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# contents

Pediatrics in Review® Vol.30 No.3 March 2009

## Articles

83

### Drug Abuse by Adolescents: General Considerations

Ximena Sanchez-Samper, John R. Knight

94

### The Nephrotic Syndrome

Roberto Gordillo, Adrian Spitzer

107

### Index of Suspicion

Case 1: Susanna Martin

Case 2: Kellie Waters

Case 3: Miriam K. Perez, Bradley T. Kleman, Linda S. Nield

114

### In Brief: Achondroplasia

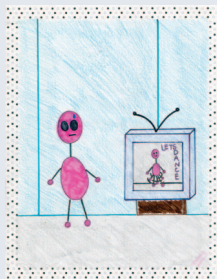
## Internet-Only Article

Abstract appears on page 106.

e11

### Cultural Influences on Infant Feeding Practices

Suzinne Pak-Gorstein, Aliya Haq, Elinor A. Graham



Cover: The artwork on the cover of this month's issue is by one of the winners of our 2007 Cover Art Contest, 15-year-old Tracey Ellin of Leonardtown, Md. Tracey's pediatrician is Kirk Patel, MD.

# Drug Abuse by Adolescents: General Considerations

Ximena Sanchez-Samper, MD,\* John R. Knight, MD\*

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Drs Sanchez-Samper and Knight have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

**Objectives** After completing this article, readers should be able to:

1. Discuss current trends in adolescent substance use and the specific substances used most commonly among 8th, 10th, and 12th graders.
2. Identify risk and protective factors, including genetic and environmental correlates, for the initiation of substance use in adolescents.
3. Discuss the most common concomitant mental health disorders and how they can affect the course of diagnosis and treatment for substance abuse.
4. Delineate the variety of treatment options available.
5. Describe the role of the pediatrician in educating patients and families on substance abuse prevention; performing screening and initial assessments; and providing support, brief counseling, or referrals for in-depth treatment.

## Introduction

Adolescence is a time of physical, emotional, and psychological maturation as well as a period of searching for independence and experimentation. One area of experimentation associated with adolescence is substance use. (1) Although many adolescents experiment with drugs and alcohol from time to time without enduring problems, those who develop the disorders of substance abuse and dependence make substance use a major public health concern.

## Epidemiology

The Monitoring the Future Study (MTFS) is a nationwide survey measuring smoking, drinking, and illicit drug use among nearly 50,000 8th, 10th, and 12th graders in more than 400 secondary schools in the United States each year. (2)(3) According to the 2006 overview of findings from the MTFS, approximately one fifth (21%) of today's 8th graders, more than one third (36%) of 10th graders, and nearly half (48%) of all 12th graders reported using an illicit drug at least once during their lifetimes. Despite a minimum legal age requirement to purchase alcohol, 6% of 8th graders, 19% of the 10th graders, and 30% of the 12th graders self-reported drunkenness during the month prior to being interviewed. (2)(3)

Among the problems experienced by adolescents who use alcohol and drugs are impaired peer relations, depression, anxiety, low self-esteem, acquisition of sexually transmitted infections, teenage pregnancy, date rape, and overall involvement in high-risk sexual behaviors. (4)(5) Motor vehicle crashes, suicide, and homicide also have been linked closely to adolescent substance use. In the United States, approximately 75% of all deaths among 10- to 24-year-olds result from only four causes: motor vehicle crashes, suicide, homicide, and other unintentional injuries, all of which are preventable and can be linked to substance use. (6)

Unfortunately, the adolescent's misconception that pre-

## Abbreviations

<b>AA:</b>	Alcoholics Anonymous
<b>ADHD:</b>	attention-deficit/hyperactivity disorder
<b>ART:</b>	acute residential treatment
<b>CBT:</b>	cognitive behavioral therapy
<b>CM:</b>	contingency management
<b>FDA:</b>	United States Food and Drug Administration
<b>LSD:</b>	lysergic acid diethylamide
<b>MDFT:</b>	multidimensional family therapy
<b>MET:</b>	motivational enhancement therapy
<b>MST:</b>	multisystemic therapy
<b>MTFS:</b>	Monitoring the Future Study
<b>NA:</b>	Narcotics Anonymous
<b>PCP:</b>	phencyclidine
<b>THC:</b>	D9-tetrahydrocannabinol

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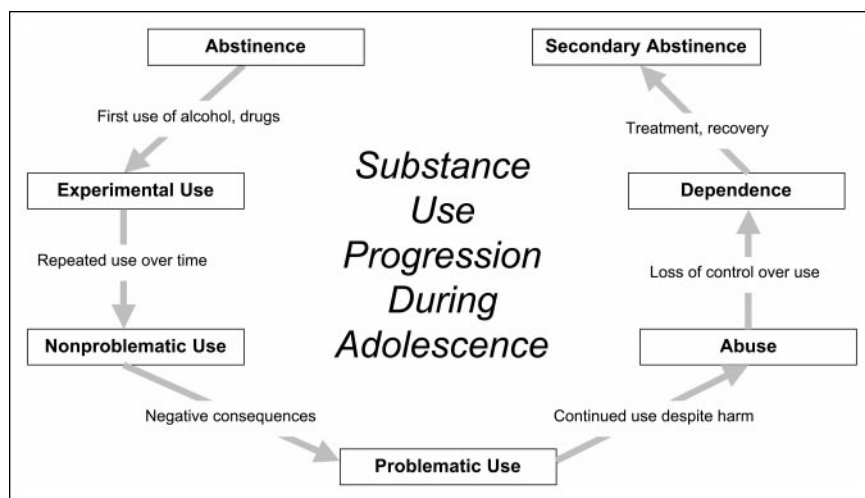


Figure 1. Substance use progression during adolescence.

scription medications are safe because they are prescribed by a physician has contributed tragically to a recent steady increase in misuse of prescription medications such as narcotics, stimulants (methylphenidate, dextro-amphetamine), tranquilizers, and sedatives. (7) The annual prevalence for oxycodone use has reached its highest rate so far in younger users, with an annual prevalence of 2.6% in 8th graders, 3.8% in 10th graders, and 4.4% in high school seniors. Over-the-counter cough and cold medications containing dextromethorphan account for yet another category of recent increase, with teens not fully appreciating the risk because these medicines are so easily accessible. (3)(7) The percent of students reporting use within the past year “with the intent to get high” was estimated to be 4%, 5%, and 7% in 8th, 10th, and 12th graders, respectively. (3)

Alcohol is the most commonly abused licit substance by adolescents today, despite being illegal for use in the adolescent age group. (3)(6) Approximately 30% of 12th graders, 19% of 10th graders, and 6% of 8th graders reported being intoxicated or “experiencing drunkenness” during the past 30 days. Marijuana, on the other hand, continues to be the most common illicit drug of abuse, with an annual prevalence of 12% in 8th graders, 25% in 10th graders, and 32% in high school seniors. (1)

## Stages of Use

Substance use occurs on a continuum from the “developmental variation” of experimentation through “substance use problems” to the disorders of abuse and dependence. (8) Figure 1 illustrates a developmental model of substance use progression.

“Abstinence” is defined as the stage when adolescents

have not yet begun to use any psychoactive substances. An initial trial of tobacco, alcohol, or other drugs defines “experimental use,” characterized by occasional use of alcohol or marijuana, usually with peers. At this stage, the teenager may experience good feelings without serious adverse consequences. However, experimentation still can be hazardous. Teenagers have insufficient experience to know safe “doses” of alcohol, and they may consume toxic quantities rapidly without realizing the potential danger. They may put themselves and others at risk by participating in hazardous activities such as operating a motor

vehicle. “Nonproblematic use” is characterized by the intermittent, continuing use of alcohol or drugs in the absence of negative consequences. In addition to alcohol, most nonproblematic users tend to use marijuana and, occasionally, prescription drugs. Because of the rapidly addictive nature of some prescription drugs (eg, opioids), however, teens using them may progress rapidly to dependence.

“Problematic use” is defined by the occurrence of adverse consequences as a result of use, although the individual may not see any causal link. Substance-related problems include school failure, suspensions, relationship problems with parents or peers, motor vehicle crashes, injuries, emergency department visits, physical or sexual assaults, and legal problems. These behaviors may be accompanied by significant changes in dress, behavior, and peer group. At this stage, some individuals still can reduce or stop their use with limited intervention.

“Substance abuse” is a maladaptive pattern of substance use that impairs social or school functioning, causes recurrent physical risk or legal problems, and involves continued use despite harm occurring over a 12-month period, with no diagnosis of dependence. (9) “Substance Dependence” is a disorder characterized by a maladaptive pattern of compulsive use, negative consequences, loss of control over use, preoccupation with use, and tolerance or withdrawal symptoms. (9) Tolerance and withdrawal symptoms can be physiologic, psychological, or both. Dependence is synonymous with “addiction,” which is manifested by continual use of substances when available, solitary use, disrupted family relationships, and loss of outside supports. Referral to an

intensive treatment program usually is required at this stage.

### Etiology: Risks and Protective Factors

Numerous studies conducted over the past 3 decades have contributed to an understanding of the etiology of drug use, highlighting both the biopsychosocial risks and protective factors involved. (10) A dynamic interplay between individual, peer, family, and community risk factors is involved. Risk factors are those that precede drug use and increase the probability of later drug use and abuse; protective factors are those that either mitigate the effect of these risk factors or enhance the effect of other protective factors, leading to less drug use. (11)(12)

From a developmental perspective, a positive mutual attachment in the parent-child relationship is essential to preventing drug use. Children who are capable of identifying with healthy parental attitudes and behaviors are more likely to internalize these characteristics and express them in their own lives. As a result, such adolescents are less likely to drift toward affiliations with peers who use drugs and are more likely to select a pathway of abstinence for themselves. Conversely, conflicted parent-child relationships (low perceived parental support, poor communication), parental ineffectiveness (insufficient parental monitoring, inconsistent discipline, child abuse/neglect), and parental alcohol or drug use all have been found to be robust correlates and predictors of adolescent substance use. (11)

The presence of concomitant childhood psychopathology is another risk factor for the development of substance use disorders during adolescence or later in life. Some of the most frequently identified psychiatric disorders linked to substance use include conduct disorder, attention-deficit/hyperactivity disorder (ADHD), mood disorders, anxiety disorders, and learning disorders. (13) A more rapid progression through the stages of use is common among those who experience early-onset substance use and heightened exposure to peer groups and environments where drugs and alcohol are readily available. (14)

Long-term outcomes can vary over time. Although adolescents who meet criteria for a diagnosis of abuse may decrease or discontinue use later in life, those in whom dependence is diagnosed are likely to be the individuals who have higher risk factors and fewer protective factors and are more prone to extending substance use into their adult years. (15)(16) Early onset of use also has been shown to correlate significantly with the risk of developing alcohol dependence later in life. Those

who begin drinking alcohol younger than 13 years of age are five times more likely to have a lifetime diagnosis of alcohol dependence compared with those who delay drinking to age 21 years or older. (17)

Most of the literature about the influence of biologic factors on addiction has focused on the familial transmission of possible genetic markers for alcoholism. As a result, the “disease model” of alcoholism has become central to expanding understanding of the biologic underpinnings of addiction as an illness. Genetic predisposition plays an instrumental role in determining a person’s risk for developing alcohol dependence, more so if the family history is positive in first- and second-degree relatives. In fact, children of alcohol-dependent parents are four to six times more prone to developing alcohol dependence compared with others in the general population who have no positive family histories. (18)

Although earlier twin studies had proposed that the heritability of alcoholism was approximately 50% in men, (18) a recent study of Australian twins suggested that approximately 66% of the risk is mediated genetically in both men and women, with the remainder being determined by environmental factors. (19) Currently, the strongest ties linking genes to alcoholism lie in the finding of specific polymorphisms of the alcohol dehydrogenase genes (*ADH2* and *ADH3*), which encode for one of the key enzymes responsible for the breakdown of alcohol. When these alleles are expressed, they encode forms of alcohol dehydrogenase that metabolize alcohol to acetaldehyde quickly, leading to accumulation and toxicity. Symptoms of toxicity often include flushing, nausea and vomiting, sweating, head throbbing, hypotension, or palpitations, although cardiovascular collapse, convulsions, and death may occur in severe cases. A partial protective effect against the development of alcoholism can be seen in Asian populations in whom these alleles are common. (20)(21) Unfortunately, little information supports or refutes the possibility of biologic transmission for other psychoactive drugs.

### Identification of At-risk Adolescents

The primary factors that appear to contribute to a teenager’s choice to select one drug over another are its perceived availability, the perceived degree of social approval associated with its use, and how risky the drug is perceived to be. The riskier and less accepted a drug is believed to be, the less likely it will be abused by adolescents; conversely, if a substance is readily available and is considered socially acceptable, an increased trend in use can be expected. (3)(22) For example, Ecstasy use increased by 71% between 1999 and 2001 such that by



the end of 2001, more than 1 in 10 teenagers reported using Ecstasy regularly. However, as the dangers associated with Ecstasy became more apparent, its popularity and social acceptance declined to just 4% by the end of 2005. (2) Clinicians must not disregard, however, the concept of “generational forgetting,” whereby knowledge of a drug’s adverse consequences fades throughout the years, allowing that drug to experience a comeback in subsequent generations long after falling from popularity. Phencyclidine (PCP), lysergic acid diethylamide (LSD), methamphetamine, and heroin are a few examples of drugs that have resurfaced from the 1960s, with a strong resurgence in heroin use due to its increased purity and use through noninjectable routes (snorting).

## Making the Diagnosis

Substance abuse should be screened for as part of routine adolescent medical care. (23)(24) Pediatricians also should consider substance use when adolescents present with behavioral problems, school failure, or emotional distress. The most effective method of screening is a confidential history, taken without parents present in the room. Teenagers reliably report use of alcohol and drugs if they are assured of confidentiality. (25)(26)(27) Information they provide should be kept confidential unless their safety or someone else’s safety is at risk. A common approach for obtaining a structured, developmentally appropriate psychosocial history is by performing a HEADSS assessment, which facilitates communication about an adolescent’s Home life, Education/Employment, Activities, Drug use, Sexuality, and risk for Suicide/depression. (28) The interview should begin with general questions about health and progress to psychosocial functioning, including how things are at home and at school, recreational activities, psychological and emotional well-being, tobacco use, alcohol and drug use, and sexual behavior.

A screening can begin with three usage questions. “During the past year (or since your last clinic visit), have you consumed any alcohol? Have you smoked marijuana? Have you used any other drug to get high? By ‘other drug,’ I mean street drugs such as Ecstasy or heroin, prescription drugs such as OxyContin or Klonopin that were not prescribed by your doctor or taken the way he or she said, over-the-counter drugs such as dextromethorphan, or inhalants such as glue or nitrous oxide from spray cans.” If the answer to all three questions is “no,” only the CAR question from the CRAFFT screen (Fig. 2) need be asked; if the answer to any of the three questions is “yes,” the entire CRAFFT screen should be administered. The CRAFFT screen

During the past 12 months:

- 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 your family or FRIENDS ever tell you that you should cut down on your drinking or drug use?
- Have you ever gotten into TROUBLE while you were using alcohol or drugs?”

Two or more “yes” answers define a positive “screen,” indicating a need for additional assessment.

Figure 2. The CRAFFT screening test.

consists of six orally administered yes/no questions that are easy to score (each “yes” answer=1). Key words in the test’s six items form its mnemonic (CRAFFT).

A CRAFFT total score of two or higher has a sensitivity of 80% and a specificity of 86% for identifying substance abuse or dependence. (29) However, the CRAFFT is only a screen, and a positive CRAFFT result should be followed by additional assessment. The assessment interview with the adolescent should include a thorough alcohol and drug use history, including age of first use, current pattern of use (quantity and frequency), impact on physical and emotional health as well as school and family, and negative consequences from use (eg, school problems, accidents, injuries, altercations, legal problems). The assessment also should include a screening for concomitant mental disorders, parent/sibling alcohol and drug use, and other risk behaviors. (24) A parental interview may be included as part of a substance use assessment, although parents typically underestimate their teenage children’s severity of use. (30)

A complete physical examination should be performed. When performing the eye examination, pupil size should be noted. The nasal mucosa should be examined for inflammation or erosion characteristic of drug insufflation (“snorting”). The liver should be palpated for tenderness or enlargement. The skin examination may reveal needle marks, although this finding is uncommon among adolescents presenting for regular medical care. Abnormal breath sounds, such as wheezing, may result from smoking tobacco, marijuana, cocaine, or heroin. Urine and serum toxicologic examinations are of limited usefulness for screening and generally are less sensitive than a good history. Except in emer-

gencies, laboratory testing should not be performed without the knowledge and consent of the competent adolescent. (31)

Pediatricians should avoid performing drug screens at the request of parents because the clinical information yielded by screens is very limited and performing such testing risks damaging the doctor-patient relationship when adolescents are pressured into providing specimens. Laboratory tests for drugs may be an important adjunct to outpatient substance abuse treatment when the results are available only to the patient and treatment team. Results always must be interpreted cautiously, and pediatricians should be familiar with the sensitivity and specificity (threshold values) for specific drugs and the different methods of testing. Urine specimens must be collected by using direct observation or according to the Mandatory Guidelines for Federal Drug Testing Programs (information available online at <http://www.drugfreeworkplace.com>).

Urine specific gravity and the creatinine concentration always must be obtained because urine concentration affects the validity of the drug test directly. All positive screen results must be confirmed by gas chromatography and mass spectrometry. In general, serum half-lives of drugs of abuse are brief, and urine testing only reflects drug use within the last 48 hours. A notable exception is marijuana, whose active ingredient, D9-tetrahydrocannabinol (THC), and its carboxylic acid metabolite may be detected in the urine for several weeks after discontinuation of daily use. (32) Therefore, when drug testing for THC is being performed as part of a treatment program, serial urine specimens must be obtained for quantitative THC and creatinine (as a measure of urine concentration/dilution) measurements. Abstinence is supported by a finding of serial decreases in the THC:creatinine ratio.

In the acute setting, adolescent patients may present with symptoms of acute or pathologic intoxication. Table 1 provides a comprehensive overview of the signs and symptoms of intoxication and withdrawal as well as treatments for common drugs of abuse. (The table can be accessed at [pedsinreview.aappublications.org/cgi/data/30/3/83/DC1/2](http://pedsinreview.aappublications.org/cgi/data/30/3/83/DC1/2).)

Following the assessment, the clinician must determine the severity of the problem and the need for treatment. Individuals who are experimental users or non-problematic users do not necessarily need to be referred to mental health specialists. They may respond favorably to brief office interventions. On the other hand, teenagers who seem likely to have a diagnosis of dependence should be referred to specialized treatment as soon as

possible. Clinicians also should refer those who have signs or symptoms of a concomitant mental disorder, such as major depression, bipolar disorder, bulimia, or ADHD. In all cases, the most important aspect of the assessment is the safety of the patient. If the patient is in any jeopardy, immediate admission to a hospital should be arranged.

