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A 7-Month-Old Who Has a Persistent Rash

Angel Alberto Herrera Guerra, MD,* Russell J. Osguthorpe, MD,† Angelica Putnam, MD,§ Sheryll L. Vanderhooft, MD‡

Presentation
A 7-month-old boy presents to the pediatric infectious diseases clinic with an unusual rash for the past 4 weeks. The rash appeared first on the back of his neck as a reddish-brown raised “spot” (Fig. 1). Over the past month, other reddish-brown macules and papules have appeared on his anterior trunk that later have developed a fine scale, followed in some places by erosions and black eschar formation. These lesions were neither vesicular nor pustular in appearance before eroding. The eschars eventually healed, leaving hypopigmented scars.

The infant has been asymptomatic otherwise and has gained weight during this time, maintaining his normal appetite and activity. There is no history of fever or discomfort. Initially, a pediatrician thought the infant had scabies and prescribed permethrin cream, but there was no improvement of the infant’s condition. The pediatrician then prescribed two courses of antibiotics (cephalexin and amoxicillin) for a presumed varicella infection complicated by bacterial superinfection. Again, there was no improvement. Because of the continued appearance of new lesions the infant was referred to a pediatric infectious diseases clinic.

The infant’s past medical history is unremarkable. He was delivered vaginally without complications at term and has been healthy otherwise until the rash appeared. There has been no animal exposure or travel. There is no history of a respiratory or gastrointestinal infection or administration of any medications before the onset of the rash. His immunizations are up to date, and he does not have any allergies. The family history is unremarkable.

Physical examination reveals a playful, smiling infant in no distress who has a heart rate of 112 beats/min, respiratory rate of 24 breaths/min, temperature of 36.4°C, and weight of 8.8 kg (75th percentile). Skin examination reveals reddish-brown papules and plaques measuring 0.5 to 1.5 cm in diameter (Fig. 2). The lesions

Figure 1. Reddish-brown raised “spot” on back of thigh similar to the “spot” that first appeared on the back of infant’s neck.

Author Disclosure
Drs Herrera Guerra, Osguthorpe, Putnam, and Vanderhooft 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.
appear to be in different stages of development; some are covered with a fine white scale, while others show erosion and black eschars. There is mild scarring and hypopigmentation where the earliest lesions had appeared. Most of the lesions are localized to the anterior trunk, especially in the periumbilical area and under the right axilla. No involvement of the palms, soles, or mucosal surfaces is appreciated. The posterior torso is spared. The rest of the examination is unremarkable.

A complete blood cell count shows a hemoglobin concentration of 12.4 g/dL, hematocrit of 35%, white blood cell count of 6,800/mm³ (1% bands, 13% neutrophils, 74% lymphocytes, 6% monocytes, 4% eosinophils, and 2% basophils), and platelet count of 434,000/mm³. C-reactive protein concentration is ≤0.5 mg/dL.

Consultation with a pediatric dermatologist and a medical procedure confirm the clinical diagnosis.
Diagnosis: Pityriasis lichenoides et varioliformis acuta

A skin biopsy showed focal parakeratosis overlying a spongiotic epidermis, with occasional dyskeratotic keratinocytes and extravasated red blood cells in the epidermis and papillary dermis (Figs. 3 and 4). The reticular dermis contained a lymphocytic infiltrate that extended to the lower portion of the dermis and surrounding adnexal structures. These findings were compatible with pityriasis lichenoides et varioliformis acuta (PLEVA), an idiopathic acquired dermatosis characterized by evolving erythematous, scaly papules that develop vesiculation, ulceration, and necrosis.

Discussion

Etiology

PLEVA commonly is preceded by an upper respiratory or gastrointestinal tract infection. Epstein-Barr virus, Mycoplasma pneumoniae, Streptococcus pyogenes, Toxoplasma gondii, parvovirus B19, and adenovirus are among the infectious agents associated with the onset of this rash. Other potential triggers include antibiotics, antipyretics, and vaccines. These observations, plus biopsy findings of immune complexes composed of immunoglobulin M and complement component C3 in the dermoepidermal junction and blood vessels, support the hypothesis that PLEVA represents a hypersensitivity reaction to an infectious or noninfectious antigen. Recently, it has been suggested that in some cases the eruption represents a true cutaneous lymphoproliferative disorder due to the demonstration of monoclonal CD8+ lymphocytes infiltrating the skin.

Epidemiology

Once thought to be uncommon in children, recent reports suggest that the incidence of PLEVA may be underestimated in the pediatric population. The incidence of PLEVA peaks twice during childhood; the first peak occurs at 24 to 36 months of age and the second peak between 5 and 7 years of age. PLEVA rarely occurs before the second year after birth, although newborn cases have been described. No ethnic group seems to be affected predominantly over another. PLEVA has a milde male preponderance, with a male to female ratio close to 1.5:1. The incidence may be higher during the winter and fall.

Clinical Presentation

PLEVA usually presents acutely with crops of brown or reddish papules about 1 cm in diameter that have sur-
rounding erythema. New lesions appear rapidly, most frequently affecting the trunk, flexor surfaces, and proximal extremities. The soles, palms, and mucosal surfaces usually are spared. Facial and scalp involvement, although rare in adults, occur in 40% of children. Lesions usually change over time, and multiple stages of development coexist at any point. The lesions can acquire white scale; they evolve into vesicles, pustules, and then erosions and ulcers. The ulcer generally will develop a necrotic appearance and finally a black eschar before healing. Healing of the lesion usually results in a scar (“varioliform,” or “resembling smallpox”) and hypopigmentation or, less commonly, hyperpigmentation.

The presence of necrosis, vesiculation, and ulceration rather than the duration of symptoms distinguish PLEVA from pityriasis lichenoides chronica (PLC), the chronic form of pityriasis lichenoides. PLC is characterized by asymptomatic reddish-brown papules with white scale that usually do not erode, ulcerate, or necrose. Histologically, PLC is similar to PLEVA, but the observed changes are milder in PLC. It is common for patients to have lesions of PLEVA and PLC simultaneously. This coincidence suggests that both forms represent different ends of the spectrum of the same disease. Constitutional symptoms accompany PLEVA in two thirds of cases. Pruritus is the most common symptom, occurring in 50% of cases. Fever, arthralgias, and malaise occur less commonly.

Differential Diagnosis

The differential diagnosis of PLEVA includes scabies, varicella, erythema multiforme, secondary syphilis, Gianotti-Crosti syndrome, tularemia, echyma, papular urticaria, and vasculitis. In an immune competent host, varicella lesions appear within a 2-week period and usually develop rapidly, evolving from macule to papule to vesicle to crust in 2 to 3 days, whereas PLEVA lesions evolve more slowly. Scabies, secondary syphilis, and Gianotti-Crosti syndrome seldom show necrosis. Lymphomatoid papulosis, a form of cutaneous lymphoma, may be impossible to differentiate from PLEVA on clinical grounds; this distinction generally is made by skin biopsy, which usually shows the presence of CD30+ lymphocytes having the atypical features of LyP.

Classification

If PLEVA affects the trunk, head, and inguinal region, it is classified as central; if the eruption affects only the limbs, it is classified as peripheral. PLEVA is classified as diffuse if there is central and peripheral involvement. The diffuse form represents 60% to 74% of PLEVA cases, the central form 5% to 21%, and the peripheral form 18% to 20%.

Evaluation

There is often a delay in making the diagnosis of PLEVA due to its polymorphic appearance, indolent course, and broad differential diagnosis. Skin biopsy is the gold standard for diagnosis and always should be performed when PLEVA is suspected. Inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate, and white blood cell count can be elevated as well as liver transaminases, but these findings are nonspecific.

Course

PLEVA is considered a self-limited disease. Ersoy-Evans et al (1) reported a median resolution time of 18 months (range 2 to 108 mo) for PLEVA and 20 months (range of 3 to 132 mo) for PLC. Relapses are common before complete resolution. Although initial reports suggested that the diffuse form had the fastest resolution rate and the peripheral form the slowest, this distinction has not been corroborated in more recent reports.

Complications

Febrile Ulceronecrotic Variant of Mucha–Habermann Disease

Febrile ulceronecrotic variant of Mucha–Habermann disease (FUMHD) is characterized by high fever and progression of the typical PLEVA lesions to larger (5 to 10 cm) and more painful ulcerative lesions with extensive necrosis as well as multiorgan involvement, including liver, central nervous system, and coagulation abnormalities. This condition carries a fatality rate as high as 25%. Sepsis can complicate this presentation because of bacterial superinfection of the lesions. Mucosal involvement is more common in this condition. Skin biopsy is critical for making a timely diagnosis.

Malignancy

Although rare, cutaneous T-cell lymphoma can arise from PLEVA lesions. Some researchers have suggested that PLEVA is a premalignant condition representing the mildest end of a spectrum that includes PLEVA, PLC, lymphomatoid papulosis, and cutaneous T-cell lymphoma.

Associated Conditions

Juvenile idiopathic arthritis, immune thrombocytopenic purpura, nonskin lymphomas, and hemophagocytic syndrome have been associated with PLEVA.
**Treatment**

Evaluating the efficacy of therapies for PLEVA is difficult due to lack of randomized controlled trials and the relapsing and self-limited nature of the disease. Ultraviolet B phototherapy is the most effective treatment; however, long-term carcinogenic concerns in children preclude this treatment as first-line therapy.

Oral erythromycin at standard doses is the most prescribed medication for PLEVA and has demonstrated a 25% to 87% response rate in children. Tetracyclines also have been used in older children and adults. Clinical response may be obtained within 2 weeks, but it may take up to 2 months. If response is obtained, the antibiotic should be tapered to prevent flares; in most cases, the taper can be completed within 1 to 4 months after clinical response is obtained. There are reports of clinical success with azithromycin in erythromycin-refractory cases. It is unclear why antibiotics are effective in treating PLEVA, but it has been suggested that the immunomodulatory properties of the macrolides may play an important role in the improvement of lesions. Because PLEVA usually follows a benign course, some experts advocate observation without further intervention if antibiotics are unsuccessful.

Therapy with topical tacrolimus, systemic corticosteroids, and methotrexate has been successful in case reports. Symptomatic relief of pruritus with emollients, antihistamines, and topical corticosteroids is an important component of treatment; however, these medications have minimal, if any, effect on the skin lesions’ evolution.

In FUMHD, methotrexate can be life saving. Intravenous immunoglobulin, cyclosporine, and systemic corticosteroids also have been successful.

**Patient Course**

The patient was started on oral erythromycin three times a day and was scheduled for a 1-month follow-up visit with a dermatologist. Unfortunately, the patient did not show up to this appointment. Six months later he was evaluated in the emergency department for a viral gastroenteritis and was found to be free of skin lesions at that time.

**Summary**

- PLEVA should be considered in children who present with coexisting papules, ulcers, and eschars. These skin lesions heal, leaving a hypopigmented scar.
- Most children who have PLEVA are nontoxic in appearance and are healthy otherwise.
- If systemic symptoms are prominent, FUMHD should be considered.
- A skin biopsy is mandatory to confirm the diagnosis and exclude more serious conditions, such as malignancy or vasculitis.
- Erythromycin is the medication most commonly used as first-line therapy.
- Most PLEVA cases are self-limited, although some cases can have a relapsing course before resolving.

**Reference**


**Suggested Reading**


QUESTION FROM THE CLINICIAN

Author Disclosure
Drs Carmody and Carmody have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Management of Prenatal Hydronephrosis

J. Bryan Carmody, MD,* Rebecca B. Carmody, MD†

Question
During a prenatal visit, a mother states that ultrasonography shows “something wrong with the baby’s kidney.” On checking with the obstetrician, it is learned that the female infant has hydronephrosis of the left kidney on screening ultrasonography done at 20 weeks of gestation, with the renal pelvis having an anteroposterior diameter (APD) of 10 mm; there is a normal volume of amniotic fluid. What is the significance of this finding, and what should the mother and pediatrician anticipate doing when the infant is born?

