomic dysregulation causing orthostatic pulse changes are almost universal in anorexia nervosa. Abnormally low sympathetic tone when supine, coupled with failure of the parasympathetic system to decrease tone when standing, can lead to dramatic orthostasis and syncope. These abnormalities correct approximately 3 weeks into the refeeding phase or when patients approach 80% of ideal body weight. Other cardiac changes include decreased left ventricular mass, mitral valve prolapse, QTc prolongation, arrhythmias, and sudden death.

Gastrointestinal complications: Patients with anorexia nervosa have many gastrointestinal complaints. Purging is associated with esophagitis, dental enamel erosion and caries, and enlargement of the parotid and submandibular glands. The round face accompanying parotid gland hypertrophy can be particularly troubling to patients, reinforcing the drive for thinness. Rare complications such as pneumomediastinum, Mallory-Weiss tears, or gastric perforation have been reported. Abdominal pain and bloating are almost universal complaints early in the weight restoration phase of treatment due to delayed gastric emptying. Metoclopramide or other prokinetic agents may be useful in severe cases. Constipation, another common complaint, is best dealt with nutritionally. Mild elevations in liver enzymes reverse with refeeding and increased intestinal motility. Elevation in serum cholesterol is a result of increased liver production due to low fat and protein intake. Pancreatitis and cholelithiasis are complications seen with dramatic, rapid weight loss.

Menstrual changes: The secondary amenorrhea seen in female patients with anorexia nervosa reflects hypogonadotropic hypogonadism, or suppressed secretion of gonadotropin-releasing hormone (GnRH). Serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol are correspondingly low. If the diagnosis of anorexia nervosa is unclear, the initial evaluation of amenorrhea should include measurement of serum LH, FSH, prolactin, thyroid-stimulating hormone (TSH), and a urine pregnancy test. Within 3 and 6 months of achieving weights within 90% of ideal, 36% and 86%, respectively, of female adolescents with anorexia nervosa will resume menses. Although those with persistent amenorrhea may have normal serum levels of LH, FSH, and progesterone, studies suggest that their estradiol and leptin levels, fat intake, and body image remain lower than those of menstruating control patients. Other studies have linked depression to persistent amenorrhea in patients with histories of anorexia nervosa. Long-term follow-up studies have shown no increased risk of infertility in those women who achieve a healthy weight and return of menses.

Bone mineral density (BMD): In both females and males with anorexia nervosa, bone mineral loss is inversely associated with BMI and directly associated with illness duration. Within 1 year of onset, up to 40% of patients have BMD measurements that are low compared with age-matched control standards. BMD measurement by dual-energy X-ray absorptiometry (DEXA) is therefore recommended for patients with anorexia nervosa who have been amenorrheic for 6–12 months.

Although studies in healthy women demonstrate the positive effects of oral contraceptives on BMD, there are no data supporting their use for this purpose in females with anorexia nervosa. Preliminary studies of bisphosphonates and BMD in adolescents with anorexia nervosa do not demonstrate efficacy and, like oral contraceptives, their use for this purpose is not considered routine. Weight-bearing exercise in patients with anorexia nervosa demonstrates a dose-related effect on BMD, with exercise interfering with weight restoration. Calcium intake has not demonstrated consistent associations with BMD improvement and therefore should meet, but not exceed, the U.S. dietary guidelines. All adolescents should receive 1200–1500 mg calcium daily from calcium-rich foods or, alternatively, from oral supplementation.

Studies of BMD in adolescents who have recovered from anorexia nervosa vary in their findings. Some demonstrate normalization of BMD with weight gain and resumption of menses, whereas others demonstrate improvement without complete normalization.

Laboratory findings: Leukopenia, thrombocytopenia, and normocytic anemia are common in patients with anorexia nervosa and tend to resolve with improved nutrition and weight gain. Thyroid function studies typically reveal low serum thyroxine (T4) and triiodothyronine (T3) levels and normal levels of TSH, consistent with a "euthyroid sick" pattern. Thyroid replacement is *not* indicated in these patients and is likely to interfere with weight gain. Cortisol levels are generally high and patients

demonstrate blunted responses to adrenocorticotropic hormone (ACTH) stimulation testing. All of these abnormalities reverse with restoration of weight.

BULIMIA NERVOSA

Definition

Bulimia nervosa (Box 35-4) is defined as recurrent episodes of binge eating and compensatory behaviors to prevent weight gain, accompanied by an undue influence of body weight on self-esteem. The diagnosis can only be made in a patient who does not meet criteria for anorexia nervosa and should be distinguished from binge eating disorder, which has been proposed for inclusion as a formal DSM-IV diagnosis (Box 35-5). The diagnostic criteria for bulimia nervosa require an established frequency and duration of the episodes, which should be classified as purging or nonpurging types.

Epidemiology

Bulimia nervosa has a prevalence of 1–3% in the general female population, and its incidence does not appear to have increased over the past two decades. First-degree relatives of individuals with bulimia nervosa are at four-fold risk for bulimia and 12-fold risk for anorexia. Long-term follow-up of patients with bulimia nervosa demonstrate recovery in 50%, improvement in 30%, and persistence in 20%.

Pathophysiology

The cause of bulimia is not known. As noted previously, there is a strong family disposition but neither a pattern of inheritance nor a gene locus has been identified. Depressive symptoms are reported in 75% of patients with bulimia, substance use in 25%, and personality disorders in up to 50%.

Evaluation

The detection of bulimia nervosa represents the greatest challenge in its evaluation. Unlike the adolescent with anorexia nervosa who comes to medical attention with visible physical signs of illness, the adolescent with bulimia nervosa typically is normal weight and well-appearing. Between binge/purge episodes, which are usually covert, eating may appear relatively normal. The health care visit therefore tends to be precipitated by the patient's increasing emotional turmoil or by discovery of the purge episodes by family or friends. Clinician sensitivity to the adolescent's embarrassment and upset are of paramount importance in the development of an effective therapeutic relationship, particularly when the adolescent has not initiated the care.

The evaluation should include discussion of growth in height and weight, change in self-esteem or body image, peak and trough weight, fluctuation in weight, eating frequency and pattern, dieting, exercise, use of appetite suppressants or laxatives, and thoughts about food and eating. Most patients with bulimia describe excessive weight fluctuation, obsessive thinking about food, and

Box 35-4 Diagnostic Criteria for Bulimia Nervosa

- Recurrent episodes of binge eating in which the person:
  - Eats an amount of food that is larger than most people would eat during a similar period of time.
  - Senses a lack of control over eating.
- Recurrent unhealthy compensatory behavior in order to prevent weight gain.
- The binge eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 months.
- Self-evaluation is unduly influenced by body shape and weight.
- Patient does not currently meet criteria for anorexia nervosa:
  - Purging type: person regularly engages in self-induced vomiting or misuse of medications (e.g. laxatives, enemas, or diuretics).
  - Nonpurging type: person uses other inappropriate behaviors, such as fasting or excessive exercise, but has not regularly engaged in purging.

Adapted from: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. TR. (DSM-IV-TR). Washington, D.C., American Psychiatric Association, 2000.

Box 35-5 Proposed Diagnostic Criteria for Binge Eating Disorder

- Recurrent episodes of binge eating that:
  - Occur without any compensatory behaviors (e.g. no purging).
  - Occur, on average, at least 2 days per week for 6 months.
- Binge eating episodes are out of control as indicated by the presence of at least three of the following:
  - Eating more rapidly than normal.
  - Eating until feeling uncomfortably full.
  - Eating large amounts of food even when not hungry.

Adapted from: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. TR. (DSM-IV-TR). Washington, D.C., American Psychiatric Association, 2000.

anxiety about eating. The history should attempt to elicit symptoms consistent with dual diagnoses such as major depressive disorder, obsessive-compulsive disorder, and substance use given their high prevalence in patients with bulimia.

The physical examination in bulimia may reveal hand abrasions from self-induced vomiting, dental caries from enamel erosion caused by gastric acid, and parotid enlargement. The most common laboratory findings are hypokalemia and metabolic alkalosis in patients with the binge/purge subtype.

Management

Medical complications are much more common in patients with the purging than nonpurging type of bulimia nervosa. Repeated self-induced vomiting is associated spontaneous gastroesophageal reflux, loss of the gag reflex, dental enamel erosion, gingivitis, parotid gland enlargement, submandibular gland enlargement, esophagitis, Mallory-Weiss tears, and spontaneous pneumothorax. Constipation and atonic colon are associated with chronic use of laxatives. Electrolyte imbalance and dehydration are more common with purging but may also occur with severe binge eating, and is the leading cause of fatal arrhythmia in patients with bulimia nervosa.

The primary treatment for bulimia nervosa in adults is cognitive-behavioral therapy (CBT). Manual-based treatment, originally developed by Christopher Fairburn, has been studied extensively in adults with bulimia nervosa and has demonstrated higher efficacy than other treatment strategies. CBT decreases binge eating by 73–93%, decreases purging by 77–94%, and improves body image. The use of an antidepressant medication in adults with bulimia nervosa and binge eating disorder yields short-term resolution in 25%, with relapse in one-third despite continuation of the medication. In one study, the combination of CBT and an antidepressant demonstrated higher efficacy than either CBT or antidepressant alone.

Medication trials in bulimia nervosa have consistently found antidepressants a useful adjunct to treatment independent of any patient symptoms of depression. Placebo-controlled trials of tricyclic antidepressants, monoamine oxidase inhibitors, and sustained serotonin reuptake inhibitors (SSRIs) have all demonstrated significant decreases in binge and purge episodes. Due to their safety and tolerability, SSRIs are preferred by many clinicians for the treatment of patients with bulimia nervosa. Fluoxitine trials demonstrate that patients receiving 60 mg daily reporting fewer episodes of binge eating and/or vomiting than those receiving 20 mg/day. Positive results have also been demonstrated with use of ondansetron.

Medication alone for the treatment of bulimia nervosa is not recommended, and clinicians should emphasize the importance of counseling. In a randomized study of CBT and desipramine, 18% of subjects on desipramine alone vs. 78% on desipramine and CBT were binge/purge-free at 1-year follow-up. The practice guidelines of the American Psychiatric Association recommend medication continuation for at least 6, and preferably 12, months. At least one study supports continued CBT after medication withdrawal to prevent relapse.

EATING DISORDER NOT OTHERWISE SPECIFIED

DSM-IV defines eating disorders not otherwise specified (NOS) as abnormal eating behaviors, dissatisfaction with body weight or shape, and harmful weight control behaviors in the absence of full criteria for anorexia nervosa or bulimia nervosa. This is the most common set of eating disorders during adolescence, and management strategies are similar to those described previously.

MAJOR POINTS

- Eating disorders are life-threatening mental health illnesses that require an interdisciplinary approach to treatment.
- Early diagnosis and intervention improves outcome in all eating disorders.
- Most adolescents with eating disorders respond best to outpatient, team-based care delivered by medical, mental health, and nutritional health providers.
- Indications for hospitalization include body weight below 75% of ideal, severe dehydration or electrolyte imbalance, bradycardia, hypotension, hypothermia, suicidal ideation, and uncontrollable binge eating or purging.
- Individual and family therapy are effective in adolescents with anorexia nervosa; findings from medication trials are inconsistent.
- CBT with or without an SSRI appears to be the most effective therapy for bulimia nervosa.

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CHAPTER 36

Mood Disorders

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INTRODUCTION

Mood disorders, also referred to as affective disorders, affect 7–14% of children and adolescents by age 15 years and are associated with significant morbidity and mortality. The diagnosis and management of adolescent affective disorders increasingly are the responsibilities of primary care physicians. The objectives of this chapter are to review the diagnostic criteria, evaluation, and primary care management of adolescent mood disorders. The chapter utilizes the categorization of mood disorders established in the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, TR (DSM-IV-TR). The first section focuses on depressive disorders and the second on bipolar disorders.

DEPRESSIVE DISORDERS

The depressive disorders are further divided into major depressive disorder (MDD), dysthymic disorder, and depressive disorder not otherwise specified (NOS). Diagnostic criteria for MDD are shown in Box 36-1 and for dysthymic disorder in Box 36-2. Depressive disorder NOS is used when the number and/or duration of criteria for MDD or dysthymic disorder are not fully met or when the manifestations may reflect an underlying general medical condition or substance use disorder.

Epidemiology

The point prevalence of MDD more than doubles between childhood and adolescence, from approximately 2% to 5%. The increase in dysthymic disorder may be even more dramatic, from less than 2% in children to as much as 8% in adolescents. The incidence, or new case rate, of MDD over the course of adolescence is 15–20%, which approximates the lifetime prevalence of MDD. These rates suggest that most adult depression begins during adolescence.

Risk factors for adolescent depression are listed in Box 36-3. Most depressive episodes during adolescence resolve spontaneously within 6 to 9 months, and 90% resolve within 2 years. However, 40% of adolescents who experience a major depressive episode relapse within 2 years and 72% relapse within 5 years. The rates of depression in males and females are the same before puberty but diverge sharply during adolescence, with females outnumbering males by two to one.