## Substance Use and Comorbid Mental Health Disorders

Psychiatric comorbidity in adolescents who misuse psychoactive substances often is the rule rather than the exception, with comorbidities including unipolar or bipolar depression, anxiety, conduct disorder, oppositional-defiant disorder, and ADHD (Table 2). (33)(34)(35)(36) Evidence suggests that adolescents who have substance use disorders also are more prone to report a history of trauma, as evidenced by physical or sexual abuse, than are adolescents who have no substance use disorder. (46) In addition, psychiatric disorders in

### Table 2. Comorbidity Diagnosis Pearls

- Conduct disorder occurs concomitantly with substance use disorders (abuse or dependence) in 60% to 80% of cases; depression occurs concomitantly in 15% to 25% of cases; anxiety disorders occur concomitantly in 25% to 35% of cases. (37)(38)
- Conduct disorder is the most common psychiatric disorder in adolescents who abuse alcohol and is considered one of the strongest predictors of those who eventually develop alcohol abuse or dependence later in life. (37)
- 25% to 50% of teens who have attention-deficit/hyperactivity disorder (ADHD) also meet criteria for conduct disorder, a comorbidity that elevates their risk of consuming alcohol at any age. (37)
- Teenagers who smoke cigarettes are at increased risk for using other drugs (in adolescence, substance use disorders frequently occur concomitantly with nicotine dependence). (39)(40)
- Adolescents who smoke frequently or who begin smoking before age 13 years are at greater risk of developing a substance abuse problem at some point in their lifetimes (males more than females). (41)
- Teens who have ADHD and smoke cigarettes are more likely to use alcohol or illicit substances than are teens who have ADHD and do not smoke. (42)
- The risk of developing a substance use disorder decreases when ADHD is treated appropriately. (43)(44)(45)

adolescents often predate the substance use disorder, and once the substance use disorder develops, the psychiatric disorder may be exacerbated. (33)

Use of substances of abuse can induce, mimic, or exacerbate an underlying mental illness. For example, cocaine and alcohol use both can cause and be a consequence of depression and can result in (or exacerbate) anxiety or psychosis. Substance use is linked directly to a higher frequency of inpatient hospitalization among those who have concurrent mental illness. (47)(48) Adolescents who have concomitant disorders are more likely to be less compliant with medications, more likely to drop out of treatment, and at higher risk of relapse. (48) Although comorbidity complicates the treatment of both disorders and is associated with a poorer prognosis overall, simultaneous treatment of the psychiatric disorder often helps to alleviate the substance use disorder and vice versa. (48)(49)

Diagnostically and therapeutically, it is important to clarify whether an adolescent is struggling with a concomitant mental illness (eg, major depressive disorder or psychotic disorder) or if he or she is presenting with a substance-induced psychiatric disorder (eg, cocaine-induced psychotic disorder or alcohol-induced anxiety disorder). Inquiring in detail about the presence or absence of psychiatric symptoms during “windows” of abstinence from drugs or alcohol can help distinguish between the two types of disorders. Regardless, if in doubt, it always is best to treat what appears to be the primary psychiatric disorder. (50)

## Substance Abuse Treatment for Adolescents

Adolescent substance use differs from that of adult abuse in that progression from casual use to dependence occurs more quickly, teenagers are more likely to use multiple substances, and adolescents often are at higher risk of presenting with psychiatric comorbidities. Because no single approach is suitable for all individuals, treatment always should be tailored to each adolescent’s particular needs. A thorough assessment that evaluates his or her problems multidimensionally (biopsychosocially) is critical to matching youngsters to programs that are adolescent-specific and formulating treatments that are age-appropriate. (2) Physicians should inquire about the patient’s readiness for change, relapse potential, recovery environment, withdrawal risk, medical complications, and psychiatric or behavioral comorbidities prior to determining the most optimal, least restrictive treatment setting. The American Academy of Child and Adolescent Psychiatry has developed a list of principles for adolescent treatment (Table 3). (50)

### Table 3. Recommendations for the Assessment and Care of Adolescents Who Have Substance Use Disorders

1. The adolescent must be assured of an appropriate level of confidentiality.
2. Assessment must include developmentally appropriate screening questions regarding the use of alcohol and drugs.
3. A positive screen necessitates a more formal evaluation.
4. Toxicology (ie, drug testing) must be a routine part of assessment and ongoing treatment.
5. Adolescents who have substance use disorders need specific treatment for them.
6. Substance use disorders should be treated in the least restrictive setting.
7. Family therapy or substantial family involvement should be included in treatment of adolescents who have substance use disorders.
8. Treatment programs should strive to engage adolescents fully and maximize treatment completion.
9. Medication to manage craving or withdrawal or for aversion therapy can be used as indicated.
10. Treatment of adolescents who have substance use disorders must include help to develop peer support.
11. Involvement with 12-step groups, such as Alcoholics Anonymous (AA) or Narcotics Anonymous (NA), should be encouraged.
12. Programs should provide comprehensive services, eg, vocational, recreational, medical.
13. Adolescents who have substance use disorders require comprehensive psychiatric assessment to evaluate for comorbid disorders.
14. Concomitant psychiatric disorders require treatment.
15. Programs must provide or arrange for aftercare.

Adapted from American Academy of Child & Adolescent Psychiatry (AACAP). Practice parameter for the assessment and treatment of children and adolescents with substance use disorders. *J Am Acad Child Adolesc Psychiatry*. 2005;44:609–621.

Drug addiction is a complex illness that can affect every aspect of an adolescent’s functioning in the family, at school, and in the community. Because of addiction’s pervasive consequences, treatment typically involves several components, including rehabilitation, counseling, behavioral therapy, psychopharmacology, case management, family therapy, and other types of services. Options range and vary from outpatient office-based management to residential inpatient treatment or hospital care, with or without detoxification. (50)(51).

## Outpatient Care

For patients deemed to be medically and behaviorally stable, outpatient treatment is the mainstay of substance abuse treatment and consists of individual therapy, group therapy, family therapy, or a combination of these. Day treatment programs such as intensive outpatient programs or partial hospitalization also may be implemented when an adolescent is making the transition from a more intensive level of care or needs greater supervision than can be provided by outpatient visits. Treatment can be delivered by a variety of practitioners, including certified drug abuse counselors, physicians, psychologists, nurses, and social workers. Although specific treatments often are associated with particular settings, a variety of therapeutic interventions or services can be included in any setting. (50)(51)

**COGNITIVE BEHAVIORAL THERAPY (CBT).** CBT is a structured, goal-oriented therapeutic approach designed to teach patients specific skills for maintaining abstinence by identifying and modifying thoughts and feelings that precede drug use. Through repeated recognition of high-risk situations, patients gradually are able to engage in healthy decision-making that results in substituting risky behaviors with behaviors other than drug use or avoiding high-risk situations altogether. Although the particular therapeutic techniques vary, they commonly include keeping a diary of significant events and associated feelings, thoughts, and behaviors; questioning and testing assumptions or habits of thoughts that might be unhelpful and unrealistic; gradually facing activities that might have been avoided; and trying out new ways of behaving and reacting. Relaxation and distraction techniques often are included. CBT sometimes is used with groups of people as well as individuals, and the techniques commonly are adapted for self-help manuals. CBT may be used alone or in combination with motivational enhancement therapy. (52)(53)

**MOTIVATIONAL ENHANCEMENT THERAPY (MET).** MET is a patient-centered counseling approach for initiating behavior change that aims to help adolescents resolve ambivalence about engaging in treatment and stopping drug use. MET employs strategies that evoke rapid and internally motivated change by eliciting self-motivational statements. Motivational interviewing principles are employed to strengthen motivation and struc-

Table 4. Stages of Change (54)(55)

Precontemplation	Not yet acknowledging that there is a problem behavior that needs to be changed
Contemplation	Acknowledging that there is a problem but not yet ready or sure of wanting to make a change
Preparation/Determination	Getting ready to change
Action/Willpower	Changing behavior
Maintenance	Maintaining the behavior change
Relapse	Returning to older behaviors and abandoning the new changes

ture a plan for change. The core constructs around which MET is organized are the “stages of change” (2) (Table 4), which represent categories along a continuum of motivational readiness to change a problem behavior. MET moves away from the belief that one is either “ready or not ready to change” and invites patients to accept a process in which motivation for change is more dynamic and fluctuates. Therapists work closely with patients on establishing decisional balances (the pros and cons of change), strengthening self-efficacy (confidence in the ability to change across problem situations), identifying situational temptations to engage in the problem behavior, and modifying behaviors that are specific to the problem area. Coping strategies for managing high-risk situations are reviewed; in subsequent sessions, the therapist monitors change, reviews cessation strategies being used, and continues to encourage commitment to change or sustained abstinence. (55)

**GROUP THERAPY.** Group therapy offers adolescents a safe environment where concerns about peer pressure, relationships, prevention of relapses, and other treatment issues can be addressed. The dynamics of group therapy set the stage for interpersonal and intrapersonal growth and differ from the dynamics played out in one-to-one interactions with an individual therapist. Teens also may find safety in numbers and become more involved with the encouragement and example of their peers. Gathering with other adolescents who share similar struggles not only provides some reassurance to the teen that he or she is “not the only one with a problem,” but also coincides with the developmentally normal preference of adolescents to be together. In addition, in the context of limited resources, group therapy is cost-effective, as long as potential group members are screened carefully to guarantee appropriateness for each of its members. (50)

**TWELVE-STEP FELLOWSHIPS.** Another form of peer-based support may be found in 12-step fellowships, such



as Alcoholics Anonymous (AA), Narcotics Anonymous (NA), and Alateen, which often form part of a substance abuse treatment program. (51) Many adolescents begin to attend AA while they are hospitalized and often are encouraged to continue their attendance on discharge. Although not every patient affiliates with AA, it is important to make efforts to understand which patients are more likely to attend and benefit from attendance. The body of research into the characteristics and factors that predict success from self-help group attendance is limited, but evidence to suggest that AA/NA programs lead to higher levels of commitment to abstinence is growing. (56) Hohman and LeCroy (57) found 12-step affiliation to be associated with having prior alcohol or drug treatment, having friends who did not use drugs, having less parental involvement in treatment, and possessing more feelings of hopelessness (depression). Ideally, adolescents should attend young people's meetings and, as is generally recommended for people early in recovery, obtain a sponsor who is aware of his or her individual developmental level when progressing through the 12 steps. (15)

**FAMILY THERAPY.** Multiple forms of family therapy have been studied in randomized clinical trials, including functional family therapy, (58) brief strategic family therapy, (59) family systems therapy, (60) multidimensional family therapy (MDFT), (61)(62)(63) and multisystemic therapy (MST). (64) Two of the modalities implemented most commonly are MDFT and MST. MDFT was developed to treat adolescents who have substance abuse and behavioral problems. This manual-based therapy is characterized by individual and family sessions occurring up to four times per week, coupled with interim phone contact and intensive advocacy with the adolescent's school and the court system, when pertinent. (61)(62)(63) MST is an intensive 4-month program developed to address the needs of adolescents at high risk of incarceration or foster care. Therapists work closely with parents to identify the goals for treatment, ascertain the causes of the substance disorder, and implement solutions. MST includes comprehensive psychiatric and substance abuse services, with sessions held in the family's home. (64)

**DRUG COURT.** A successful juvenile drug court uses the case management system, which includes positive reinforcement for compliance as well as clearly outlined consequences that are swiftly enforced for violation of court-ordered program guidelines. Limited studies indicate that juvenile drug court involvement reduces recid-

ivism and substance use, arrests, and criminal behavior while simultaneously improving school and vocational outcomes. (65)

**CONTINGENCY MANAGEMENT.** Contingency management (CM) treatments are based on a simple behavioral principle that if a good behavior is rewarded, it is more likely to be repeated in the future. (66) The premise behind CM is to use these and other reinforcement procedures systematically to modify behaviors of substance-abusing adolescents in a positive and supportive manner. Patients are called at random to provide urine specimens at least once a week, and rewards are provided for each specimen that tests negative for drugs. These rewards often consist of vouchers that can be exchanged for gift certificates, clothing, music, sports equipment, theater tickets, or other items of interest to adolescents. (52) Although several studies have demonstrated that CM is efficacious in retaining patients in treatment, reducing substance use, increasing group attendance, and improving adherence to medications, additional research with adolescent populations is needed. (52)(67)

**PHARMACOTHERAPY.** Developing medication treatments for substance use disorders continues as an area of research. Unfortunately, opioids and alcohol are the only substances for which corresponding pharmacotherapies exist for treatment in adults. To date, the United States Food and Drug Administration (FDA) has not yet granted approval for treatment in adolescents. (68) Following the introduction of methadone as agonist replacement therapy in the mid-1960s, the treatment of opioid dependence in adults has relied primarily on the establishment of methadone maintenance programs, strictly monitored by federal guidelines. (69)(70) However, in the past decade, newer medications (levomethadyl acetate [LAAM] and buprenorphine) have been found to be similarly effective. (71) Concern regarding cardiotoxicity with levomethadyl acetate has led to cessation of its use, (72) thus opening the door for buprenorphine to gain popularity as an office-based alternative for opioid maintenance. Buprenorphine is a partial opioid agonist and, therefore, may have some advantages over methadone, including fewer withdrawal symptoms and a lower risk of overdose. (73) In addition, its availability as a buprenorphine-naloxone preparation lessens the risk for diversion or abuse and marks a milestone as a medication with the potential to increase the safety, availability, and acceptance of opioid abuse treatment in the United States. (74)(75)(76) (Additional information

can be obtained at <http://www.samhsa.gov>.) Finally, although disulfiram, naltrexone (oral and intramuscular), and acamprosate have received FDA approval for the treatment of alcohol dependence in adults, (77) they are not approved for use in adolescents.

### Inpatient Care

**DETOXIFICATION.** Although most adolescents typically do not experience physical withdrawal symptoms from the most commonly used substances (eg, cannabis), those who are dependent on alcohol, other sedative-hypnotics (eg, benzodiazepines), or opioids often experience withdrawal symptoms that require monitored medical management in an inpatient facility. (50) Detoxification in a hospital should be considered for all patients who meet criteria for alcohol, opioid, or sedative-hypnotic dependence and who display symptoms of physical withdrawal from these substances (Table 1).

**PSYCHIATRIC HOSPITALIZATION AND ACUTE RESIDENTIAL TREATMENT.** Psychiatric hospitalization may be warranted for adolescents struggling with concomitant mental illness that either has preceded substance use, occurred simultaneously, or been exacerbated by persistent use of drugs and alcohol. In a structured 24-hour psychiatric treatment facility, adolescents are offered services ranging from assessment and consultation to psychopharmacology, family therapy, and recommendations and referrals for aftercare. Once medically stable, an adolescent may be a candidate for step-down to acute residential treatment (ART) as an alternative to prolonging inpatient hospitalization. Based on a multimodal approach and therapeutic milieu model, ARTs work closely with parents and teens to build and strengthen interpersonal relationships, learn more about themselves through groups and classroom experience, and reinforce emerging healthy alternative behaviors for managing feelings and impulsive behaviors rather than engaging in substance use. When deemed necessary, additional evaluation to address specific concerns such as childhood trauma, eating disorders, learning disabilities, and school conflict can be coordinated. The goal is to collaborate with each adolescent and his or her family to promote the smoothest possible transition from the therapeutic milieu back to the community. (50)(51)

**LONG-TERM RESIDENTIAL TREATMENT.** As occurs with ARTs, long-term residential programs provide a variety of daily therapeutic sessions, including individual, group, and family therapy, as well as psychological edu-

cation and psychopharmacology over an average of 6 to 12 months. These programs can accommodate adolescents who have both psychiatric and substance use disorders and have been unable to stop using substances or may have other self-injurious behaviors such as “cutting” or a history of suicide attempts. Some residential programs are “locked” for the most at-risk youths. (50)(51)

**THERAPEUTIC COMMUNITIES.** Therapeutic communities provide treatment for adolescents who have severe chemical dependency and behavioral difficulties, have failed less intensive treatments, and are unable to live at home. This treatment modality generally is longer in duration (18 to 24 months) and potentially may serve as a step-down for adolescents who have completed more intensive treatment elsewhere. (50)(51)

**THERAPEUTIC SCHOOLS.** Therapeutic schools are designed to meet the academic and therapeutic needs of adolescents who have a variety of mental health and behavioral problems. Although these schools are not designed exclusively for substance abuse treatment, many have substance abuse services as part of their curricula. Therapeutic schools may be residential (include a boarding component) or function solely as a day school, with adolescents living at home. (50)

**WILDERNESS THERAPY.** Wilderness therapy programs typically serve adolescents who have a variety of behavior problems and have resisted changing their behaviors despite multiple treatments. Wilderness therapy promotes group living in an unfamiliar environment, with application of outdoor-living skills and physical challenges as vehicles for boosting personal and social responsibility and encouraging emotional growth. Although not specifically designed to treat drug problems, drug use is common among teens in these programs, and most such programs have some specific drug treatment component. Wilderness therapy programs generally last 3 to 8 weeks. Despite their growing popularity, however, they have not been studied adequately. Parents should inquire carefully about such programs, including whether the program is licensed by the state, before deciding which to use for their teenager. (50)

*To view references and Table 1 for this article, visit [pedsinreview.aappublications.org/cgi/content-embargo/full/30/3/83/DC1](http://pedsinreview.aappublications.org/cgi/content-embargo/full/30/3/83/DC1).*

## Summary

- Research evidence shows that early onset of substance use is significantly correlated with risk of developing alcohol dependence later in life. (17)
- Research evidence shows that the primary factors appearing to contribute to a teenager's choice of selecting one drug over another are its perceived availability, the perceived degree of social approval associated with its use, and how risky the drug is perceived to be. (3)(22)
- Strong research evidence shows that the CRAFFT is a valid and reliable method of screening adolescents for substance abuse in medical settings. (27)(29)
- Strong research evidence shows that psychiatric comorbidity in adolescents who misuse psychoactive substances is the rule rather than the exception, with comorbidities, including unipolar or bipolar depression, anxiety, conduct disorder, oppositional-defiant disorder, and ADHD. (33)(34)(35)(36)
- Adolescent substance use differs from that of adults in that progression from casual use to dependence occurs more quickly, adolescents are more likely to use multiple substances, and adolescents often are at higher risk of presenting with psychiatric comorbidities. Treatment always should be tailored to each adolescent's particular needs.
- Strong research evidence shows that family-based treatments are effective for adolescents who abuse substances and depend on them. (58)(59)(60)(61)(62)(63)(64)

## Useful Web Sites

- [www.drugstrategies.com](http://www.drugstrategies.com). Drug Strategies is a non-profit research foundation that promotes more effective ways of dealing with the nation's drug and alcohol problems. Drug Strategies also sponsors [www.bubblemonkey.com](http://www.bubblemonkey.com), a confidential Web site dedicated to answering teens' questions about drugs and alcohol.
- [www.reclaimingfutures.org](http://www.reclaimingfutures.org). This Web site provides information about Reclaiming Futures sites that provide research-based interventions for teens who have substance use disorders.
- [www.dea.gov/pubs/abuse](http://www.dea.gov/pubs/abuse). This site provides text of *Drugs of Abuse*, a publication that offers straightforward information about drugs.
- [www.buprenorphine.samhsa.gov](http://www.buprenorphine.samhsa.gov). This Web site provides information about the use of buprenorphine in treating opioid dependence as well as a "physician locator" to help patients and families find treatment.

## PIR Quiz

Quiz also available online at [www.pedsinreview.aappublications.org](http://www.pedsinreview.aappublications.org)

1. The latest stage in the progression of drug use at which a teenager might be able to reduce or stop using with limited intervention is:
  - A. Abstinence.
  - B. Abuse.
  - C. Experimentation.
  - D. Nonproblematic use.
  - E. Problematic use.
2. Substance abuse is considered to be the result of both genetic and environmental predisposing factors. According to recent studies, the heritability of alcoholism is *closest* to:
  - A.  $\leq 1\%$ .
  - B. 5%.
  - C. 10%.
  - D. 25%.
  - E.  $\geq 50\%$ .
3. Among the following, the *most* effective method of screening for drug or alcohol use is (a):
  - A. Adherence to an athletic code of conduct.
  - B. Confidential medical interview.
  - C. Health questionnaire.
  - D. Serum toxicology screen.
  - E. Urine toxicology screen.
4. The presence of which of the following is the *strongest* indication for hospitalization of a teenage substance user?
  - A. Bipolar disorder.
  - B. Drug dependence.
  - C. Eating disorder.
  - D. Jeopardized safety.
  - E. Major depression.
5. A 16-year-old boy became addicted to morphine following a skiing accident in which he lost his leg. You tell him and his parents that addiction can be treated medically. Among the following, the drug that is *most* likely to be helpful is:
  - A. Acamprosate.
  - B. Buprenorphine.
  - C. Disulfiram.
  - D. Levomethadyl acetate (LAAM).
  - E. Methadone.



# The Nephrotic Syndrome

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**Objectives** After completing this article, readers should be able to:

1. Explain the mechanism and the consequences of proteinuria.
2. Make a presumptive diagnosis of minimal-change nephrotic syndrome.
3. Interpret the signs associated with steroid resistance.
4. Ascertain the timing and the indications for a kidney biopsy.
5. Gauge the indications for referral to a pediatric nephrologist.
6. Determine the adequacy of the therapy.
7. Predict the disease course.

## Introduction

The word “nephrosis” was introduced in the medical literature at the beginning of the 20th century in an attempt to distinguish diseases of the kidney characterized by exudation and proliferation from those characterized by inflammation (nephritis). As it became apparent that this is not a single disease, not even a group of related diseases, the term “nephrosis” was supplanted by “nephrotic syndrome.” The clinical features that characterize the nephrotic syndrome result from alterations of the glomerular capillary wall and consist of heavy proteinuria and hypoalbuminemia, often associated with edema and generalized hyperlipidemia.

## Pathophysiology

### Proteinuria and Hypoalbuminemia

Proteinuria is the result of alterations in the integrity of the glomerular filtration barrier. This barrier is composed of three layers in series: the fenestrated endothelium, the glomerular basement membrane, and the visceral glomerular epithelium, comprised of podocytes and their slit diaphragms. Podocyte is the name of the epithelial cell, and foot process is the segment of the cell that extends into the urinary space. (In the nephrotic syndrome, there is effacement of the foot process, but the rest of the cell usually is preserved.)