Assessment
Abnormalities of the kidneys and genitourinary tract are the most common abnormalities identified on routine screening prenatal ultrasonography, and among these, hydronephrosis—dilation of the proximal urinary collecting system with fluid—is the single most common abnormality identified, (1) occurring in approximately 0.6% of all scans. (2) With the increased use of high-resolution screening ultrasonography, pediatricians are confronted more and more frequently with the issue of how to interpret abnormal findings and manage these infants postnatally.

In approximately 35% of all cases of prenatal hydronephrosis, a pathologic condition can be identified postnatally, such as ureteropelvic junction (UPJ) obstruction, vesicoureteral reflux (VUR), posterior urethral valves (PUV), megaureter, or ureterocele. However, in approximately 50% of cases, the prenatal hydronephrosis is transient and not identified on postnatal evaluation; in an additional 15% of cases, hydronephrosis persists but is not associated with urinary tract obstruction (so-called “physiologic” or nonrefluxing, nonobstructive hydronephrosis). Only 10% of these infants will ever require surgery due to the development of obstruction; for the rest, the hydronephrosis improves or resolves entirely, typically by age 3. (3) Much less frequently, other processes may be interpreted as hydronephrosis on prenatal imaging, including multicystic dysplastic kidney, nonrenal cystic abdominal masses (eg, ovarian, urachal, adrenal, mesenteric, and intestinal duplication cysts), or extrarenal obstruction (eg, sacrococcygeal teratoma, hydrometrocolpos). (4)

The degree of prenatal hydronephrosis can be assessed by using either the measurement of the APD of the renal pelvis (5) or the radiographic criteria of the Society for Fetal Urology. The latter evaluation assesses the presence of calyceal blunting, caliectasis, or cortical thinning and assigns a grade of 1 to 5, with higher grades indicating greater severity. (6) Standards for the measurement of the APD are more variable and depend on the infant’s gestational age: for the second trimester, an APD <7 mm is considered mild, 7 to 10 mm moderate, and >10 mm severe, whereas for the third trimester, the standards are <9 mm, 9 to
If oligohydramnios is present, a voiding cystourethrogram should be performed to evaluate the presence of VUR. This test will also evaluate the bladder and urethra, and may identify an ureterocele, urethral stricture, or PUV (an especially important consideration in male infants who have bilateral hydronephrosis). The optimal timing for the VCUG is determined by the infant’s clinical situation; for more severely affected infants, it is prudent to obtain this study early. 

In infants in whom hydronephrosis is persistent postnatally and a UPJ or ureterovesical junction obstruction is suspected, a diuretic renal scan should be obtained. The most frequently used is the mercapto-acetyl tri-glycine (MAG-3) scan with furosemide. In this study, a tracer labeled with Tc-99m is injected intravenously and taken up rapidly by the kidneys; a dose of diuretic is then given to “wash out” the tracer. When obstruction is present, the tracer washout time exceeds 20 minutes; washout times of 15 to 20 minutes are indeterminate.

This study also provides information regarding the split or differential renal function (the percentage of total kidney function performed by each kidney). In cases of unilateral hydronephrosis, values <35% indicate impaired function and constitute an indication for surgery.

The use of antibiotics to prevent urinary tract infections in infants with hydronephrosis remains controversial. In many centers, the standard of care remains to provide prophylactic antibiotics, particularly for those infants in whom the possibility of high-grade VUR has not been excluded. Typical regimens include amoxicillin (10 to 20 mg/kg once daily), nitrofurantoin (1 to 2 mg/kg once daily), or, for older infants, trimethoprim-sulfamethoxazole (2 mg/kg trimethoprim once daily). However, the role of prophylactic antibiotics may be changing due to the difficulty in establishing a clear benefit to their use, especially in cases of mild hydronephrosis.

In the case described, the infant’s hydronephrosis is unilateral and moderate; the most likely pathologic diagnosis is UPJ obstruction. If the infant is well appearing and subsequent prenatal ultrasonography shows stable findings, an urgent evaluation is not required. Renal ultrasonography should be obtained at around 1 week of age, and if hydronephrosis

15 mm, and >15 mm, respectively. (7)

Obtaining accurate information from the obstetrician about the nature and degree of hydronephrosis is critical in allowing the pediatrician to manage the infant postnatally. Higher grade hydronephrosis is much more likely to be associated with serious pathology. In one study, lesions requiring surgery or long-term follow up were present in 94% of patients who had an APD >20 mm at 20 weeks’ gestation, but only in 3% of those demonstrating an APD of <10 mm³. Additionally, the differential diagnosis changes depending on the severity of the hydronephrosis. For example, when the APD is >10 to 15 mm in the second trimester, the most likely diagnosis is UPJ obstruction, whereas VUR is most likely when the hydronephrosis is milder (APD 5 to 9 mm). (4)

When hydronephrosis is severe, bilateral, or occurs in a single kidney, serious consideration should be given to obtaining a prenatal consultation from a pediatric urologist; a nephrology referral also may be warranted to discuss the natural progression, complications, and long-term management of chronic kidney disease. Consultation with a neonatologist may be helpful when oligohydranmnios is present, given the risk of pulmonary hypoplasia or potential need for preterm delivery.

The postnatal assessment of an infant demonstrating prenatal hydronephrosis begins with a careful physical examination. Significant findings include a palpable abdominal or flank mass (UPJ, multicystic dysplastic kidney), distended bladder (PUV or urethral stricture), or absent abdominal musculature and undescended testicles (“prune belly” syndrome).

The infant’s initial voiding pattern also may be helpful because oligohydramnios within the first 48 hours after birth in an otherwise healthy infant strongly suggests the presence of an obstructive lesion (such as PUV in a male infant). Importantly, however, spontaneous voiding (even with a normal urinary stream) does not exclude the possibility of obstructive uropathy, and radiographic evaluation still is required if the prenatal history is suggestive. (8)

Laboratory evaluation of renal function may be of limited value because the serum creatinine will be normal or near normal even in cases of severe unilateral obstruction; testing is warranted in infants with bilateral hydronephrosis, hydronephrosis in a single kidney, a history of oligohydramnios, or oliguria.

Renal ultrasonography is mandatory in infants who have shown prenatal hydronephrosis. This study is obtained ideally at around 1 week of age because studies obtained in the first 48 hours after birth may underestimate the degree of hydronephrosis due to the relative oliguria in this period. Some authors have suggested performing ultrasonography before discharge from the nursery (so significant problems are not missed), with a repeat study at 4 to 6 weeks of age to ensure the absence of hydronephrosis. (9)

When postnatal hydronephrosis is present, a voiding cystourethrogram (VCUG) should be obtained to evaluate the presence of VUR. This test will also evaluate the bladder and urethra, and may identify an ureterocele, urethral stricture, or PUV (an especially important consideration in male infants who have bilateral hydronephrosis). The optimal timing for the VCUG is determined by the infant’s clinical situation; for more severely affected infants, it is prudent to obtain this study early.

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In the case described, the infant’s hydronephrosis is unilateral and moderate; the most likely pathologic diagnosis is UPJ obstruction. If the infant is well appearing and subsequent prenatal ultrasonography shows stable findings, an urgent evaluation is not required. Renal ultrasonography should be obtained at around 1 week of age, and if hydronephrosis
is present, a VCUG should be performed. If the hydronephrosis remains moderate to severe, a MAG-3 scan also should be obtained to evaluate for a UPJ obstruction. Patients who have significant abnormalities identified should be referred to a pediatric urologist.

References
Commentary

Change is in the Air

Although the primary goal of Pediatrics in Review (PIR) is to keep the pediatrician up to date across the broad spectrum of pediatric knowledge, the journal serves other purposes.

One function is to allow the reader to earn continuing medical education (CME) credits. Reading the journal and taking the quizzes, learners can earn up to 36 credits per year; taking the companion PREP Self-Assessment in learning mode can add up to 43 additional credits. Many physicians can fulfill all of their CME requirements by using these two learning tools.

As most readers are aware, specific criteria must be met before accrediting educational organizations will grant CME credit. For instance, the Accreditation Council for Continuing Medical Education (ACCME) in 2011 awarded the American Academy of Pediatrics accreditation “with commendation” for the next 6 years, based on the quality of its CME offerings, which continue to meet the ACCME requirements for outcomes-based learning designed to improve quality of care.

Another key agency, the American Medical Association (AMA), in 2010 strengthened its requirements by issuing several new standards and reinterpreting a few old ones, in order for accredited CME providers to cocertify activities for AMA PRA Category 1 Credits™. Among these is the requirement of a minimum performance level (a minimum passing score) and a “1 article = 1 credit” rule. Both are designed to ensure mastery of content. Both will entail changes for PIR readers.

Currently, all quiz questions are written by designated question writers, must undergo peer review, and are published only after final approval by the authors and editors. Each question is designed to help readers focus on salient elements of the CME article and on general pediatric knowledge. Questions are constructed to help learners evaluate information and select a course of action, recommend treatment modalities, or entertain a diagnosis. This approach will not change.

What will change is the method for submitting quiz answers and claiming credit. Until now, readers have been able to submit answers in two ways: on a paper form or online. The print version of the journal had listed the correct answers inside the front cover. The online quiz had indicated the correct answers electronically and highlighted the part of the article that forms the basis for the answer.

Starting in January 2012, readers may submit quiz answers online only. Online confirmation of the correct answer will remain the same, but in the print issues, correct answers will not appear until the following month.

An advantage of the online method of answering is that readers may review the material and retake the quiz until questions are answered correctly. Not only will repeated attempts reinforce the correct information, but the reader will be able to achieve the percentage of correct answers required to claim CME credit. The minimum passing score that must be achieved is 60% for each article designated for credit. Once learners achieve a 60% score, they will be prompted to claim credit.

Under new requirements, each quiz that follows a specific article will be worth 1 AMA PRA Category 1 Credit™; the older method of stating the hours spent reading each issue will no longer apply. With few exceptions, the articles chosen to have quizzes will be full-length reviews. Occasionally, quizzes may be appended to shorter articles.

Readers should know that there is a strong trend toward measuring changes that learners might make in their practice habits. Going a step further, efforts will be made to measure changes in outcomes that result from participating in PIR as an educational activity.

We trust these changes will not require a great deal of adaptation on the part of our learners and that they will result ultimately in an improvement of our educational capability.

Lawrence F. Nazarian
Editor-in-Chief
Eating Disorders

Mark A. Goldstein, MD,* Esther J. Dechant, MD,† Eugene V. Beresin, MA, MD§

Author Disclosure
Drs Goldstein, Dechant, and Beresin 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. Identify behaviors in an adolescent that suggest an underlying eating disorder.
2. Recognize the physical findings that can be seen in patients who have an eating disorder.
3. Understand the medical complications seen in teens who have anorexia and bulimia.
4. Be informed about the types of therapies available for adolescents who have anorexia and bulimia.
5. Know the definition of the female athlete triad.

A 15-year-old girl is admitted to the pediatric intensive care unit with a long history of weight loss and a serum sodium concentration of 189 mmol/L. She has been following a meal plan to gain weight and recently has stopped running 5 miles a day. Her fluid intake is approximately 16 oz of water a day. She denies fear of weight gain and body image disturbances, and a symptom review is negative. Physical examination reveals an alert and cooperative adolescent girl. Weight is 68 lb (53%); height, 62.75 in (34%); body mass index (BMI), 12.14 (53%); blood pressure, 113/74 mm Hg; heart beat, 67 beats/minute; and axillary temperature, 36°C. She has no signs of pubertal development and is mildly dehydrated. After extensive evaluation, she is determined to have an underlying eating disorder with no primary medical diagnosis. She is discharged from the hospital on day 16 without any complications, with follow-up care by an adolescent medicine specialist and therapist.