Pathophysiology

Evidence thus far demonstrates that depression results from a combination of genetic predisposition, biological factors, and environmental influences. Depression is not likely to result from a single defective gene, but rather multiple defects in minor genes of varying penetrance and expression. Several studies point to defects in the serotonin transporter gene as important in the pathogenesis

Box 36-1 DSM-IV-TR Criteria for the Diagnosis of Major Depressive Disorder (MDD)

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. **Note:** Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.
   1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
   3. Significant weight loss when not dieting, or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.
   4. Insomnia or hypersomnia nearly every day.
   5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
   6. Fatigue or loss of energy nearly every day.
   7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
   8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
   9. Recurrent thoughts of death (not just fear of dying); recurrent suicidal ideation without a specific plan; or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a mixed episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, or a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by bereavement (i.e., after the loss of a loved one), the symptoms persist for longer than 2 months, or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

From: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. [Text Revision] (DSM-IV-TR). Washington, D.C., American Psychiatric Association, 2000.

Box 36-2 DSM-IV-TR Criteria for the Diagnosis of Dysthymic Disorder

A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 years. **Note:** In children and adolescents, mood can be irritable and duration must be at least 1 year.

B. Presence, while depressed, of two (or more) of the following:
   1. Poor appetite or overeating.
   2. Insomnia or hypersomnia.
   3. Low energy or fatigue.
   4. Low self-esteem.
   5. Poor concentration.
   6. Feelings of hopelessness.

C. During the 2-year period (1 year for children or adolescents) of the disturbance, the person has never been without the symptoms in Criteria A and B for more than 2 months at a time.

D. No major depressive episode has been present during the first 2 years of the disturbance (1 year for children and adolescents) (i.e., the disturbance is not better accounted for by chronic major depressive disorder or major depressive disorder in partial remission). **Note:** There may have been a previous major depressive episode provided there was a full remission (no significant signs or symptoms for 2 months) before development of the dysthymic disorder. In addition, after the initial 2 years (1 year in children and adolescents) of dysthymic disorder, there may be superimposed episodes of major depressive disorder, in which case both diagnoses may be given when the criteria are met for major depressive episode.

E. There has never been a manic episode, a mixed episode, or a hypomanic episode, and criteria have never been met for cyclothymic disorder.

F. The disturbance does not occur exclusively during the course of a chronic psychotic disorder, such as schizophrenia or delusional disorder.

G. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse or a medication) or a general medical condition (e.g., hypothyroidism).

H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

- Early onset: if onset is before age 21 years.
- Late onset: if onset is age 21 years or older.

Specify (for most recent 2 years of dysthymic disorder):

- With atypical features (i.e., mood reactivity and 2 or more of the following: increased appetite or weight gain, hypersomnia, leaden paralysis, long-standing pattern of extreme sensitivity to perceived interpersonal rejection).

From: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. [Text Revision] (DSM-IV-TR). Washington, D.C., American Psychiatric Association, 2000.

Box 36-3 Risk Factors for Adolescent Depression

- Prior episodes of depression
- Attention-deficit/hyperactivity disorder (ADHD)
- Learning disorders
- Anxiety disorders
- Depressive disorder in parent or sibling
- Family dysfunction
- Loss of significant adult in early childhood
- Low parent–teen connectedness
- Low school connectedness
- Difficulty with peer relationships

of stress-induced depression. Family studies show that parental depression increases a child's risk of depression four-fold, but the genetic and environmental contributions to this risk remain controversial.

Neurohormonal dysfunction plays a role in the pathogenesis of depression, and pharmacotherapy usually targets neurotransmitters such as serotonin, norepinephrine, and acetylcholine. Table 36-1 summarizes the neuroreceptor effects of tricyclic antidepressants (TCAs), sustained serotonin reuptake inhibitors (SSRIs), bupropion, venlafaxine, and mirtazepine.

Dysregulation of the neuroendocrine system may also play a role in depression. The hypothalamic-pituitary-adrenal axis is overactive in some adults with depression, as evidenced by elevated levels of corticotropic-releasing hormone. A few studies in adolescents with depression have shown elevated levels of evening cortisol compared with controls. Finally, studies indicate that depressed children and adolescents have blunted growth hormone secretion in response to stimulation.

Evaluation

There is no single diagnostic test for depression. The diagnosis rests on the patient and family history, observations of the adolescent's mood and behavior, and evidence of a change from the baseline level of function. The history should be obtained from the adolescent alone, the adolescent and parent/guardian together, and available medical and/or school records. It should include a discussion of present symptoms; review of past mental and medical illness, including evaluation, diagnoses, hospitalizations, and response to treatment; current medications; family history of mental illness; social history, including school performance and attendance; current or past use of alcohol or drugs; current or past abuse or neglect; peer relationships; sexual history; and mental status examination (Table 36-2).

Common manifestations of adolescent depression (Box 36-4) include irritability (the most common complaint), decreased school performance, social withdrawal, and increased conflict with peers or family.

Many adolescents with depression present to their primary care providers with unexplained somatic complaints, such as headache or abdominal pain. The most common sleep disturbances associated with depression in adolescents are delayed sleep onset, frequent nocturnal awakening, difficulty with morning awakening, and daytime fatigue. Energy typically declines, although some adolescents complain of restlessness and agitation. Changes in appetite and weight are highly variable, with anorexia and weight loss in some teens and emotional eating with weight gain in others. There may be decreased interest in usual activities (i.e., apathy), a change in attitude toward school, refusal to attend school, feelings of hopelessness, and/or recurrent thoughts of death or suicide.

Medical causes of depression or symptoms that may be misinterpreted as depression need to be considered in the evaluation. Examples include anemia; hypothyroidism; malnutrition due to an eating disorder, inflammatory bowel disease, or other chronic illness; infectious mononucleosis; adrenal insufficiency; and lupus cerebritis. It is particularly important to evaluate adolescents for use of alcohol, marijuana, and other illicit substances

Table 36-1 Neuroreceptor Effects of Antidepressant Medications

	TCAs	SSRIs	Bupropion	Venlafaxine	Mirtazepine
Serotonin reuptake inhibitor	+ +	+ + + +	+ / −	+ + +	−
Norepinephrine reuptake inhibitor	+ + +	+	+	+ + +	+ +
Dopamine uptake inhibitor	−	+ Sertraline	+ +	+	−
Cholinergic antagonist	+ + +	+ Paroxetine	−	−	+ +

TCAs, tricyclic antidepressants; SSRIs, sustained serotonin reuptake inhibitors.
+ mild effect; ++ moderate effect; +++ strong effect; ++++ strong, predominant effect; − no effect; +/− minimal to no effect

Table 36-2 Mental Status Examination

Component	Descriptors
Appearance, behavior	Overall presentation, appropriateness, grooming, eye contact, interpersonal interaction, relatedness
Speech, language	Volume, pace, pressure level, articulation
Mood	As perceived by the patient (e.g., happy, sad, hopeless)
Affect	As perceived by others about the patient (e.g., labile, euphoric, bright, full, constricted, blunted, flat)
Thought process	Logical or disorganized, goal-directed or tangential, circumstantial, flight of ideas
Thought content	Suicidal, homicidal, paranoid ideations, delusions
Perception	Hallucinations
Cognition	Estimated intelligence
Insight, judgment	Patient's understanding of his or her illness, ability to make good decisions

Box 36-4 Symptoms of Depression in Adolescents

- Depressed or irritable mood
- Declining academic performance
- Delayed sleep onset, difficulty waking up
- Decrease energy level
- Restlessness or agitation
- Decreased appetite or weight loss
- Frequent somatic complaints
- Loss of interest in usual activities/withdrawal
- Low self-esteem, feelings of guilt
- Hopelessness or suicidal ideation or behavior

and to recognize that a diagnosis of depression should not be made when the adolescent is actively using drugs or alcohol. Treating the substance use disorder will alleviate the depressive symptoms in many, but not all, cases.

Several screening tools for depression have been validated for use in adolescents, including the Children's Depression Inventory, the Beck Depression Inventory, and the Reynolds Adolescent Depression Scale. These instruments can be helpful in confirming a diagnosis of depression and monitoring response to treatment but should not replace a thorough history and physical examination.

Management

The mangement of depressive disorders in adolescents is multimodal and should address individual as well as environmental issues. Family therapy is recommended when there is a high level of family conflict. Psychoeducation should be included during these sessions. When school is causing excessive amounts of stress for the adolescent, the provider may collaborate with the school to help ensure that appropriate adjustments are made. Psychological testing may be helpful to determine whether there is comorbid attention-deficit/hyperactivity disorder (ADHD) and/or learning disability that may be contributing to the depression. Referral to a support group such as those dealing with divorce, grief and loss, sexuality, chronic illness, or anger management is recommended. If the stresses are interpersonal, individual psychotherapy is recommended. Cognitive behavioral therapy (CBT) and interpersonal psychotherapy have been shown to reduce symptoms of mild to moderate depression in adolescents. If the depression is more severe or if the adolescent fails to respond to these modes of treatment alone, pharmacological treatment may be necessary.

SSRIs are the first-line pharmacological treatment for unipolar depression. Two randomized, placebo-controlled trials have shown that fluoxetine is both safe and effective in the treatment of depression in children and adolescents. This finding was replicated in the Treatment for Adolescents with Depression Study (TADS), a multicenter, randomized, clinical trial comparing fluoxetine with and without CBT to CBT alone and placebo. Results based on the Children's Depression Rating Scale–Revised (CDRS-R) were as follows: Rate of response was highest in the fluoxetine plus CBT group (71.0%), followed by fluoxetine alone (60.6%), then CBT alone (43.2%), and lastly placebo (34.8%).

It is generally recommended to start with a low medication dosage (i.e., fluoxetine 10 mg) and titrate to effect. Dose of fluoxetine used in TADS ranged from 20 to 40 mg. If an adolescent fails to respond to a therapeutic dose of an SSRI after 4 to 6 weeks, switching to an alternative SSRI may result in clinical improvement. Other SSRIs that may be used include sertraline, citalopram, escitalopram, or paroxetine. If the adolescent fails two SSRIs, then an alternative antidepressant should be considered.

Augmentation therapy, or the addition of a second medication, can be considered if a comorbid condition exists with the depression or if the depressive symptoms do not respond adequately to an SSRI alone. One such strategy is the addition of bupropion (SR or XL). This can be particularly helpful in adolescents with comorbid ADHD. In adolescents and adults with depression that is resistant to the inhibition of serotonin reuptake alone,

the inhibition of both serotonin and norepinephrine reuptake with venlafaxine may yield improvement. Lithium carbonate plus an antidepressant has demonstrated effectiveness in adults with treatment-resistant depression but should be used with caution in adolescents because of side effects, potential toxicity, and suicidal risk. Tricyclic antidepressants generally are not recommended for use in adolescents for these same reasons, as well as limited evidence of efficacy. Other potential augmentation strategies include the addition of a psychostimulant (e.g., methylphenidate) or thyroid hormone (i.e., liothyronine or levothyroxine) to the antidepressant.

As discussed in Chapter 39, the U.S. Food and Drug Administration issued a black-box warning in 2004 regarding to suicidal ideation when antidepressants are used for patients under age 18. This warning must be discussed with parents, and close monitoring for agitation and suicidal thoughts is recommended.

BIPOLAR DISORDER

A diagnosis of bipolar disorder (BPD) can be difficult to establish during adolescence. The manifestations commonly evolve during the second decade of life, and years may separate the first depressive and manic episodes. Consequently, the initial diagnosis given is often unipolar depression, anxiety, Panic disorder, or ADHD. It may be many years before the recognition and diagnosis of BPD.

Definitions

DSM-IV-TR classifies BPD as BPD Type I, BPD Type II, Cyclothymic Disorder, and BPD NOS. Criteria for BPD Type I are listed in Boxes 36–5 and 36–6. Criteria for BPD Type II are listed in Box 36–7.

Cyclothymic disorder is defined by numerous periods of hypomania and mild depression lasting at least 1 year (2 years for adults). The patient is not without symptoms for more than 2 months at a time. Adolescents with cyclothymia often progress to BPD Type I or II. BPD NOS includes those patients with bipolar features who do not meet the full DSM-IV-TR criteria. Children and adolescents are often given this diagnosis, as they often fail to meet full DSM-IV-TR criteria. Older adolescents may present with a more classic, adult-like presentation meeting all the criteria. As with depressive disorder NOS, BPD NOS can also be used when it is unclear whether the symptoms may be due to a medical condition or substance use disorder.

Box 36-5 DSM-IV-TR Criteria for the Diagnosis of BPD Type I, Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).
B. During the period of mood disturbance, 3 (or more) of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree:
   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli).
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
   7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
C. The symptoms do not meet criteria for a mixed episode.
D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism). **Note:** Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of BPD Type I.

From: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. [Text Revision] (DSM-IV-TR). Washington, D.C., American Psychiatric Association, 2000.