Endothelial cells have numerous openings that are 70 to 100 nm in diameter, called fenestrae, which form a physical barrier for passage of macromolecules from plasma into the renal tubule. Electron microscopic studies led to the identification of negatively charged particles (heparan sulfate proteoglycans) in the glomerular basement membrane, which preclude the passage of anionic macromolecules, such as albumin. Removal of these charges in animals by in situ perfusion of heparitinase resulted in proteinuria.

Until recently, the podocytes were considered to play a passive role in the process of glomerular filtration. This concept changed dramatically with the discovery that muta-

## Abbreviations

<b>ACE:</b>	angiotensin-converting enzyme
<b>BSA:</b>	body surface area
<b>CNF:</b>	congenital nephrotic syndrome of the Finnish type
<b>CNS:</b>	congenital nephrotic syndrome
<b>FSGS:</b>	focal segmental glomerulosclerosis
<b>HDL:</b>	high-density lipoprotein
<b>Ig:</b>	immunoglobulin
<b>IL:</b>	interleukin
<b>ISKDC:</b>	International Study of Kidney Disease in Children
<b>LDL:</b>	low-density lipoprotein
<b>MCNS:</b>	minimal-change nephrotic syndrome
<b>MN:</b>	membranous nephropathy
<b>MPGN:</b>	mesangioproliferative glomerulonephritis
<b>RAA:</b>	renin-angiotensin-aldosterone
<b>SLE:</b>	systemic lupus erythematosus
<b>UPr/Cr:</b>	urine protein/creatinine ratio
<b>VLDL:</b>	very low-density lipoprotein

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tion of a protein located at the slit diaphragm, named nephrin, is the cause of the congenital nephrotic syndrome of the Finnish type (CNF). (1) The slit diaphragm is a thin membrane that bridges the filtration pores between adjacent podocytes and is anchored to the cell cytoskeleton by adaptor proteins such as podocin and CD2AP. Podocytes have been found to affect the structure and function of the glomerular basement membrane and to regulate the integrity and survival of glomerular endothelial cells. A number of acquired and inherited diseases now are attributed to defects of the slit diaphragm protein complex (Table 1).

### Edema

The classic theory is that edema formation results from a decrease in plasma oncotic pressure due to loss of serum albumin, causing water to extravasate into the interstitial space. Such movement reduces the intravascular volume, leading to renal hypoperfusion and stimulation of the renin-angiotensin-aldosterone (RAA) system. Aldosterone increases reabsorption of sodium, particularly at the level of the distal segments of the nephron. This hypothesis, although attractive, is not supported fully by clinical findings. Plasma volume has been shown to be decreased only in some children who have minimal-change nephrotic syndrome (MCNS), particularly during the initial phase of a relapse. The decrease is absent in others and almost always absent in adults who have nephrotic syndrome. In addition, studies have failed to demonstrate elevation of RAA hormones, and increased sodium reabsorption was found to continue when albumin was infused or angiotensin-converting enzyme (ACE) inhibitors were administered to suppress renin production. An intrinsic renal abnormality leading to

retention of sodium is postulated. Vasopressin excess also contributes to the retention of water.

### Hyperlipidemia

Increased concentrations of very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) result in elevated serum cholesterol and triglycerides concentrations. The high-density lipoprotein (HDL) fraction is normal. Consequently, the LDL/HDL cholesterol ratio is increased. Several mechanisms allegedly contribute to nephrotic syndrome dyslipidemia: overproduction due to low plasma albumin concentration and low oncotic pressure and impaired catabolism of apolipoprotein B and VLDL chylomicrons.

### Epidemiology

The incidence of idiopathic nephrotic syndrome in the United States has been reported to be 2.7 new cases per 100,000 children per year, and the cumulative prevalence rate is 16 per 100,000 children. The ratio of males to females is approximately 2:1 during childhood, but the sex difference wanes by adolescence. There is an increased familial incidence, particularly among siblings. The mean age at onset has been reported to be 3.4 years in Asians and 4.2 years in Europeans. Compared with other populations, African American and Hispanic children have a greater incidence of nephrotic syndrome, a more severe form of disease, and a poorer prognosis. (2)

### Classification

Nephrotic syndrome can be primary (idiopathic) or secondary. Among children, 90% of cases are primary and the rest are secondary (Table 2). The advent of percutaneous renal biopsy in the 1950s and 1960s led to the identification of three histologic types of idiopathic nephrotic syndrome: MCNS, focal segmental glomerulosclerosis (FSGS), and membranous nephropathy (MN). Whereas the incidence of nephrotic syndrome has remained stable for decades, the distribution of histologic types apparently has changed due to an increase in the incidence of FSGS.

MCNS is the most common form of disease in children, accounting for approximately 85% of cases. On light microscopy, the glomeruli appear normal; electron microscopy allows detection of fusion of the epithelial foot processes, a finding common to all proteinuric states. FSGS accounts for 10% to 15% of all cases of nephrotic syndrome. Scar tissue develops initially in segments of some glomeruli, leading eventually to global,

**Table 1. Genetic Forms of Nephrotic Syndrome**

Gene/Protein	Location	Phenotype	Inheritance
<i>NPHS</i> /nephrin	Slit diaphragm	CNF	AR
<i>NPHS2</i> /podocin	Slit diaphragm	FSGS	AR
<i>CD2AP</i> / <i>CD2AP</i>	Near slit diaphragm	FSGS	
<i>TRPC6</i> / <i>TRPC6</i>	Podocyte	FSGS	AD
<i>WT1</i>	Podocyte	FSGS	AR
<i>ACTIN4</i>	Foot process	FSGS	AD
<i>tRNA<sup>Leu</sup></i>	Podocyte	FSGS	
<i>COQ2</i>	Podocyte	FSGS	

AD=autosomal dominant, AR=autosomal recessive, CNF=congenital nephrotic syndrome of the Finnish type, FSGS=focal segmental glomerulosclerosis

Table 2. Secondary Causes of Nephrotic Syndrome

## Infections

- Hepatitis B, C
- Human immunodeficiency virus
- Malaria
- Toxoplasmosis
- Syphilis

## Drugs

- Gold
- Non-steroidal anti-inflammatory drugs
- Pamidronate
- Interferon
- Heroin
- Lithium

## Malignancies

- Lymphoma
- Leukemia

## Miscellaneous

- Systemic lupus erythematosus
- Mesangioproliferative glomerulonephritis
- Immunoglobulin A nephropathy
- Diabetes mellitus

extensive glomerular sclerosis and tubular atrophy. MN is characterized histologically by diffuse thickening of the glomerular capillary walls and accounts for approximately 4% of nephrotic syndrome cases in children.

Other glomerulopathies that can be associated with nephrotic syndrome are mesangioproliferative glomerulonephritis (MPGN), lupus nephritis, and immunoglobulin A (IgA) nephropathy. In the first two conditions, nephritic findings (hematuria, hypertension, decreased renal function) predominate; in the third, microscopic hematuria is interspersed with episodes of macroscopic hematuria (Table 3). In all of these diseases, the occurrence of nephrotic syndrome is associated with a guarded-to-poor prognosis.

## Steroid-sensitive Nephrotic Syndrome

In the 1970s, a series of prospective, controlled, multicenter studies performed under the aegis of the International Study of Kidney Disease in Children (ISKDC) resulted in a better understanding of the relationships between the clinical course and histologic characteristics of various forms of nephrotic syndrome. Definitions of terms (Table 4), such as nephrotic level albuminuria and hypoalbuminemia, response to therapy, and indications for renal biopsy, were established. Various therapeutic regimens were tested, and prevention of relapse became the primary goal of therapy for patients who had MCNS. Care shifted from the hospital to the home, with emphasis on daily monitoring of the urine to detect proteinuria and initiate prednisone therapy early. Today, hospitalization should be necessary only when there is incapacitating edema (which is preventable) or infection.

A major conclusion of these studies was that the best

Table 3. Differential Diagnosis of Nephrotic Syndrome

Diagnosis	Physical Findings	Renal Function	Serum Albumin	C3 Complement	UPr/Cr	Other
MCNS	Edema	Normal	Low	Normal	>3.0	Hyperlipidemia
FSGS	Edema	Normal or low	Low	Normal	1.0 to 3.0	Hyperlipidemia Hematuria?
CNS	Anasarca	Normal or low	Very low	Normal	>3.0	Hyperlipidemia
MN	Edema	Normal or low	Very low	Normal	>3.0	Hematuria?
MPGN	Edema?	Normal or low	Low	Low	>3.0	Hematuria Hypertension
PSGN	Edema	Low	Normal	Low	<1.0	Hematuria Hypertension
HSP	Purpuric rash Arthritis	Low	Normal or low	Normal	1.0 to 3.0	Hematuria Hypertension?
LN	Butterfly rash Arthritis	Low	Normal or low	Low	1.0 to 3.0	Hematuria Hypertension
IgA	Edema?	Normal or low	Normal or low	Normal	1.0 to 3.0	Hematuria

CNS=congenital nephrotic syndrome, Cr=creatinine, FSGS=focal-segmental glomerular sclerosis, HSP=Henoch-Schönlein purpura, LN=lupus nephritis, IgA=immunoglobulin A nephropathy, MCNS=minimal-change nephrotic syndrome, MN=membranous nephropathy, MPGN=mesangiocapillary glomerulonephritis, PSGN=poststreptococcal glomerulonephritis, UPr=urine protein

Table 4. Definition of Terms

**Responder:** Protein-free urine for >3 days during initial treatment

**Infrequent relapser:** Fewer than three relapses within 6 months of the initial response or fewer than four relapses within any 12-month period

**Frequent relapser:** Three or more relapses within 6 months following initial response or four relapses within any 12-month period

**Steroid-dependent:** Recurrence of proteinuria on alternate-day steroid therapy or within 2 weeks after cessation of treatment

**Steroid-resistant:** Failure to respond to initial prednisone therapy or to 4 weeks of daily prednisone for relapse

prognostic indicator in children who have nephrotic syndrome is steroid responsiveness. Ninety-five percent of children who eventually respond to steroids do so within the first 4 weeks of treatment (Fig. 1). (3) As a result of this observation, children who fulfill the clinical criteria of MCNS (heavy proteinuria, hypoalbuminemia, and hyperlipidemia) are started on prednisone therapy without undergoing a renal biopsy. A renal biopsy at the time of diagnosis is indicated for patients who have macroscopic hematuria, severe hypertension, persistent renal insufficiency, or a low serum C3 complement value (Table 5). These signs may be indicative of MPGN, systemic lupus erythematosus (SLE), or postinfectious glomerulonephritis. A biopsy also should be performed if proteinuria persists at the end of 4 weeks of daily steroid

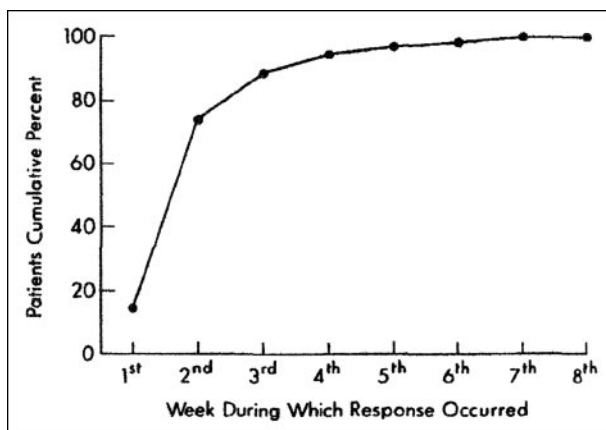


Figure 1. Cumulative distribution of time to response for initial responders. Note that approximately 95% of the children who eventually respond do so by 4 weeks of daily prednisone therapy. Reprinted with permission from *J Pediatr*. 1981;98:561–564.

Table 5. Indications for Renal Biopsy in Nephrotic Syndrome

## At Time of Diagnosis:

Two or more of the following:

- Age >10 years
- Persistent or gross hematuria
- Hypertension
- Renal insufficiency
- Low C3 complement values

## Subsequently:

- Persistent proteinuria (at the end of 4 weeks of daily prednisone therapy)

therapy, when the chance of subsequent response is approximately 5%. It is worth noting that microscopic hematuria is present during the first few weeks of illness in as many as one third of children who have MCNS. Persistence or recurrence of hematuria often is a sign of impending steroid resistance.

## Clinical Features

The hallmark of nephrotic syndrome is heavy proteinuria, and the most common presenting sign is edema that becomes visible when fluid retention exceeds 3% to 5% of body weight. Usually, edema appears initially in areas of low tissue resistance (ie, periorbital, scrotal, and labial regions). Ultimately, it becomes generalized and can be massive (anasarca). Edema is characteristically dependent. In the morning, it is periorbital, frequently misinterpreted as being caused by an allergy, and later in the day is localized primarily to the lower extremities. Anorexia, irritability, fatigue, abdominal discomfort, and diarrhea are common symptoms. A respiratory tract infection preceding the onset of the disease by a few days often is reported, but its pathogenetic role is doubtful. A history of allergy is reported by as many as 50% of children who have MCNS.

## Laboratory Findings

Plasma protein concentration is reduced markedly, due primarily to the loss of albumin in the urine; the serum albumin concentration usually is below 2.5 g/dL (25 g/L). The low concentration of albumin stimulates synthesis of lipids by the liver, resulting in high concentrations of cholesterol, triglycerides, and lipoproteins. Serum sodium may be decreased, due, in part, to hyperlipidemia and, in part, to the retention of water caused by hypovolemia and increased secretion of antidiuretic



hormone. The total calcium value may be low because of hypoalbuminemia, but the ionized calcium concentration is normal.

The concentration of protein in the urine can be estimated by the dipstick method. The strips are impregnated with tetrabromophenol blue, which reacts preferentially to albumin. The color change allows the reader to distinguish between a protein concentration of approximately 30 mg/dL (300 g/L) (1+), 100 mg/dL (1,000 g/L) (2+), 300 mg/dL (3,000 g/L) (3+), and 1,000 mg/dL (10,000 g/L) (4+). False-positive results may occur when the urine is alkaline (pH >7) or contains blood, pus, mucus, semen, or vaginal secretions. By this method, severity of proteinuria may be underestimated when the urine is diluted or overestimated when the urine is concentrated.

Patients who have a positive dipstick result should have a quantitative measurement of urinary protein excretion. Conventionally, this evaluation is performed on a 12- or 24-hour timed urine sample. An excretion of more than 50 mg/kg per day or 40 mg/m<sup>2</sup> per hour is considered indicative of nephrotic syndrome.

Accurate collections of urine are cumbersome, particularly in children, which explains the wide acceptance of the urine protein/creatinine ratio (UPr/Cr) as a reliable substitute. A strong correlation has been found between the UPr/Cr obtained in random specimens of urine and the 24-hour excretion of protein, corrected for body surface area (BSA). For children older than 2 years of age, a UPr/Cr of less than 0.2 is considered to be normal, a value of less than 0.5 is accepted as normal for children between 6 months and 2 years of age, and a value of more than 3.0 is consistent with nephrotic syndrome. Actual protein excretion (g/m<sup>2</sup> per day) can be calculated by the formula:  $0.63 \times (\text{UPr/Cr})$ . Due to circadian variations, the accuracy of the measurements can be increased by using a first-voided morning specimen.

### Cause

The cause of MCNS remains unknown. A decrease in immune responsiveness or disorders affecting T-lymphocyte number or function has been postulated. (4) Also, there are reports of increased expression of interleukin-2 (IL-2) receptors on

T-lymphocytes; increases in IL-8, IL-13, insulin-like growth factor-1, transforming growth factor-beta, and interferon-gamma; abnormalities in nephrin expression or distribution; and the presence of a circulating "vascular permeability factor." One such factor may be an active isoform of hemopexin, a plasma protein that can increase glomerular permeability by enhancing protease activity.

Recently, a group of investigators developed a humanized animal model of idiopathic nephrotic syndrome by injecting CD34<sup>+</sup> stem cells or CD34<sup>-</sup> peripheral blood mononuclear cells from patients afflicted with MCNS or FSGS into immunocompromised mice. (5) Only the injection of CD34<sup>+</sup> stem cells induced albuminuria and effacement of the podocyte foot processes. This finding suggests that the cells responsible for the pathogenesis of MCNS, as well as FSGS, are likely immature cells undergoing differentiation into T cells.

### Treatment and Course of MCNS

Prednisone is the drug of choice and should be started as soon as a presumptive diagnosis of primary nephrotic syndrome has been made, and infection, including tuberculosis, has been ruled out (Fig. 2). The treatment proposed by the ISKDC consisted of 60 mg/m<sup>2</sup> BSA per day, calculated on the basis of ideal weight for height (not to exceed 80 mg/day), divided in three doses. Daily administration was continued for 4 weeks, followed by 40 mg/m<sup>2</sup> BSA per day, given as a single dose in the morning, on alternate days, for an additional 4 weeks. Of

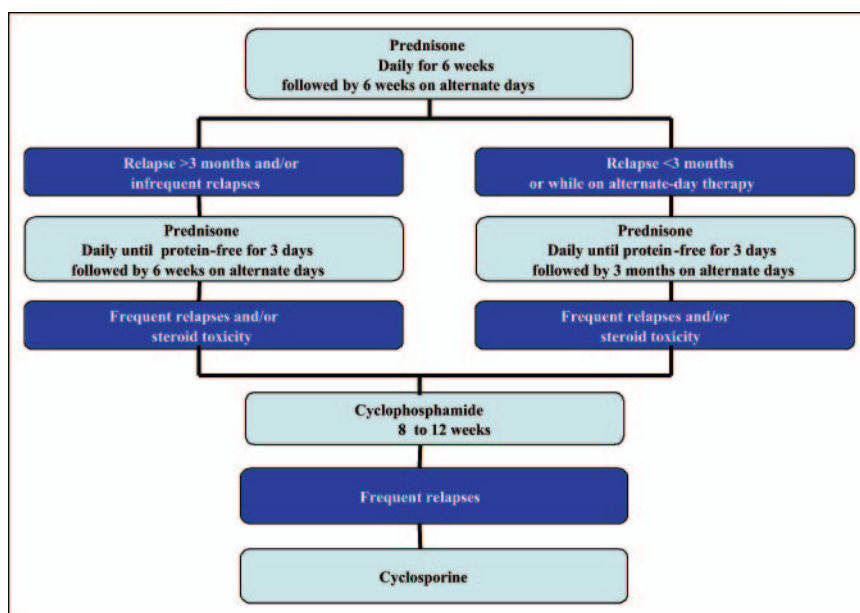


Figure 2. Treatment of minimal-change nephrotic syndrome.

the patients afflicted with MCNS, about 90% responded to steroids, and of those, about 60% relapsed. Subsequent studies of small numbers of children have revealed that similar rates of initial response can be achieved with twice-daily or even once-daily administration of prednisone. There are exceptions to this rule, however. A minority of children who fail to respond to a twice-daily regimen respond when given the daily prednisone in three divided doses.

In a retrospective analysis of 389 children included in the ISKDC studies who had MCNS, 80% were in remission at 8 years. Seventy-five percent of initial responders who remained in remission during the first 6 months after initial response either continued to be in remission or relapsed rarely. In contrast, initial “relapsers,” both frequent and infrequent, achieved a nonrelapsing course only after an average of 3 years. (6) Absence of hematuria at presentation, remission within 7 to 9 days from the start of treatment, and age older than 4 years have been reported to be predictive of few relapses. (7)

A prolonged initial treatment with prednisone (6 weeks of daily followed by 6 weeks of alternate-day administration) has been found to decrease the frequency of relapses. (8) In a Cochrane Review of the subject, the authors concluded that the higher the relapse rate with 2 months of initial treatment, the greater the effect of subsequent prolonged administration of prednisone. (9) Beginning with a relapse rate of 68% in children treated for 2 months, the relapse rate fell by an average of 7.5% with every 1-month increase in the length of treatment (approximately 30% at 6 months).

The treatment regimen used currently by most nephrologists consists of 6 weeks of daily prednisone, given in two divided doses, followed by 6 weeks of alternate-day prednisone given as a single dose in the morning. A relapse is treated with prednisone, 60 mg/m<sup>2</sup> BSA per day, given in two divided doses until the urine is protein-free for 3 consecutive days, followed by 40 mg/m<sup>2</sup> BSA per day, on alternate days, given as a single dose in the morning for 6 additional weeks, when the first relapse occurs more than 3 months after the initial response and for 12 additional weeks when the first relapse occurs within 3 months after the initial response.