Introduction
Eating disorders in children, adolescents, and young adults represent serious mental health problems. These disorders can cause significant morbidity to body systems as well as devastating effects on the child’s psychosocial development, family dynamics, and education. Anorexia nervosa has the highest fatality rate of any mental health disorder. The hallmark of anorexia is the refusal or inability to maintain a normal body weight. The current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV TR) (1) definition of anorexia nervosa also includes amenorrhea of 3 months’ duration as part of this disorder; however, if the onset of the eating disorder occurs before menarche, the patient will have, by definition, primary amenorrhea.

Other important psychological symptoms of anorexia include body image distortions and fears of weight gain. Bulimia nervosa, on the other hand, is marked by recurrent binges (eating a large amount of food in a short period of time in a way that feels out of control) along with “compensatory” mechanisms such as purging, food restriction, and exercise to prevent weight gain. Patients who have bulimia often are at or above normal weight but still have concerns about their weight and shape.

Abbreviations

BMI: body mass index
CBT: cognitive behavioral therapy
DEXA: dual energy radiograph absorptiometry
DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
EDNOS: eating disorder not otherwise specified
IOP: intensive outpatient treatment
OCD: obsessive compulsive disorder

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Eating disorder not otherwise specified (EDNOS) includes clinically significant eating disorders that do not meet the DSM-IV TR criterion for anorexia or bulimia. For example, EDNOS includes patients with symptoms of anorexia who do not meet the 85% of expected weight criterion, or the amenorrhea criterion, as well as patients who experience bingeing and compensatory behaviors that occur less than twice a week on average. The patient described in the above vignette, who lacked the psychological symptoms of eating disorders, would be classified as having EDNOS. Of note, patients who have binge eating disorder, which is marked by recurrent bingeing without compensatory behaviors, currently are classified under EDNOS. Because most patients who have binge eating disorder are adults, this disorder will not be discussed in this article.

Anorexia and bulimia are fairly rare conditions. The prevalence of anorexia is 0.9% in women and 0.3% in men; the prevalence of bulimia is 1.5% in women and 0.5% in men. (2) The prevalence of EDNOS is 3.5% in women and 2% in men. (2) The onset of eating disorders usually occurs in mid adolescence for anorexia and late adolescence for bulimia. However, a majority of patients report body image concerns and disordered eating before adolescence.

The causes of anorexia and bulimia are complex and include biologic, psychological, and environmental components. The biologic underpinnings of eating disorders are not well understood. In studies of twins (usually comparing disordered eating), there is reasonable evidence that eating disorders have moderate to substantial heritability and that the inheritance pattern is multifactorial. Eating disorders occur more frequently in patients who have a family history of eating disorders, obesity, and mood disorders.

Girls who experience early puberty or are obese (who often were teased) are at increased risk for developing eating disorders. In fact, eating disorders often arise in the context of starting a diet to lose weight. Frequent comorbid psychiatric disorders are present, as well as personality traits such as perfectionism, concerns over self-control, sensitivity to rejection, and low self-esteem.

A past history of abuse, often sexual, is frequent among patients with eating disorders. It is unclear how much of the onset of an eating disorder during adolescence is due to environmental influences (eg, stress from developmental tasks of adolescence or pressure by explicit or implicit demands of the family for performance or appearance) or biologic factors (eg, increased hormones such as estrogen).

Social factors, such as the increase in obesity juxtaposed with the stigmatization of obesity and media images of ever-thinner women, clearly are important. Finally, some sports, such as cheerleading, figure skating, gymnastics, wrestling, crew, dance, and long distance running, may promote weight loss or thinness, thereby encouraging an eating disorder to develop. Although eating disorders more often are diagnosed in girls, boys are presenting with these problems increasingly.

Pediatricians can facilitate better outcomes for their patients who have eating disorders by early diagnosis and the institution of appropriate referrals and treatments. Screening for eating disorders should be part of the annual examination of adolescents. To facilitate early diagnosis, pediatricians should educate parents and others who interact with adolescents to recognize symptoms of eating disorders in youth.

Suspicious Behavior
Adolescents who have an eating disorder may develop changes in behavior. Behaviors include the assumption of a vegetarian, vegan, low fat, or “healthier” diet, scrutiny of ingredient lists, initiation of precise calorie counting, or weighing one’s self several times daily. Mealtime may demonstrate an emerging pattern of taking smaller portions or taking a longer period of time to eat. Some teens lose weight by increasing the duration and intensity of exercise in an attempt to utilize more energy.

As the eating disorder becomes more severe, an affected teen may have difficulty eating in social settings and will avoid eating with family and friends or develop deceptive or secretive behaviors, such as hiding food during social meals. Signs of purging activity include frequent trips to the bathroom after meals and discovery of empty containers of diet pills or laxatives. An adolescent who has an eating disorder may dress with extra layers of clothing to cover up signs of emaciation and to retain body heat.

Psychological Symptoms
The psychological symptoms of eating disorders are prominent, especially in patients who have anorexia. Perhaps most striking are the quasi-psychotic body image distortions that frequently accompany anorexia. A majority of patients perceive their bodies as large and unattractive, despite their emaciated state. This image distortion often makes maintaining a healthy weight very uncomfortable and sometimes intolerable for the affected patient. Fears of weight gain, wishes to lose weight, feelings of being “fat,” and discomfort with weight or figure, or both, arise from a negative body image. These psychological symptoms fuel food restric-
tion, food avoidance, and other behaviors that cause weight loss. The illness is worsened by the oft-present behavior of “denial about the seriousness of the illness” that makes patients resistant to treatment.

Anorexia is an ego-syntonic illness; that is, patients often do not want to give up what they see as acceptable behavior. Patients who have bulimia also have body image concerns but often to a lesser degree. However, “self-image unduly influenced by weight and shape” is a core symptom of bulimia and is the reason for the compensatory behaviors, such as vomiting and the usual restricting behaviors to prevent weight gain. Bulimia is an ego-dystonic illness; patients do not want their illness and often experience considerable shame.

Suggestive Physical Findings
Certain physical findings, some of which are medical complications, suggest that an adolescent may have an eating disorder (Table 1). In anorexia, nutritional insufficiency eventually will affect most body systems on both physical and functional levels. For example, decreased serum estrogen in females can cause delay of puberty, atrophy of the external genitalia, and bone demineralization. In males, decreasing testosterone concentrations may cause reduced beard growth. Increased vagal tone in males and females can produce bradycardia and orthostasis. Significant weight loss also can cause loss of muscle mass, resulting in diminished muscle strength and decreased cardiac muscle mass.

The key physical parameters in anorexia are the adolescent’s height, weight, and BMI, which should be tracked on a growth chart. Falling off from the usual percentiles is the earliest signal of a significant problem. Because the physical findings in bulimia are more subtle (if present at all), historical information and laboratory testing are particularly important to confirm the diagnosis. The physical findings of an eating disorder usually diminish when the patient has appropriate weight gain.

Questions to Ask
If an adolescent falls off the weight curve, slows down in statural growth, demonstrates a delay in onset of puberty or progression of pubertal development, has primary or secondary amenorrhea, or displays suspicious behaviors or certain physical findings, further questioning is indicated. Questioning should address weight history, body image concerns, exercise history, menstrual history, diet history, and a system review focused on eating disorders (Table 2). Another useful tool for evaluating the symptoms of an eating disorder, including behaviors and psychological symptoms, is the Eating Disorders Examination–Questionnaire, which can be found at the following website under assessment measures: http://

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Table 1. Physical Findings in Adolescents Who Have an Eating Disorder

<table>
<thead>
<tr>
<th>System</th>
<th>Anorexia</th>
<th>Bulimia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>Cheilosis, acrocyanosis, hypercarotenimia, alopecia, xerosis, acne, lanugo, pallor</td>
<td>Periorbital petechiae, Russell sign (calluses over the PIP joints in the hands)</td>
</tr>
<tr>
<td>Orofacial</td>
<td>Halitosis</td>
<td>Injury to the palate and posterior pharynx, dental caries, enamel erosion, parotid gland enlargement, submandibular adenopathy</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Palpable stool secondary to constipation, rectal prolapse, scaphoid abdomen</td>
<td>Abdominal fullness, gastric dilatation</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Bradycardia, orthostatic hypotension, arrhythmia, mitral valve prolapse/murmur</td>
<td>Arrhythmia, orthostasis</td>
</tr>
<tr>
<td>Breasts and genitourinary</td>
<td>Breast atrophy, atrophic vaginitis and atrophy of the female external genitalia</td>
<td>Pneumothorax, pneumon Mediastinum, aspiration</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pneumothorax or aspiration secondary to vomiting, pulmonary edema during refeeding</td>
<td>Pneumothorax, pneumon Mediastinum, aspiration</td>
</tr>
<tr>
<td>Bone</td>
<td>Fractures due to bone mineralization loss</td>
<td></td>
</tr>
<tr>
<td>Endocrine and metabolic</td>
<td>Delayed puberty, arrested growth, hypothermia, weakness, reduced beard growth in males</td>
<td></td>
</tr>
<tr>
<td>Neurologic and mental status</td>
<td>Neurocognitive deficit, diminished muscle strength, peripheral neuropathy, movement disorder</td>
<td></td>
</tr>
</tbody>
</table>

PIP = proximal interphalangeal.
Comorbid Mental Illness

Comorbid mental disorders are present in the majority of patients who have anorexia and bulimia. The most common comorbid disorders in anorexia include major depression, anxiety disorders such as obsessive compulsive disorder (OCD), generalized anxiety disorder, and social phobia. Patients who have bulimia often have comorbid mood disorders (both major depression and bipolar disorder), anxiety disorders, and substance use disorders. Bulimic patients tend to be more volatile and impulsive and may exhibit high-risk behaviors, such as tobacco smoking, excessive use of drugs or alcohol, sexual promiscuity, or stealing.

It is important to differentiate symptoms due to a comorbid mental illness from symptoms due to the eating disorder itself. For example, patients who have anorexia often have low or irritable moods, impaired sleep, loss of energy, impaired concentration, and withdrawal. These symptoms may be due to malnutrition or may be due to a major depressive disorder. It is useful to determine whether these symptoms of depression were present before the eating disorder or arose after the eating disorder began. OCD symptoms related to food and eating should not be confused with symptoms of a coexisting OCD condition.

Assess Psychosocial Impact

Eating disorders disrupt the developmental trajectory of children and teens, which then places them under increased stress. In the case of anorexia, the time taken up by the eating disorder can make it difficult for the patient to partake in extracurricular and social activities. Typically, patients who have anorexia are compliant, dutiful, and hard-working, particularly in academics and sports. They rarely break rules or cause upsets with family or friends. However, the progression of anorexia may result in isolation from friends and families. Those around them do not know how to react to the weight loss.

Patients who have bulimia often hide their illness more and continue to function more normally on the surface, while suffering with their eating disorder. Disrupted schooling due to time spent attending treatment appointments or undergoing hospitalizations may stress a teen further. Academic performance and functioning at school may or may not be disrupted.

All children and teens should be considered in the context of stress in the family: the family’s messages about eating, food, and weight; the family’s pressure for perfectionist performance in a variety of areas; family history of mental illness or eating disorders; and how the eating disorder is affecting the family. Families often report increased stress and more difficult relationships because of the eating disorder.

Triage for Medical Stability and Safety

Some patients, particularly patients who have anorexia and are at low weight or purging and patients who have bulimia who are purging significantly, need immediate medical attention. Suicidality is more common in patients who have bulimia than in the general population.