Epidemiology

The prevalence of BPD in adolescents is thought to be similar to that found in adults and is estimated to be about 1%. Lewinsohn et al. evaluated rates of BPD in high school youth aged 14 to 18 years. The lifetime prevalence was approximately 1%, and another 5.7% had subsyndromal symptoms warranting a diagnosis of BPD NOS. These adolescents had high rates of impairment similar to those

Box 36-6 DSM-IV-TR Criteri for the Diagnosis of BPD Type I, Mixed Episode

A. The criteria are met both for a manic episode and for a major depressive episode (except for duration) nearly every day during at least a 1-week period.
B. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism). **Note:** Mixed-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of BPD Type I.

From: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. [Text Revision] (DSM-IV-TR). Washington, D.C., American Psychiatric Association, 2000.

who received the diagnosis of BPD, Type I or II. In retrospective studies of adults with BPD, as many as 60% experienced the onset of symptoms before the age of 20 years; 10–20% had onset before age 10 years. The authors conclude that the diagnosis of BPD is often delayed by as much as 10 years.

Pathophysiology

As with the depressive disorders, BPD is likely the result of multiple genetic variations as well as environmental factors. Although twin and adoption studies indicate that adult BPD is a heritable disease, studies in children and adolescents are limited. Some authors believe that early-onset BPD may have an even stronger genetic link. Adolescents with a family history of BPD in a first-degree relative are two to three times more likely to develop a mood disorder.

Brain imaging studies in adolescents with BPD have shown white matter hyperintensities predominantly in the frontal cortex and smaller amygdala volumes compared with normal controls. The frontal cortex is involved in control of impulses, judgment, sexual behavior, and socialization. The amygdala plays a key role in processing and storage of emotional stimuli.

Evaluation

As with MDD, the diagnosis of BPD is made by clinical interview of patient and guardian. Careful analysis of present symptoms and family history will lead to the diagnosis. There is no single diagnostic test for BPD. Useful clinician scales include the Wash-U-KSADS and Young Mania Rating Scale. The Child Behavior Checklist is a useful parent rating scale. Adolescents often present with mood lability, extreme irritability, behavior changes, and/or aggressiveness. Mania, which is a criterion for the

Box 36-7 DSM-IV-TR Criteri for the Diagnosis of BPD Type II, Hypomanic Episode

A. A distinct period of persistently elevated, expansive or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood.
B. During the period of mood disturbance, 3 (or more) of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree:
   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli).
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
   7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.
D. The disturbance in mood and the change in functioning are observable by others.
E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.
F. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism). **Note:** Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of BPD Type II.

From: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. [Text Revision] (DSM-IV-TR). Washington, D.C., American Psychiatric Association, 2000.

diagnosis of BPD Type I, is characterized by the symptoms noted in Box 36-8.

Although older adolescents may have moods that cycle over weeks to months, younger adolescents may present with rapid, ultrarapid, or ultradian (daily) mood cycling. Classic euphoric mania is rare in both children and adults. The mood in BPD is more often irritable or dysphoric. Differential diagnosis is difficult and includes ADHD, oppositional defiant disorder, conduct disorder, and anxiety disorders. Each of these diagnoses can be comorbid with BPD. Warning signs that an adolescent who presents with depression may in fact have BPD are listed in Box 36-9.

Early age of onset (before age 25 years) of a depressive episode is a risk factor for BPD. Frequent episodes of depression, failure to respond to antidepressant therapy, or tendency toward activation (worsening) with antidepressants are also warning signs for later development of BPD. Family history of BPD in a first-degree relative is a major risk factor (two to three times more likely).

Medical conditions that might present with manic symptoms include hyperthyroidism, closed head injury, temporal lobe epilepsy, multiple sclerosis, systemic lupus erythematosus, and Wilson disease. It is important to screen for symptoms or family history of these conditions. Routine screening labs might include complete blood count, liver panel, renal panel, and thyroid-stimulating hormone (TSH). If there are neurological signs, especially if they are localizing, brain imaging is indicated.

As is the case with the depressive disorders, a careful substance use history should be obtained. Adolescents abusing stimulants such as cocaine, amphetamine, psychostimulants, dextromethorphan, or steroids can present with manic symptoms. In addition, many adolescents with BPD may self-medicate with alcohol and other drugs. If substance use or abuse is suspected, it is useful to get a urine drug screen and blood alcohol concentration.

Box 36-8 Symptoms of Mania in Adolescents

- Euphoric, elated, or extremely irritable mood
- Grandiosity
- Decreased need for sleep
- Pressured speech
- Racing thoughts or flight of ideas
- Distractibility
- Increased goal-directed activity (e.g., drawing or writing excessively)
- Excessive involvement in pleasurable or risky behaviors (e.g., hypersexuality)
- Psychosis (auditory or visual hallucinations or delusions)

Box 36-9 Risk Factors for BPD in Adolescents with Unipolar Depression

- Early age of onset of a depressive episode
- Frequently recurring depression
- Poor response to antidepressant therapy
- Activation (worsening) with antidepressant
- Substance abuse
- Psychotic symptoms
- Family history of BPD

Management

Pharmacotherapy is usually indicated for the management of BPD. However, most of the mood-stabilizers and atypical antipsychotics (see Chapter 39) used to manage BPD are considered off-label in children and adolescents due to the paucity of randomized controlled data in pediatric populations.

In 2005, Kowatch, et al. published expert consensus guidelines for the acute management of BPD Type I with and without psychosis in patients aged 6 to 17 years. Guidelines were not developed for BPD Type II because the expert panel decided that the existing evidence base in children and adolescents was insufficient to support reliable recommendations. The algorithms for BPD Type I call for 4–8 week trials of each medication or combination of medications before moving on to another regimen. The expert panel emphasized that factors other than medication failure should be considered for patients who do not respond to treatment. These factors may include incorrect diagnosis of BPD, comorbid conditions, non-adherence to medication, and environmental or physiologic stressors.

The algorithm for the acute manic or mixed phases of BPD Type I without psychosis calls for rapid initiation of monotherapy (stage 1) with a traditional mood stabilizer (e.g., lithium carbonate, valproate, or carbamazepine) or atypical antipsychotic (e.g., olanzapine, quetiapine, or risperidone). Although the panel leaned toward lithium or valproate because of their longer history and larger evidence base, the atypical antipsychotics may be better tolerated and do not require the monitoring of blood levels. If lithium or valproate is used, the controlled release formulation may help minimize side effects. The panel could not recommend the atypical antipsychotics ziprasidone and aripiprazole as initial monotherapy because of insufficient supporting data. If initial monotherapy yields partial improvement, augmentation therapy (addition of a second mood stabilizer or atypical antipsychotic) is recommended. For those with no response or significant side effects to initial monotherapy, alternative monotherapy (stage 2) with a drug not used previously is recommended. Failure to respond at this

level should prompt either a third trial of alternative monotherapy or a combination of two mood stabilizers (stage 3). Failure to respond at this level should be followed by a trial of three mood stabilizers (stage 4) and, finally, by trials of alternate monotherapy with oxcarbazepine, ziprasidone, or aripiprazole (stage 5). Non-response or intolerable side effects to stage 5 is followed by the stage 6 recommendation for clozapine or electroconvulsive therapy.

The treatment algorithm for the acute manic or mixed phases of BPD Type I with psychosis is more aggressive than that for acute BPD Type I without psychosis. When psychosis is present, the expert panel recommends stage 1 therapy with both a traditional mood stabilizer (e.g., lithium or valproate) and an atypical antipsychotic (risperidone, olanzapine or quetiapine). This can be augmented by the addition of a third medication (i.e., another atypical antipsychotic) prior to the progression through the subsequent stages.

Although the consensus panel did not develop a treatment algorithm for the acute depressed phase of BPD Type I, it did note that data in adults support the use of lithium in adolescents which is approved for age 13 years and older. Lamotrigine has also been shown to be effective treatment for the depressed phase in adults with BPD, but it must be initiated very slowly to decrease the risk of erythema multiforme major. Alternatively, bupropion or an SSRI may be added once the patient has improved on a mood stabilizer. Care should be taken with SSRIs because of potential mood destabilization and suicidal risk (see Chapter 39).

Alternatively, bupropion SR or an SSRI may be added in once the mood has been stabilized with medication. Caution must be used with SSRIs because they can be mood destabilizing.

It is important to treat comorbid conditions once adequate mood stabilization has been achieved. ADHD is the most common comorbid condition and should be treated with psychostimulants, atomoxitine, bupropion, or alpha-2-agonists (clonidine or guanfacine).

Psychotherapy for adolescents with BPD should be supportive with a focus on skill building for the adolescent. The therapist should aim to build rapport, which will improve compliance. As with the depressive disorders, psychoeducation of the family is critical. Emphasis should be on the importance of medication compliance and early recognition of relapse.

OUTCOME

BPD typically follows an episodic course, with higher chronicity and poorer prognosis for earlier-onset disease. In a 4-year follow-up study of 86 youth with BPD, Geller et al. reported recovery and relapse rates of 87% and 64%, respectively. Risk factors for recurrence include low socioeconomic status, rapid cycling, mixed episodes, psychosis, and family conflict.

MAJOR POINTS

- Mood, or affective, disorders are categorized as MDD, Dysthymic Disorder, Depressive Disorder NOS, BPD Type I, and BPD Type II, Cyclothymic Disorder, and BPD NOS.
- lAlthough most depressive episodes during adolescence resolve spontaneously within 6–9 months, nearly three-quarters of adolescents who experience a major depressive episode will relapse within 5 years.
- Common manifestations of adolescent depression include irritability, decreased school performance, social withdrawal, and conflict with peers or family.
- Individual, interpersonal, and cognitive-behavioral therapy are considered first-line treatment options for adolescents with depressive disorders. Adolescents who do not respond may benefit from treatment with a low-dose SSRI or alternate antidepressant, titrated to effect (see Chapter 39).
- BPD is difficult to diagnose during adolescence. The 1% prevalence is thought to be similar to that of adults, but the recognition and diagnosis is commonly delayed by as much as 10 years.
- First-line treatment of BPD is pharmacologic, beginning with monotherapy with a mood stabilizer or atypical antipsychotic. More severe illness or the presence of psychotic symptoms may require combination drug therapy. Mood stabilization is the major goal of initial therapy.
- Once mood stabilization is achieved in adolescents with BPD, additional pharmacotherapy should be considered for comorbid conditions. Psychotherapy should be provided with a focus on skill building.
- Rates of episode remission and relapse in BPD are high, and earlier-onset disease follows a more chronic course and carries a poorer prognosis.

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CHAPTER 37

Psychotic Disorders

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INTRODUCTION

Psychosis in children or adolescents presents physicians with perhaps the most challenging of clinical situations. These are young people who have difficulties across all lines of development and suffer interpersonal difficulties, perceptual disturbances, cognitive delays, and maladaptive functioning. The diagnosis of psychosis in young people can be devastating for families and costly for society.

Psychosis has various definitions, but a common thread among them is severe impairment of mental functioning with disturbance in reality testing, or the inability to evaluate the external environment and differentiate it from one's internal world. Reality testing requires accurate perception, organized thought processes, and flexibility in interpersonal interactions. Hallucinations and delusions, along with impairments in reality testing, are the classic characteristics of psychosis.

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision (DSM-IV-TR) divides psychotic disorders into the following diagnoses: schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, substance-induced psychotic disorder, and psychotic disorder not otherwise specified (NOS). Psychotic features may be associated with mood disorders, trauma-related disorders, pervasive developmental disorders (PDDs), and personality disorders, but manifestations other than psychosis predominate.

This chapter focuses on schizophrenia during adolescence. Its distinction from pervasive developmental and autistic disorders is discussed, followed by a review of its manifestations, evaluation, and management.

HISTORICAL PERSPECTIVE

The classification and diagnosis of psychosis in children has a long history of controversy. The first documented description by DeSanctis in 1906 identified a group of children who had significant developmental delays associated with social isolation, language abnormalities, and bizarre, inappropriate affect. Kraeplin subsequently noted that adult schizophrenia, which he termed dementia praecox, often began to manifest during adolescence. Kanner, Kolvin, and Rutter were the first to differentiate pervasive developmental delay (PDD) and autism as distinct from schizophrenia. PDD and autism spectrum disorders were described as early-onset, with high rates of mental retardation and seizure disorders, and rarely associated with hallucinations, delusions, and thought disorders. Childhood schizophrenia was described as later-onset symptoms, often associated with family schizophrenia, and predominated by thought disorders, hallucinations, and delusions.

DSM-IV-TR does not differentiate adult-onset from childhood-onset schizophrenia, reflecting evidence over the past 40 years demonstrating the evolution of symptoms over time. It does differentiate schizophrenia from diagnoses in the category of PDD (e.g., autistic disorder, Asperger syndrome, childhood disintegrative disorder, and Rett disorder). Although the cause of schizophrenia

remains unknown, it is generally considered a neurodevelopmental disorder.