Children who are frequent relapsers may benefit from an alkylating agent, such as cyclophosphamide (2 mg/kg per day), generally given for 8 to 12 weeks (Fig. 3). (10) A meta-analysis revealed that the relative risk of relapse in children who received this treatment is reduced by 60%. (11) The cumulative dose of cyclophosphamide should not exceed 200 mg/kg because of gonadal toxicity. Levamisole, chlorambucil, cyclosporine, and

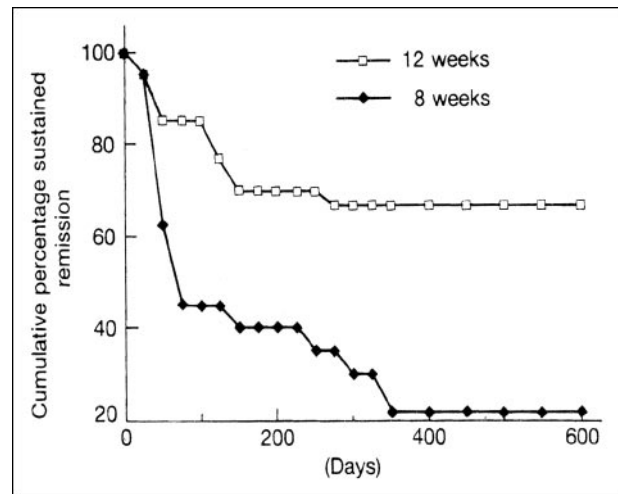


Figure 3. Actuarial remission rate after treatment with cyclophosphamide in steroid-dependent nephrotic syndrome. Reprinted with permission from *Arch Dis Child*. 1987;62:1102–1106.

mycophenolate-mofetil also have been found to reduce the frequency of relapses. In a number of uncontrolled studies, cyclosporine has been reported to reduce the incidence of relapses in 75% to 90% of patients who have steroid-dependent nephrotic syndrome. The drug has serious adverse effects (hypertension, hyperkalemia, hypertrichosis, gingival hyperplasia). Renal insufficiency, initially transitory, can become permanent due to interstitial fibrosis. Often, proteinuria recurs when the treatment is discontinued. (12) Cyclosporine administration requires careful monitoring of serum concentrations and should be undertaken only by experienced physicians. The frequency of relapses usually decreases with time, becoming rare at or after puberty. Nonetheless, as many as 52% of patients have been reported to have at least one relapse during adulthood. Pregnancy apparently is a predisposing factor. As long as the patient responds to steroid therapy, the risk of progression toward renal insufficiency remains negligible.

### Steroid-resistant Nephrotic Syndrome

Steroid-resistant nephrotic syndrome may occur at birth or during the first postnatal year, but is more common after the age of 2 years. This group of patients represents no more than 10% of the entire population of children who have nephrotic syndrome, but their prognosis usually is bleak. Their renal function deteriorates, and eventually they become candidates for dialysis or renal transplantation.

### Congenital Nephrotic Syndrome (CNS)

The name implies the presence of proteinuria at birth, leading to clinical symptoms shortly thereafter. Yet, an arbitrary limit of 3 months after birth is being used to separate the congenital from the infantile form of nephrotic syndrome.

The most common type of CNS is the Finnish type. CNF is an autosomal recessive disease, its incidence in Finland being 1 per 8,200 live births. However, patients who have CNF have been reported all over the world. In a subgroup of Mennonites from Lancaster, Pennsylvania, the incidence is 1 in 500, almost 20 times that encountered in Finland. In 1998, a gene (*NPHS1*) that codes for a protein (nephrin) located on podocytes was found to be mutated in CNF. (1) Soon thereafter, it became apparent that CNF also can be caused by mutations in *NPHS2*, which codes for another podocyte protein (podocin), and that mutations in *NPHS1* sometimes may cause mild, rather than severe, nephrotic syndrome.

The “typical” form of CNF is characterized by massive proteinuria that starts during fetal life. Elevated concentrations of alpha-fetoprotein in the amniotic fluid and normal fetal ultrasonographic findings serve to make a presumptive diagnosis of CNF. A definitive diagnosis requires genetic analysis of placental tissue or amniotic cells. Most affected children are born preterm, weighing a mean of 2,500 g. The amniotic fluid often is meconium stained, and the placenta is large. Edema and abdominal distention become evident soon after birth. The serum albumin concentration usually is below 1.0 g/dL (10 g/L). Albuminuria is massive and related directly to the concentration of albumin in the blood. Many other proteins, such as IgG, transferrin, antithrombin III, lipoprotein lipase, vitamin D-binding protein, and thyroid-binding protein, also are lost in the urine. These losses lead to metabolic disturbances, including lipid abnormalities that can produce atherosclerotic changes as early as the first postnatal year.

During the first months of extrauterine life, renal pathology is limited to slight-to-moderate mesangial cell proliferation by light microscopy and effacement of foot processes and thin glomerular basement membranes by electron microscopy. During the ensuing months, the renal tubules become dilated, mesangial hypercellularity increases, the Bowman capsule thickens, the interstitium becomes fibrotic, and glomeruli sclerose. Electron microscopy reveals the disappearance of the slit diaphragms.

Initial treatment aims to sustain a good nutritional state, control edema, and prevent complications such as infections and vascular thrombosis. Unilateral or bilateral nephrectomy (followed by peritoneal dialysis) often is

required to curtail the massive loss of protein. Successful treatment results in satisfactory growth and development and the chance for eventual kidney transplantation. In some patients, the nephrotic syndrome recurs, due to the development of antinephrin antibodies against the foreign antigens in the graft. Rare forms of CNS are those associated with diffuse mesangial sclerosis, specifically, the Denys-Drash, Galloway-Mowat, and Pierson syndromes. CNS also can be associated with infections such as syphilis, toxoplasmosis, cytomegalovirus, congenital rubella, and hepatitis B.

### Focal-Segmental Glomerular Sclerosis

FSGS was identified half a century ago as a postmortem finding in 20 children who had nephrotic syndrome. The significance of this observation became apparent years later when the advent of renal biopsy allowed investigators to associate FSGS with steroid resistance. Initially, the disease consists of hyalinization or sclerosis of some glomeruli (focal) that involves only part of the glomerular tuft (segmental). The lesion appears in the juxtamedullary nephrons and extends to the cortex, resulting in progressive loss of renal function. The location of the lesion within the glomerulus may have prognostic significance. Peripheral lesions opposite the origin of the proximal tubule (“tip lesions”) appear to have a better prognosis than do hilar lesions, particularly those characterized by capillary collapse (collapsing glomerulopathy) that occur in immunocompromised patients. FSGS is fourfold more common and more aggressive in African Americans than in Caucasians or Asians. (2)

As in MCNS, the major signs of disease are edema and albuminuria. Hematuria is more frequent in FSGS than in MCNS, but the overlap diminishes its value as an element of diagnosis. Results of blood chemistries are indistinguishable from those in MCNS. The age at onset also is similar in the two conditions. Because of these similarities, FSGS cannot be diagnosed at presentation, and children commonly are started on standard prednisone therapy. Lack of response at 4 weeks prompts a renal biopsy, which often reveals the specific histologic lesion of FSGS. The lesion may be missed, however, if the tissue sample contains a small number of glomeruli or does not include juxtamedullary glomeruli, which are affected first. In addition, about 20% of children who have FSGS respond to steroid therapy and do not undergo a renal biopsy.

The relationship between MCNS and FSGS remains controversial. Some believe that these are two distinct entities; others believe that FSGS is a severe form of MCNS. The latter opinion is supported by the observa-

tion that some children who initially respond to steroids become steroid-resistant, with a renal biopsy revealing focal-segmental lesions.

FSGS is a heterogeneous condition, the histologic expression of a variety of diseases, including heroin-associated nephropathy, acquired immunodeficiency syndrome, multiple myeloma, Alport syndrome, reflux nephropathy, diabetic nephropathy, and obesity. Heterogeneity also applies to “idiopathic” FSGS. Some patients respond to steroid therapy; most do not. In some patients, disease progression is slow, reaching end stage in about 10 years; in others, it reaches that point in about 2 years. Moreover, in this latter group, the disease has a high likelihood of recurring in the transplanted kidney, probably due to the presence of a blood-circulating factor. Despite sustained efforts, no factor has been isolated. The heterogeneity of FSGS has been amplified by the recognition that some cases of FSGS are due to genetic abnormalities.

**GENETIC FORMS OF FSGS.** In recent years, impressive progress has been made in describing the molecular structure of the podocytes and the slit diaphragms that link them. Specifically, a number of proteins have been identified that work in concert to control the permeability of the glomerular membrane. Mutations in the genes that encode these proteins are associated with nephrotic syndrome and focal-segmental glomerular lesions. The impetus for this exploding field of research has been the discovery that lack of nephrin, a protein located at the slit-diaphragm, accounts for CNF. Table 1 summarizes the current state of knowledge. Genetic forms account for only a small percentage of FSGS. Genetic diagnosis, although commercially available, is expensive, is performed in only a few laboratories, and is justified only in isolated circumstances.

Despite the impressive progress made in identifying genetic types of FSGS, the cause of the disease still has not been identified in most patients. It has been proposed that genetic variants in two or more podocyte genes that alone do not produce disease may interact to cause FSGS. This concept, although enticing, is yet to be proved.

**TREATMENT.** The therapy for FSGS, regardless of variety, has been and continues to be a frustrating en-

deavor. It is reasonable to assert that no agent that could conceivably be of benefit to these patients has escaped clinical experimentation. Alas, no definitive evidence has emerged that any of these drugs is effective, although a few facts have been learned from these trials. Pulse methylprednisolone, hailed as being salutary for most children who have steroid-resistant nephrotic syndrome, has proven to be of minimal benefit. Alkylating agents such as cyclophosphamide also have been shown to have little therapeutic effect, but they continue to be used. In uncontrolled trials, cyclosporine has been reported to induce remission in 25% to 50% of patients who have steroid-resistant FSGS, but patients relapse promptly when the drug is discontinued and develop serious adverse effects if the treatment is sustained for long periods. A multicenter, prospective, controlled, randomized trial, sponsored by the National Institutes of Health, is in progress. Patients younger than 40 years of age who have biopsy-proven FSGS are assigned to treatment with either pulse steroids plus mycophenolate-mofetil or to

**Infections are frequent and serious complications of nephrotic syndrome . . . The most common infection is peritonitis . . .**

cyclosporine. The results of this therapeutic trial will not be known for several years.

Recurrence of disease in transplanted kidneys is a major problem; it has been reported to occur in as many as 50% of children who have FSGS. Being older than 6 years of age at onset and progression to end-stage renal disease in fewer than 3 years are considered risk factors. For most affected children, proteinuria develops within hours after transplantation, although it may start as late as 3 months later. High-dose cyclosporine, plasmapheresis, or a combination of both is associated with partial or total remission in a minority of cases. The outcome of the treatment is unpredictable.

### Membranous Nephropathy

MN was identified initially postmortem as a diffuse, irregular thickening of the glomerular basement membranes in the absence of any inflammatory changes. With the introduction of acid-silver-methenamine stain and electron microscopy, it became evident that the distor-



tion of the basement membranes is due to the presence of blobs of silver-negative, electron-dense deposits. The deposits are located exclusively in the subepithelial area and are flanked by silver-positive tissue, giving the appearance of spikes. MN is very rare in children and can manifest at any age. It presents as either asymptomatic proteinuria or nephrotic syndrome. Microscopic hematuria and hypertension are rare. No clinical or laboratory findings allow a positive identification; the diagnosis rests ultimately on the specific histologic findings.

The disease can be either primary or due to a variety of conditions, including infections (hepatitis B, malaria, syphilis), autoimmune diseases (SLE, Crohn disease), drugs (penicillamine), tumors (Wilms, neuroblastoma), and other disorders. The pathogenesis of MN has not been determined precisely, although evidence points toward binding of an antibody to an in situ glomerular basement membrane antigen. In several cases of neonatal MN, a podocyte antigen, neutral-endopeptidase, (13) served as the pathogen. Antibodies to this protein originated in pregnant women who lacked the neutral endopeptidase epitope due to a mutational deletion. No similar findings have been reported in older patients.

The course of the disease is variable. Spontaneous remissions occur in 25% to 50% of children, whereas 25% to 30% develop renal insufficiency. Treatment with steroids and immunosuppressive drugs is common, although the results have been discouraging.

## Complications of Nephrotic Syndrome

Some patients exhibit signs of acute renal failure (ie, reduction in glomerular filtration rate and oliguria). These signs usually are reversed when the intravascular volume is expanded by infusion of salt-poor human albumin and diuresis is induced by furosemide or other diuretic drugs. Rarely, acute renal failure can be caused by bilateral renal vein thrombosis. The diagnosis is made by ultrasonography. Thromboembolic complications also can affect the lungs, the brain, and the peripheral vessels. The overall incidence of thromboembolic events is about 3%. Such events are caused by loss of antithrombin III and protein S in the urine as well as an increase in fibrinogen concentration, leading to a hypercoagulable state.

The antiphospholipid syndrome also has been incriminated as a cause of thromboembolic complications in some patients who have nephrotic syndrome. This disorder is characterized by persistently elevated concentrations of antibodies directed against membrane anionic phospholipids (eg, anticardiolipin antibody, antiphosphatidylserine) or their associated plasma proteins, pre-

dominantly beta-2 glycoprotein I (apolipoprotein H). A circulating anticoagulant also may be present. The mechanism of thrombosis in this syndrome has not yet been defined. Emerging evidence from murine models suggests that antiphospholipid-mediated complement activation may be the primary event. Irrespective of cause or pathogenesis, the first line of treatment is low-molecular weight heparin. If the thrombosis extends, thrombolytic drugs, such as tissue plasminogen activator, followed by warfarin should be considered. Warfarin should be discontinued as soon as the nephrotic syndrome resolves.

Infections are frequent and serious complications of nephrotic syndrome. Urine loss of factor B (which contributes to opsonization of bacteria), a decrease in IgG synthesis, and impaired T-cell function contribute to the susceptibility to infection. The most common infection is peritonitis, which used to be due primarily to *Streptococcus pneumoniae*. Vaccination has reduced infections with *S pneumoniae* substantially and increased the relative frequency of gram-negative organisms. There also has been an increase in penicillin-resistant *S pneumoniae*.

A high degree of suspicion must be maintained when caring for patients who have ascites. Fever and chills occur in as many as 80% of patients who have peritonitis. Abdominal pain or discomfort is found in as many as 70% of patients and often is accompanied by ileus or diarrhea. Peritoneal fluid must be analyzed for any patient in whom peritonitis is considered. An ascitic fluid neutrophil count of more than 500 cells/mcL is the single best predictor of infection, with a sensitivity of 86% and specificity of 98%. Lowering the ascitic fluid neutrophil count to more than 250 cells/mcL results in an increased sensitivity (93%) but a lower specificity (94%). Notably, steroids do not mask the signs and symptoms of peritonitis. (14)

A combination of an aminoglycoside and ampicillin provides empiric coverage of more than 90% of cases of peritonitis caused by gram-negative aerobes or gram-positive cocci. The third-generation cephalosporin cefotaxime is as efficacious and is not nephrotoxic but does not treat enterococci. Subsequently, antibiotic therapy should be guided by the results of ascitic fluid cultures and sensitivities.

Cellulitis, meningitis, and pneumonitis also may occur in patients who have nephrotic syndrome. Anasarca and pulmonary edema are preventable complications of nephrotic syndrome and reflect massive retention of sodium and water, consequent to the loss of albumin in the urine and its leakage into the extravascular compartment. Diuretic drugs and salt-poor albumin infusions are only

partially effective. The primary goal of therapy should be diminution of protein loss. Stunting of growth, a complication of prolonged steroid administration, is well recognized. Thirty-four patients who had a frequently relapsing course and a mean age of 8.0 years at onset were found to have a mean height 2.5 cm below the target height, when evaluated 13 years later. (15) Growth rate should be monitored closely in frequent relapsers or steroid-dependent children, and an alternative therapy (cyclophosphamide, mycophenolate-mofetil, cyclosporine) should be considered as soon as the growth curve plateaus.

Reduced mineral bone density, a recently recognized complication of MCNS, is due to the prolonged administration of steroids and, possibly, to vitamin D deficiency. In a randomized, controlled study of 40 children who had MCNS, daily administration of 400 IU of vitamin D and 1 g of calcium diminished, but did not end, the decrease in bone mineral density.

### Ancillary Therapy of Nephrotic Syndrome

Edema in nephrotic syndrome requires treatment only when it is associated with severe ascites, peritonitis, respiratory distress, or heart failure. The first line of therapy is diuretic drugs. Commonly used are loop diuretics (furosemide, ethacrynic acid), which block reabsorption of sodium in the loop of Henle, and thiazide diuretics (hydrochlorothiazide), which block reabsorption of sodium in the distal tubule. For patients who fail to respond to diuretics, concomitant administration of salt-poor albumin (0.5 to 1 g/kg body weight up to 25 g, in a 25% solution administered intravenously over 30 to 60 minutes) may induce diuresis. This treatment appears to be particularly effective in children who have very low serum albumin concentrations ( $<1.5$  g/dL [ $15$  g/L]) and in those who have clinical signs of intravascular volume contraction. Aggressive administration of diuretic drugs may induce hypovolemia and secondary renal failure, thromboembolism, or electrolyte disturbances. Hypovolemia can be prevented or treated by administration of salt-poor albumin.

Approximately 20 years ago, it was noticed that angiotensin II inhibitors diminished proteinuria, independently of their effect on blood pressure and glomerular filtration rate. As a result, ACE inhibitors and angiotensin receptor blockers, given alone or in combination, have become important components of the antiproteinuric therapy. Twelve weeks of treatment were reported to reduce proteinuria by about 1 g/24 hours. Recently, it has been found that ACE inhibitors prevent loss of podocytes and preserve nephrin expression; they also

may slow progression of renal disease. A protective effect on renal function also was seen with angiotensin receptor blockers.

Hyperlipidemia is one of the primary features of the nephrotic syndrome that may persist well beyond remission. Several studies have revealed premature coronary atherosclerosis and increased incidence of myocardial infarction in patients who have nephrotic syndrome. Hyperlipidemia also may contribute to progression of renal disease. These observations have prompted many physicians to use statins in patients who have had persistent hyperlipidemia. Statins also have been found to slow the progression of chronic renal disease, albeit to a trivial extent. These effects may be due to improvement of endothelial function, systemic or intrarenal anti-inflammatory actions, amelioration of oxidative stress, and inhibition of macrophage recruitment and function.

Vaccination of children who have nephrotic syndrome has been found to be generally effective. Antibody responses to pneumococcal, influenza, varicella, and hepatitis vaccines have been adequate, and the adverse effects have not been found to be different from those reported in the general population. However, pneumococcal and hepatitis antibody concentrations were reported to decline faster in children who had nephrotic syndrome than in the general population. The Committee on Infectious Diseases of the American Academy of Pediatrics recommends vaccination with the conjugated pneumococcal vaccine. The state of immunity to varicella should be assessed for patients who have not been vaccinated, and treatment with acyclovir should be started as soon as an at-risk patient is exposed to the virus.

Retention of sodium is paramount to water retention and the development of edema. Thus, a low-sodium diet is warranted, although fluid intake does not need to be restricted as long as sodium intake is limited. Prolonged loss of proteins in the urine may compromise the nutritional status of the children and must be prevented by an adequate diet and, when necessary, the addition of high-protein products. Vitamin D and calcium supplementation also are advisable.

### Summary and Conclusions

Nephrotic syndrome encompasses a diverse group of conditions that share the common denominator of massive loss of protein in the urine. Progress in identifying the cause and pathogenesis of each of these conditions has been slow. The current identification of various forms of nephrotic syndrome is based primarily on histologic findings, which are not always pathognomonic.

Treatment has and still depends on drugs that lack specificity and have numerous, often serious, adverse effects.