### Table 2. Questions for Adolescents With a Possible Eating Disorder

<table>
<thead>
<tr>
<th>Weight History</th>
<th>Weight History Questions</th>
<th>Body Image</th>
<th>Are you satisfied, dissatisfied, distressed with your current weight; body shape?</th>
<th>Have you every thought that you were too fat or in danger of getting too fat?</th>
<th>At what weight would you like to be?</th>
<th>How often do you weigh yourself?</th>
<th>What percent of the day are your thoughts occupied with food, eating, body size, or shape?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Image</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise History</td>
<td>Exercise History Questions</td>
<td>Do you exercise? If so, how frequently do you exercise?</td>
<td>What exercises do you do?</td>
<td>How long are your workouts?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual History</td>
<td>Menstrual History Questions</td>
<td>When was your very first menstrual period?</td>
<td>When was your last menstrual period?</td>
<td>How many menstrual periods have you had in the past 6 months?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet and Eating History:</td>
<td>Diet and Eating History Questions</td>
<td>Do you restrict your calories?</td>
<td>Do you restrict or avoid certain foods?</td>
<td>Do you have problems controlling your food intake?</td>
<td>Do you engage in any of these behaviors: vomiting, spitting, ruminating, use of laxatives, diuretics, use of diet pills or syrup of ipecac?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom Review:</td>
<td>Symptom Review Questions</td>
<td>Have you experienced: sensitivity to cold, thinning hair, swollen glands in cheek, lightheadedness, irregular heart beat, weight loss, loss of periods, vomiting, or constipation?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

suicide and cardiac complications are the leading causes of death. All patients should be assessed for medical stability (including laboratory evaluation) and for safety. Patients with suicidality may require inpatient psychiatric hospitalization; patients with medical instability may need a medical admission.

**Anorexia Nervosa**

**Case History**

A 12-year-old boy who had a previous weight of 93 lb (60%) and a BMI of 19.6 (75%) is admitted to the pediatric gastroenterology service with a history of a 20-lb weight loss over 5 months, early satiety, and decreased appetite. Physical examination reveals a thin adolescent with a weight of 72.6 lb (14%), height of 57.8 in (34%), and a BMI of 15.6 (11%). His calculated ideal weight was 84.9 lb (see formula below), and he is at 87.9% of ideal weight. Screening laboratory tests, abdominal ultrasonography, and upper and lower endoscopies are unremarkable. The patient displays anxiety around meals, voices increasing concerns about caloric counts and weight gain, and has initiated restriction of his caloric intake with deceptive behaviors. He continues to lose weight in the hospital. A diagnosis of anorexia is established, and the patient is placed on an eating disorder treatment protocol. Over 3 weeks, he gains weight and is transferred to residential care for treatment of anorexia.

**Definition**

In the restrictive type of anorexia, the patient does not engage in binge eating or purging behaviors such as self-induced vomiting or using laxatives, diuretics, or enemas. In the binge-eating/purging type, the patient regularly engages in binge eating or purging behaviors. Most adolescents fall into the restrictive type. Table 3 lists the current *DSM-IV-TR* and proposed *DSM-V* diagnostic criteria for anorexia.

**Ideal Body Weight Calculation**

For adolescents, the ideal body weight (in kilograms) is calculated by the formula: Square of the height in meters multiplied by the 50th percentile BMI for age and sex.

\[
\text{BMI} = \frac{\text{Calculated ideal weight}}{(\text{Height in meters})^2} = \frac{84.9}{(1.626)^2} = 19.4 \text{ kg/m}^2
\]

For example, the ideal weight of a 14-year-old girl who is 64 in (1.626 m) in height is calculated as follows:

\[
(1.626 \times 1.626 \times 19.4 = 51.3 \text{ kg (112.9 lb})
\]

**Conditions That May Cause Weight Loss**

Adolescents who have anorexia may not disclose a complete or truthful history. Therefore, it is important for the

---

**Table 3. Diagnostic Criteria for Anorexia Nervosa**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>DSM-IV-TR 2000</th>
<th>Proposed for DSM-V 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>Refusal to maintain a body weight more than 85% of weight expected for height and age; failure to gain weight during a period of growth with body weight less than 85% expected for height and age.</td>
<td>Restriction of energy intake relative to requirements leading to a markedly low body weight (less than that minimally expected for age and height).</td>
</tr>
<tr>
<td>Menstruation</td>
<td>In postmenarchal females, the absence of three consecutive menstrual cycles (hormonally induced menstruation is excluded).</td>
<td>This criterion is likely to be deleted.</td>
</tr>
<tr>
<td>Fear of weight gain</td>
<td>Although underweight, an intense fear of gaining weight or becoming fat.</td>
<td>Intense fear of gaining weight or becoming fat, although underweight, or persistent behavior to avoid weight gain, although at a markedly low weight.</td>
</tr>
<tr>
<td>Body image</td>
<td>A disturbance in the way one's body weight or shape is experienced; denial of the seriousness of low body weight; an undue influence of body weight or shape on self-evaluation.</td>
<td>No change from DSM-IV-TR.</td>
</tr>
</tbody>
</table>

*DSM-IV-TR* = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; *DSM-V* = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.
To consider and rule out other medical and mental health conditions that could lead to weight loss or amenorrhea. Such conditions are listed in Table 4. The initial laboratory evaluation should include a complete blood count with sedimentation rate; general chemistries; amylase, lipase, magnesium, phosphorus, calcium, and thyroid stimulating hormone concentrations; urinalysis; and serum human chorionic gonadotropin (HCG) concentration for females. If there are concerns about celiac disease, an immune globulin A and serum tissue transglutaminase determination are helpful; a baseline electrocardiogram is useful, especially if bradycardia, hypotension, arrhythmia, or other cardiac problems are present. Besides the human chorionic gonadotropin test, measuring follicle-stimulating hormone, luteinizing hormone, prolactin, and estradiol concentrations may help elucidate the cause of amenorrhea.

Anorexia: Complications
Medical complications of anorexia are listed in Table 5 (see Table 1 also). The likelihood of these complications increases as the anorexic patient further loses weight from his or her ideal weight. Generally, medical complications begin to resolve once appropriate weight gain occurs, and achieving an adolescent’s ideal weight typically corrects most complications. However, bone loss due to hypothalamic amenorrhea in female patients or secondary to low testosterone in male patients does not automatically correct with weight gain, although some improvement does occur. Fluctuations in the patient’s weight, recurrent periods of amenorrhea, elevated cortisol concentrations, and lower than optimal insulin growth factor-I concentrations during recovery may lead to incomplete catch-up.

Although weight gain with resumption of normal menstruation is the most effective means of increasing bone density in adolescent females who have anorexia, a recent research study has determined that physiologic estrogen replacement is effective in increasing bone mass and may be a therapeutic option in girls with anorexia nervosa and low bone density who are refractory to multidisciplinary therapy and are unable to gain weight. (3) Oral estrogen has not been shown to help prevent or treat bone demineralization in females; indeed, withdrawal bleeding from oral contraceptive use may falsely reassure the patient who is not gaining weight that bone density is recovering.

Anorexia: When to Hospitalize
The care for an adolescent with anorexia depends on the pediatrician’s initial review of the history, physical findings, and laboratory data. Guidelines for the hospitalization of adolescents and young adults who have anorexia are listed in Table 6. Adolescents who are medically unstable and require admission often are 75% or less of their ideal weight and have other signs of medical instability; in addition, the failure of outpatient treatment is an indication in itself for medical admission.

<table>
<thead>
<tr>
<th>Table 4. Conditions That May Cause Weight Loss With or Without Amenorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal:</strong> Inflammatory bowel disease, celiac disease, achalasia</td>
</tr>
<tr>
<td><strong>Endocrine:</strong> Hyperthyroidism, Addison disease, hypopituitarism, type 1 diabetes mellitus</td>
</tr>
<tr>
<td><strong>Malignancy:</strong> Lymphoma, central nervous system tumor, occult malignancies</td>
</tr>
<tr>
<td><strong>Infectious:</strong> Human immunodeficiency virus, tuberculosis</td>
</tr>
<tr>
<td><strong>Mental Health:</strong> Depression, substance abuse, use of medications such as diet pills</td>
</tr>
<tr>
<td><strong>Other:</strong> Pregnancy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5. Medical Complications of Anorexia Nervosa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>System</strong></td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Hematologic</td>
</tr>
<tr>
<td>Endocrine and metabolic</td>
</tr>
<tr>
<td>Renal</td>
</tr>
<tr>
<td>Neurologic</td>
</tr>
</tbody>
</table>
Anorexia: Inpatient Medical Management

In many settings, an adolescent medicine specialist, a hospitalist, or a psychiatrist will manage the inpatient medical rehabilitation of an adolescent afflicted with anorexia. However, in some circumstances the pediatrician will serve as the treating physician. The goals of a medical admission are several: initiate correction of the adolescent’s malnourished state, promote healthy eating and weight gain, correct metabolic disturbances, prevent the refeeding syndrome, rule out psychiatric comorbidities, and develop a plan of care after hospital discharge.

A multidisciplinary team consisting of a medical specialist, psychiatrist, nutritionist, and social worker achieves such care best. Using a written eating disorder protocol helps prevent misunderstandings among all parties; cooperation and weight gain allow the patient to gain privileges and serve as incentives. See the references for an example of an eating disorder protocol (5) as well as the American Psychiatric Association guidelines for care. (6) A copy of the eating disorder protocol at MassGeneral Hospital for Children is available in the online edition of this issue of Pediatrics in Review.

At our institution, initially we place the adolescent on bed rest with a bedside commode. An intravenous line is established to provide quick intravenous access should an emergent situation develop. Administering intravenous fluids may account for initial weight gain on admission; it is important to establish a baseline weight the morning after supplemental intravenous fluids are discontinued. In the acute hospital setting, the patient is expected to gain approximately ½ lb daily.

Our procedure is to calculate the goal number of calories for weight gain; the starting daily calorie intake is determined by estimating the patient’s 24-hour caloric intake in the day before admission and adding 250 calories. Typically, the initial 24-hour meal plan is no higher than 1,250 calories, and the caloric intake is increased by 250 calories daily until goal calories are reached and appropriate daily weight gain occurs. Naso-gastric feedings may be used if the teenager refuses to take in appropriate calories or becomes medically unstable. Nutritional rehabilitation of adolescents who have anorexia very rarely requires parenteral nutrition.

The Refeeding Syndrome

The refeeding syndrome describes the metabolic disturbances that occur as a result of reinstatement of nutrition to patients who are starved or severely malnourished. Reintroducing food to a patient with anorexia may cause a rapid fall in phosphate, magnesium, and potassium, along with an increasing extracellular volume, that can lead to a variety of complications. As the adolescent’s caloric intake increases, low levels of serum phosphorus can lead to rhabdomyolysis, decreased cardiac motility, cardiomyopathy, respiratory and cardiac failure, edema, hemolysis, acute tubular necrosis, seizures, and delirium. Serum phosphorus, magnesium, and electrolyte concentrations should be measured daily during the first week in the hospital. Some clinicians begin oral supplementation with phosphorus on the first hospital day, while some wait until the serum phosphorus concentration begins to decline.

### Table 6. Criteria for Hospitalization of Adolescents and Young Adults Who Have Eating Disorders (4)

<table>
<thead>
<tr>
<th>Anorexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight &lt;75% of ideal body weight for age, gender, and stature</td>
</tr>
<tr>
<td>Continued weight loss despite intensive outpatient therapy</td>
</tr>
<tr>
<td>Acute weight decline and refusal of food</td>
</tr>
<tr>
<td>Hypothermia (body temperature &lt;96°F)</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;90 mm Hg</td>
</tr>
<tr>
<td>Resting heart rate &lt;50 beats/min during the day and &lt;40 beats/min during the night</td>
</tr>
<tr>
<td>Orthostatic changes in blood pressure (&gt;10 mm Hg)</td>
</tr>
<tr>
<td>Orthostatic changes in pulse (&gt;20 beats/min)</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
</tr>
<tr>
<td>Arrhythmia</td>
</tr>
<tr>
<td>Suicidality (ideation, plan, or attempt)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bulimia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
</tr>
<tr>
<td>Electrolyte disturbances: serum potassium &lt;3.2 mEq/L</td>
</tr>
<tr>
<td>or serum chloride &lt;88 mEq/L</td>
</tr>
<tr>
<td>Esophageal tears</td>
</tr>
<tr>
<td>Cardiac arrhythmias including prolonged QTc</td>
</tr>
<tr>
<td>Hypothermia</td>
</tr>
<tr>
<td>Suicide risk</td>
</tr>
<tr>
<td>Intractable vomiting</td>
</tr>
<tr>
<td>Hematemesis</td>
</tr>
<tr>
<td>Failure to respond to outpatient treatment</td>
</tr>
</tbody>
</table>

AAP=American Academy of Pediatrics.
Adapted from AAP, Committee on Adolescence. Identifying and treating eating disorders. Pediatrics. 2003;111:204–211.
Anorexia: Discharge Planning

Generally, when an adolescent achieves a steady weight gain of about ½ lb daily, stabilizes vital signs, and has normal serum chemistries and a plan of care in place, discharge to the next level of care is appropriate. Inpatient medical admissions often range in duration from 7 to 10 days.