EPIDEMIOLOGY

Schizophrenia is much more likely to be diagnosed in adolescents and adults than in children. The adolescent and adult rates are 2–4 per 10,000, compared with 2 per 100,000 before puberty. The age of onset peaks at 15–30 years. The male-to-female ratio decreases from approximately 2:1 during childhood to 1:1 during adolescence and adulthood.

Premorbid factors that have been associated with schizophrenia include abnormal motor development, inattention, difficulty with information processing, diminished cognitive capacity, language delay, poor school performance, social isolation, and anxiety. However, no single factor demonstrates a consistent association and no set of factors reliably predicts the development of schizophrenia.

PATHOPHYSIOLOGY

Psychosis presents with manifestations that can be classified as positive and negative. Positive manifestations represent overproductions or distortions of normal functions (e.g., hallucinations, delusions, and disorganized speech). Negative manifestations represent deficiencies of normal functions, such as flattened affect, avolition, and diminished speech (i.e., alogia). The onset of schizophrenia is typically gradual, and the effect tends to be cumulative over time. Acute onset has been described but is unusual.

Auditory hallucinations are described by 75% of patients with schizophrenia and constitute the most common presenting symptom. The hallucinations are usually brief phrases or a few words and often carry a negative message or command. The voices may be familiar or unknown, single or multiple, and engaged in conversation apart from the patient or directed toward the patient. Visual hallucinations are less common in schizophrenia than are auditory hallucinations, particularly after puberty. When present, they tend to be vivid, moving, and well defined.

Delusions are reported in 50–85% of children and adolescents with schizophrenia. Abstract themes, paranoia, and mind control are more common in adolescents and adults than in children, who are more likely to describe delusions involving animals, ghosts, monsters, or unspecified fears. Formal thought disorders present as irrational, illogical, or tangential thinking; loose associations; magical thinking; and frank incoherence when severe. The presence of negative manifestations (e.g., flattened affect, diminished energy, social withdrawal, inattention, and apathy) tends to distinguish schizophrenia from other illnesses with psychotic features, such as bipolar disorder (BPD).

Neurological findings in youth with schizophrenia are similar to those found in adults and include abnormal eye movements and cognitive delay. The most common manifestations of the cognitive delay are difficulties with information processing, attention, executive functioning, and memory. It has been estimated that 10–20% of patients with early-onset schizophrenia have borderline or mild mental retardation. The most common finding on computerized tomography (CT) or magnetic resonance imaging (MRI) in patients with schizophrenia is enlargement of the ventricular system with decreased brain volume and cortical gray matter, particularly in the medial temporal lobe, superior temporal gyrus, cingulate gyrus, thalamus, hippocampus, parahippocampus, and frontal lobe. The structural changes reflect abnormal neuronal migration and precede the onset of psychosis, supporting the view of schizophrenia as a neurodevelopmental disorder.

Heritability is strong and consistent in family studies of schizophrenia. The risk of disease is 10-fold in first-degree biological relatives of adopted individuals with schizophrenia. Fifty percent of offspring develop schizophrenia when both parents are affected, and the concordance rate in monozygotic twins is 50% as compared with 17% in dizygotic twins. Childhood-onset schizophrenia demonstrates stronger family associations than adult-onset schizophrenia. For example, disease rates among parents of affected individuals are 25% for childhood-onset schizophrenia compared with 11% for adult-onset schizophrenia. Although susceptibility genes have not yet been identified, studies have demonstrated several chromosomal regions of interest.

Environmental factors, such as low socioeconomic status, have been associated with schizophrenia, but there is little evidence supporting their role as causative. Although low socioeconomic status may contribute to disease development, it is also possible that disease in family members contributes to difficulties with employment and education. Studies of family function have demonstrated associations of high expressed emotion (e.g., hostility, criticism, overinvolvement, unclear communication, conflict) with both the development of schizophrenia during adulthood and relapse during adulthood.

EVALUATION

All areas of biological, psychological, and social functioning should be assessed in a child or adolescent with psychosis to ensure proper diagnosis and treatment (Box 37-1). The assessment requires collateral information from

Box 37-1 Evaluation of the Adolescent with Psychosis

History

- History of present illness
- Age of symptom onset
- Course and nature of symptoms
- Precipitants
- Premorbid functioning
- Past psychiatric history
- School academic functioning
- Adaptive living skills
- Family history of psychiatric disorders
- Family stressors
- Family and cultural beliefs concerning illness
- Family strengths
- History of abuse, neglect, exposure to trauma
- Substance use history
- Developmental history—prenatal to current age

Mental Status Examination

- Appearance
- Psychomotor activity
- Speech, communication, language, functioning
- Mood and affect
- Form and content of thinking
- Thought disturbances (i.e., delusions, ideas of reference)
- Perceptual disturbances (i.e., hallucinations)
- Level of consciousness and orientation
- Concentration
- Memory
- Fund of knowledge
- Insight
- Judgment
- Suicidality and/or homicidality
- Assessment of dangerousness and impulsive activity

Psychological Testing

- Projective testing for evaluation of thought disturbance, hallucinations, etc.
- IQ and formal educational testing for assessment of achievement
- Assessment of adaptive living skills
- Assessment of communication/speech and language

Medical Evaluation

- Physical examination for associated medical conditions
- Laboratory assessment (e.g., complete blood count; electrolytes; renal, liver, and thyroid function studies; toxicology screen)
- Electroencephalogram
- Neuroimaging

Adapted from: Sorter MT: Psychotic disorders. In Klykylo WM, Kay J (eds): *Clinical Child Psychiatry,* 2nd ed. London, John Wiley & Sons, 2005, pp. 433–446.

multiple informants and may take place over several sessions. It is important for the clinician to build a working alliance with family members because they will provide most of the historical information and contribute to the patient's course and outcome.

Although a thorough diagnostic evaluation may take several sessions, the initial evaluation must rule out delirium, organic conditions requiring immediate attention (e.g., drug overdose), and suicidal or homicidal ideation. Evaluation of hallucinations, delusions, thought disorder, the presence or absence of negative symptoms, and the duration and intensity of mood disturbance will often help distinguish primary psychotic disorders from affective disorders with psychotic features. There are many validated psychiatric interview schedules to assess psychotic symptoms and provide systematic evaluation of other key symptom areas. The Schedule for the Assessment of Positive Symptoms (SAPS) evaluates hallucinations, delusions, bizarre behavior, and formal thought disorder. The Schedule for the Assessment of Negative Symptoms (SANS) evaluates flat affect, anergy, avolition, asociality, and inattention. The Kiddie PANSS is a modification of the Adult Positive and Negative Syndrome Scale.

Psychological testing, including projective testing, may help clinicians assess the severity and nature of psychosis. Evaluation of cognitive ability, educational achievement, and adaptive living skills may reveal weaknesses that require attention, as well as strengths that will be relied upon in treatment. Evaluation of speech and language is especially useful in young patients because new-onset, extreme disorganization in speech supports a diagnosis of schizophrenia or other underlying psychosis.

Box 37-2 summarizes the differential diagnosis of schizophrenia. The medical evaluation begins with a thorough history and physical examination, often with neurology consultation. Baseline laboratory assessment should include a complete blood count; serum electrolytes, calcium, magnesium, and phosphorous; serum blood urea nitrogen and creatinine; erythrocyte sedimentation rate or C-reactive protein; serum liver and thyroid function tests, and toxicology screen. Substance use leads the differential diagnosis of psychosis in adolescents. Causes include the use of cocaine, amphetamines, hallucinogens, cannabis, phencyclidine, inhalants, and alcohol, as well as withdrawal from alcohol, barbiturates, benzodiazepines, and other sedatives. Chaotic family and social environments that place patients at risk of schizophrenia may also place them at risk for substance use and human immunodeficiency virus (HIV) infection. HIV screening is indicated for any adolescent with a history of substance use, sexual abuse, or consensual sexual activity.

BPD and schizophrenia present with similar manifestations, including delusions, hallucinations, paranoia, and ideas of reference. BPD tends to be more episodic than

Box 37-2 Differential Diagnosis of Schizophrenia

Autistic Spectrum Disorders

- Asperger disorder
- Autistic disorder
- Childhood disintegrative disorder
- Pervasive developmental disorder (NOS)

Psychosis Associated with Mood Disorder

- Bipolar disorder
- Major depressive disorder

Other Psychotic Disorders

- Psychotic disorder, NOS
- Schizoaffective disorder

Obsessive-Compulsive Disorder

Post-Traumatic Stress Disorder

- Dissociative disorder

Personality Disorders

- Schizotypal
- Schizoid
- Borderline
- Paranoid

Communication Disorders

- Substance-Induced Psychosis (e.g., amphetamines, cocaine, phencyclidine, marijuana, hallucinogens, alcohol, organic solvents, sedative withdrawal)
- Toxic Encephalopathy (e.g., corticosteroids, anticholinergics, heavy metals)

Medical Conditions

- Delirium
- Epilepsy
- Central nervous system (CNS) trauma or neoplasm

Infectious Diseases

- Human immunodeficiency virus (HIV) infection
- Herpes encephalitis
- Neurosyphilis
- Encephalitis meningitis

Neurodegenerative Disease

Metabolic Disorders

schizophrenia during adolescence, whereas negative symptoms appear more common in schizophrenia than BPD. The rates of positive symptoms, behavioral difficulties, and dysphoria do not appear to differ in adolescents with schizophrenia, BPD, and psychosis not otherwise specified (NOS). Children with early-onset schizophrenia, compared with those with BPD or psychosis NOS, have higher rates of premorbid social withdrawal, more global impairment in function, and fewer friends. Long-term follow-up often is needed before a diagnosis of schizophrenia can be established (Box 37-3).

Other diagnoses of childhood and adolescence that may be confused with schizophrenia include pervasive developmental disorders (PDDs), obsessive-compulsive disorder (OCD), and dissociative states. PDDs typically are apparent in early childhood and follow a chronic course, with significant impairments in language and social function. Delusions and hallucinations may occur in PDDs but tend to be less persistent than in schizophrenia. It is also important to recognize that illogical and immature patterns of communication may not reflect an underlying thought disorder. OCD is manifested by perseveration of thought, speech, and behavior. Although hallucinations are uncommon in OCD, obsessive thoughts and compulsive behaviors can accompany schizophrenia. Dissociative states and brief episodes of hallucination or distorted thinking may accompany post-traumatic stress disorder (PTSD) and borderline or schizotypal personality disorders. However, the symptoms tend to be more transient and intermittent in these disorders than in schizophrenia.

MANAGEMENT

The treatment of schizophrenia requires the integration of multiple strategies to relieve psychotic symptoms, minimize developmental deviation, and maximize adaptive function. The care plan typically includes pharmacotherapy for the patient, counseling and education for the patient (see Chapter 39) and caregivers, and community resources to help relieve the emotional and financial strain on the family. Many studies have established the efficacy of neuroleptic medications in the management of schizophrenia during adulthood. The few studies conducted in children and adolescents demonstrate that medications are more effective than placebo for the control of hallucinations and delusions, but that the rates of relapse and side effects are high.

Recent studies of atypical, or second-generation, antipsychotic medications in children and adolescents have been encouraging. A double-blind, randomized trial of clozapine demonstrated its superiority to haloperidol for mood stabilization and the management of psychosis. Open-label studies of children and adolescents have demonstrated the effectiveness of clozapine, risperidone, and olanzapine for the control of the positive and negative symptoms of schizophrenia. Common side effects are fatigue and weight gain for all three medications; nonspecific electroencephalographic changes and hypersalivation for clozapine; and extrapyramidal symptoms for risperidone. Open-label studies in adolescents with psychosis have demonstrated that quetiapine, aripiprazole,

Box 37-3 DSM-IV-TR Diagnostic Criteria for Schizophrenia

A. **Characteristic symptoms:** Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):
   1. Delusions
   2. Hallucinations
   3. Disorganized speech (e.g., frequent derailment or incoherence)
   4. Grossly disorganized or catatonic behavior
   5. Negative symptoms (i.e., affective flattening, alogia, or avolition)

Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.

B. **Social/occupational dysfunction:** For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or, when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. **Duration:** Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. **Schizoaffective and mood disorder exclusion:** Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. **Substance/general medical condition exclusion:** The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse or a medication) or a general medical condition.

F. **Relationship to a pervasive developmental disorder:** If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

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and ziprasidone are effective and well tolerated over the long term.

Clinicians should educate patients and families about the risks, benefits, and side effects of all medications prescribed, particularly when the use is extrapolated from adult data and approval by the U.S. Food and Drug Administration (FDA) is lacking. Informed consent of the parent/guardian must be obtained, as well as assent of the patient when possible. Long-term potential side effects of antipsychotic medications, such as extrapyramidal side effects, tardive dyskinesia, weight gain, excessive sedation, cognitive blunting, hyperglycemia, changes in electrocardiogram (ECG), endocrine effects on thyroid hormones or prolactin elevation, hematological changes, and neuroleptic malignant syndrome require baseline and periodic evaluation. Each evaluation should include the determination of body mass index, a structured evaluation such as the Abnormal Involuntary Movement Scale (AIMS) to measure the presence or absence of any involuntary movements, appropriate laboratory data, and ECG.