The following conclusions are worth remembering:

- Most children who have nephrotic syndrome have MCNS, which is responsive to prednisone therapy.
- Response to steroid therapy is the best prognostic indicator.
- Most (~60%) of children who have MCNS relapse, some of them frequently. Cyclophosphamide and cyclosporine decrease the incidence of relapses.
- Compelling evidence suggests that renal biopsy should be performed at onset only in children who, in addition to proteinuria, have macroscopic hematuria, hypertension, persistent renal insufficiency, or low C3 complement values. Another indication is failure to respond to steroid therapy (proteinuria still present at the end of 4 weeks of daily prednisone therapy).
- Most children who have nephrotic syndrome and fail to respond to steroids have FSGS. Most alkylating agents are ineffective. Cyclosporine has been reported, in uncontrolled studies, to induce remission in 20% to 50% of patients who failed to respond to steroids. The drug requires monitoring of serum values and has serious adverse effects. Proteinuria recurs in most patients as soon as the treatment is discontinued.
- Several genetic forms of FSGS, due to mutations that encode proteins at the level of the podocytes, have been identified. They account for a small minority of patients who have nephrotic syndrome, and none responds to treatment.
- Dialysis and transplantation have improved the long-term prognosis of patients who reach end-stage renal disease, even infants who have CNS.
- Some glomerulopathies, such as FSGS, MPGN, and possibly CNS, may recur in renal transplants. Treatment with immunosuppressive agents and plasmapheresis is effective in about 30% of such patients.

## References

1. Trygvason K, Patrakka J, Wartiorova J. Hereditary proteinuria syndromes and mechanisms of proteinuria. *N Engl J Med*. 2006; 354:1387–1401

2. Ingulli E, Tejani A. Racial differences in the incidence and renal outcome of idiopathic focal segmental glomerulosclerosis in children. *Pediatr Nephrol*. 1991;5:393–397
3. The primary nephrotic syndrome in children: identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A Report of the International Study of Kidney Disease in Children. *J Pediatr*. 1981;98:561–564
4. Shalhoub RJ. Pathogenesis of lipoid nephrosis: a disorder of T cell function. *Lancet*. 1974;2:556–559
5. Sellier-Leclerc AL, Duval A, Riveron S, et al. A humanized mouse model of idiopathic nephrotic syndrome suggests a pathogenic role for immature cells. *J Am Soc Nephrol*. 2007;18: 2732–2739
6. Tarshish P, Tobin JN, Bernstein J, Edelmann CM Jr. Prognostic significance of the early course of minimal change nephrotic syndrome: report of the International Study of Kidney Disease in Children. *J Am Soc Nephrol*. 1997;8:769–776
7. Constantinescu AR, Shah HB, Foote EF, Weiss LS. Predicting first-year relapses in children with nephrotic syndrome. *Pediatrics*. 2000;105:492–495
8. Brodehl J. The treatment of minimal change nephrotic syndrome: lessons learned from multicentre cooperative studies. *Eur J Pediatr*. 1991;150:380–387
9. Hodson EM, Knight JF, Willis NS, Craig JC. Corticosteroid therapy in nephrotic syndrome: a meta-analysis of randomized controlled trials. *Arch Dis Child*. 2000;83:45–51
10. Cyclophosphamide treatment of steroid dependent nephrotic syndrome: comparison of 8-week with 12-week course: report of the Arbeitsgemeinschaft für Pädiatrische Nephrologie. *Arch Dis Child*. 1987;62:1102–1106
11. Durkan AM, Hodson EM, Willis NS, Craig JC. Immunosuppressive agents in childhood nephrotic syndrome: a meta-analysis of randomized controlled trials. *Kidney Int*. 2001;59:1919–1927
12. Niaudet P, Habib R. Cyclosporine in the treatment of idiopathic nephrosis. *J Am Soc Nephrol*. 1994;5:1049–1056
13. Dubiec H, Guignon V, Mougenot B, et al. Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. *N Engl J Med*. 2002;346:2053–2060
14. Krensky AM, Ingelfinger JR, Grupe W. Peritonitis in childhood nephrotic syndrome: 1970–1980. *Am J Dis Child*. 1982;136: 732–736
15. Motoyama O, Iitaka K. Final height in children with steroid sensitive nephrotic syndrome. *Pediatr Int*. 2007;49:623–625

## Suggested Reading

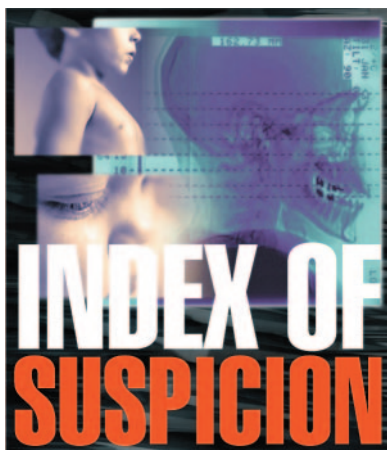
- Eddy AA, Symons JM. The nephrotic syndrome. *Lancet*. 2003;362: 629–639
- Shankland SJ. The podocyte's response to injury: role of proteinuria in glomerulosclerosis. *Kidney Int*. 2006;69:2131–2147

## PIR Quiz

Quiz also available online at [www.pedsinreview.aappublications.org](http://www.pedsinreview.aappublications.org).

6. A 4-year-old boy presents with swelling of the face and extremities of 2 days' duration. Physical examination reveals an otherwise happy child who has swelling of the face and pitting edema of all extremities. Vital signs and the rest of the physical examination findings are normal. Urinalysis shows 4+ proteinuria and 5 red blood cells per high-power field. Of the following, the *most* likely abnormality on histologic examination of this boy's kidney is:
  - A. Deposition of immunoglobulin A in mesangium.
  - B. Diffuse thickening of glomerular capillary walls.
  - C. Fusion of epithelial foot processes only.
  - D. Mesangial cell proliferation and thickening of Bowman capsule.
  - E. Scar tissue in segments of some glomeruli.
7. A 4-year-old boy presents with swelling of the face and extremities of 2 days' duration. Physical examination reveals an otherwise happy child who has swelling of the face and pitting edema of all extremities. Vital signs and the rest of the physical examination findings are normal. Urinalysis shows 4+ proteinuria and 5 red blood cells per high-power field. Of the following, the *best* indicator of good outcome for this child is:
  - A. Normal C3 complement value.
  - B. Normal serum creatinine concentration.
  - C. Resolution of symptoms with prednisone treatment.
  - D. Serum cholesterol less than 500 mg/dL (13.0 mmol/L).
  - E. Urine protein:creatinine ratio less than 5.
8. You are treating a 9-year-old girl who has nephrotic syndrome with prednisone. Which of the following is the *strongest* indication for performing renal biopsy?
  - A. Lack of response to therapy after 1 week.
  - B. Microscopic hematuria showing more than 5 red blood cells per high-power field in urine.
  - C. Reduced serum concentration of C3 complement.
  - D. Serum albumin less than 1.5 g/dL (15 g/L).
  - E. Urine protein:creatinine ratio of 1 at presentation.
9. A 6-year-old girl is admitted for swelling of her face and extremities. Findings on her physical examination and vital signs are normal except for generalized anasarca. Urinalysis shows 4+ protein with no casts or red blood cells. Serum albumin is 1.3 g/dL (13 g/L), cholesterol is 550 mg/dL (14.2 mmol/L), and creatinine is 0.4 mg/dL (35.4  $\mu$ mol/L). This patient is at *greatest* risk for:
  - A. Centrilobular hepatic necrosis.
  - B. Cerebral edema.
  - C. Congestive heart failure.
  - D. Myoglobinuric renal failure.
  - E. Peritonitis.





The reader is encouraged to write possible diagnoses for each case before turning to the discussion. We invite readers to contribute case presentations and discussions. Please inquire first by contacting Dr. Deepak Kamat at [dkamat@med.wayne.edu](mailto:dkamat@med.wayne.edu).

#### Author Disclosure

Drs Martin, Waters, Perez, Kleman, and Nield have disclosed no financial relationships relevant to these cases. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

### Case 1 Presentation

A 9-year-old boy presents to the ED with a 1-day history of increased work of breathing and cough. Over the past few days, he also has experienced increasing lethargy and fatigue. His past history is significant for situs inversus and asplenia. He has had multiple prior admissions for pneumonia and had a gastric volvulus at age 3 years, which was treated with an esophagojejunal anastomosis. He had been fed by a jejunal tube, but this was removed. The patient subsequently was lost to follow-up until recently. Current medications include fluticasone 125 mcg, 1 puff twice daily via spacer, and amoxicillin 125 mg by mouth daily; his compliance is questionable.

The physical examination reveals a pale child who does not appear toxic. His temperature is 98.6°F (37°C), heart rate is 110 beats/min, respiratory rate is 32 breaths/min, blood pressure is 104/54 mm Hg, and oxygen saturation is 92% on 6 L of oxygen/min. His height and weight are at the 40th and 25th percentiles, respectively. He has diffuse wheezing and crackles in the left base. The rest of the examination findings are unremarkable.

A chest radiograph demonstrates a left lower lobe infiltrate. Blood cultures are ordered and broad-spectrum antibiotics begun. A complete blood count demonstrates a Hgb of 5.8 g/dL (58 g/L), mean corpuscular volume (MCV) of 133.8 fL, mean corpuscular hemoglobin concentration (MCH) of 45.4 pg, WBC count of  $3.16 \times 10^3/\text{mcL}$  ( $3.16 \times 10^9/\text{L}$ ) ( $1.55 \times 10^3/\text{mcL}$  neutrophils,  $1.51 \times 10^3/\text{mcL}$  lymphocytes,  $0.1 \times 10^3/\text{mcL}$  basophils), and platelets of  $70 \times 10^3/\text{mcL}$  ( $70 \times 10^9/\text{L}$ ). The peripheral smear shows Howell-Jolly bodies, multi-lobulated neutrophils, large platelets,

macro-ovalocytes, and nucleated red blood cells. Values for serum electrolytes, alkaline phosphatase, AST, and ALT are normal. The lactate dehydrogenase concentration is 1,670 U/L, and the bilirubin is 1.3 mg/dL (22.0  $\mu\text{mol/L}$ ). An additional investigation reveals the cause of his anemia.

### Case 2 Presentation

A 6-year-old girl presents with excessive daytime sleepiness and school difficulties. She had enjoyed normal health during infancy and the preschool years. Over the past 2 years, however, the mother reports that her daughter has experienced excessive daytime sleepiness to the extent that she frequently falls asleep on the drive to school. She seems to tire more easily than her peers and has difficulty keeping up when playing team sports. The mother also describes several “drop attacks,” when her daughter suddenly loses muscle tone and collapses to the floor. She does not lose consciousness with these episodes and does not have seizure activity. The school reports that the girl is inattentive and immature and recommends that she repeat first grade. Her past medical history is otherwise unremarkable, and her development is normal. Findings on physical examination, including neurologic assessment, are within normal limits. Normal results are documented on MRI; EEG (nonsleep-deprived); CBC; and measurement of serum electrolytes, creatinine, BUN, ESR, and C-reactive protein.

### Case 3 Presentation

A 17-year-old boy presents with a 3-day history of worsening sore throat and dysphagia. He was seen in the ED yesterday, had a negative rapid strep test result, and was pre-

scribed azithromycin and told to follow-up in the clinic today. He has to sit up continuously and catch his saliva because he cannot swallow it, and he cannot lie down because he has difficulty breathing when he is recumbent. He has no fever.

The boy is fully immunized, including vaccination against *Haemophilus influenzae* type B (Hib) and *Neisseria meningitidis*. One week ago, he had oral and vaginal intercourse. His 15-year-old sister was admitted to the hospital yesterday with a nonhealing axillary abscess infected with community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA).

Physical examination reveals a distressed young man who is crying and leaning against his mother for support. His temperature is 100.0°F (37.8°C), respiratory rate is 16 breaths/min, and pulse oximetry is 100% on room air. His tonsils are slightly swollen bilaterally and erythematous without discharge. The uvula is in the midline. He is unable

to open his mouth fully because of increased right-sided ear and neck pain. His neck is supple, with 1-cm tender anterior cervical lymph nodes bilaterally. He has normal range of motion at the neck without any stiffness, but he complains of pain when looking upward with cervical extension. The rest of his examination findings are unremarkable. A radiologic study reveals the diagnosis.

### Case 1 Discussion

The boy's serum vitamin B<sub>12</sub> value was less than 60 pg/mL (44 pmol/L) (normal, 187 to 1,059 pg/mL [138 to 781 pmol/L]), confirming a diagnosis of megaloblastic anemia caused by vitamin B<sub>12</sub> deficiency. His red blood cell folate concentration was 256 ng/mL (579 nmol/L) (normal, 160 to 714 ng/mL [362 to 1,617 nmol/L]). Additional questioning revealed that he had not received prophylactic vitamin B<sub>12</sub> since his gastrectomy 6 years ago.

Macrocytic anemias, defined as an MCV greater than 100 fL, are rare. Megaloblastic anemia is defined as a macrocytic anemia associated with macro-ovalocytosis and hypersegmented neutrophils. Importantly, not all macrocytic anemias are megaloblastic. Macrocytosis without macro-ovalocytes and hypersegmented neutrophils defines a normoblastic anemia, causes of which include increased immature cells (identified by an increased reticulocyte count) and Diamond-Blackfan anemia.

### Differential Diagnosis

The differential diagnosis of megaloblastic anemia includes vitamin B<sub>12</sub> and folate deficiency. Both vitamins are involved in DNA synthesis, and their absence leads to ineffective erythropoiesis. There is marrow erythroid hyperplasia but also reticulocytopenia because the precursors die

in the marrow. Granulocytes and megakaryocytes also may be involved, leading to neutropenia and thrombocytopenia. Various drugs, including zidovudine, 6-mercaptopurine, cytosine arabinoside, azathioprine, and hydroxyurea, also can cause megaloblastic anemia. Rarely, orotic aciduria, Lesch-Nyhan syndrome, and thiamine-responsive megaloblastic anemia present in infancy with normal vitamin B<sub>12</sub> and folate values.

Folate is absorbed rapidly in the jejunum. Deficiencies can result from dietary inadequacy. Sources of folate include fruit and green leafy vegetables, liver, and fortified flour. Human milk is adequate, although raw goat milk is deficient. Other causes of folate deficiency include disorders leading to impaired absorption, such as inflammatory bowel disease. Folate antagonists, such as methotrexate and trimethoprim, can cause deficiency, as can several rare genetic enzyme or receptor deficiencies. Phenobarbital and phenytoin generally do not cause clinical deficiency, although increased folate supplementation is recommended for pregnant women receiving anticonvulsants to reduce the risk of neural tube defects.

Rare causes of folate deficiency include severe eczema, exfoliative dermatitis, and chronic hemolysis because of increased cellular turnover and DNA synthesis in these conditions. Diagnosis is made by measuring erythrocyte folate because serum concentrations are variable. Folate storage is limited, and deficiency develops within 2 to 3 months of a dietary deficit.

### The Condition

Dietary vitamin B<sub>12</sub> is complexed with binding proteins in saliva and gastric juices, then liberated in the duodenum by pancreatic proteases,

#### Frequently Used Abbreviations

<b>ALT:</b>	alanine aminotransferase
<b>AST:</b>	aspartate aminotransferase
<b>BUN:</b>	blood urea nitrogen
<b>CBC:</b>	complete blood count
<b>CNS:</b>	central nervous system
<b>CSF:</b>	cerebrospinal fluid
<b>CT:</b>	computed tomography
<b>ECG:</b>	electrocardiography
<b>ED:</b>	emergency department
<b>EEG:</b>	electroencephalography
<b>ESR:</b>	erythrocyte sedimentation rate
<b>GI:</b>	gastrointestinal
<b>GU:</b>	genitourinary
<b>Hct:</b>	hematocrit
<b>Hgb:</b>	hemoglobin
<b>MRI:</b>	magnetic resonance imaging
<b>WBC:</b>	white blood cell

where it binds with intrinsic factor (IF), which is derived from gastric parietal cells. This complex is absorbed in the ileum, is bound to a plasma carrier (transcobalamin II [TCII]), enters the cells, and is converted to active forms.

Because vitamin B<sub>12</sub> is widely available in animal food sources, dietary deficiency usually occurs only in individuals consuming a vegan diet. Because of relatively large hepatic stores, it can take years for clinical deficiency to manifest, as demonstrated in this patient.

Other causes of vitamin B<sub>12</sub> deficiency include any abnormalities of the previously mentioned pathway. Congenital pernicious anemia is an autosomal recessive disorder resulting from abnormal or deficient IF, with symptoms beginning near the end of the first postnatal year. This condition differs from juvenile pernicious anemia, which includes gastric atrophy and achlorhydria and is believed to be an autoimmune disorder resulting from antiparietal cell and anti-IF autoantibodies, similar to the adult form. There may be associated immunologically mediated endocrine deficiencies. Both forms of pernicious anemia are relatively uncommon in childhood.

Gastric disorders (gastrectomy, gastritis) also may result in absent IF and clinical vitamin B<sub>12</sub> deficiency. Pancreatic insufficiency can cause vitamin B<sub>12</sub> deficiency by impairing cleavage and IF complex formation. Disorders of the distal small intestine can impair absorption of the vitamin B<sub>12</sub>-IF complex and include inflammatory bowel disease, celiac disease, ileal resection, and bacterial overgrowth. Rare cases of abnormalities of the vitamin B<sub>12</sub>-IF receptor in the terminal ileum have been described, and affected individuals also may have proteinuria. In endemic areas, infection with the fish tapeworm

*Diphyllobothrium latum* can result in a deficiency.

When vitamin B<sub>12</sub> absorption is normal, deficiencies of the TCII transport protein can occur. These conditions usually are inherited in an autosomal recessive pattern and present in early infancy. Serum vitamin B<sub>12</sub> concentrations typically are normal, and diagnosis is made by demonstrating reduced TCII values. Other causes of vitamin B<sub>12</sub> deficiency that should be apparent from the history include medications such as proton pump inhibitors, neomycin, and metformin.

Symptoms of vitamin B<sub>12</sub> deficiency relate to the anemia and include pallor, fatigue, decreased appetite, and irritability. Glossitis, a smooth painful tongue, is characteristic. There may be coexisting neurologic symptoms (absent in folate deficiency) as a result of posterior and lateral spinal column degeneration. These effects include ataxia, paresthesias, and difficulty walking. Decreased reflexes, vibration, and position sense may be found. Late stages may be characterized by altered mental status. Neurologic changes may coexist with anemia or occur in its absence.

### Diagnosis

Vitamin B<sub>12</sub> deficiency anemia is diagnosed by recognizing the classic findings of megaloblastic anemia (macrocytosis with hypersegmented neutrophils) and is confirmed by low serum vitamin B<sub>12</sub> values. Increased serum lactate dehydrogenase and bilirubin concentrations are usual findings, reflecting ineffective erythropoiesis. Methylmalonic acid is elevated in the urine, but is low in folate deficiency. Homocysteine is elevated, and the reticulocyte count is low (for the degree of anemia). Thrombocytopenia and neutropenia frequently are associated, although

such findings indicate the need to scrutinize the peripheral smear to rule out other conditions. A bone marrow examination may be indicated to exclude disorders such as acute myeloid leukemia or aplastic anemia.

The specific cause can be determined by considering the differential diagnosis in the individual patient. Pernicious anemia can be tested for by examining for antibody to IF. The classic Schilling test no longer is regarded as the diagnostic test.

### Treatment and Prognosis

Treatment of this deficiency is via parenteral administration of vitamin B<sub>12</sub>, unless the cause is dietary deficiency. Clinical response usually follows the administration of 100 to 1,000 mcg intramuscularly daily for 1 to 2 weeks, followed by 50 to 1,000 mcg monthly. For an individual undergoing complete gastric or ileal resection, vitamin B<sub>12</sub> should be started prophylactically. Where there is uncertainty, close follow-up is mandated. Surveillance must continue long-term because typical hepatic storage allows for a delay in clinical presentation of up to 5 years in cases of malabsorption and up to 20 years in dietary deficiency.

Following treatment, reticulocytosis should occur within 72 hours, followed by an increase in Hgb within 7 to 10 days and a subsequent decreased MCV. Potassium concentrations should be monitored in cases of severe anemia because significant hypokalemia may develop as a result of potassium incorporation into new cells. Neurologic symptoms resolve much more slowly, over the next 6 months, but can be irreversible. Therefore, prevention in a susceptible child, as described here, is warranted.

### Lessons for the Clinician

This case emphasizes the importance of a careful history, which immediately led to the suspected diagnosis. Any child undergoing gastric or distal ileal resection should receive vitamin B<sub>12</sub> prophylactically. Examination of the red blood cell indices, including MCV and MCH, and a peripheral smear can give valuable clues as to the cause of the anemia. (*Susanna Martin, MDCM, FRCP(C), Royal University Hospital, University of Saskatchewan, Saskatoon, Saskatchewan, Canada*)

### Case 2 Discussion

Because of the history of daytime sleepiness, the girl was referred to a sleep specialist. She underwent overnight polysomnography (PSG) and a multiple sleep latency test (MSLT), which demonstrated a pattern diagnostic of narcolepsy.