Most adolescents do not go directly home after hospitalization for anorexia. Although stabilization of vital signs, initiation of weight gain, and initiation of healthy eating are goals for the hospitalization, the work around disordered thinking and eating and body image requires a therapeutic milieu that is more appropriate for treating these problems such as a residential program devoted to the treatment of eating disorders. The pediatrician can guide the family in finding the most appropriate programs that are covered by the family’s health insurance.

Anorexia: Levels of Care

Patients who have anorexia may be treated as an outpatient or may require residential or partial hospitalization. If a patient is treated as an outpatient, it is helpful to have a back-up plan for a hospitalization if the patient is unable to make reasonable weight gains. Ideally, outpatient treatment should consist of a treatment team of at least a mental health therapist (psychiatrist, psychologist, or social worker), nutritionist, and pediatrician who work in close collaboration. Often, a psychopharmacologist and family therapist are needed to complete the treatment team.

Levels of care for anorexia other than inpatient medical hospitalization include placement in inpatient psychiatric hospitals, acute residential hospitals, partial or day hospitals, intensive outpatient treatment (IOP), outpatient treatment, long-term residential centers, and therapeutic boarding schools. Acute residential programs provide treatment for weeks to months in an unlocked hospital setting. Partial or day hospitalization provides several hours a day of structured time at a hospital, including some meals, with the patients leaving the program at night. IOP consists of group therapy, and possibly a meal for a few hours a day, several days a week. Long-term residential treatment centers or therapeutic boarding schools can provide long-term (ie, months to years) treatment for difficult or intractable cases.

Anorexia: Pediatrician Role in Outpatient Management

The pediatrician may serve as coordinator of the patient’s care or as referring doctor to an adolescent medicine specialist or psychiatrist, depending on his or her comfort level with adolescents who have eating disorders. Some pediatricians prefer to coordinate care with another specialist and see the patient periodically for weight checks.

Initially, it is helpful to place patients who have anorexia into mild, moderate, or severe categories. An adolescent who is 85% to 95% of ideal body weight is mildly ill, 75% to 85% of ideal body weight is moderately ill, and <75% of ideal body weight is severely ill. Severely ill adolescents who have anorexia usually require a higher level of care. In general, as the teen’s percent of ideal weight decreases, more medical issues arise and more intervention is necessary. However, each teen afflicted with anorexia has a unique set of medical, mental, family, and social issues.

As noted, a key element in the outpatient management of teens who have anorexia is the establishment of a treatment team. Each member of the team should be comfortable working with adolescents who have an eating disorder and each should have a clearly defined role. If there is a question of comorbidity, a psychiatric consultation is warranted. It is critical that team members communicate frequently with each other (often by email) for updates and to prevent miscommunication and team splitting. In this setting, the pediatrician can monitor the teen’s medical stability, weight, and laboratory data and counsel the teen and his or her family. The pediatrician can answer questions regarding medications, exercise, laboratory testing, menstruation, and diet. Pediatrician visits frequently are on a weekly basis until steady progress occurs.

Patients who have anorexia should have a daily multivitamin supplementation with at least 400 to 800 IU of vitamin D; 1,200 mg elemental calcium is recommended daily also. Because low bone density is seen often in anorexia, a dual energy radiograph absorptiometry (DEXA) scan is recommended for those adolescents who have sustained 6 months of amenorrhea. The DEXA usually is repeated on an annual basis if amenorrhea continues.

Teens who have mild anorexia should have a nutritional plan that will ensure weight gain of ½ to 1 lb weekly. Exercise usually is restricted, especially if weight gain does not occur or if the adolescent weighs less than 90% of his or her ideal weight. The pediatrician should evaluate the teen every few weeks, and the teen should have ongoing visits with the therapist and nutritionist. Clear guidelines, based on medical parameters (such as weight, blood pressure, and pulse), should be given to the patient and his or her family as to when a higher level of care is warranted.
Weekly medical evaluations generally are indicated if the teen is moderately ill with anorexia (75% to 85% ideal weight). No exercise should be allowed. Clear guidelines should be set for a higher level of care and clearly communicated to the adolescent, his or her family, and other team members. Typically, some patients may need IOP, partial hospitalization, or even residential care if outpatient care is not helpful.

Adolescents who weigh 75% or less than their ideal weight generally are hospitalized at a residential treatment center. If medically unstable, they usually are stabilized in an inpatient medical setting and then transferred to a residential treatment center.

It is important to have parents as allies in the treatment effort. At times, parents may not be helpful due to subtle, complex child–parent relationships that are counterproductive. In this situation, family therapy may be helpful.

**Anorexia: Psychopharmacology**

A review of randomized controlled trials for the treatment of anorexia and bulimia was published in 2007 by the Evidence-based Practice Center of the University of North Carolina at Chapel Hill. It was concluded that the evidence for medication treatment for anorexia was “sparse and inconclusive.” (7) In general, medications are used in patients who have anorexia to treat their comorbid psychiatric conditions or psychiatric symptoms. In addition, care must be taken to avoid, or use cautiously, medications that cause weight loss or weight gain, appetite suppression, hypotension, or prolonged QTc interval. There are no medications indicated for weight maintenance; a randomized, controlled trial comparing time to relapse in patients on fluoxetine versus placebo showed no difference. (8)

**Anorexia: Therapies**

The types of therapies commonly used to treat patients who have eating disorders include cognitive behavioral therapy (CBT), dialectic behavioral therapy, psychodynamic therapy, and different modalities of family therapy. Nutritional therapy includes helping patients eat a variety of foods (ie, stop food avoidance), improve eating habits, stop compensatory behaviors, and gain weight. The expected weight gain for outpatients is ½ to 1 lb a week; for inpatient or residential patients, expected weight gain is up to 4 lb a week.

Good evidence exists for family-based therapy in the treatment of anorexia in children and adolescents, but not adults, (7) especially in children and adolescents who have early onset and short duration of illness. Family-based therapy as developed at the Maudsley Hospital in London is an outpatient treatment designed to avoid hospitalization. In the first stage of the treatment, the family takes control over food and eating and helps the child or teen begin to restore his or her weight and normal eating habits. In stage two, control is transferred back to the patient as recovery begins. Phase three is a termination phase that focuses on developmental issues and relapse prevention. (9)

**Bulimia**

**Case History**

An 18-year-old college freshman is seen for recurrent vomiting on recommendation by the college Dean’s office after her roommates report witnessing her behavior of frequent vomiting. She has a history of restrictive anorexia that evolved into bulimia. Physical examination is remarkable for 105% of ideal weight and right parotid gland enlargement. Laboratory examination reveals mild hypokalemia. Despite enrolling in an IOP eating disorder program, she continues to induce vomiting twice daily. A college administrator observed her eating eight desserts at one meal and going to the bathroom after each dessert was consumed. The college administration mandates that she leave college and enter residential care for the eating disorder. After 1 year of residential and outpatient care, she is symptom-free. On return to college, she immediately begins to induce vomiting twice a day.

**Definition**

The current criteria for diagnosing bulimia and the *DSM* proposed changes in those criteria are listed in Table 7. Bulimia is divided into two subtypes, purging and nonpurging. Binge eating is seen in both subtypes. The purging subtype describes an individual who engages regularly in self-induced vomiting or the misuse of laxatives, diuretics, or enemas. The nonpurging subtype describes an individual who uses other inappropriate compensatory behaviors, such as excessive exercise or fasting to burn calories. It is important to note that patients who have bulimia often are not low weight and thus may easily hide their eating disorder.

**Bulimia: Medical Complications**

As noted in Table 1, several physical findings signal a medical complication from bulimia, such as periorbital petechiae, Russell sign (calluses over the proximal interphalangeal joints in the hands), injury to the palate and posterior pharynx, dental caries, enamel erosion, parotid gland enlargement, submandibular adenopathy, arrhythmia, orthostasis, pneumothorax, pneumonmediastinum, and aspi-
ration. Table 8 lists specific gastrointestinal, cardiac, metabolic, endocrine, and dental complications. Electrolyte disturbances, depending on the method of purging, are common in bulimia secondary to induced vomiting or the use of laxatives and diuretics. Syrup of ipecac can cause cardiomyopathy; ipecac is still available for purchase through the Internet. Dentists may notice perimylolysis (loss of dental enamel), a sign indicative of purging activities.

### Indications for Inpatient Hospitalization for Adolescents Who Have Bulimia

Adolescents with bulimia may face life-threatening events. Of most concern are electrolyte disturbances (particularly hypokalemia) and cardiac issues, such as syncope or a prolonged QTc interval. Table 6 lists guidelines for the hospitalization of adolescents who have bulimia. Self-destructive actions such as cutting or suicidal ideation generally warrant inpatient admission.

### Bulimia: Pediatrician Role in Outpatient Management

For patients who have bulimia, the pediatrician can coordinate the services of an interdisciplinary team that includes a nutritionist and therapist. Adolescents who have bulimia should be seen periodically to assess medical stability; teens who are purging may need to be seen weekly to monitor electrolyte levels. Hypokalemia is corrected either by oral potassium supplementation or intravenous supplementation, depending on the severity of the hypokalemia. Indications for calcium and vitamin D supplementation are the same as those for patients who have anorexia. Administration of a proton-pump inhibitor may help teens who have reflux disease caused by recurrent vomiting. Promoting hydration, a high fiber diet, and moderate exercise (unless contraindicated because of medical instability) may help improve the health of patients who are dependent on laxatives. Tooth brushing with sodium bicarbonate toothpaste after vomiting may improve dental hygiene. Teens who have bulimia who have been amenorrheic for 6 months or more should have a DEXA scan.

### Bulimia: Levels of Care

Patients who have bulimia generally respond to outpatient treatment, although patients experiencing escalating or severe symptoms that do not respond often warrant acute residential or partial hospitalization, or IOP.

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**Table 7. Diagnostic Criteria for Bulimia Nervosa**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>DSM-IV-TR 2000</th>
<th>Proposed for DSM-V 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binge eating</td>
<td>Eating an amount of food in a discrete period of time (2 h) that is definitely larger than most people would eat</td>
<td>No changes</td>
</tr>
<tr>
<td>Compensatory behavior</td>
<td>Recurrent inappropriate compensatory behavior in order to prevent weight gain such as self-induced vomiting, misuse of laxative, diuretics, enemas, or other medications; fasting; or excessive exercise</td>
<td>No changes</td>
</tr>
<tr>
<td>Frequency of above behaviors</td>
<td>Binge eating and inappropriate compensatory behaviors occur, on average, twice weekly for the previous 3 mo</td>
<td>Binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 mo</td>
</tr>
<tr>
<td>Self-evaluation</td>
<td>Unduly influenced by body shape and weight</td>
<td>No changes</td>
</tr>
<tr>
<td>Relation to anorexia nervosa</td>
<td>The disturbance does not occur exclusively during episodes of anorexia nervosa</td>
<td>No changes</td>
</tr>
</tbody>
</table>


**Table 8. Medical Complications of Bulimia Nervosa**

<table>
<thead>
<tr>
<th>System</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Gastroesophageal reflux, Mallory-Weiss tear, gastritis</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Cardiomyopathy secondary to ipecac poisoning, arrhythmia</td>
</tr>
<tr>
<td>Metabolic</td>
<td>↑↓ sodium, ↓↑ potassium, ↑↓ chloride, ↑↓ bicarbonate, ↑↓ pH</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Irregular menstruation</td>
</tr>
<tr>
<td>Dental</td>
<td>Caries, enamel loss</td>
</tr>
</tbody>
</table>
Acute residential care is particularly indicated when patients with bulimia are unable to control their behaviors at night.