The psychosocial treatment plan must be well integrated and tailored to meet the specific needs of the individual patient at the appropriate developmental level. Children with schizophrenia may benefit from supportive psychotherapy, but traditional, insight-oriented psychotherapy generally is not recommended in the acute phases of illness.

The combination of psychoeducational family treatment, medication, and social skills training has been shown to decrease relapse. Supportive and cognitive behavioral therapy has been shown to improve adaptive function, and cognitive enhancement therapy has been shown to improve neurocognition and processing speed in adults. Focused individual and group therapy may target deficits in activities of daily living, conflict resolution, problem solving, and social skills. Children and adolescents with schizophrenia often require special educational accommodations developed jointly by school and mental health professionals.

The management of schizophrenia often requires a step-down strategy from hospitalization to day treatment to intensive outpatient care. Community mental health services may include in-home therapeutic care, therapeutic recreation, case management, and vocational rehabilitation for older adolescents and young adults.

OUTCOME

Outcome data for children and adolescents with schizophrenia are limited. A review of 57 children and adolescents with onset prior to age 14 revealed improve-

MAJOR POINTS

- Psychosis is a severe impairment of mental functioning with disturbance in reality testing, or the ability to evaluate the external environment and differentiate it from one's internal world. Psychotic disorders include schizophrenia, schizophreniform disorder, schizoaffective disorder, and substance-induced psychotic disorder.
- Psychotic features may be associated with mood disorders, trauma-related disorders, pervasive developmental disorders (PDDs), and personality disorders, but manifestations other than psychosis predominate.
- PDD and autism spectrum disorders are of earlier onset than schizophrenia and are more likely to be associated with mental retardation and seizure disorders. Schizophrenia in children is often associated with family schizophrenia and is characterized by thought disorders and delusions.
- Bipolar disorder and schizophrenia present with similar manifestations, including delusions, hallucinations, paranoia, and ideas of reference. Bipolar disorder tends to be more episodic during adolescence than is schizophrenia, whereas negative symptoms appear more commonly in schizophrenia than in bipolar disorder.
- Schizophrenia is much more likely to be diagnosed in adolescents and adults than in children. The adolescent and adult rates are 2–4 per 10,000, compared with 2 per 100,000 before puberty. The onset of schizophrenia is typically gradual, and the effect tends to be cumulative over time.
- The evaluation of an adolescent with psychosis must rule out delirium, organic conditions requiring immediate attention (e.g., drug overdose), and suicidal or homicidal ideation.
- The treatment of schizophrenia typically includes pharmacotherapy for the patient, counseling and education for the patient and caregivers, and community resources to help relieve the emotional and financial strain on the family.
- Recent studies of atypical, or second-generation, antipsychotic medications (e.g., clozapine, risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone) in children and adolescents with schizophrenia have been encouraging. However, side effects are common and FDA approval for use in children is often lacking.
- Although schizophrenia tends to become less disruptive and easier to manage with age, core symptoms and difficulties with social function typically persist in adulthood.

ment in one-quarter of patients, remission in one-quarter, and severe deficit in one-half. Other studies have demonstrated that up to 90% of patients remain on antipsychotic medication and that the rates of repeat hospitalization and residential placement are high. Adult studies have documented increased rates of early death from suicide or injury and low levels of employment and/or education. Factors that have been associated with poor outcome include poor premorbid functioning, early age of onset, and nonacute, insidious onset. Although schizophrenia does become less disruptive and easier to manage over the years, core symptoms and difficulties with social function persist.

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CHAPTER 38

Anxiety Disorders

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INTRODUCTION

Anxiety is an emotion that combines cognitive symptoms, such as apprehension and fear, with physical symptoms of sympathetic nervous system activation, such as sweating and tachycardia. It may be a normal response to a real environmental stress that improves alertness and readiness for reaction, or an abnormal response to an imagined or misperceived threat that impairs function. Anxiety disorders are chronic and/or recurrent manifestations of stress and worry that do not serve health and positive development.

Box 38-1 lists the diagnostic categories of anxiety according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision (DSM-IV-TR). This chapter focuses on those disorders that are common during adolescence: panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, and generalized anxiety disorder.

DEFINITIONS

Agoraphobia is persistent concern about or avoidance of places or situations that might trigger panic and in which help might be unavailable or escape difficult. It may occur with or without panic disorder.

Panic is defined as intense apprehension, fear, or terror; a sense of impending doom; and physical symptoms of breathlessness, palpitations, chest pain, choking, or smothering.

Panic attacks develop abruptly, peak within 10 minutes, and include at least four of the symptoms listed in Box 38-2.

Panic disorder consists of recurrent panic attacks and persistent worry about the attacks or their consequences over at least a 1-month period. It may occur with or without agoraphobia and is not attributable to a medication, drug, or underlying medical condition.

Specific phobias involve persistent and excessive or unreasonable anxiety provoked by the presence or

Box 38-1 Anxiety Disorders Defined by DSM-IV-TR

- Panic disorder without agoraphobia
- Panic disorder with agoraphobia
- Agoraphobia without history of panic disorder
- Specific phobia
- Social phobia
- Obsessive-compulsive disorder
- Post-traumatic stress disorder
- Acute stress disorder
- Generalized anxiety disorder
- Anxiety disorder due to a general medical condition
- Substance-induced anxiety disorder
- Anxiety disorder not otherwise specified

From: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. [Text Revision] (DSM-IV-TR). Washington, D.C., American Psychiatric Association, 2000.

Box 38-2 DSM-IV-TR Symptoms of Panic

- Sweating
- Trembling or shaking
- Breathlessness or choking sensation
- Chest pain or discomfort
- Nausea or abdominal distress
- Lightheadedness
- Feelings of unreality or detachment
- Fear of losing control or going crazy
- Fear of dying
- Paresthesias
- Chills or hot flashes
- Palpitations or pounding heartbeat

From: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. [Text Revision] (DSM-IV-TR). Washington, D.C., American Psychiatric Association, 2000.

Box 38-3 DSM-IV-TR Definitions of Obsessions and Compulsions

Obsessions

1. Recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress.
2. The thoughts, impulses, or images are not simply excessive worries about real-life problems.
3. The person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action.
4. The person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without, as in thought insertion).

Compulsions

1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly.
2. The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive.

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anticipation of specific objects or situations and often leading to avoidance of those objects and situations. Adults with specific phobias typically present with panic attacks and perceive the anxiety as unreasonable. Children often do not perceive the anxiety as unreasonable and often present with crying, tantrums, or clinging behavior persisting at least 6 months. Avoidance or endurance of the phobic stimulus causes significant distress and interferes with daily function.

Social phobia is anxiety provoked by exposure to certain social or performance situations and often leading to avoidance. The situations typically involve unfamiliar people, potential scrutiny, and potential humiliation. The diagnosis of social phobia in childhood requires the anxiety to occur in peer rather than adult settings. The fear or avoidance cannot be triggered by a medical or other mental health disorder, and if another disorder is present, the anxiety must be considered a separate entity.

Obsessive-compulsive disorder (OCD) is characterized by obsessive thoughts that cause marked distress or anxiety and compulsive behaviors that serve to neutralize the anxiety (Box 38-3). The obsessions and compulsions consume more than an hour per day; interfere significantly with function; are recognized by adults and some children as unreasonable or excessive; and are not attributable to a medication, drug, or other condition.

Post-traumatic stress disorder (PTSD) is characterized by re-experiencing a traumatic event, simultaneous symptoms of increased arousal, and the avoidance of trauma-associated stimuli. PTSD during adolescence requires history of exposure to an event(s) involving actual or threatened death or serious injury and a response to that event involving intense fear, helplessness, or horror (Box 38-4). The episodes of re-experience must recur for at least 1 month and must cause significant distress or social impairment.

Generalized anxiety disorder (GAD) is characterized by at least 6 months of persistent and excessive worry that causes significant distress or functional impairment; is not explained by medication use, drug use, or another medical or mental health condition; and is associated with the symptoms shown in Box 38-5.

Separation anxiety disorder (SAD) is excessive, developmentally inappropriate anxiety about separation from home or from objects/people to which the patient is attached. The diagnosis requires at least three symptoms (Box 38-6), onset before age 18 years, persistence at least 4 weeks, and no evidence that the condition is caused by medication, drug use, medical illness, or another mental health disorder.

Box 38-4 DSM-IV-TR Criteria for Post-Traumatic Stress Disorder (PTSD) Symptoms

The traumatic event is persistently re-experienced in one (or more) of the following ways:

- Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.
- Recurrent distressing dreams of the event. In children, there may be frightening dreams without recognizable content.
- Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated). **Note:** In young children, trauma-specific re-enactment may occur.
- Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
- Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:

- Efforts to avoid thoughts, feelings, or conversations associated with the trauma.
- Efforts to avoid activities, places, or people that arouse recollections of the trauma.
- Inability to recall an important aspect of the trauma.
- Markedly diminished interest or participation in significant activities.
- Feeling of detachment or estrangement from others.
- Restricted range of affect (e.g., unable to have loving feelings).
- Sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span).

Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:

- Difficulty falling or staying asleep.
- Irritability or outbursts of anger.
- Difficulty concentrating.
- Hypervigilance.
- Exaggerated startle response.

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Box 38-5 DSM-IV-TR Anxiety Symptoms for Generalized Anxiety Disorder (GAD)

- Restlessness or feeling keyed up or on edge
- Being easily fatigued
- Difficulty concentrating or mind going blank
- Irritability
- Muscle tension
- Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)

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Box 38-6 DSM-IV-TR Criteria for Separation Anxiety Disorder (SAD)

- Recurrent excessive distress when separation from home or major attachment figures occurs or is anticipated.
- Persistent and excessive worry about losing, or about possible harm befalling, major attachment figures.
- Persistent and excessive worry that an untoward event will lead to separation from a major attachment figure (e.g., getting lost or being kidnapped).
- Persistent reluctance or refusal to go to school or elsewhere because of fear of separation.
- Persistently and excessively fearful or reluctant to be alone or without major attachment figures at home or without significant adults in other settings.
- Persistent reluctance or refusal to go to sleep without being near a major attachment figure or to sleep away from home.
- Repeated nightmares involving the theme of separation.
- Repeated complaints of physical symptoms (such as headaches, stomachaches, nausea, or vomiting) when separation from major attachment figures occurs or is anticipated.

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EPIDEMIOLOGY

The estimated prevalence of anxiety disorders during adolescence varies depending on the population studied and the methods used for diagnosis. Gender differences are small in childhood, but all anxiety disorders except OCD are more common in females than males by adolescence. The overall community prevalence of anxiety disorders in children, adolescents, and young adults is

5–20%. When limited to adolescents, the overall community prevalence is 1–9%. The prevalence of anxiety disorders increases during adolescence and young adulthood, but the 4-year mean duration of symptoms at the time of diagnosis suggests under-recognition at younger ages.

PTSD is probably the most common anxiety disorder of adolescence, affecting 24–35% of youth in urban settings. Risk factors for PTSD during childhood and adolescence include exposure severity, exposure timing, and parental reaction to their child's exposure. Once symptoms appear, they may persist for many years. However, spontaneous recovery from PTSD may occur.

Studies suggest that up to two-thirds of adolescents experience panic attacks and up to 15% of adolescents in clinical settings have social anxiety disorder. Community prevalence rates among adolescents for other anxiety disorders are as follows: GAD, 3–5%; SAD, 2–5%; panic disorder, 1–5%; specific phobia, 2–3%; and OCD, 1%.

PATHOPHYSIOLOGY

Genetics and Neurochemistry

Comorbidity, family predisposition, and responsiveness to sustained serotonin reuptake inhibitors (SSRIs) and other antidepressant medications suggest that anxiety and depressive disorders overlap in their genetic and/or neurochemical pathways. Key lines of evidence supporting genetic transmission of anxiety include the higher concordance of anxiety disorders in monozygotic than dizygotic twins; the association of anxiety traits with the short allele of the serotonin transporter gene; and the association of anxiety disorders and noradrenergic transmission with a region of chromosome 15.

The genetics of OCD may differ from that of other anxiety disorders. For example, family studies indicate that OCD, but not other anxiety disorders, is strongly associated with tic disorders. Although other anxiety disorders respond to SSRIs as well as other types of antidepressants, OCD responds only to SSRIs. OCD, but not the other anxiety disorders, may occur as a pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAs) due to genetic vulnerability of the immune system.

Neuroimaging

Neuroimaging studies indicate that PTSD and panic disorder are associated with baseline increases in right-sided hippocampal blood flow. Decreased cerebral blood flow occurs during hyperventilation, with even greater decreases during panic attacks. Decreased hippocampal volume has been noted on magnetic resonance imaging (MRI) of adults with PTSD and depressive disorders, and lower left-brain activity has been reported in association with negative affect.