PSG records a number of physiologic measures during sleep, including EEG activity; eye, chest wall, and leg movements; oxygen saturation; and electrocardiographic activity. In narcolepsy, overnight PSG documents that the patient had enough sleep time before the MSLT and rules out other sleep disorders that may interfere with sleep quality. Specifically, no findings should suggest obstructive or central apnea events that could interfere with the patient's quality of sleep and induce daytime sleepiness. Other abnormalities that should be ruled out on PSG include seizures and periodic limb movements.

The MSLT should demonstrate objectively the degree of daytime sleepiness in the child by providing four or five regularly scheduled nap opportunities, each separated by approximately 2 hours. EEG demonstrating sleep-onset rapid eye movement (REM) periods (SOREMPs) in

two or more naps is considered suggestive for narcolepsy. SOREMPs are diagnosed when REM sleep occurs within 15 minutes of sleep onset. MSLTs are not validated in children younger than age 8 years.

### The Condition

Narcolepsy is defined as a disorder of daytime sleepiness combined with cataplexy, hypnagogic hallucinations, and sleep paralysis. The condition affects 1 in 2,000 people (equally across sexes) and is diagnosed most commonly in the teens or early 20s. The condition has been diagnosed in children as young as 5 years of age. Many people who have narcolepsy demonstrate only two or three of the characteristic symptoms:

- **Daytime Sleepiness:** Any school-age child who regularly falls asleep during a 30-minute car ride or while watching television or who requires a nap after school suffers from inappropriate daytime sleepiness. Such children should be evaluated for a sleep disorder that affects their sleep quality.
- **Cataplexy:** Cataplexy should be suspected when a child describes suddenly falling or completely losing all muscle tone associated with some strong emotion. This patient described such an episode associated with the excitement of being involved in her first soccer game. These "drop attacks" tend to become more frequent when the child is suffering from an intercurrent illness.
- **Hypnagogic Hallucinations:** These vivid, frequently unpleasant hallucinations occur just before the onset of sleep. The hallucinations may be simple (seeing colored shapes or hearing unexplained noises) or complex (hearing threatening statements or having the sensation of being touched by someone or

something). They are made more terrifying when accompanied by sleep paralysis, which is the feeling that the child cannot move. Some patients who have narcolepsy suffer from hypnopompic hallucinations, which are similar but occur just on waking from sleep.

- **Sleep Paralysis:** Patients may describe a feeling of being unable to move certain parts of their bodies or to speak just before falling asleep or on waking. This sensation can be especially frightening when combined with hypnagogic or hypnopompic hallucinations.

The differential diagnosis for narcolepsy should include other causes of excessive daytime sleepiness. Social stresses and recent changes (eg, divorce, new baby, foster care) that may interfere with sleep quantity or quality should be explored. Similarly, obstructive sleep apnea syndrome and circadian rhythm disorders may present with poor nighttime sleep and daytime sleepiness. Many medications, such as those used for epilepsy and behavior disorders, may cause drowsiness. Daytime sleepiness can be confused with attention-deficit/hyperactivity disorder, epilepsy (especially absence seizures), depression, or learning disability. The drop attacks of cataplexy may look very similar to atonic seizures.

### Diagnosis

Narcolepsy ideally is diagnosed by combining overnight PSG with an MSLT the following day. The PSG should rule out sleep apnea and many other causes of daytime sleepiness. It also may show an earlier-than-normal entry into REM sleep. The MSLT assesses the severity of excessive daytime sleepiness and whether the patient's naps involve REM sleep. The appearance of REM sleep



in at least two naps is highly suggestive of narcolepsy.

### Treatment

The treatment of narcolepsy involves lifestyle modifications as well as medications. Affected children are encouraged to adhere to regular sleep and wake times. In addition, allowance must be made for them to take one or two planned 30-minute naps during the day. This adjustment may require modifications to the school schedule. The naps should occur in a quiet, dark room that feels comfortable to the child.

Medications are used in conjunction with these lifestyle changes to increase daytime alertness. The mainstay of pharmacologic treatment for daytime sleepiness for affected patients is stimulant therapy. Methylphenidate and dextroamphetamine have been used widely, with great success, to treat excessive daytime sleepiness that is associated with narcolepsy. Newer once-daily formulations have made these medications more convenient to use. Modafinil is an attractive new therapy because of its safety profile and its being an uncontrolled substance. However, it is a very expensive alternative and has not been approved by the United States Food and Drug Administration for use in children. Other medications, including tricyclic antidepressants, venlafaxine, fluoxetine, and gamma-hydroxybutyrate, have been used in treating cataplexy in adults, with limited off-label use in children.

### Lessons for the Clinician

Any child who has excessive daytime sleepiness (which can manifest as drowsiness, inattention, or hyperactivity) should be evaluated for a sleep disorder. The history and physical examination should rule out the common causes such as behaviorally

induced insufficient sleep syndrome, circadian rhythm disorder, medication effects, and other conditions. Although uncommon, narcolepsy is underdiagnosed in children, and a significant proportion of patients diagnosed in adulthood have had symptoms in childhood. Any child suspected of having narcolepsy should be referred to a sleep specialist for additional evaluation. Narcolepsy is a lifelong condition with psychosocial consequences that can be managed, although not cured, with medication and lifestyle changes. (Kellie Waters, MD, Stollery Children's Hospital, Edmonton, Alberta, Canada)

### Case 3 Discussion Differential Diagnosis

Pharyngitis due to viral or bacterial agents (Epstein-Barr virus, group A *Streptococcus*, *Neisseria gonorrhoeae*), retropharyngeal abscess, peritonsillar abscess, and epiglottitis were considered in the differential diagnosis. Because the patient was alert and in adequate control of his airway, the decision was made to obtain a lateral radiograph of the soft tissues of the head and neck (Fig. 1). Compared with a radiograph from 4 months prior (Fig. 2), obtained following a motor vehicle crash, development of thickening of the epiglottis and the aryepiglottic folds was noted, consistent with a "thumb sign" and a diagnosis of epiglottitis.

### The Condition

Epiglottitis is inflammation of the epiglottis, aryepiglottic folds, and other supraglottic tissues. Today, no predominant infectious agent causes epiglottitis in the United States. In the pre-Hib vaccine era, almost all cases were caused by Hib. Rarely, fully vaccinated children may develop Hib epiglottitis, but inadequately immunized individuals (eg,

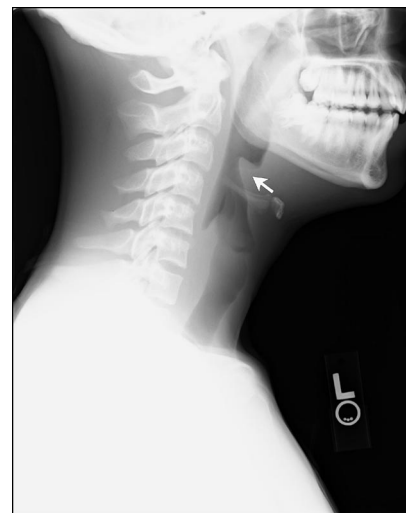


Figure 1. Lateral neck radiograph showing an enlarged epiglottis protruding from the anterior wall of the hypopharynx (the "thumb sign"). The hypopharynx appears dilated and the cervical spine straightened instead of the usual mild cervical lordosis.

immigrants) are at higher risk. Other bacterial causes include *H influenzae* nontype b strains; *Streptococcus pneumoniae*; *Staphylococcus aureus*, and beta-hemolytic streptococci groups A, B, and F. Group A *Streptococcus*



Figure 2. Lateral neck radiograph of the same patient obtained 4 months earlier shows normal epiglottis, hypopharynx, and normal cervical lordosis.



epiglottitis has been reported as a complication of varicella infection. Although the incidence of CA-MRSA is on the rise, this organism has not been associated with increased cases of epiglottitis. Sexually transmitted infections have not been reported as causes of epiglottitis. *Pseudomonas aeruginosa* and *Candida* sp may be associated rarely with epiglottitis in immunocompromised hosts. Viral causes include herpes simplex type 1, parainfluenza type 3, and influenza B. Noninfectious causes of thermal injury, specifically corrosive ingestion, posttransplantation lymphoproliferative disease, and graft versus host disease, also have been reported in children.

The peak age of affected individuals during the pre-Hib vaccine era was 3 years; today, the median age is older than 10 years. (1)(2)(3)(4) Adults also can suffer from epiglottitis, with a somewhat different presentation. Abrupt onset and rapid progression of fever, sore throat, dysphagia, drooling, and toxic appearance are the hallmarks in children. The affected child experiences a choking sensation and is anxious, restless, and irritable. Speech is muffled, often described as a “hot potato” voice. Hoarseness and stridor may be present. The child usually assumes a sitting position, with the trunk leaning forward, neck hyperextended, and chin thrust forward in an effort to maximize the diameter of the obstructed airway. As the disease progresses, airway obstruction can advance to the point of hypoxia, hypercapnia, and acidosis that can lead to cardiorespiratory arrest and death. Interaction with the child suspected of having epiglottitis should minimize anxiety and stress. Adults afflicted with epiglottitis are less toxic-appearing and less likely to have

dyspnea, fever, or cough. They tend to complain more of painful swallowing and neck pain.

### Diagnosis

The diagnosis of epiglottitis must be considered clinically and subsequently confirmed by the appearance of the fiery red, edematous epiglottis. Unnecessary physical examination and diagnostic testing should be omitted in the general pediatric clinic; cardiorespiratory arrest has occurred during such efforts. The epiglottis must be viewed in a controlled setting, typically by an otolaryngologist with continuous monitoring by clinicians (eg, anesthesiologists) able to perform resuscitation, including tracheal intubation. In an older child who is stable and able to open the mouth adequately without the use of a tongue blade, inspection of the posterior pharynx and epiglottis in a controlled setting may be possible.

A classic teaching point is that radiologic studies should *not* be obtained prior to viewing the epiglottis and establishing an artificial airway in a controlled setting for individuals in whom epiglottitis is strongly suspected based on clinical findings. In this particular case, clinical judgment guided the decision to obtain radiographs because the adolescent was cooperative and stable and the diagnosis less certain. If a lateral neck radiograph is obtained, it displays an enlarged epiglottis protruding from the anterior wall of the hypopharynx (the “thumb sign”). The hypopharynx may appear dilated and the cervical spine straightened instead of having the usual mild cervical lordosis.

Again, obtaining such radiographs or attempting additional gross inspection in the general pediatric clinic can lead to delays in management or life-threatening compli-

cations and should be undertaken only after strong consideration of the risks. The etiologic diagnosis is confirmed by culture of a pathogenic organism from the blood or the surface of the epiglottis. Cultures are obtained only after the airway is secured.

### Treatment and Prognosis

Key aspects of treating acute epiglottitis are maintaining the airway and administering the appropriate antimicrobial agent. The recommended practice has been to establish an artificial airway as soon as possible. Tracheotomy is reserved for instances in which intubation cannot be accomplished due to severe epiglottic edema. Patients who are not intubated, as in this case, must be monitored closely.

Antibiotic therapy should be initiated before the results of cultures are available. Preferred regimens include one of the following antimicrobials: oxacillin, nafcillin, cefazolin, clindamycin, or vancomycin PLUS a third-generation cephalosporin. Once culture and susceptibility results are available, the regimen should be adjusted to provide optimal coverage for the isolated organism. The optimal duration of therapy is unknown and typically is guided by patient response, although it usually is 2 to 4 days (until extubation), after which antibiotics can be continued orally. Most patients recover completely. Most deaths are the result of cardiorespiratory arrest or delays in securing the airway.

This patient was hospitalized, monitored closely, and started on intravenous clindamycin and ceftriaxone. A contrast computed tomography scan confirmed the diagnosis of epiglottitis. Surface cultures of the

epiglottitis were obtained during endoscopy by the otolaryngologist. After 3 days, the patient was discharged on oral clindamycin, dexamethasone, and ibuprofen, with symptoms virtually resolved. The cultures did not grow any organisms, and the underlying cause of the epiglottitis remained undetermined.

### Lessons for the Clinician

Although clinicians in the United States in recent times do not have much, if any, experience with epiglottitis, they still need to be aware of its presentation and treatment. Epiglottitis is a potentially life-threatening illness, and proper man-

agement is crucial. Classic teaching warns that the child who is suspected of having epiglottitis should undergo immediate endoscopy under controlled circumstances for examination and stabilization of the airway by an experienced clinician. The older child may have a less toxic appearance, but still requires aggressive monitoring and treatment due to the risk of respiratory compromise. (Miriam K. Perez, MD, West Virginia University School of Medicine, Morgantown, W.V., Bradley T. Kleiman, MD, AP&S Pediatrics, Terre Haute, Ind., Linda S. Nield, MD, West Virginia University School of Medicine, Morgantown, W.V.)

### References

1. Faden HS. Treatment of *Haemophilus influenzae* type b epiglottitis. *Pediatrics*. 1979;63:402–407
2. Cohen SR, Chai J. Epiglottitis. Twenty-year study with tracheotomy. *Ann Otol Rhinol Laryngol*. 1978;87:461–467
3. Gorelick MH, Baker MD. Epiglottitis in children, 1979 through 1992. Effects of *Haemophilus influenzae* type b immunization. *Arch Pediatr Adolesc Med*. 1994;148:47–50
4. Shah RK, Roberson DW, Jones DT. Epiglottitis in the *Haemophilus influenzae* type B vaccine era: changing trends. *Laryngoscope*. 2004;114:557–560

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# In Brief

## Achondroplasia

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### Author Disclosure

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**Health Supervision for Children With Achondroplasia.** American Academy of Pediatrics: Clinical Report. *Pediatrics*. 2005;116:771-783

**Achondroplasia.** Horton WA, Hall JG, Hecht JT. *Lancet*. 2007;370:162-172

**Mortality in Achondroplasia Study: A 42-Year Follow-Up.** Wynn J, King TM, Gambello MJ, et al. *Am J Med Genet*. 2007;143A:2502-2511

**Weight for Age Charts for Children with Achondroplasia.** Hoover-Fong JE, McGready J, Schulze KJ, et al. *Am J Med Genet*. 2007;143A:2227-2235

Achondroplasia is the most common of the skeletal dysplasias and the most common condition associated with disproportionate short stature. The incidence is 1 in 10,000 to 1 in 30,000 live births, with more than 250,000 people affected worldwide. The disorder is transmitted as an autosomal dominant trait with complete penetrance. However, in more than 75% of affected infants, achondroplasia results from a new mutation. The genetic defect in more than 95% of cases is an arginine-

for-glycine substitution in amino acid 380 in the gene, mapped to band 4p16.3, that codes for fibroblast growth receptor 3 (FGFR3). This substitution results in a gain of function of the *FGFR3* gene and decreased endochondral ossification and chondrocyte inhibition in growth plate cartilage. Advanced paternal age, especially older than 35 years, has been associated in sporadic cases. Homozygous mutation is fatal. A rare mutation leads to a condition known as severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN). Hypochondroplasia is a milder form of achondroplasia.

Fetal diagnosis often is suspected when long-bone foreshortening is discovered during third-trimester ultrasonography. However, families may be counseled inaccurately because other explanations for the ultrasonographic findings exist. Molecular diagnosis is available for confirmation. At birth, the condition can be confirmed radiologically with a skeletal survey that shows a contracted skull base, square-shaped long bones, trident hands, proximal femur radiolucency, and rhizomelic (proximal segment) long-bone shortening. Additional clinical features that aid in the diagnosis of newborns include macrocephaly and frontal bossing. The diagnosis has been delayed in up to 20% of patients when the condition is not suspected at birth. Additional characteristics noted during the first postnatal year include hypotonia and delay in motor development, although normal development usually is achieved eventually.

Life expectancy can reach close to the average, but newer evidence adds to the concern that age-specific mortality is increased at all ages. Abnormal

linear bone growth leads to many predictable complications, some of which can be modified through anticipatory guidance and close monitoring.

Neurologic complications are the most concerning. Infants have large heads and can develop craniocervical junction narrowing. Spinal cord compression at the cervical medullary junction can lead to sudden death in infancy and, more commonly, causes hypotonia, which leads to developmental motor delays. Mechanical swings and carrier slings must be avoided to minimize movement of the infant's head. Surgical suboccipital decompression is indicated for lower limb hyperreflexia, clonus, and central hypopnea on polysomnography. Head size measurements and, if indicated, head ultrasonography are recommended at birth and regularly during early childhood to monitor ventricular size due to the risk of hydrocephalus. Vertebral bodies have short pedicles and narrow interpedicular distance. The spinal canal size decreases in relation to the size of the spinal cord as patients age, which can lead to lumbar spinal stenosis. Indications for laminectomy include claudication and lower extremity hyperreflexia.

Among the orthopedic complications are thoracolumbar gibbus deformity (hump), which typically develops by 4 months of age. Bowing of the lower extremities is present early, and external rotation of the hips, typically seen at birth, resolves after the patient begins to bear weight. Persistent kyphosis worsens with age, exacerbating spinal stenosis.

Brainstem compression may lead to central apnea, and midface underdevelopment can lead to obstructive apnea. Tonsil and adenoid tissue can obstruct

breathing by restricting space, and patients may benefit from tonsillectomy. Respiratory dysfunction can result in abnormal gas exchange and is associated with increased risk for cognitive deficits. Patients who have achondroplasia otherwise typically would have near-normal intelligence. Eustachian tubes are short, and recurrent otitis media is common. Some degree of conductive hearing loss is found in up to 40% of affected adults. Speech delay and problems with articulation can result.

Obesity is common and particularly troublesome for the patient who has achondroplasia because it worsens lumbar lordosis and contributes to a higher rate of cardiac morbidity. Early degenerative joint disease and upper

airway obstruction are exacerbated by obesity. Weight-for-height-and-age growth curves have been developed specifically for patients who have achondroplasia, and consultation with a dietitian is recommended.

Growth hormone has been used in clinical trials, but its long-term benefits are questionable, and such therapy currently is not recommended. Limb-lengthening surgical procedures are somewhat effective yet arduous and, therefore, controversial. Research into FGFR3 tyrosine kinase inhibitors is underway with animal models; success has been limited thus far.

**Comment:** Dr Stratbucker outlines the anticipatory guidance and surveillance that pediatricians must perform

to identify and prevent morbidity early. Pediatricians also must be aware of the psychosocial issues that children who have achondroplasia may face, such as the potential for low self-esteem and mental health issues. Referral to family support groups such as the Little People of America Web site at [www.lpaonline.org](http://www.lpaonline.org), or introduction of families to others who have children of short stature may be helpful. Implementing home and school adaptations can help a child of shorter stature to function independently, and occupational therapists can be of assistance.

*Janet R. Serwint, MD*  
Consulting Editor

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# Cultural Influences on Infant Feeding Practices

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**Objectives** After completing this article, readers should be able to:

1. Provide examples of specific cultural beliefs and traditions that affect infant feeding practices.
2. Describe the influence of acculturation in the United States (US) on infant feeding practices among immigrant mothers.
3. Recognize the problem of infant overfeeding among particular groups.
4. Outline a culturally sensitive approach to elicit personal and cultural beliefs regarding infant feeding and to provide effective infant feeding counseling for mothers from different cultural backgrounds.

*“... all different cultures, whether in a tropical village or in a highly urbanized and technologically sophisticated community, contain some practices and customs which are beneficial to the health and nutrition of the group, and some which are harmful. No culture has a monopoly on wisdom or absurdity.”* *Jelliffe D. Child Nutrition in Developing Countries: A Handbook for Fieldworkers. Washington, DC: United States Public Health Service; 1968*

## Introduction

Healthy infant feeding practices, including exclusive breastfeeding and delayed introduction of complementary foods, are promoted by health clinicians as well as by numerous national and international organizations. However, mothers base their infant feeding decisions on an array of factors, including their experiences, family demands, socioeconomic circumstances, and cultural beliefs.

As the number of children from immigrant families in the US increases, more pediatric clinicians are working not only with families of color who have a long heritage of living in the US spanning many generations, but also with families new to the US whose cultural backgrounds are markedly different from their own. Health professionals are faced with a growing challenge to appreciate the cultural beliefs influencing infant feeding practices for both recent immigrants as well as for resident US ethnic groups. Discussions regarding infant feeding often are the initial interaction between clinician and mother and, as such, are important in building a foundation of trust and rapport necessary for successful well child visits leading to optimal development of the infant through childhood.