**Bulimia: Psychopharmacology**

Reasonable evidence indicates that fluoxetine helps reduce the core symptoms of bingeing and purging. A daily dose of 60 mg appears to be more efficacious than a dose of 20 mg. Of note, these trials were time-limited, and the medication treatments resulted in symptom reduction not remission (ie, absence of symptoms). If fluoxetine is not tolerated, other selective serotonin reuptake inhibitors at maximal approved doses may be used for symptom reduction.

**Bulimia: Psychotherapy**

Strong evidence indicates that CBT helps treat bulimia. CBT aims to change both patient cognition and behavior. In the CBT program by Fairburn, the core pathology of the eating disorder is “over-evaluation of shape and weight and its control.” In this time-limited treatment, the patient’s eating disorder is assessed and the patient learns about eating disorders. After forming a personalized plan for treating the eating disorder, the patient starts “real time monitoring” of food intake and behaviors. The patient tries to establish “regular eating,” eating meals and snacks in a normal way at normal times, without using behaviors to compensate for food intake. After establishing a pattern of regular eating, the patient learns “maintaining mechanisms” to address dietary restricting or restraint, over-evaluation of weight and shape, control over eating, and monitoring events or mood changes in eating behaviors.

**Eating Disorder Not Otherwise Specified and Disordered Eating**

Patients given a diagnosis of EDNOS whose symptoms resemble anorexia should receive the same care and treatment as patients who have anorexia. Similarly, patients having EDNOS whose symptoms resemble bulimia should receive the same care and treatment as patients who have bulimia. Care must be taken not to view EDNOS as a less serious illness than anorexia. In addition, a patient’s eating disorder often is dynamic and changes with illness progression and treatment.

Disordered eating refers to eating disorder behaviors such as occasional restricting, fasting, overeating, avoidance of risk foods, use of purgatives, and heavy exercise to lose weight. If the symptoms are transient and not accompanied by the psychological symptoms of eating disorders, these behaviors may represent a variant of normal. On the other hand, these behaviors may be a harbinger of the development of an eating disorder. Patients who exhibit disordered eating should be monitored closely and evaluated for psychological symptoms associated with eating disorders.

**Female Athlete Triad**

The term “female athlete triad” describes the constellation of low energy availability with or without an eating disorder, hypothalamic amenorrhea, and osteoporosis in a female athlete. Energy availability refers to dietary energy intake minus exercise energy expenditure. Energy availability is the amount of dietary energy remaining for other bodily functions. Some athletes develop abnormal eating patterns, such as dietary restriction, fasting, binge eating, and purging or may use diet pills, laxatives, diuretics, or enemas to maintain or lose weight, thereby creating low energy availability.

Most of these affected athletes develop low body fat composition, which contributes to a hypoestrogenic state and amenorrhea. Athletes who participate in sports in which leanness is emphasized, such as gymnastics, ballet, diving, figure skating, aerobics, and running, are at risk for developing the female athlete triad. Unfortunately, low body weight and continued strenuous training often is encouraged in certain sports, thereby making it difficult for the patient to decrease her training to increase energy availability and restart menstrual cycles.

As in patients who have anorexia, hypogonadotropic hypogonadism along with estrogen deficiency contribute to reduction in bone mineralization density. As noted, there are no data to support the use of oral contraceptives in the prevention of bone loss. At times, the female athlete may have a normal weight but still present with low body fat and amenorrhea, placing her at risk for bone demineralization.

The pediatrician should consider the possibility of a patient having the female athlete triad during a preparticipation physical examination or if an athlete presents with low weight, amenorrhea, stress fracture, or disordered eating. Treatment should be multidisciplinary, especially if an eating disorder is present, and may require limiting or eliminating participation in athletics. It is important for the pediatrician to work with the athlete’s coach to most effectively treat the patient. A written contract that includes the athlete, pediatrician, and coach may be necessary to enforce treatment strategies.

The athlete’s energy availability must be increased and eating habits improved. Daily calcium (1,200 mg) and vitamin D (400 to 800 IU) supplementation along with weight bearing exercises are recommended to help pre-
serve bone health. A DEXA scan is indicated if there is a stress fracture or a cumulative total of 6 months or more of amenorrhea. The best protection for the female athlete’s bone health is to remain eumenorrheic and maintain a healthy balance between exercise, energy availability, and body weight.

Pro-Mia and Pro-Ana Sites
Some patients who have eating disorders visit Internet sites such as Pro-Mia or Pro-Ana that promote and encourage eating disorders as a chosen lifestyle. Parents should be educated about the presence of these sites, and, if possible, block access to these sites on home computers. Ultimately preventing a patient from searching such Internet sites depends on the patient’s motivation, or lack thereof, to recover from his or her eating disorder.

Prevention
Pediatricians play an integral role in the early detection and prevention of eating disorders. Prevention includes assessing for mental illness as well as stress that may predispose a child or teen to an eating disorder, as well as referring a patient early for mental health evaluation and treatment. Pediatricians also should screen children and teens who are obese (especially those who are teased) and those who have experienced early puberty for behaviors suggestive of an eating disorder. Patients who are struggling with obesity should be encouraged to improve their diet and activity rather than simply “lose weight.” Routine screening for body image concerns or “disordered eating” practices by pediatricians often can preempt eating disorders. Finally, to facilitate early detection and treatment, pediatricians should be vigilant for symptoms and signs of eating disorders, such as new onset “healthy dieting,” weight loss, weight fluctuations, or electrolyte abnormalities.

Prognosis
Steinhausen conducted an analysis of multiple outcome studies for anorexia (12) and bulimia (13): 46% of patients who had anorexia and 45% of patients with bulimia recovered from their illnesses; 33% of patients who had anorexia and 27% of patients who had bulimia showed improvement; and 20% of patients who had anorexia and 23% of patients who had bulimia had a chronic course. The mean crude mortality rates from these studies were 5% for patients who had anorexia and 0.32% for patients who had bulimia. Steinhausen noted great variation in outcome parameters. Of note, Crow et al. used the National Death Index and records from an outpatient eating disorders clinic to complete an analysis of mortality over 8 to 25 years for 1,885 individuals who had anorexia nervosa. (14) In this analysis, they found crude mortality rates of 4.0% for anorexia, 3.9% for bulimia, and 5.2% for EDNOS, highlighting that the risks of the latter two illnesses go against the general thought that these disorders are less fatal than anorexia.

Acknowledgment
The authors would like to express their gratitude to Dr. David B. Herzog for his careful review of this article.

Summary
- Based on widely accepted clinical practice, pediatricians should monitor patients for warning signs of anorexia. Warning signs include rapid or severe weight loss, falling off of growth percentiles, excessive dieting or exercising, constriction of food choices, calorie counting, and excessive concern with weight or body shape.
- Pediatricians should monitor patients for warning signs of bulimia, which include weight cycles, excessive concern with weight or body shape, trips to the bathroom after meals, electrolyte abnormalities, swollen parotid glands, or knuckle abrasions.
- Based on strong research evidence, girls who have anorexia have a high prevalence of hemodynamic, hematologic, endocrine, and bone density abnormalities. (15)
- Based on good research evidence, medication treatment for anorexia is “sparse and inconclusive.” (7)
- Based on widely accepted clinical practice, patients who have anorexia should refeed to a healthy weight range at a rate of 0.5 to 1 lb a week and may need hospitalization if they are unable to improve as an outpatient.
- Based on some research evidence, fluoxetine is helpful in reducing some symptoms of bulimia. (10)
- Based on strong research evidence, CBT is helpful for bulimia. (11)
- Based on good research evidence, disordered eating, eating disorders, and amenorrhea occur more frequently in sports that emphasize leanness. (16)
- Based on some research evidence, the long-term medical consequence of anorexia is largely restricted to bone loss, if the patient can restore weight. There are no long-term medical consequences of bulimia if the patient can recover without damaging his or her teeth or gastrointestinal tract or endure cardiac damage.
References


Suggested Reading

## PIR Quiz

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

NOTE: Beginning in January 2012, learners will be able to take *Pediatrics in Review* quizzes and claim credit online only. No paper answer form will be printed in the journal.

<table>
<thead>
<tr>
<th>Question</th>
<th>Details</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>A 15-year-old girl is hospitalized because of anorexia nervosa, with a BMI at 75% of ideal body weight. She gains weight and is discharged to a residential treatment setting. Her parents ask you if there are any medical complications that they need to monitor in the future. Your best response is that, if she maintains a normal body weight, she</td>
<td>A. Does not need medical monitoring.</td>
</tr>
<tr>
<td>2.</td>
<td>A 14-year-old girl is hospitalized because of anorexia nervosa, with a BMI at 65% of ideal body weight. Tube feedings are initiated, and she receives vitamin and mineral supplements. The supplement she is most likely to require is</td>
<td>A. Phosphorus.</td>
</tr>
<tr>
<td>3.</td>
<td>The characteristic MOST common to individuals with bulimia is</td>
<td>A. Binge eating.</td>
</tr>
<tr>
<td>4.</td>
<td>A 14-year-old girl is an elite gymnast. She experienced menarche at age 12 but has had no periods in the past year. Her weight is 85% of ideal body weight. Her coach has prescribed a strict dietary regimen, but she limits her intake to 75% of the portions recommended by her coach. This girl is at highest risk for</td>
<td>A. Cardiac arrest.</td>
</tr>
</tbody>
</table>
Objectives

1. Describe how the approach to the patient who has a staphylococcal infection varies by age, immune status, and clinical presentation.
2. Recognize that the management of staphylococcal infection in the pediatric patient relies on prompt diagnosis and localization of focus.
3. Utilize susceptibility data to plan antimicrobial therapy for staphylococcal infection.
4. Delineate the pharmacokinetic and pharmacodynamic data that guide therapy for specific infections.
5. Understand that vancomycin continues to be the cornerstone of therapy for methicillin-resistant Staphylococcus aureus infection in children.

Introduction

Long recognized as a ubiquitous environmental organism, Staphylococcus aureus is a well-known cause of both local and invasive infection. Distinguished in the laboratory by the production of coagulase and having a distinctive Gram stain appearance of grapelike clusters, S. aureus colonizes the nares and skin in 30% to 50% of children and adults. Higher rates are noted for healthcare personnel and for those having skin disorders or burns or in individuals who use needles frequently (diabetes, hemodialysis). The percentage of children colonized with methicillin-resistant S. aureus (MRSA) remains relatively low and has been estimated to be between 1% and 10%, despite the fact that most experienced practitioners find that they have drained more skin abscesses in the last 5 years than cumulatively in their entire careers.

Common infections involve skin (S. aureus is the primary cause of both bullous and crusted impetigo), soft tissue, or lymph nodes; but if the organism seeds the bloodstream, dissemination to joints, bones, kidney, liver, muscles, lung, and heart valves may occur, causing substantial morbidity and potential mortality. Although there are instances when an underlying immunodeficiency should be considered in patients who have repeated staphylococcal infection, an immunodeficiency evaluation is not recommended routinely because most infections, including those caused by MRSA, occur in previously healthy individuals. In the event that a child with recurrent skin infections is noted to have an additional risk factor for immunodeficiency (eg, prior invasive bacterial infection), a diagnostic evaluation should focus on diseases associated with neutrophil defects. The intrinsic capacity of S. aureus to bind to tissue and foreign bodies via surface-based adhesive matrix molecule receptors allows low inoculum bacteremia to produce infections related to catheters and prosthetic devices and clearly makes such infections more difficult to eradicate.