Psychological Perspectives

During infancy, the primary caregiver responds to the infant's cries of hunger, fatigue, cold, fear, etc. Over time, the child internalizes an expected pattern of relief from distressing sensations. Psychodynamic theories posit that inconsistent caregiving produces a learned pattern of anxiety. Studies suggest that this inconsistency may be caused by traumatic disruption of the parent–child relationship, negligence on the part of the caregiver, or temperamental inhibition on the part of the child.

SAD and withdrawn behavior during childhood are associated with PTSD, social phobia, specific phobia, and agoraphobia during adolescence. It remains unknown, however, whether early intervention in childhood can prevent or ameliorate the adolescent disorders.

EVALUATION

The evaluation of an adolescent with anxiety begins with a detailed history to establish symptom onset, context, frequency, and severity. The environmental or cognitive triggers, emotional responses, and associated physical manifestations should be determined. A thorough physical examination, including a mental status examination, should note common physical findings associated with anxiety disorders such as hypervigilance, autonomic arousal, and psychomotor agitation. Persistent tachycardia or hypertension, however, should raise suspicion of an underlying medical condition (e.g., hyperthyroidism), substance use, or medication affect.

Patients with anxiety disorders should always be evaluated at baseline and monitored for the development of comorbid conditions such as depressive disorders, suicidal ideation or behavior, and substance use. Box 38-7 lists screening tools that may help identify and monitor anxiety. Although many of these scales are not designed specifically for adolescents, they can help with the assessment of symptom severity and response to treatment.

Other mental health disorders that should be included in the differential diagnosis of anxiety include affective disorders; psychotic disorders with delusions; avoidant personality disorder; disruptive behavior disorders such as attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, and conduct disorder; and substance use disorder. Two-thirds of children with one anxiety disorder meet criteria for another, and one-third have at least three disorders. Of particular concern is the high prevalence of major depressive disorder and/or substance use disorder in adolescents with anxiety disorders.

Box 38-7 Screening Tools to Help Identify and Monitor Anxiety

- Vanderbilt Scales for Parent and Teacher Assessment
- Multidimensional Anxiety Scale for Children
- Screen for Child-Related Emotional Disorders (SCARED)
- Revised Children's Manifest Anxiety Scale
- Hamilton Rating Scale for Anxiety
- Social Anxiety Scale
- Yale-Brown Obsessive-Compulsive Scale
- Acute Panic Inventory

MANAGEMENT

Individual, group, and/or family counseling generally constitute the initial treatment for adolescents with anxiety disorders. Cognitive behavioral therapy (CBT) may be useful in younger adolescents with mild to moderate anxiety of recent onset. Older adolescents with severe anxiety or significant comorbidity typically require pharmacotherapy (see Chapter 39) in addition to CBT or psychotherapy.

SSRIs are considered first-line pharmacotherapy for the treatment of anxiety disorders. Most SSRIs are used off-label in children and adolescents because of inadequate pediatric data to support approval by the U.S. Food and Drug Administration (FDA). Data are most convincing for fluoxetine, fluvoxamine, and sertraline, but citalopram and escitalopram are also widely used for the treatment of anxiety. Randomized trials in adults support the use of fluoxetine and fluvoxamine for SAD, GAD, and social phobia; and the use of sertraline for generalized anxiety disorder. Regardless of which SSRI is used, adolescents and parents should be informed of the FDA's black-box warning that SSRIs may increase the risk of suicidal ideation or behavior in adolescents (see Chapter 39). They also should be aware that treatment with SSRIs may require dosage adjustment over a 6– to 12– week period to achieve maximum effectiveness without undue side effects.

Clomipramine and other tricyclic antidepressants have demonstrated efficacy in adults with various anxiety disorders, but SSRIs are generally regarded as safer and better tolerated. SSRIs and clomipramine are the only antidepressants shown to be effective for the treatment of OCD. Venlafaxine has proven efficacious for the treatment of GAD in adults but is not recommended for use in adolescents.

Anxiety often improves with treatment of comorbid conditions. For example, the combination of SSRIs and stimulants may be used to treat comorbid anxiety and ADHD. Comorbid bipolar and anxiety disorders represent one of the most challenging therapeutic dilemmas in psychiatry, given the effectiveness of SSRIs for the control of anxiety and their simultaneous potential to induce mania in bipolar disorder. The usual approach is to optimize mood-stabilizing agents prior to initiating SSRIs.

Other medications that have been used to manage anxiety include benzodiazepines, buspirone, beta blockers, and clonidine. Placebo-controlled trials of benzodiazepines in adults with anxiety disorders have failed to consistently demonstrate long-term efficacy and, given the risk of addiction and abuse, they should be avoided in adolescents. For patients with severe anxiety uncontrolled by SSRIs, benzodiazepines can be used on a short-term, episodic basis. Limited data in adolescents suggest that buspirone may be effective for generalized anxiety disorder and that clonidine may be effective for the hyperarousal and re-experiencing symptoms of PTSD. Beta blockers have been used in adults with performance anxiety or panic disorder, but their use in adolescents has not been systematically studied.

OCD should be treated with an SSRI for at least 12–18 months after achieving symptom remission before attempting gradual discontinuation over an 8-month period. Although relapse rates are as high as 90% within a few months of discontinuation, studies suggest that ongoing or maintenance CBT during the period of declining dosage may help sustain remission.

OUTCOME

Longitudinal and retrospective studies suggest that spontaneous remission is unusual in patients with anxiety disorders, particularly if the symptoms are long-standing or severe. The best prognoses are for children with SAD or phobias. As noted earlier, adolescents with anxiety disorders often have been symptomatic for years prior to diagnosis and, even with treatment, experience a remitting and relapsing course of illness. The prepubertal onset of anxiety disorders has been shown to increase the risk of later mental health problems, including substance use disorder.

GAD and panic disorder in children tend to be chronic and are associated with major depressive disorder during adolescence and GAD during adulthood. SAD in childhood increases the risk of separation difficulties, depression, and agoraphobia in adulthood. Social phobia in childhood negatively affects education, adult employment, and adult relationships and may increase the risk of adolescent substance use. The course of PTSD during adolescence is highly variable, as noted previously. Spontaneous remission is associated with mild symptoms that develop soon after the traumatic event, early intervention, and family support. AU8

MAJOR POINTS

- Anxiety is an emotion that combines cognitive symptoms, such as apprehension and fear, with physical symptoms of sympathetic nervous system activation, such as sweating and tachycardia.
- Anxiety disorders affect 1–9% of adolescents. The most common diagnoses during adolescence are PTSD, GAD, SAD, panic disorder, specific phobia, and OCD.
- Comorbidity, family predisposition, and responsiveness to SSRIs suggest that anxiety and depressive disorders overlap in their genetic and/or neurochemical pathways. OCD differs from other anxiety disorders in its familial association with tic disorders and its autoimmune association with streptococcal infection.
- Other mental health disorders, such as depression, substance use, and ADHD, should always be considered in the differential diagnosis and as comorbidities of anxiety disorders.
- Counseling, CBT, and SSRIs constitute the major therapies for anxiety disorders.
- Spontaneous remission is more likely with SAD, phobias, and PTSD than with GAD, panic disorder, and OCD.

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CHAPTER 39

Psychiatric Pharmacotherapy

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INTRODUCTION

The aim of this chapter is to provide an overview of the psychotropic agents used most commonly in the treatment of adolescents with mental health and/or behavior problems. It is important to recognize that the pediatric literature on psychopharmacotherapy is scant, resulting in off-label use of these medications in patients of younger age or with different conditions than approved by the U.S. Food and Drug Administration (FDA). In addition, primary care providers often are asked to assume responsibility for adolescent pharmacotherapy due to a shortage of child psychiatrists. Clinicians who care for youth are therefore expected to provide first-line mental health care in the office setting and to help patients and parents make educated decisions about the types, risks, and benefits of medication.

The number of prescriptions for psychotropic medications administered to youth has increased steadily over the past two decades. An estimated 6% of U.S. children and adolescents younger than age 20 years are prescribed psychotropic medications. The challenges faced by these youth and their families are considerable. Comorbidity, social stigma, home and school disruption, parental difficulty controlling their children's behavior, and side effects contribute to delayed and erratic use of psychiatric medications. A team approach, shared by physicians, nurses, psychologists, and social workers, facilitates adherence to the treatment plan and provides support for patients, families, and health care providers.

The medications discussed in this chapter are divided into the following five categories: antidepressants, psychostimulants, antipsychotics, mood stabilizers, and adjuncts to care. Generic names are used throughout the text, and common trade names are noted in the tables.

ANTIDEPRESSANTS

Selective serotonin reuptake inhibitors (SSRIs) are approved by the FDA for the treatment of adults with major depressive disorder (MDD), generalized anxiety disorder (GAD), social anxiety, eating disorders, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), premenstrual dysphoric disorder (PMDD), panic disorder, trichotillomania, and migraine headaches. One SSRI (fluoxetine) is approved for the treatment of children and adolescents with MDD. All SSRIs carry black-box warning of increased risk for suicide. The warning was based on a pooled analysis of nine antidepressants in 4400 adolescents showing a slight increase in suicidal ideation and behavior and no cases of actual suicide. The FDA recommends that the use of antidepressants in adolescents include face-to-face contact weekly during the initial month, biweekly until week 12, and then as clinically indicated. Telephone contact between visits is also encouraged.

The usual treatment of mild to moderate depression is individual psychotherapy, without medication. For more severe depressive symptoms in the absence of bipolar disorder (BPD), the recommended approach is an SSRI combined with psychotherapy. SSRIs can precipitate mixed or manic episodes in patients with BPD and should be avoided when the diagnosis is suspected.

Most adolescents with MDD respond to low or moderate doses (Table 39-1). Treatment should continue for at least 4 weeks before increasing the dose, followed by an additional 2 to 4 weeks at a higher dose before assessing the drug's effectiveness. Once an effective drug and dose are determined, treatment should continue at least 6–12 months before considering a taper off the medication for adolescents with no previous depressive episodes. Extrapolation from the adult literature has led to recommendations for 1- to 3-year maintenance pharmacotherapy for adolescents with two or more previous episodes or an episode accompanied by psychosis, severe impairment, or significant suicidality prior to treatment.

General recommendations pertaining to the use of SSRIs in adolescents are listed in Box 39-1. The half-lives of various SSRIs, potential drug interactions, and common side effects, are shown in Table 39-2.

Specific SSRIs

Fluoxetine (Prozac) is approved by the FDA for the treatment of MDD and OCD in children ages 7 years and above, as well as for MDD, OCD, bulimia nervosa, panic disorder, and PMDD in adults. Based on comparative efficacy data, it is considered first-line pharmacotherapy for the treatment of pediatric depression. The usual starting dose is 5–10 mg daily, although doses up to 20 mg daily are commonly begun in adolescents who do not have anxiety. The maximum dose is 1 mg/kg/day, or 80 mg daily. Prozac Weekly is an enteric-coated, delayed-release formulation, with a starting dose of 90 mg weekly. A 1-week hiatus is recommended between the last immediate-release dose and the first delayed-release dose.

Sertraline (Zoloft) is approved by the FDA for the treatment of OCD in children ages 6 years and above, as well as for MDD, panic disorder, PTSD, PMDD, and social anxiety disorder in adults. There are at least two randomized, double-blind, placebo-controlled trials showing its efficacy in treating MDD in children as young as 6 years. The starting dose is 25 mg daily for children or 50 mg daily for adolescents, with a maximum dose of 3 mg/kg/day, or 200 mg daily.

Paroxetine (Paxil) is indicated in adults for the treatment of MDD, OCD, panic disorder, social anxiety disorder, social phobia, PTSD, and GAD. There is some evidence of its efficacy over placebo in treating pediatric OCD (ages 7–17 years) and social anxiety disorder (ages 8–17 years). The starting dose in children is 10–20 mg daily. The maximum dose is 0.7 mg/kg/day, or 60 mg daily. Although paroxetine has some anticholinergic effects and is mildly sedating, it has not demonstrated efficacy in the treatment of sleep disturbances. These side effects, its potent inhibition of CYP2D6, and the lack of placebo-controlled data in children make it a less desirable option in the treatment of pediatric depression.

Citalopram (Celexa) is approved by the FDA for the treatment of adult MDD. It has shown efficacy over placebo in the treatment of MDD in children ages 7–17 years. The starting dose is 10–20 mg daily. The maximum dose is 0.7 mg/kg/day or 60 mg daily. Citalopram is often preferred for patients with medical problems or those on other medications because of its minimal CYP450 interactions.

Escitalopram (Lexapro) is the active S-enantiomer of citalopram (which is a racemic mixture) and is indicated in the treatment of adult MDD. There are no pediatric placebo-controlled studies of escitalopram, but it is commonly used in pediatric patients to minimize potential side effects. Dosing is half that of citalopram, with a starting dose of 5–10 mg daily and a maximum dose of 20 mg daily.