This article illustrates cultural influences on infant feeding practices through four cases and reviews the evidence for effective, culturally appropriate interventions to improve infant feeding.

## Case Study 1: Breastfeeding Initiation

*The mother of a term 18-hour-old infant girl who is rooming in requests a bottle of formula. Although she plans to breastfeed, she does not want to put her infant to the breast in the first 2 days after birth, saying she just “doesn’t have enough milk.” After starting to develop a rapport with the mother, you inquire about her family support and learn that although her husband provides help, her own mother and extended family are in their native country. You probe further and ask about her personal experience with infant feeding, what makes her feel that she does not have adequate human milk, her understanding of the benefits of breastfeeding, and how you can support her and her newborn.*

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## Immigrants to the US

Across racial and ethnic groups, foreign-born mothers, particularly those from low-income countries, generally possess higher breastfeeding initiation and duration rates than do US-born mothers, even after accounting for socioeconomic and demographic differences. (1) Factors that facilitate acculturation, such as longer residence in the US, maternal US birth, and decreased maternal use of native language, affect breastfeeding rates negatively. (2)(3) Children whose Hispanic parents were born outside of the US have a greater likelihood of being breastfed, with the odds of breastfeeding reduced by 4% for each year that the parents reside in the US. (2)

**COLOSTRUM AND PRELACTEAL FEEDINGS.** Many of the world's infants are given liquids other than mother's milk in the first few days after birth, including those who eventually are breastfed exclusively. This practice of feeding infants nonmilk liquids before the first breastfeeding stems from concerns about the nutritional value of and the cultural taboos against colostrum. Although immunologic and nutritional benefits of colostrum are evident from scientific literature, its thinner consistency and yellowish color (compared with the later human milk) likely encourages these beliefs. Also, some groups believe that feeding sugared water, honey, teas, sweet oils, or butter "cleanses" the newborn's gut by promoting the elimination of meconium, which is believed to be harmful.

Prelacteal fluids fed in some traditional societies described in the literature are listed in Table 1. Infants in Durango, Mexico, have been reported to be fed an infusion of sugar water mixed with herbs 30 minutes after birth because mothers believe their milk is muy fuerte (too strong) for the baby. In Vietnam, colostrum

often is viewed to be "old milk" and discarded, and infants are fed either ginseng herbal-root tea or boiled sugar water for the first 2 to 3 postnatal days. In several African countries, common water-based prelacteal feedings given to infants in the first 3 postnatal days include sugar water, water, salty liquids, and teas as well as milk, porridge, and honey.

Although high rates of hospital deliveries make it unlikely that US-born infants will be fed prelacteal fluids in the first few days, early home discharge still raises the possibility of prelacteal fluids being fed at home. Honey is a common prelacteal feeding for many cultures, and clinicians may be unaware of such practices unless they specifically ask about its use at home to screen for the risk of infantile botulism. In addition, an underlying cultural acceptance of prelacteal feedings and avoidance of colostrum leads to delayed breastfeeding and more requests for formula to feed the newborn. Both factors interrupt the hormonal feedback to stimulate human milk production, setting up the mother for inadequate human milk production. Consistent messages regarding the benefits of early breastfeeding coupled with lactation support and the discouragement of formula supplements have been shown to increase initiation rates of breastfeeding.

**HOT AND COLD CLASSIFICATION.** A classification of foods as hot and cold prevails worldwide among many cultural groups and affects the desire to breastfeed the newborn. Traced to roots in ancient India, the "hot-cold" concepts are prevalent in many areas of the world, including parts of southeast Asia (more widely known as the Chinese principle of yin/yang or am/duong in Vietnam) and through Central and South America (simply referred to as caliente/frio). Inherent in this classification

Table 1. Examples of Prelacteal Feedings Given to Infants

Culture/Geographic Area	Liquids or Foods
Migrant farm workers in northern Colorado	Sugar water, water, juice, milk
Jamaica	Sugar water, mint tea, castor oil drops
Mayan-Indians in the Yucatan	Sugar water
Mexico, rural	Sugar water and freshly picked, unwashed herbs, Manzanilla (chamomile) or oregano tea with sugar (4)
Egypt	Sugar or caraway water, herbal teas, dried seeds with sugar (5)
Somalia	Sugar water, goat milk, other livestock milk, reconstituted powdered milk
Eastern Uganda	Sugar water, salty water, water, milk, porridge, honey (52%)
Zaire	Premasticated rice, mashed or pounded rice, infant formula
Rural India	Honey, butter, diluted animal milk, sugar, water, jaggery (crude brown sugar)
Vietnam	Ginseng tea, herbal-root tea or boiled sugar water (6)
This table is not meant to be comprehensive but to cover a few ethnic groups and to demonstrate the diversity of beliefs regarding prelacteal foods.	

is a belief that a state of health depends on a balance of bodily forces. Health is viewed to be a state of equilibrium between hot and cold and wet and dry. In accordance with the Greek theory of body humors and the philosophies of Confucianism and Taoism, a person's vital force, or qi, is at risk if exposed to excessive cold or heat, leading to specific types of illness.

Following this "hot-cold" belief system, some Asian mothers consider pregnancy a state of excessive heat for the body, with birth signifying an important loss of heat that leaves the mother in a vulnerable state. Cold foods are avoided in the postpartum period, and a variety of heating rituals and foods are described to help the mother regain her balance. The production of human milk requires much of this vital energy, and an "imbalanced" maternal body is believed to produce unhealthy human milk. Lack of family support for traditional postnatal heating rituals and specially prepared healing foods lead many immigrant mothers, particularly those from China and Southeast Asia, to switch to infant formula for fear that the lactating mother will suffer from a cold disease and the baby may not have access to abundant, healthy milk. In this way, the inability to continue culturally prescribed postpartum practices that are linked intimately to cultural beliefs about maternal health and production of nutritious human milk underlie the growing rates of formula supplementation among many of these immigrant mothers. Such cultural beliefs run strong among certain groups, and the clinician is more likely to be successful in counseling the parents by first identifying such belief systems and then working with the family on identifying how traditional healing and nutrition may occur simultaneously with breastfeeding.

**POSTPARTUM SUPPORT.** Called different names in different cultures—afatanbah/Umol bah in Somalia, d'sai kchey in Cambodia, and Chollish din in Bengali—many societies practice a 30- to 40-day postpartum period of intensive family support that keeps the mother and infant indoors to receive healing rituals and nurturing. Such practices have supported postpartum maternal survival in less advantaged societies. This period also permits sanctioned support by family and friends to help the mother and infant focus on bonding and breastfeeding. Migration to the US without establishment of a new supporting community disrupts this cultural network of support, and the lack of this support system has been identified as an important factor inducing some immigrant women to abandon breastfeeding.

The immediate postpartum period of support also is viewed by many cultures as a means to protect the mother and baby from the "evil eye." Human milk is regarded as a source of nurturance that is vulnerable to becoming tainted by a "shadow" or "evil eye" encountered while outside the home, which would be detrimental to the nursing infant. Mothers may be compelled by family members to stop breastfeeding for fear that such tainted milk may cause their children to fall ill.

### Ethnic Groups of US Heritage

**AFRICAN AMERICANS.** African American mothers have lower rates of breastfeeding than do other US ethnic groups, but similar to European Americans, breastfeeding is more likely to occur among African American mothers who are older, married, and possess high levels of education. Cultural and personal influences overlay these factors significantly, as observed by ethnographic studies of low-income African American women. Inner-city African American women are likely to have been raised without ever witnessing an African American mother breastfeed an infant within their family or community. (7) Without the presence of breastfeeding role models and family and friends with whom to share personal experiences, myths about negative effects and the physical pain associated with nursing further fuel a tradition of formula feeding.

In-depth ethnography also reveals a value for independence among inner-city, low-income African American mothers, interpreted as a culturally evolved response to the daily unpredictable stresses and losses in life. Breastfeeding, therefore, is viewed to foster the baby's early dependence on the mother, which potentially would lead to an overly "needy" or "spoiled" personality. Such cultural and experiential barriers to breastfeeding are unlikely to be addressed in a medical environment where physicians are seen as not understanding or not able to relate to the mothers' financial concerns or personal experiences.

**HISPANICS.** Although Hispanic mothers in the US are more likely to breastfeed than are their white or African American counterparts, these rates are significantly lower than rates in Mexico, where most of the US Hispanic population originated. (8) A survey of Mexico in 1999 showed high breastfeeding rates, with more than 90% of mothers initiating breastfeeding and 33% of mothers still breastfeeding their children at 1 year postpartum. (9) Acculturation, commonly measured by using indicators

such as duration of US residence or language use, has a significant influence on breastfeeding rates, with less acculturated women being more likely to breastfeed exclusively. (10) US-born Mexican women are more likely to supplement breastfeeding with formula and more likely to discontinue any breastfeeding compared with Mexican-born women who have immigrated to the US. Interestingly, measures of income have little or no impact on breastfeeding compared with the impact of having lived in the US for more years. (11)

It is important for clinicians and lactation consultants to be aware that cultural beliefs discouraging breastfeeding also may exist in the setting of relatively high breastfeeding rates. Some mothers may believe that negative maternal emotions can taint the mother's milk. (12) Women of Mexican descent may be influenced by traditional beliefs and reduce or cease breastfeeding if they encounter folk illnesses associated with anger or fright (*coraje, susto*) because of concern that emotions can be transferred via maternal milk and harm the infant or cause diarrhea in the infant. (13)

Finally, cultural influences on breastfeeding vary widely by specific group because Hispanic people comprise a widely heterogeneous population. For example, lower rates of breastfeeding are reported among women of Puerto Rican compared with women of Mexican heritage. The association between acculturation and breastfeeding patterns varies by country of origin and may not be significant in all subgroups, possibly due to differing measures of acculturation, native beliefs and practices, and varying responses to acculturation. (14) (15)(16)

### Suggestions for Counseling and Newborn Feeding Support

**GENERAL APPROACH TO COMMUNICATION.** The first step in effective infant feeding counseling is to reach a common understanding between the mother's and the clinician's perspectives, which involves a communication approach that is open-ended and empathetic. The mother may not reveal cultural beliefs with initial closed-ended questions if she feels that the US clinician might not understand or agree with traditional perspectives on breastfeeding. The practice of nonjudgmental probing with an open-minded, interested approach and more time spent listening to the mother's point of view regarding infant health and nutrition early in the clinician-patient discussions will unveil obstacles to breastfeeding. Once this common ground of understanding is reached, effective direct discussions about infant feeding and

other topics regarding infant care can be based on a stronger foundation of trust and understanding.

**PRENATAL APPROACHES.** Breastfeeding counseling during prenatal care visits can be key to preparing and educating mothers to breastfeed. (17) Several studies have supported the positive impact of prenatal counseling on breastfeeding initiation, exclusivity, and duration. (17)(18)(19) Prenatal care clinicians and newborn nursery nurses, therefore, may play critical roles in promoting and supporting breastfeeding as the preferred method of infant feeding. Furthermore, breastfeeding counseling during prenatal Women, Infants, and Children (WIC) program visits may have a significant impact on these families by providing consistent, culturally sensitive messages in their own languages.

**MATERNAL/INFANT CARE HOSPITAL POLICIES.** Written policies on breastfeeding for all staff that include education, training, encouragement of early breastfeeding initiation, and restriction of supplements and pacifiers have been shown to be critical in determining breastfeeding rates in the US. Hospitals may gain "Breastfeeding-Friendly" designation by complying with the UNICEF/WHO-sponsored "Ten Steps to Successful Breastfeeding" and by including cultural mediators and cultural competence training for staff. (20) Such steps improve understanding of the cultural beliefs and traditions surrounding childbirth and early feeding. Hospital videos and written material presented in the hospital alone, however, will not necessarily improve breastfeeding initiation and duration. African American mothers of US heritage report having been exposed to written material and even videos about breastfeeding at the hospital, but without any discussions regarding their own individual personal beliefs or experiences to help tailor the information to their needs, the positive influence of these materials are minimal. (21)

Another approach to hospital-based infant feeding is the use of midwives or doulas from the mothers' cultural community. For example, in Minnesota, immigrant Somali are supported by trained Somali midwives during labor and delivery, with early encouragement to breastfeed the newborn. (22) Nursing staff are provided in-house training on working with the midwives and are taught key Somali words useful in supporting delivery and infant feeding. Similar community-based breastfeeding peer counseling programs have been effective in increasing rates of breastfeeding initiation in Puerto Rican mothers in the US.

## Case Study 2: Mixed Feedings/Maintaining Breastfeeding

*A 2-month-old infant is brought by his mother to his pediatrician for his health supervision visit and immunizations. The infant was born at term by vaginal delivery to a 32-year-old woman who immigrated to the country with her husband and three other children 2 years ago. The pregnancy was uncomplicated. With the aid of an interpreter, the mother reports that she is breastfeeding through the night and day while supplementing with formula to “top him off” because he still appears hungry after breastfeeding. The baby’s weight for height is at the 95th percentile. She reports some vomiting following feeding as well as episodes when the infant appears to gag, becomes red in the face, and cries. She interprets this behavior as hunger and feeds more often. You explore her beliefs and attitudes about infant feeding.*

The protective benefits of breastfeeding are duration-dependent, so a longer duration of exclusive breastfeeding results in a greater beneficial effect. (23) However, few studies have differentiated between exclusive and mixed breastfeeding patterns. A national study of low-income WIC participants revealed that very few infants were breastfed exclusively (13% of infants at 1 month, with rates declining thereafter). (24) The median age at which formula was introduced was 16 days by African American mothers, 12 days by white mothers, and 20 days by Hispanic mothers.

The mother in this case is following a common practice of overfeeding by supplementing breastfeeding with formula, resulting in rapid weight gain and reflux in the infant.

### Immigrants to the United States

Many immigrant women from low-income countries make significant sociocultural and economic transitions when they move to the US. Many leave a traditional setting with parenting and family support and become isolated in the US. The influences of acculturation work to reduce traditional infant feeding beliefs within the first generation of residence. Mothers attempt to assimilate in their new social settings as they are exposed to advertisements of formula and are aware of formula made available for free through government-sponsored family support agencies such as WIC and at many hospitals after delivery. Many women also are in new situations involving work and school that separate them from their infants.

Furthermore, unlike US-born mothers, many immigrant mothers possess little or no past experience with human milk pumping or storage. The concept that hu-

man milk can be placed in a bottle and fed to the infant when the mother is not available may be completely foreign to them. Finally, immigrant mothers in the US typically have limited exposure to health education messages such as the “breast is best” campaigns that may be found in their native countries because promotional messages in the US are not in their own language and not specifically designed to relate to them.

Although breastfeeding rates are typically high in many low-income countries, rates of exclusive breastfeeding may be very low, depending on governmental and cultural reinforcement of breastfeeding and the existence of commercial interests that sell formula. Several studies have revealed the frequent practice of supplementing human milk with other fluids among mothers related to the impact of large-scale milk distribution programs. Reasons for mixed feeding of infants in these groups include a belief that human milk is an incomplete food that does not increase the infant’s weight significantly and a belief that human milk alone is inadequate to “fatten the baby” as a means of protecting the baby’s health. (25)

**RELIGION, PRIVACY, AND BREASTFEEDING.** Healthy infant feeding practices encouraged by cultural traditions and religion may be overlooked and not reinforced by US clinicians. For example, the Islam religion formally recognizes the fundamental value of breastfeeding for the welfare of the child and family. The holy script of the Qu’ran (holy book of Muslims) contains references that recommend breastfeeding for 2 years: “The mothers shall give suck to their offspring for two whole years for those who desire to complete the term (2:233).”

Another important religious aspect of breastfeeding for Muslims that may interfere with breastfeeding in the US is the mother’s emphasis on privacy during breastfeeding. The Islamic tradition to keep body parts covered when in front of nonfamily members can prompt Muslim women to offer formula to their infants, particularly as they face having to return to work or school or feed in more public locations. Similarly, mothers from other cultural groups view breastfeeding in public as embarrassing and potentially dangerous, often abandoning breastfeeding when the mother returns to school or work. (26)

**PAST EXPERIENCES.** Cultural and past experience with fears regarding infant undernutrition may drive subsequent feeding practices. So strong are these fears that cases of infant overfeeding leading to gastrointestinal reflux, oral aversion, and subsequent failure to thrive



have been reported among Somali refugee immigrants in Seattle and Minnesota as well as high corresponding rates of obesity among these groups. Focus group interviews of the Somali mothers have revealed strong community and family pressure to supplement human milk with formula to keep their infants “chubby.”

### Ethnic Groups of US Heritage

**AFRICAN AMERICANS.** The lack of African American breastfeeding role models and support from family and community to nurse has led to short durations of breastfeeding. One study found the duration of breastfeeding to be shortest for African American mothers (median of 42 days) compared with white (52 days) and Hispanic (72 days) mothers. Interestingly, the median breastfeeding duration for immigrant mothers was twice that of US-born mothers. (24)

Perceived barriers to breastfeeding among African American mothers include the uncertainty in knowing that the baby is getting enough to eat, breastfeeding in public, concerns that human milk would leak onto clothes, and fear that no one else would be able to feed the baby, which would “tie you down.” (24)

**HISPANICS.** Hispanic mothers have been found to have the most favorable attitudes toward breastfeeding and correspondingly highest rates of breastfeeding initiation and longest duration. (2) Hispanic mothers tend to agree that breastfeeding brings a mother closer to her baby and helps protect babies from diseases, and they are more likely to believe that breastfeeding is easier than bottle feeding (75% of Hispanic mothers compared with 43% of white and 40% of African American mothers). (24) High rates of breastfeeding among Hispanic mothers has been offered to help explain the “Hispanic paradox,” in which health outcomes are better than might be expected based on socioeconomic status, an effect attributed to the protective effects of breastfeeding. (24)

### Suggestions for Counseling and Infant Feeding Support

Despite what may appear to be overwhelming obstacles to encouraging successful breastfeeding, support from clinicians improves breastfeeding initiation and increases the likelihood that mothers will continue breastfeeding. (27) Mothers who reported having received encouragement to breastfeed from a doctor, nurse, or breastfeeding consultant during the first 12 weeks postpartum were more likely than other mothers to continue breastfeeding. Culturally sensitive communication skills are an im-

portant component to conveying infant feeding messages effectively.

**THE MOTHER'S PERSONAL PERSPECTIVES, EXPERIENCE, AND PLANS.** Gathering such information before counseling allows the development of a trusting rapport with the mother and shaping of the clinician's advice. If a mother's world view is not clear, a few culturally based questions might help clarify her perspectives:

- “*How did you feed your other children? How have other children in your family been fed?*” These questions may yield information on a mother's beliefs about feeding her infant.
- “*What are your plans about how and what to feed your baby in the next 2 months?*” This information may help the clinician gauge how confidently the mother is prepared to breastfeed her infant exclusively in the first 6 months after birth, open the opportunity for the mother to discuss her own perspectives, and ensure that the clinician offers appropriate healthy infant feeding suggestions prior to establishment of contrary behaviors.
- “*How do you feel about these suggestions?*” Asking this question gives the mother a chance to express whether any new information matches her world view and life.

**A CULTURALLY COMPETENT HEALTH-CARE SETTING.** Such a setting can be welcoming to all patients.

- Use interpreters and include posters, handouts, and pamphlets in the languages that your patients speak. Ensure that all staff receive ongoing education and training in culturally and linguistically appropriate service delivery.
- Use trained community members to counsel parents.

**GENERAL CULTURAL INFLUENCES IN THE POPULATION SERVED.** It is helpful to gain an understanding of such influences on infant feeding practices among the primary population that you serve, while avoiding cultural stereotypes. However, strictly held generalizations about specific groups of people can be divisive rather than helpful. There is great variety within any large ethnic group with regard to language and culture, socioeconomic status, proximity of immigration and degree of assimilation, geographic location, special needs, and personal experiences.

**COLLECTING DETAILED INFORMATION.** Rather than making assumptions, it is more efficient to collect detailed information.



- If a mother states that she is breastfeeding, the clinician may be quick to assume that she is exclusively breastfeeding and move onto another part of the visit's discussion. It may be more informative to ask, "*What has your baby been fed in the past 24 hours?*"
- Knowledge of the common fluids and foods other than human milk given to infants of different cultural groups may be obtained by asking specific questions, such as "*What are your feelings about giving infants honey?*" or "*Have you heard of infants being fed tea?*"
- Don't assume that certain cultural groups who tend to breastfeed in their home country are doing so in the US (eg, Hispanics). Remember that as families live longer in the US, they become less likely to breastfeed exclusively.