In the preantibiotic era, deaths from invasive staphylococcal infection were virtually inevitable. The availability of penicillin in the early 1940s, which proved to be an effective
drug for *S. aureus* infection, changed the outlook for such patients; but, not surprisingly, less than 10 years later, 65% to 80% of strains were noted to be resistant. It is rare to identify a penicillin-susceptible *S. aureus* strain today because nearly all isolates now produce penicillinase.

The introduction of methicillin, one of the first semi-synthetic penicillinase-resistant penicillins, was heralded as a welcome addition to the clinicians’ treatment armamentarium once strains became penicillin resistant, but reports of methicillin resistance swiftly followed its approval in 1959. MRSA resistance emerged initially from the hospital setting, becoming an important cause of healthcare-acquired infections over the next 4 decades. Clonal spread of MRSA with different dominant phage types was first reported in the 1960s, and outbreaks of disease, such as staphylococcal scalded skin syndrome types was first reported in the 1960s, and outbreaks of disease, such as staphylococcal scalded skin syndrome due to phage type 3-containing *S. aureus*, were well documented in hospital nurseries and surgical and intensive care units.

The early reports of invasive community-associated MRSA infection in 1999 focused attention on MRSA isolates that were from a single clonal strain and caused the deaths of four otherwise healthy children (12 mo to 13 y) from Minnesota and North Dakota. The community-associated strains were found later to produce a unique SCCmec, type IV cassette (a large mobile genetic element used for subtyping MRSA), which is smaller than that associated with healthcare-associated MRSA. Susceptibility data confirmed that such strains were uniformly susceptible to clindamycin and trimethoprim-sulfamethoxazole (TMP-SMX). The unique antibiogram (in vitro sensitivity) of community-associated MRSA distinguished such strains and was explained easily because the SCCmec cassette from hospital-associated strains is larger and usually carries genes associated with clindamycin and TMP-SMX resistance. Both hospital-associated and community-associated strains have more resistance genes than the classic methicillin-susceptible *S. aureus*.

Since then, so-called community-associated MRSA has become a common gram-positive infection causing both local and invasive infections in the pediatric population. This new, distinct community-associated MRSA clone has been called USA 300, based on the Centers for Disease Control and Prevention (CDC) nomenclature. The unique resistance pattern and the organism’s capacity to produce severe local infections as well as invasive infections are notable. The exact mechanism of enhanced virulence is not completely clear; but initial in vitro and clinical studies have pointed to extracellular proteins, including Pantron Valentine leucocidin, phenol soluble modulin peptides, or other products produced by these isolates.

This article will describe the diverse presentations of local and invasive staphylococcal infection in children and define management and prevention strategies. Focused discussion of skin and soft tissue infection, lymph node infection, pneumonia, septic arthritis, and osteomyelitis will be presented along with management recommendations highlighting the evidence supporting these recommendations. Lastly, less common manifestations of *S. aureus* infections, including cardiac and central nervous system infection, will be discussed.

It is crucial to note that occult bacteremia caused by *S. aureus* does not occur, and any time a blood culture grows this organism (methicillin-sensitive *S. aureus* [MSSA] or MRSA) a search for a focus of infection (skin, soft tissue, lymph node, or concealed sites, including bone, joint, lung, liver, kidney, heart) should commence. Although MRSA infections clearly have increased, data from our institution demonstrate that MSSA remains an important cause of invasive infection in more than 50% of such cases. Currently available agents that will be discussed include vancomycin, daptomycin, linezolid, clindamycin, doxycycline, and TMP-SMX (Table 1). Newer agents will be described, including cefitiprole, tigecycline, televancin, and quinupristin-dalfpristin but will not be discussed in detail because utilization in the pediatric population is limited.

**Simple Skin and Soft Tissue Infections**

Most experienced clinicians have mastered the art of abscess drainage in the last 5 years because MRSA-associated skin abscesses have emerged as a common childhood malady. It is estimated that 90% of all community-associated MRSA infections are skin and soft tissue in origin. That being said, practitioners should be able to classify specific skin and soft tissue processes skillfully, including cases in which necrotizing infection is present and should understand when pathogens other than *S. aureus* should be considered, targeting cases when simple incision and drainage and oral antibiotics are insufficient.

Recommendations for management of children who acquire pustules, furuncles, carbuncles, and simple skin abscesses have been published by the American Academy of Pediatrics (Fig. 1). The algorithm highlights the importance of recognizing the variable types of skin and soft tissue infections and advocates grading the severity of the infection clinically and taking into account the patient’s age and other risk factors for more serious infection before implementation of the clinical plan (Table 1).
In the previously healthy child who does not appear ill and has a pustule, furuncle, or a small abscess (<5 cm) drainage alone is curative and should be performed along with a request for culture. In cases of neonatal pustulosis, drainage with culture and topical treatment with mupirocin could be considered if the infant is full term, has local pustules and is well. In general, newborns with large areas of pustule involvement, or any systemic signs, any child afflicted with an immunocompromising condition, or any previously healthy child who appears toxic or has extensive limb involvement should have further evaluation and hospitalization for management.

In the previously healthy child, selecting the patient who requires drainage plus empirical antibiotic treatment requires factoring in additional, specific host and clinical features. In the following four circumstances, antibiotic treatment should be provided for the child with a simple skin or soft tissue infection: 1) the child has high fever or other systemic symptoms; 2) the abscess is larger than 5 cm, or is located in a critical location or in a difficult to drain area; 3) there are multiple abscesses or a carbuncle (a localized bacterial skin infection larger than a boil that usually has several openings through which pus can drain); or 4) signs and symptoms persist following incision and drainage.

Although nearly 70% of staphylococcal skin infections currently are related to MRSA, the availability of culture and susceptibility information is important because rates of resistance to certain antibiotics, including clindamycin, appear to be increasing nationally. Further, not every skin and soft tissue infection is staphylococcal in origin.

Cellulitis, which is diagnosed when the practitioner identifies a well-defined area of tender, erythematous swelling of the skin and soft tissue, is by nature an infection for which drainage is not feasible and antibiotic treatment is essential (Fig. 2). Although cellulitis may be staphylococcal in etiology, especially when it involves a traumatic lesion (insect bite, injury), erysipelas is a diagnosis that should be considered when the margins of the cellulitis are distinctly raised, the lesion is extremely painful (commonly named “St. Anthony’s fire” in the past), or the consistency of the involved area has an orange peel appearance (“peau d’orange”). In such instances, *group A Streptococcus* (GAS) is the usual pathogen and penicillin is the drug of choice. In the past, erysipelas occurred primarily on the face, but more recently, and particularly in children, such infections are most common on the extremities, and individuals who have preexisting lymphedema appear to be at particularly high risk (Fig. 3).

There are basically three choices of empiric antibiotics for treating potentially MRSA-infected skin or soft tissue infection in a child who is well enough to be treated as an outpatient: clindamycin, doxycycline (in children older than 8 y of age), and TMP-SMX. If both staphylococcal and streptococcal coverage is deemed appropriate, clindamycin alone generally is the drug of choice. Neither doxycycline nor TMP-SMX is appropriate for treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose, mg/kg per day (max daily dose)</th>
<th>Total Daily Dose Divided Route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP/SMX</td>
<td>8–12</td>
<td>Every 12 h Oral</td>
<td>No coverage GAS</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>4 (200 mg/d)</td>
<td>Every 12 h Oral</td>
<td>&gt;8 y</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>40 (4.8 g)</td>
<td>Every 6 h IV</td>
<td>Poor palatability</td>
</tr>
<tr>
<td></td>
<td>30 (1.8 g)</td>
<td>Every 8 h Oral</td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>6–10</td>
<td>Once daily IV</td>
<td>Consult infectious diseases; after first dose, adjust based on renal function</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>60</td>
<td>Every 6 h IV</td>
<td>Consult infectious diseases; not appropriate for pneumonia</td>
</tr>
<tr>
<td>Linezolid</td>
<td>30: &lt;12 y</td>
<td>Every 8 h IV/Oral</td>
<td>Consult infectious diseases; same dose for oral transition; myelosuppressive, expensive</td>
</tr>
<tr>
<td></td>
<td>20: :12 y</td>
<td>Every 12 h IV/Oral</td>
<td></td>
</tr>
<tr>
<td>Oxacillin</td>
<td>200 (12 g)</td>
<td>Every 6 h IV</td>
<td>MSSA only</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>100 (12 g)</td>
<td>Every 6 h IV</td>
<td>MSSA only</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>50 (4 g)</td>
<td>Every 8 h Oral</td>
<td>MSSA only; oral transition: 100 mg/kg/d for skeletal infection</td>
</tr>
</tbody>
</table>
| GAS = *group A Streptococcus*, IV = intravenous, MSSA = methicillin-sensitive *Staphylococcus aureus*

### Table 1. Drugs Appropriate for Treatment of Pediatric Staphylococcal Infection
of a skin or soft tissue infection if there is a high likelihood that GAS is a pathogen. In this scenario, cephalexin or penicillin should be added to TMP-SMX. Cephalexin remains a good empiric choice for MSSA and GAS infections or in situations when combined infection with these two pathogens is suspected.

**Pneumonia and Empyema**

Community-acquired pneumonia is common, and pneumococcus remains the most common bacterial pathogen outside of the neonatal period. However, *S aureus* is an important cause of pneumonia and is more likely to cause an illness that involves multisystem dysfunction. Pneumatoceles have been reported to be associated with complicated and uncomplicated *S aureus* pneumonia. Three types of complicated *S aureus* pneumonia can be observed: necrotizing pneumonia, pneumonia with empyema, and pneumonia with lung abscess. Pulmonary involvement from septic emboli also may occur in disseminated staphylococcal disease or when there is endocarditis. The clinical presentation in children with staphylococcal pneumonia is typical of any bacterial pneumonia, including high spiking fevers and signs of respiratory distress (hypoxemia, tachypnea, retractions, nasal flaring, chest pain, splinting, etc). The hallmark of staphylococcal pneumonia in young infants, however, may be the rapidity with which the disease progresses.

When the child with pneumonia is toxic appearing, has significant respiratory distress, or has a sizeable pleural effusion, a complicated process, including empyema, should be considered. With the emergence of MRSA, an increase in necrotizing pneumonias with empyema...
has been observed in certain geographic regions. Empyema, defined as an accumulation of pus in the pleural space, can be identified by chest ultrasonography (preferred method based on Infectious Diseases Society of America/Pediatric Infectious Diseases Society [IDSA/PIDS] Guidelines) or computed tomographic scan; imaging will demonstrate loculated fluid, which is the typical feature of complicated pleural space infection. Pleural fluid should be analyzed for features of empyema, which include pH < 7.1, lactic acid dehydrogenase concentration > 1,000, and bacteria on gram-stained smear or culture.

Finally, *S. aureus* can manifest as an intraparenchymal lung abscess. Although the majority of lung abscesses are observed in patients with underlying conditions and likely are due to aspiration of anaerobic bacteria, normal healthy children can have lung abscesses that result from a *S. aureus* infection. These infections cause cavity lesions within the lung parenchyma, and often air-fluid levels are present on plain radiograph. The clinical presentation of children who have lung abscesses is daily fevers with or without respiratory symptoms. The largest review of this entity observed a majority of patients presenting predominantly with fever and cough; so imaging is the major method of identification and differentiation from other forms of lung infection.