Fluvoxamine (Luvox) is approved by the FDA for the treatment of OCD in children ages 8 years and above. Dosing is divided twice daily. The starting daily dose is 25–50 mg and may be increased slowly every 4–7 days to a maximum daily dose of approximately 4 mg/kg, or 200 mg. Fluvoxamine has multiple and strong CYP450 interactions, making its concomitant administration with

Table 39-1 SSRI Dosing

Trade Name	Generic	Common Daily Dose Range	Available Formulations
Prozac	Fluoxetine	5–40 mg	Capsule, liquid (mint)
Paxil	Paroxetine	10–60 mg	Tablet, liquid (orange)
Zoloft	Sertraline	25–200 mg	Tablet, syrup
Celexa	Citalopram	10–40 mg	Tablet, liquid (mint)
Lexapro	Escitalopram	5–20 mg[a]	Tablet, oral solution
Luvox	Fluvoxamine	50–300 mg[b]	Tablet

[a]10 mg and 20 mg of Lexapro is bioequivalent to 20 mg and 40 mg of Celexa, respectively.
[b]Divided BID.

Box 39-1 General Recommendations for the Use of SSRIs

- The selection of a particular SSRI must take into account potential drug–drug interactions associated with the SSRI half-life and effect on the cytochrome P450 (CYP450) enzyme system.
- Initiating SSRI treatment at low doses minimizes common, early side effects (e.g., restlessness, dizziness, diarrhea, sweating, nausea, headaches, initial insomnia) and promotes compliance.
- Failure to respond is defined as inadequate control of symptoms after at least 6 weeks on the maximum tolerated dose.
- Anxiety disorders typically require very low starting doses, higher maintenance doses than for MDD, and longer intervals between dose increases.
- Children who are fast vs. slow metabolizers (which can be determined by laboratory testing) differ in their therapeutic SSRI doses.
- Serum SSRI levels do not correlate with response and are not clinically indicated.
- Discontinuation syndrome can occur when an SSRI with a short half-life is stopped abruptly. Symptoms can include dizziness, nausea, insomnia, headache, vivid dreams, nervousness, asthenia, diarrhea, worsening mood, vomiting, irritability, visual disturbances, lethargy, anorexia, tremor, and paresthesias.
- Serotonin syndrome can occur when an SSRI is used with other serotonergic agents, such as tricyclic antidepressants. Symptoms can include agitation, excitation, muscle twitching, nausea, vomiting, diarrhea, chills, fever, confusion, diaphoresis, and dizziness.
- The risk of suicidal ideation is highest following SSRI initiation or change in dose.
- For adolescents with bipolar depression, the dose of lithium or valproate should be maximized and lamotrigine or an atypical antipsychotic should be added before considering SSRIs.

other medications difficult. Twice-daily dosing is also a disadvantage in pediatric patients. Fluvoxamine may be more likely than other SSRIs to cause nausea and vomiting.

Non-SSRI Antidepressants

Buproprion (Wellbutrin, Wellbutrin SR, Wellbutrin XL) has both noradrenergic and dopaminergic effects. It is approved by the FDA for the treatment of MDD and smoking cessation in adults. There is some evidence suggesting modest efficacy in the treatment of pediatric attention-deficit/hyperactivity disorder (ADHD). The starting dose is 50–100 mg daily. The maximum dose is 150 mg daily in children weighing less than 150 lbs and 300 mg daily in those over 150 lbs. The sustained-release (SR) form is divided twice daily, and the XL form is administered once daily. Interval doses exceeding 200 mg and daily doses exceeding 400 mg are associated with increased risk of seizure. Buproprion has a lower incidence of sexual dysfunction than SSRIs.

Mirtazapine (Remeron) is approved by the FDA for the treatment of MDD in adults, but there are no placebo-controlled trials to support its use in youth. An open-label study in adolescents demonstrated good efficacy and tolerability with few side effects (most commonly fatigue, increased appetite, weight gain, and dizziness). Clinically, mirtazapine can be used for the treatment of MDD in adolescents when better-studied agents are not tolerated, or as an adjunctive agent in patients with insomnia because of its beneficial effect on sleep.

Venlafaxine (Effexor XR) is FDA-approved for the treatment of MDD, GAD, and panic disorder in adults. Placebo-controlled trials in the pediatric population have failed to show efficacy.

Duloxetine (Cymbalta) is a dual serotonin-norepinephrine reuptake inhibitor approved by the FDA for the treatment of MDD and diabetic peripheral neuropathy in adults. There are no studies of its use in youth.

Nefazadone (Serzone), tricyclic antidepressants (TCAs), and ***monoamine oxidase inhibitors (MAOIs)*** are considered third- or fourth-line treatment choices in pediatric populations because of their lack of clear efficacy (there are more than a dozen negative trials with TCAs in youth with MDD), side effect profiles, and potential lethality in overdose. The use of these agents or a combination thereof to treat pediatric psychiatric disorders should take place in consultation with a pediatric psychiatrist. Table 39-3 lists common dose ranges for non-SSRI antidepressants.

PSYCHOSTIMULANTS

Psychostimulants have been used to treat ADHD since 1937 and are approved by the FDA for use in patients aged 6 years and older. Chapter 32 discusses in detail the manifestations of ADHD, the behavioral and pharmacological strategies for its management, and the risks and side effects associated with psychostimulant use. Tables 39-4 and 39-5 summarize the pharmacokinetics of the commonly used psychostimulants. The formulations fall into three categories: methylphenidate, dextroamphetamine, and mixed salts of dextroamphetamine and amphetamine. A fourth category, pemoline, is no longer in use because of associated liver toxicity. Nonstimulant medications used in the treatment of ADHD (e.g., bupropion, atomoxetine) are discussed in Chapter 32.

Table 39-2 SSRI Half-Lives, CYP450 Effects, and Drug Interactions

Agent	Mean (Range) Half-Life	CYP450 Effects	Some Potential Drug Interactions
Fluoxetine	1–3 d (7–9 d)[a]	↓ 2D6	↑ Pimozide, phenytoin, TCAs, carbamazepine, some antiarrhythmics
Paroxetine	24 hr (IR) 15–20 hr (CR)	↓ 2D6 and metabolized by 2D6	Same as fluoxetine ↑ By cimetidine ↓ By phenobarbital and phenytoin
Sertraline	25 hr (60–70 hr)[b]	↓ 2D6	Same as for fluoxetine
Citalopram	35 hr	Weak ↓ 2D6	Minimal
Escitalopram	27–30 hr	↓ 2C9[c], ↓ 2C19[c]	Caution with anti-migraine agents
Fluvoxamine	15 hr	↓ 3A4, ↓ 1A2	↑ Theophylline, warfarin, propranolol, diazepam, alprazolam

TCAs, tricyclic antidepressants.
[a]Norfluoxetine.
[b]Multiple metabolites.
[c]Inhibition via a metabolite.
↓ Indicates enzyme inhibition or decrease of plasma drug levels.
↑ Indicates enzyme induction or increase of plasma drug levels.

Table 39-3 Non-SSRI Antidepressants

Trade Name	Generic	Common Daily Dose Range	Available Formulations
Effexor (XR)[a]	Venlafaxine	37.5–225 mg	Capsule
Wellbutrin (SR, XL)[a]	Buproprion	100–300 mg[b]	Tablet
Remeron	Mirtazipine	15–45 mg	Tablet Sol Tab—rapid dissolution
Serzone	Nefazadone	200–600 mg[c]	Tablet

[a]Use of immediate-release formulation is not recommended.
[b]Dosing of SR is divided BID.
[c]Dosing is divided BID.

Table 39-4 Methylphenidate Formulations

Trade Name	Hours to Peak	Duration (hours)	Delivery System
Ritalin	2	3–5	Immediate-release tablet
Ritalin SR	4.7	8–12	Sustained-release tablet
Ritalin LA	1–3, 5–7	8–12	Immediate-release (50%) and extended-release (50%) beads in a wax matrix
Concerta	1–2, 6–8	10–12	Immediate-release (22%) from caplet cover, osmotic-release (78%) from core
Methylin	2	3–5	Immediate-release chewable tablet, oral tablet, and oral solution
Methylin ER	4.7	8	Extended-release tablet
Metadate ER	4.5	4–8	Extended-release beads
Metadate CD	1.5, 4.5	8–10	Immediate-release (30%) and extended-release (70%) beads in a capsule
Focalin[a]	1–4	3–5	Immediate-release tablet
Focalin XR[a]	2, 6.5	12	Immediate-release (50%) and extended-release (50%) beads
Daytrana	9 or time of patch removal	12	Transdermal patch with a steady plasma concentration

[a]D-isomer of methylphenidate.

Table 39-5 Dextroamphetamine and Mixed Amphetamine Salts

Trade Name	Hours to Peak	Duration (hours)	Delivery System
Dexedrine[a]	1–3	4–6	Immediate-release tablet
Dexedrine Spansule[a]	8–10	6–10	Extended-release capsule
Adderall[b]	1–3	4–6	Immediate release tablet
Adderall XR[b]	3, 7	12	Immediate-release and extended-release beads
Vyvanse[c]	4-6	12	Pro-drug metabolized in the intestine

[a]Dextroamphetamine.
[b]Mixed salts of dextroamphetamine and amphetamine.
[c]Dextroamphetamine bound to L lysine.

Psychostimulants are classified by the U.S. Drug Enforcement Agency (DEA) as Schedule II drugs and should be given cautiously to patients with a history of drug or alcohol abuse. Interestingly, studies show that children with ADHD who are treated with psychostimulants are less likely than those who are not treated with psychostimulants to develop substance use disorders.

The FDA requires that the drug inserts for all psychostimulants include warning language about the potential risks of arrhythmia and sudden death. The evidence behind this requirement is discussed in detail in Chapter 32. Psychostimulant use is contraindicated in patients with histories of drug hypersensitivity, arrhythmia, glaucoma, or use of MAOIs within the preceding 14 days.

ANTIPSYCHOTICS

Antipsychotic medications are classified as conventional (i.e., first-generation or neuroleptic) or atypical (i.e., second-generation) according to their side effect profiles. Conventional antipsychotics are associated with extrapyramidal side effects (EPSs) such as tremor, bradykinesia, rigidity, restlessness, and tardive dyskinesia (i.e., choreoathetoid movements, usually of the face). A rare but life-threatening EPS is neuroleptic malignant syndrome, which presents with autonomic instability including severe hyperthermia, significant elevation of creatinine phosphokinase (CPK), and leukocytosis.

Studies of adults have demonstrated that atypical antipsychotics tend to have better efficacy and fewer side effects than conventional antipsychotics. Although controlled pediatric data are limited, the use of atypical antipsychotics has far surpassed that of conventional antipsychotics in children and adolescents, as well as adults. Tables 39-6, 39-7, and 39-8 summarize the side effects, monitoring, and doses of the six commonly used atypical antipsychotics. Weight gain is the most common side effect, with the associated metabolic complications of Type 2 diabetes mellitus, dyslipidemia, and elevation of liver transaminases due to hepatic steatosis. Although the weight gain is most severe with clozapine and olanzapine and the metabolic complications are not associated with aripiprazole and ziprasidone, all six atypical antipsychotics carry the same black-box warning of these side effects.

Risperidone (Risperdal) is widely used and highly effective but, compared to other antipsychotics, is associated with more pronounced elevations in serum prolactin levels and greater risk of EPS with rapid titration, use of high dose, and abrupt withdrawal. Children and adolescents should be started at the lowest possible dose, and titration must be gradual and guided by clinical response. If a decision is made to stop risperidone, the dose should be tapered gradually. It has received FDA approval for use in treatment of aggression in children with autism and for adolescents with BPD or psychosis.

Olanzapine (Zyprexa) is effective for the treatment of adolescents with BPD but causes more weight gain in adolescents than in adults. It also is associated with increases in glycosylated hemoglobin, cholesterol, triglycerides, and excessive sedation.

Quetiapine (Seroquel) is associated with excessive sedation, lightheadedness, and orthostatic hypotension. The sedation typically subsides with gradual titration to daily doses above 200 mg.

Ziprasidone (Geodon) is associated with much less weight gain in adolescents than the other atypical antipsychotics. A baseline electrocardiogram should be performed due to potential dose-dependent QTc prolongation.

Aripiprazole (Abilify) is associated with minimal risk of weight gain and EPS in adults. However, the clinical experience in adolescents has been equivocal, with case reports of both EPS and significant weight gain. It should be used with great caution when used with medications affecting 2D6-CYP450.

Clozapine (Clozaril) carries high efficacy in the treatment of patients who are resistant to other antipsychotic medications. However, because of its high risk of

Table 39-6 Antipsychotics: Comparison of Selected Side Effects

	Weight Gain	Extrapyramidal	Prolonged QTc	Prolactin	Diabetes, Lipid
Haloperidol	++	++++	++	++++	++
Thioridazine	+++	+/++	++++	++++	++++
Clozapine	++++	+/−	+	+	+
Risperidone	+++	++++	++	++++	++
Olanzapine	++++	+++	+	++	+
Quetiapine	++	+/−	++	+	++
Ziprasidone	+/−	++	+++	+	+++
Aripiprazole	+	++	++	+	++

+/− Rarely occurs or occurs only at high dose.
+ Mild effect or unlikely to occur at average doses.
++ Moderate effect or moderately likely to occur at average doses.
+++ Significant effect or likely to occur at all doses.
++++ Severe effect or highly likely to occur at all doses.