**INFANT OVERFEEDING.** Development of a trusting relationship with careful probing can help to uncover fears about undernutrition and allow for direct discussions regarding the widely divergent settings between the mother's home country and the US. Useful messages may emphasize the unlikely threat of undernutrition in the US and provide personal success stories of mothers from the same ethnic group who breastfed exclusively. Making available breast pumps and education about milk storage also can help to increase the mother's milk supply and prepare her for a smooth return to work or school. A clear explanation of stomach capacity and reflux, often with pictures, helps mothers to understand that signs they had interpreted to signify hunger actually may be from esophageal irritation due to reflux. Some mothers are concerned about the threat of obesity to the future health of the child, especially if there is a history of diabetes or obesity in the family. However, multiple studies have documented the general preference among lower income and immigrant mothers for plump or fat babies and their belief that such babies are healthy. This insight suggests that a focus on messages that promote breastfeeding as a means to avoid overweight or obesity is unlikely to be effective in changing feeding behavior.

**REALISTIC GOALS FOR AN INFANT'S WEIGHT GAIN.** Providing specific goals for weight at the next health supervision visit can reassure mothers of good infant growth and the adequacy of their human milk. Mothers who have low literacy may find growth grids hard to understand compared with having a goal for their infant's weight gain over time.

**BASIC EDUCATION ABOUT BREASTFEEDING.** Such basic education likely is lacking for many mothers, in-

cluding information on infant suckling and emptying of breasts to stimulate human milk production, impact of supplemental feedings on human milk production, on-cue feeding, and monitoring of infant elimination pattern (urine and stool).

**PEER COUNSELOR PROGRAMS.** Breastfeeding peer counselors and their clients typically share a common language/dialect, ethnic background, and socioeconomic status. (28) Because of such similarities, these counselors possess a deep understanding of a community's health beliefs and barriers to health-care services. They engage in one-on-one dialogue, hands-on demonstrations, teaching, and advising to provide personal support and promotion of healthy infant feeding patterns. Such activities by peer counselors support their roles as liaisons between the health-care delivery system and lay communities. By facilitating access to personal and environmental resources in a nonthreatening, friendly manner, peer counseling empowers the clients by providing a sense of control and self-efficacy. (29)

### Case Study 3: Introduction of Complementary Foods

*At a 4-month health supervision visit, a mother reports that she has started feeding her infant home-made rice porridge mixed with soup broth, as advised by her neighbor friends.*

The American Academy of Pediatrics (AAP) recommends that complementary foods be introduced no earlier than 6 months of age because human milk provides a complete source of nutrition. However, many cultures introduce solid or semisolid foods at an early age. These foods often are given to the infant after a breastfeeding and are intended initially to complement, rather than substitute for or interfere with milk feedings. Frequently, such feedings are viewed as a means of socializing the infant into the family's diet culture.

### Immigrants to United States

Complementary food feeding practices among US immigrants vary significantly, depending on the country of origin, prior rural-urban residence, and socioeconomic status. A list of first complementary foods is found in Table 2. The range and practices are wide. In Cairo, infants are breastfed exclusively for the first 40 days after birth except for the mint- or cumin-flavored sugar water fed to them when they are "colicky." After this time, the infant is not only allowed to be taken out of the home, but begins to be fed bread soaked in teas and milk, yogurt sweetened with honey, and the water from the family pot of rice, fava beans, and whole wheat cereal. When the

Table 2. **Examples of First Complementary Foods Given to Infants**

Culture/Geographic Area	First Foods
African American adolescents in the US	Cow milk, prechewed meat, mashed potatoes, cereal in bowl/bottle, vegetables, applesauce, juice, water with sugar
Chinese-, Vietnamese-, and Cambodian-Americans in California	Prechewed rice paste, rice, sweetened porridge
Asian Indian Americans	Rice and banana (kheer: dessert prepared with rice, banana, milk, and sugar), potato podimas (mashed potato with clarified butter), dhal laddu (cake prepared with roasted flour and sugar), rice khitchri (rice, lentil, and clarified butter), idli (fermented and cooked rice/lentil), chappati (bread prepared from wheat flour), Bengal gram sundal (germinated chickpea steamed with spices)
Migrant farm workers in northern Colorado	First vegetables, then grains and fruits
Mexico, rural	Soups, fruits (eg, pawpaw, banana), tortillas soaked in soup or sweetened vanilla, milk, caldo de frijol (red beans cooked and mashed into a watery soup), atolita or atole (a sweetened corn meal liquid)
Mayan-Indians in the Yucatan	Sweet soft drinks, atole, posole (atole with added coconut), soup-soaked tortilla, sugar cane
Egypt	Bread soaked in milk and tea; water from preparation of rice, fava beans, and whole wheat cereal; yogurt sweetened with honey
Jamaica	Corn meal with condensed milk, banana porridge, strained oats, crushed foods, thin porridge, gruels
Sudan	Starch gruel made either of rice or fermented sorghum
Eastern Uganda	Maize porridge, thinned mashed banana, millet, porridge, peas, cassava, sugar cane, black tea, rice water, goat milk
Zaire	Pap of cassava, banana, sorghum, millet, bidia (a gruel prepared with cassava and maize flour)
Rural India	Salty tea prepared by adding butter, salt, and various dried fruit to the boiled tea, sattu, chullipalchi (dried apricot that is soaked in water, then boiled and added to sattu, salt, spices, oil)
Arab Gulf	Mehallabia (rice pudding), fruit juices mixed with cereals and milk, mashed cooked vegetables in soup, yogurt
These results represent beliefs and practices of subgroups of these diverse immigrant populations and do not necessarily represent the attitudes and practices of the entire ethnic group.	

infant is older, mashed and peeled fava beans as well as vegetable soups are added gradually.

In Zaire, cassava, banana, sorghum, millet, and cassava-maize flour may be combined and fed to breast-fed infants during the first postnatal weeks because of a belief that human milk alone is insufficient. By 5 months of age, infants are eating cassava, rice, or beans and some fish or meat at least once a week, and by 1 year, they are eating the adult diet, even though they may continue to be breastfed for 2 to 4 years.

The wide range of weaning foods based on cultural practices are modified in the new US setting, where the types of food available to the mother are drastically different from those in her native country. Mothers who have limited education from developing countries likely understand “good foods” rather than “nutritional value.” In the US, they are faced with a very different

appearing set of grocery options from which to select. Community and family members serve as the mother’s guides in selecting complementary foods for her infant and advise her on when to feed these to her infant.

### Ethnic Groups of US Heritage

**AFRICAN AMERICANS.** Studies have reported that African American mothers commonly supplement their infants’ diets with cereal mixed with formula in a bottle as early as 2 weeks of age. (30) Foods that require spoon-feeding, such as cereal or applesauce, were introduced around 8 weeks of age among this same group. Reasons for introducing complementary foods were based on infant cues for hunger (eg, “he wasn’t getting full”), the mother’s own desires (“I wanted her to taste it”), concerns about infant size (thin, small), desire to influence infant sleeping, and specific beliefs (need complementary

foods during hot weather). Mothers may possess a concern that milk alone may not allow the infant's stomach to get full. (31) Many mothers introduce solid foods on the advice of others, even when in direct contradiction to their clinician's advice, which highlights the importance of including other family members as targets for messages about nutrition.

**HISPANICS.** Hispanic mothers in the US are more likely to introduce meat as well fruit and fruit juices to their infants before 6 months, compared with Anglo-Americans, although more highly educated women may tend to delay the introduction of meat. (32) Introducing solid feedings early also may be observed in periurban Mexico, where breastfeeding rates are high (91%), but solid foods are introduced well before 3 months of age. (33)

**FOOD PREPARATION AND FEEDING SETTING.** Low-income mothers from settings where jar foods are not readily available and where freshly prepared foods are the norm may be less likely to accept processed foods for their infants. For example, some Somali mothers in the US express a mistrust of infant jar foods that have been on the unrefrigerated shelves of the groceries for an unknown period. They readily accept home preparation of infant foods.

The manner in which infants are fed complementary foods also may not involve a spoon. Premasticated table foods and hand feeding are common, so messages involving spoon portion sizes may not be useful. Feeding infants seated on high chairs also may not be the norm in families from some US ethnic groups and immigrant households, where the infant is fed more commonly on the caregiver's lap. Many cultures also may emphasize controlled caregiver feeding throughout early childhood, providing little opportunity for the developing child to self-feed. There is some evidence that strong and continued parental control over infant feeding may not allow the infant to respond to his or her own sense of satiety, eventually placing the child at risk for obesity or oral aversion if forced feeding occurs.

### Suggestions for Counseling about Healthy Infant Complementary Foods

The clinician is more likely to succeed in delaying solid feedings if these plans are addressed at the 2-month health supervision visit rather than after solids have already been introduced.

The clinician should not assume that if the mother is feeding her child commercially prepared infant foods

that she is providing a well-balanced array of foods. Unaccustomed to commercial infant foods, mothers may believe that all jar foods are equally nutritious. Asking the mother what types of foods she has fed her infant in the past week may reveal that the infant is being fed only solids that are low in iron.

Do not overlook the roles of other caregivers and family members in encouraging healthy feeding practices. The mother may not be the sole person caring for and feeding the infant. Understanding the degree to which a grandmother, father, or other person is providing care for the infant currently and as the infant grows will help to identify important caregivers who should be included in discussions.

Learning about the common cultural feeding attitudes and practices can help direct questioning regarding infant foods. For example, familiarity with an ethnic group's proclivity toward prepared infant foods rather than store-bought foods may help to focus questions on proper preparation of infant foods instead of assuming that the infant will be fed fortified jar foods or processed cereals.

### Case Study 4: Weaning to a Cup

*At her toddler's 2-year health supervision visit, a mother reports that she still provides her child with cow milk from a bottle. She states that her child needs a bottle to fall asleep at night.*

The AAP recommends breastfeeding for the infant's first 12 months after birth and as long after as the mother and child desire. The AAP also advises introduction of the cup at approximately 6 months of age. If bottle-feeding, the infant should be weaned completely by 15 to 18 months of age to prevent bottle caries, iron deficiency anemia, poor weight gain, and obesity. Ethnographic studies of mothers who bottle-feed their toddlers beyond 18 months describe a desire for "easy solutions" for crying toddlers as well as a means to have special bonding time with their "toddler-babies" in the setting of increased disciplinary needs for the developing child.

### Immigrants to the United States

The age at which an infant is weaned to a cup frequently is influenced by cultural beliefs. East African mothers often continue breastfeeding well beyond 1 year of age but readily introduce a cup during the first postnatal year. Southeast Asian cultures often delay weaning from the bottle until 2 years of age. In the US, immigrants who typically breastfeed their infants may switch to bottle feeding and continue until 3 or 4 years of age. In addition, cultural preference for gradual rather than abrupt

change along with a child-raising philosophy that involves a reluctance to upset or disturb the child further encourage frequent and prolonged bottle-feeding.

Children from immigrant families may be at additional risk for caries due to a lack of appreciation for their children's primary teeth, which "just fall out anyway." They may not associate the presence of caries in primary teeth with risk for caries in permanent teeth and typically possess little concept of routine preventive dental visits. Correspondingly, immigrant children may be at higher risk for iron deficiency anemia due to a high volume of milk intake and lack of iron-rich solid foods in their diets.

### Ethnic Groups of US Heritage

In general, African American families have been reported frequently to wean their children earlier and relatively abruptly, which corresponds with the general cultural value placed on an early development of independence. Prolonged bottle feeding after 24 months of age with milk as well as sweetened beverages has been reported to occur more often among certain other ethnic groups, including Native Americans and US-born Hispanics and Southeast Asians, a practice associated with iron deficiency in these populations. (34)

### Suggestions for Counseling and Practice Regarding Weaning Toddlers to a Cup

Cultural influences on infant feeding practices necessitate culturally appropriate, nonjudgmental approaches to infant feeding discussions and education that target all family and community members who may influence feeding attitudes. Specific inquiries are necessary to identify the practice of prolonged bottle feeding as well as inappropriate nighttime bottle-feeding. However, open-ended inquiries allow the clinician to understand the setting in which transition to a cup has been delayed, such as a desire to keep the child quiet at nighttime so as not to disturb the working father's or grandparents' sleep. Certainly, the beliefs and opinions of nonparent care providers about weaning should be explored, as well as their involvement, before recommendations to the mother about changes in feeding may be expected to be successful.

Any child who is delayed in weaning from nursing or bottle at 24 months of age should be evaluated for iron deficiency anemia. Because the hematocrit is not a sensitive screening test for iron status, a zinc protoporphyrin-heme ratio may be used as an inexpensive capillary blood screening test for iron deficiency in the toddler population. (35) Finally, evaluation for dental caries is indicated

for any child taking human milk or formula at night with early, regular visits to a dentist for routine monitoring.

### Effective Public Policy

Effective strategies to promote healthy infant feeding practices in the culturally diverse US population require unified approaches from the triad of clinicians, community groups, and public organizations. Evidence-based recommendations and persistent advocacy for public policies that support healthy infant feeding practices may take the following forms:

- Advocacy against media portrayal of high-calorie formulas as a healthy option for picky eaters who have adequate weight gain patterns.
- Advocacy for culturally based, protein-rich food supplements provided through WIC to encourage mothers to make healthy, culturally appropriate food choices.
- Development of breastfeeding policies to create a supportive environment for breastfeeding in the workplace and public venues, including a private place to pump breasts and place to store milk
- Greater federal resources to WIC to support lactation support services, pumps, shields, and community-outreach campaigns.

### Web Sites

- Ethnomed.org
- La Leche League International: <http://www.llli.org/>
- Centers for Disease Control and Prevention: <http://www.cdc.gov/breastfeeding/recommendations/index.htm>
- Baby Friendly USA: <http://www.babyfriendlyusa.org>
- Academy of Breastfeeding Medicine Model Breastfeeding Policy: [www.bfmed.org/Resources/Download.aspx?filename=Protocol\\_7.pdf](http://www.bfmed.org/Resources/Download.aspx?filename=Protocol_7.pdf)

### References

1. Celi AC, Rich-Edwards JW, Richardson MK, Kleinman KP, Gillman MW. Immigration, race/ethnicity, and social and economic factors as predictors of breastfeeding initiation. *Arch Pediatr Adolesc Med.* 2005;159:255–260
2. Gibson-Davis CM, Brooks-Gunn J. Couples' immigration status and ethnicity as determinants of breastfeeding. *Am J Public Health.* 2006;96:641–646
3. Sussner KM, Lindsay AC, Peterson KE. The influence of acculturation on breast-feeding initiation and duration in low-income women in the US. *J Biosoc Sci.* 2007;29:1–24
4. Fink E. Nutrition, lactation and fertility in two Mexican rural communities. *Soc Sci Med.* 1985;20:1295–1305
5. Harrison GG, Zaghoul SS, Galal OM, Gabr A. Breastfeeding and weaning in a poor urban neighborhood in Cairo, Egypt: maternal beliefs and perceptions. *Soc Sci Med.* 1993;36:1063–1069
6. Henderson SM, Brown JS. Infant feeding practices of Vietnamese immigrants to the Northwest United States. *Sch Inq Nurs Pract.* 1987;1:153–169

7. Cricco-Lizza R. Infant-feeding beliefs and experiences of black women enrolled in WIC in the New York metropolitan area. *Qual Health Res.* 2004;14:1197–1210
8. Guzman B. The Hispanic population: *Census 2000*. Washington, DC: United States Census Bureau; 2001.
9. Gonzalez-Cossio T, Moreno-Macias H, Rivera JA, et al. Breast-feeding practices in Mexico: results from the Second National Nutrition Survey 1999. *Salud Publica Mex.* 2003;45 (suppl 4): S477–S489
10. Gorman JR, Madlensky L, Jackson DJ, Ganiats TG, Boies E. Early postpartum breastfeeding and acculturation among Hispanic women. *Birth.* 2007;34:308–315
11. Harley K, Stamm NL, Eskenazi B. The effect of time in the US on the duration of breastfeeding in women of Mexican descent. *Matern Child Health J.* 2007;11:119–125
12. Bunik M, Clark L, Zimmer LM, Jimenez LM, O'Connor ME, Crane LA, Kempe A. Early infant feeding decisions in low-income Latinas. *Breastfeed Med.* 2006;1:225–235
13. Guerrero ML, Morrow RC, Calva JJ, et al. Rapid ethnographic assessment of breastfeeding practices in periurban Mexico City. *Bull World Health Organ.* 1999;77:323–330
14. Knapp RB, Houghton MD. Breast-feeding practices of WIC participants from the former USSR. *J Am Diet Assoc.* 1999;99: 1269–1271
15. Meftuh AB, Tapsoba LP, Lamounier JA. Breastfeeding practices in Ethiopian women in southern California. *Indian J Pediatr.* 1991;58:349–356
16. Tuttle CR, Dewey KG. Determinants of infant feeding choices among Southeast Asian immigrants in Northern California. *J Am Diet Assoc.* 1994;94:282–286
17. Shaw E, Kaczorowski J. The effect of a peer counseling program on breastfeeding initiation and longevity in a low-income rural population. *J Hum Lact.* 1999;15:19–25
18. Long DG, Funk-Archuleta MA, Geiger CJ, et al. Peer counselor program increases breastfeeding rates in Utah Native American WIC population. *J Hum Lact.* 1995;11:279–284
19. Schafer E, Vogel MK, Viegas S, Hausafus C. Volunteer peer counselors increase breastfeeding duration among rural low-income women. *Birth.* 1998;25:101–106
20. Step 10: strives to achieve the WHO/UNICEF ten steps of the Baby-Friendly Hospital Initiative to promote successful breastfeeding: the Coalition for Improving Maternity Services. *J Perinat Educ.* 2007;16(suppl 1):79S–80S
21. Cricco-Lizza R. Black non-Hispanic mothers' perceptions about the promotion of infant-feeding methods by nurses and physicians. *J Obstet Gynecol Neonat Nurs.* 2006;35:173–180
22. Dundek LH. Establishment of a Somali doula program at a large metropolitan hospital. *J Perinat Neonatal Nurs.* 2006;20: 128–137
23. Hylander MA, Strobino DM, Dhanireddy R. Human milk feedings and infection among very low birth weight infants. *Pediatrics.* 1998;102:e38
24. McCann MF, Baydar N, Williams RL. Breastfeeding attitudes and reported problems in a national sample of WIC participants. *J Hum Lact.* 2007;23:314–324
25. Kakute PN, Ngum J, Mitchell P, et al. Cultural barriers to exclusive breastfeeding by mothers in a rural area of Cameroon, Africa. *J Midwifery Women's Health.* 2005;50:324–328
26. Rossiter JC, Yam BMC. Breastfeeding: how could it be enhanced? The perceptions of Vietnamese women in Sydney, Australia. *J Midwifery Women's Health.* 2000;45:271–276
27. Lu MC, Lange L, Slusser W, et al. Provider encouragement of breast-feeding: evidence from a national survey. *Obstet Gynecol.* 2001;97:290–295
28. Grummer-Strawn LM, Rice SP, Dugas K, et al. An evaluation of breastfeeding promotion through peer counseling in Mississippi WIC clinics. *Matern Child Health J.* 1997;1:35–42
29. Bronner Y, Barber T, Miele L. Breastfeeding peer counseling: rationale for the national WIC survey. *J Hum Lact.* 2001;17: 135–139
30. Black MM, Siegel EH, Abel Y, Bentley ME. Home and videotape intervention delays early complementary feeding among adolescent mothers. *Pediatrics.* 2001;107:e67
31. Bentley M, Gavin L, Black MM, Teti L. Infant feeding practices of low-income, African-American, adolescent mothers: an ecological, multigenerational perspective. *Soc Sci Med.* 1999;49: 1085–1100
32. Ziegler P, Hanson C, Ponza M, et al. Feeding Infants and Toddlers Study: meal and snack intakes of Hispanic and non-Hispanic infants and toddlers. *J Am Diet Assoc.* 2006;106(suppl 1):S107–S123.
33. Guerrero ML, Morrow RC, Calva JJ, et al. Rapid ethnographic assessment of breastfeeding practices in periurban Mexico City. *Bull World Health Organ.* 1999;77:323–330
34. Brotanek JM, Halterman JS, Auinger P, et al. Iron deficiency, prolonged bottle-feeding, and racial/ethnic disparities in young children. *Arch Pediatr Adolesc Med.* 2005;159:1038–1042
35. Graham EA, Carlson TH, Sodergren KK, Detter JC, Labbe RF. Delayed bottle weaning and iron deficiency in southeast Asian toddlers. *West J Med.* 1997;167:10–14