Table 39-7 Atypical Antipsychotics: Monitoring Recommendations of the American Diabetes Association

	Baseline	4-Week	8-Week	12-Week	Quarterly	Annually	Every 5 Years
Personal/family history	X						
Body mass index	X	X	X	X	X		
Blood pressure	X					X	
Waist circumference	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

Table 39-8 Atypical Antipsychotics: Doses and Formulations

Generic	Trade Name	Daily Dose	Available Formulations
Risperidone	Risperdal	0.25–3 mg	Tablet, rapid-disintegrating M-tab, liquid
Olanzapine	Zyprexa	2.5–20 mg	Tablet, rapid-disintegrating Zydis, intramuscular
Quetiapine	Seroquel	12.5–800 mg	Tablet
Ziprasidone	Geodon	40–160 mg	Tablet, intramuscular
Aripiprazole	Abilify	2.5–20 mg	Tablet, oral solution
Clozapine	Clozaril	100–600 mg	Tablet

agranulocytosis, it is recommended only for patients who have failed other medication trials. Other side effects are also common, such as weight gain, tachycardia, orthostatic hypotension, sialorrhea, fatigue, and constipation. The risk of seizures increases with dose, and there is evidence supporting an association with cardiomyopathy and congestive heart failure. It should be administered by psychiatrists familiar with its risks and the need for close monitoring.

MOOD STABILIZERS

Mood stabilizers are used to treat acute mania and hypomania. The medications in this class include lithium, divalproex sodium (valproate), carbamazepine, and several newer antiepilectic drugs. Details of dosing, half-lives, serum levels, monitoring, side effects, and drug interactions are summarized in Tables 39-9, 39-10, and 39-11.

Lithium carbonate is approved by the FDA for acute and maintenance therapy of patients 12 years of age and older with manic episodes associated with BPD. There is some evidence supporting its use in children and adolescents with severe aggression and in those with the dual diagnoses of bipolar and substance use disorders. The response to lithium may be delayed 6–8 weeks in children and adolescents, resulting in its frequent use with faster-acting atypical antipsychotics. The starting dose of lithium is 150–300 mg daily, with increases of 300 mg every 3 days until an adequate dose (~30 mg/kg/day) is achieved. Divided dosing (e.g., three times daily) is typically used early in treatment, but once- or twice-daily dosing is usually tolerated once a steady state is reached. The target serum level range is 0.8–1.2 mEq/L for acute treatment and 0.8–1.0 mEq/L for maintenance treatment. Discontinuation of lithium requires gradual downward titration by 300 mg every 3 days to avoid the precipitation of a manic episode.

Lithium has been shown to prevent recurrent manic episodes, provide moderate prophylaxis for depressive episodes, and reduce the long-term risk of suicide. However, severe toxicity can occur at blood levels just two to three times higher than the therapeutic range. It therefore is essential to monitor levels closely, limit patient access to large pill quantities, and repeatedly assess patient risk for suicide. Common dose-dependent side effects of lithium include polyuria (50–70%) and hypothyroidism (30%).

Valproate is approved by the FDA for the treatment of acute bipolar mania in adults. Evidence supports its use for the treatment of acute mania in youth, and it is also commonly used in youth for maintenance treatment of BPD. Valproate may be particularly advantageous in patients with mixed and rapid cycling, cyclothymia, PTSD, panic disorder, and BPD with concurrent diagnoses of migraines, seizure disorder, or developmental disability. When used for the treatment of acute mania, rapid loading can be achieved with doses of 15–20 mg/kg/day. It is often started as a divided, twice-daily dose to minimize side effects but can be given once daily when a stable dose is reached. The dose should be increased as tolerated until clinical response is achieved, which typically occurs within a fairly wide therapeutic serum-level range of 85–120 μg/ml.

Valproate carries a black-box warning for potentially lethal hepatic failure, with highest risk in patients younger than 2 years of age and in the first 6 months of treatment. Common side effects include gastrointestinal distress, cognitive dulling, weight gain, and alopecia.

Table 39-9 Mood Stabilizers: Doses and Formulations

Generic	Trade Name	Daily Dose	Available Formulations
Lithium	Eskalith, Eskalith CR, Lithobid SR	300–2400 mg	Tablet, capsule, syrup
Valproate	Depakote, Depakene, Depakon	500–1500 mg	Tablet, capsule, syrup, intravenous
Carbamazepine	Tegretol	400–1000 mg	Tablet, capsule, chewable, syrup
Lamotrigine	Lamictal	100–400 mg	Tablet, chewable

Table 39-10 Mood Stabilizers: Half-Lives, Serum Levels, and Monitoring

Agent	Half-Life (hours)	Target Serum Level	Monitoring
Lithium	24	0.8–1.2 mEq/l	Baseline BUN, creatinine, thyroid function tests, HCG, electrocardiogram; repeat every 6–12 months as indicated. Monitor serum drug level.
Valproate	9–16	85–120 μg/ml	Baseline complete blood count, liver function tests, amylase, lipase; repeat every 6–12 months as indicated. Monitor serum drug level.
Carbamazepine	18–55 initially, 5–20 ongoing*	6–10 μg/ml	Baseline complete blood count, liver and thyroid function tests, BUN, creatinine; repeat every 6–12 months as indicated.

*Due to autoinduction with chronic dosing.
BUN, blood urea nitrogen; HCG, human chorionic gonadotropin.

Table 39-11 Mood Stabilizers: Serious Side Effects and Drug Interactions

Agent	Serious Side Effects	Drug Interactions
Lithium	Interstitial nephritis, polyuria, nephrogenic diabetes insipidus, nephrotic syndrome, thyroid dysfunction, cardiac anomalies	↑ Level by thiazides (30–50%), NSAIDs, ACEIs. ↓ level by theophylline, caffeine.
Valproate	Hepatitis, pancreatitis, thrombocytopenia, neural tube defects, polycystic ovary syndrome	↑ Levels by salicylates, SSRIs, anticonvulsants, rifampin. May double level of lamotrigine and ↑ level of SSRIs.
Carbamazepine	Aplastic anemia, neutropenia, thrombocytopenia, hepatitis, SIADH, cardiac conduction delay, hypothyroidism	Auto-induction via potent ↑ of P450 enzymes. ↑ levels by SSRIs.
Lamotrigine	Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic failure, hematological anomalies[a]	Level doubled by valproate. ↓ level by other anticonvulsants.
Oxcarbazepine	Hyponatremia, hematological anomalies, hepatitis	↓ 2C19, ↑ 3A4, 3A5.

ACEIs, angiotensin-converting enzyme inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; SIADH, syndrome of inappropriate antidiuretic hormone.
[a]Risks of these side effects are greatly reduced by slow initial titration of dosage.
↓ Indicates enzyme inhibition or decrease of plasma drug levels.
↑ Indicates enzyme induction or increase of plasma drug levels.

Neural tube defects are reported in 1% of infants born to mothers treated with valproate during pregnancy.

Carbamazepine is indicated for the treatment of mania in adults. Open-label studies, case reports, and clinical experience support its use in children and adolescents with rapid-cycling BPD, acute mania, and severe impulsivity. However, there also are case reports of carbamazepine-induced mania in youth. Dosing is started at 200 mg nightly or divided twice-daily, and is increased slowly as tolerated until a therapeutic dose (10–30 mg/kg/day) is achieved. Dosing is complicated by autoinduction of metabolism after 2–6 weeks of treatment. Slow titration of dose greatly minimizes occurrence and intensity of gastrointestinal distress, ataxia, vertigo, and slurred speech. Side effects that are dose-related include hematological anomalies, transaminase elevation, sedation, cognitive dulling, and ataxia. In pregnancy, carbamazepine may increase incidence of neural tube defects, developmental delay, and craniofacial defects. Carbamazepine may reduce the effectiveness of oral contraceptives and many other psychotropics via potent CYP450 induction.

Lamotrigine (Lamictal) was recently approved for the maintenance treatment of BPD in adults to prevent recurrent depressive episodes. Pediatric data are limited, and it should be used only in those adolescents who have failed other medication trials. Side effects are common on lamotrigine. Up to 10% of patients develop a benign maculopapular, erythematous rash that resolves with discontinuation of the drug. The likelihood of rash doubles when lamotrigine is used with valproate and is three times higher in children than adults. A black-box warning states that 1% of patients younger than 16 years and 0.1% of adults on lamotrigine develop life-threatening reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or angioedema.

Slow initial dose titration minimizes the incidence of rash and other side effects. Dosing is started at 25 mg daily for 2 weeks and then is increased every 1–2 weeks by 25 mg until a maximum dose of 200 mg daily is reached. Unlike lithium and valproate, serum levels do not need to be monitored for lamotrigine. The metabolism of lamotrigine is decreased by valproate and increased by carbamazepine, and its dosing should be adjusted when used concomitantly with these drugs. When discontinuing lamotrigine, it should be tapered over 1 week.

Topiramate (Topamax) is not approved by the FDA for the treatment of any psychiatric disorder but is used off-label for the adjunctive treatment of weight gain associated with atypical antipsychotic therapy. Dosing in youth should start at 25 mg daily, with increases of 25 mg daily every 3 days until the desired effect on appetite and weight are achieved. Common side effects are cognitive dulling, memory impairment, confusion, nausea, and diarrhea. Less common effects are metabolic acidosis, nephrolithiasis, and glaucoma.

OTHER AGENTS

Alpha-2 agonists (clonidine and guanfacine) are often used in the treatment of ADHD as second-line agents or to augment psychostimulants, even though they are not approved by the FDA for these uses. Although there are limited data on their effectiveness in the treatment of ADHD, clinical experience suggests that they are more helpful in the control of ADHD-associated aggression, impulsivity, tics, and insomnia than in the control of inattention. Clonidine (Catapres) is typically started at 0.05 mg at bedtime and can be titrated up to 0.1 mg three times daily. The major side effect is sedation. Guanfacine (Tenex) is less sedating than clonidine and can be started at 1 mg per day and titrated up to 1 mg three times daily. If either alpha-2 agonist is deemed ineffective after an

MAJOR POINTS

- The pediatric literature on psychopharmacotherapy is scant, resulting in frequent off-label use of psychiatric medications in children and adolescents.
- Fluoxetine is the only SSRI approved by the FDA for the treatment of children and adolescents with MDD. SSRIs carry a black-box warning of increased risk for suicide based on studies showing a slight increase in suicidal ideation and behavior and no cases of actual suicide.
- SSRIs can precipitate mixed or manic episodes in patients with BPD and should be avoided until mood stabilization has been achieved.
- The selection of a particular SSRI depends on potential drug-drug interactions, half-life, and side effects.
- SSRI treatment should begin at low dose to minimize side effects. Discontinuation syndrome can occur with abrupt discontinuation, and serotonin syndrome can occur when the SSRI is used with other serotonergic agents.
- Psychostimulants are approved by the FDA for use in patients with ADHD ages 6 years and older. The FDA requires that drug inserts carry warning language about potential risks of arrhythmia and sudden death.
- Atypical antipsychotics tend to have better efficacy and fewer side effects than conventional antipsychotics. The most common side effect is weight gain, which is most severe with clozapine and olanzapine. There is also increased risk of developing metabolic syndrome (non-insulin–dependent diabetes mellitus, dyslipidemias). There is a need to monitor metabolic parameters (weight, fasting glucose, fasting lipid profile, insulin, body mass index, blood pressure) at baseline after 3 months and annually thereafter.
- Lithium carbonate is approved by the FDA for acute and maintenance therapy of patients aged 12 years and older with mania associated with BPD. Valproate and carbamazepine are widely used in children and adolescents with BPD but are not approved by the FDA for such use.

adequate trial, the medication should be tapered gradually over 1 to 2 weeks to avoid rebound hypertension.

Ramelteon (Rozerem), a melatonin analog that binds to the same receptors as melatonin, was recently found useful in treating initial insomnia; it is much more potent than melatonin but is not FDA-approved for use in youth.

Atomoxetine (Strattera) is a noradrenergic reuptake inhibitor used effectively in the treatment of ADHD in youth, especially those with comorbid anxiety (Chapter 32). It is considered a first-line agent in the treatment of ADHD but has a lower effect size than psychostimulants. Atomoxetine is more effective in treating inattention than hyperactivity or impulsivity at doses as high as 1.8 mg/kg (a dose higher than the manufacturer's recommendation) and has the advantage of not being a Category II agent. However, full therapeutic dose is not achieved until at least several weeks.

Modafinil (Sparlon) is a Category IV agent that is effective for treating excessive sleepiness. In March 2006, the FDA Advisory Committee for Psychopharmacologic Drugs voted not to recommend FDA approval of modafinil for the treatment of pediatric ADHD due to concerns over the risk of Stevens-Johnson syndrome and recommended that additional data be collected to support the safety of the drug in youth with ADHD.

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Index

Note: Page numbers are followed by f for figures and t for tables.