Septic emboli with secondary pulmonary involvement are a potential complication in patients with staphylococcal musculoskeletal infections, particularly multifocal infections. The pathogenesis of these emboli is vascular thrombosis, usually adjacent to the soft tissue/muscle/bone focus, with embolization to the lungs. Suspicion is higher when an area of cellulitis or myositis fails to respond as expected or the patient with a soft tissue or bone infection develops respiratory distress. On chest radiograph, small, round multifocal densities within the lungs represent foci of embolization.

Empiric coverage for children suspected of having staphylococcal pulmonary disease should be vancomycin (15 mg/kg per dose every 6 h) or clindamycin (10 mg/kg per dose every 6 h). Vancomycin should be initiated in the critically ill child who has hemodynamic instability and severe respiratory distress or failure. Clindamycin is an appropriate choice; however, the clinician needs to know the overall resistance rate of all their *S. aureus* isolates to clindamycin before its use. The recent IDSA guidelines suggest that if the overall resistance rate of *S. aureus* to clindamycin is greater than 10%, the drug should not be used for empiric therapy.

In addition to antibiotic therapy, prompt drainage of the pleural space is essential when pleural fluid is detected and empyema has been confirmed. Depending on local expertise, either video-assisted thorascopic debridement (VATS) or chest tube with intrapleural fibrinolysis (IPF) should be performed if an empyema is confirmed. Two randomized, controlled trials comparing VATS versus IPF have demonstrated equal effectiveness in terms of length of fever and duration of hospitalization and demonstrated an IPF failure rate of 16%.

No high quality, controlled data exist on the appropriate length of therapy for empyema and lung abscess, although most clinicians treat for 3 weeks. Chest tubes associated with VATS or IPF usually can be removed 3 to 4 days after insertion. Transition to oral therapy could be considered when clinical, microbiologic, and laboratory improvement have been confirmed. Therefore, when a patient has become afebrile, no longer requires oxygen, has cleared the organism from the bloodstream (in the 10% of cases where bacteremia has been confirmed), and is tolerating an oral diet without vomiting, an oral antibiotic can be utilized based on susceptibilities. A decrease in the C-reactive protein concentration also can aid in assessing improvement. In children infected with MRSA that is clindamycin resistant, linezolid is an appropriate oral agent, using standard dosing recommendations (Table 1).

**Septic Arthritis and Osteomyelitis**

Skeletal infections represent the most common invasive infection in children caused by *S. aureus* in general, and MRSA specifically. Hematogenous seeding is the mechanism for bone and joint infection in nearly all children. The rate of infection, where both bone and joint are involved, traditionally has been highest in infants and young children owing to the unique vascular supply in younger ages.

Antalgic gait is the most common clinical presentation in the ambulatory child in view of the typical pattern of bone and joint involvement. In the younger infant, irritability and limb disuse may be present. However, it may not be possible to identify the affected joint or bone on initial examination.

Osteomyelitis is diagnosed in 6 of 1,000 admissions to a children’s hospital, with 50% of the cases occurring in those younger than 5 years of age. A single long bone (femur, tibia, or fibula) is most commonly involved (over 50% of cases), followed by humerus and then pelvis. Typically, the hallmark of osteomyelitis is limp with point tenderness over the metaphysis of the affected bone, usually in the setting of fever. Septic arthritis has been noted most often in infants and toddlers and affects the knee and hip most often. Pain and swelling of a joint is...
most common, although infants may manifest with pain on movement of the hip during diaper change.

When acute skeletal infection is suspected, laboratory studies may be helpful in confirming the diagnosis. Erythrocyte sedimentation rate (elevated in 80% to 90% of cases), C-reactive protein (elevated in 98% of cases), and blood culture should be obtained in all patients; however, only 50% of blood cultures will identify the specific pathogen. Plain radiographs should be obtained but usually are not diagnostic in cases of osteomyelitis because the tell-tale periosteal bone reaction can take 2 weeks or so to develop. Magnetic resonance imaging (MRI) is sensitive and specific for skeletal infection and may direct the surgical drainage (Fig. 4). Joint fluid analysis and culture should be obtained in all cases of septic arthritis. Polymerase chain reaction for *S aureus* and *Kingella kingae* (an important pathogen in infants) is recommended on debrided tissue and synovial fluid. Incubating synovial fluid in a blood culture bottle in addition to plating it on standard culture media may enhance the identification of a pathogen.

Infections involving hips and shoulders should be surgically drained. In the setting of osteomyelitis, culture of bone can be essential but is not performed routinely; if bone is debrided in cases of osteomyelitis, culture and histopathologic examination should be performed. Debridement of necrotic bone is essential, however, for good outcome. Recently available polymerase chain reaction (PCR) assays on joint fluid for *S aureus* and *kingae* may be useful in the diagnosis of septic arthritis in regions where <50% of routine joint fluid cultures reveal a pathogen.

Disseminated MRSA infection with musculoskeletal involvement has been reported increasingly. Such infections can be limb and life-threatening and require prompt recognition and aggressive drainage and debridement in addition to prolonged antibiotic therapy. The typical patient is school-aged and presents with fever and an antalgic gait and appears toxic on examination. MRI can be essential in defining bone, joint, or muscle involvement and also may guide surgical drainage.

In some cases, deep venous septic thrombosis occurs and involves the vessels adjacent to involved bone, similar to thrombosis noted adjacent to pyomyositis sites. Pulmonary embolic phenomena similarly may complicate septic thrombophlebitis in these cases and often are evident on routine chest radiograph as diffuse nodular lesions. The common iliac, saphenous, popliteal, and femoral veins are involved most frequently, and Doppler ultrasonography or computed tomography scan are most useful for diagnosis. The typical involvement of, and association with, pelvic vasculature is so distinctive that some refer to this condition as “pelvic syndrome.”

If the child is hemodynamically stable and the pathogen has been identified as MSSA, cefazolin, oxacillin, or nafcillin can supply appropriate initial coverage. Vancomycin traditionally has been the recommended antibiotic treatment of skeletal infection in children when disease appears to be life or limb threatening. Concerns have been raised, however, regarding relatively poor penetration of vancomycin into bone, and animal model data in some cases suggest efficacy is relatively poor. Treatment failure unquestionably is greater in cases where abscesses are drained inadequately or necrotic bone is not debrided.

In light of the above data, some experts empirically add rifampin (10 mg/kg every 12 h with oral route preferred) to vancomycin because rifampin has excellent intracellular activity and penetrates bone well. Limited data suggest, at least in the animal model, that outcomes are improved in such cases. However, in vitro studies have demonstrated antagonism between vancomycin and rifampin.

In the setting of MRSA skeletal infection, alternatives to vancomycin include daptomycin, linezolid, and clindamycin. Clindamycin is considered an appropriate drug, provided that there is no evidence of intravascular infection, and that the isolate is susceptible, because this agent has excellent penetration into leukocytes, bone, and joints. Following aggressive debridement and clindamy-
cin treatment, usually for 3 to 7 days intravenously (IV), therapy can be switched to oral clindamycin and treatment continued for 4 to 6 weeks. A shorter course of therapy (3 wk) could be considered for the child who has uncomplicated septic arthritis caused by MRSA.

Although only a few small case series exist to support efficacy, linezolid does achieve good concentrations in bone, and dosing for treating osteomyelitis is similar to that used in MRSA pneumonia or soft tissue infection. IV linezolid may not be necessary because IV and oral linezolid are equivalent for all practical purposes. Due to the high risk of bone marrow suppression after 2 or more weeks of therapy, all patients require close follow-up, and complete blood counts should be performed weekly.

Daptomycin (6 to 10 mg/kg IV once daily) generally is reserved for cases in which MRSA skeletal infection has been refractory to standard therapy, keeping in mind that, as it is inactivated by surfactant, daptomycin is currently not recommended for treatment of pneumonia. This drug, however, has been used effectively in treating right-sided endocarditis and it has been suggested that daptomycin can be used in the setting of septic pulmonary emboli, which is commonly seen when there is disseminated staphylococcal infection with musculoskeletal involvement. Theoretically, embolic phenomena represents vascular rather than alveolar disease and, as such, daptomycin should be effective.

Still, we suggest that there are several limitations in the consideration of daptomycin for treatment in the pediatric patient and that this drug should, for now, be utilized only with the input of the infectious disease specialist. Efficacy data are still just evolving. Nearly all isolates have minimum inhibitory concentration values $\leq 1 \text{ mcg/mL}$, but no specific breakpoint for resistance has been assigned. Muscle pain and weakness with elevated creatinine phosphokinase (CPK) concentrations are the most commonly reported adverse events, and CPK should be monitored weekly if such therapy is considered.

**Sepsis and Toxic Shock Syndrome**

*Staphylococcus aureus*, both MRSA and MSSA, can cause severe, life-threatening disease manifesting as either a severe sepsis syndrome or toxic shock syndrome (TSS). Severe sepsis syndrome is likely the result of many different virulence factors, including multiple toxins and other factors, while the pathogenesis of TSS is based on the production of toxic shock syndrome toxin-1 (TSST-1).

Most recently, an increase in the incidence of severe sepsis syndrome has been reported in children infected with MRSA. A study from Texas Children’s Hospital observed an increase from one case of MRSA sepsis in the period 1999 to 2001 to 12 cases occurring from 2002 to 2004. The classic clinical presentation is a teenager with multifocal bone or joint infections, pulmonary findings (embolic disease, pneumatoceles, complicated parapneumonic effusions), hypotension, or coagulopathy. Additionally, patients who have had antecedent influenza have been observed to suffer from severe *S. aureus* sepsis with substantial mortality. Before the advent of varicella vaccine, both GAS and *S. aureus* were noted to be associated with severe invasive disease as a complication of wild type varicella infection. This complication continues to be seen in the vaccine era in the under immunized population. Although children who contract sepsis-like syndrome resemble those having TSS, they did not fulfill all of the established diagnostic criteria and more often may have positive blood cultures.

Similar in clinical presentation to the severe sepsis syndrome, TSS has been well described for both MSSA and MRSA infections. TSS first was described in 1978, and the first epidemic was reported in 1979 to 1980 related to the use of high absorbency tampons. Subsequently, surgical associated cases have been described as well as cases without an identifiable infectious focus; the pathogenesis of these cases has been postulated to be due to infection of hematomas or other similar pools of blood-containing secretions.

TSS is by definition a toxin-mediated illness related to *S. aureus* strains that produce TSST-1. The common denominators among patients appear to be lack of antibodies to the TSST-1 toxin produced by the bacteria, coupled with compromise in mucosal or skin integrity, as well as the presence of a foreign body (tampon, surgical implants). Importantly, TSS can be observed in children who have invasive staphylococcal disease, including pneumonia and skeletal infection, most often without a positive blood culture. In *S. aureus* TSS, blood cultures are positive in $<5\%$ of patients. The clinical case definition for staphylococcal TSS is well described.

The empiric antibiotics of choice in children presenting with potential *S. aureus* sepsis or TSS are vancomycin (15 mg/kg per dose every 6 h), oxacillin (50 mg/kg per dose every 6 h), and clindamycin (10 mg/kg per dose every 6 h). Due to recent reports of increasing MIC values of MRSA against vancomycin (vancomycin creep), all empiric dosing, especially in children who have sepsis or TSS, should be 15 mg/kg every 6 hours. The addition of oxacillin (or nafcillin) allows for a more rapid rate of killing than vancomycin (in the event that the pathogen is MSSA). Other beta-lactam antibiotics that have MSSA
coverage include cefazolin (first generation cephalosporin having good staphylococcal but limited gram-negative and inadequate CNS coverage) and cefepime (a fourth generation cephalosporin with good MSSA coverage, broader gram-negative and CNS coverage). One of these agents can be added to the regimen in place of oxacillin or nafcillin. Clindamycin abrogates the production of the toxin by the bacteria as well as having antibacterial effects in susceptible organisms and is recommended specifically for inclusion in the empiric coverage for the patient suspected of having TSS. The length of therapy is dependent on the clinical manifestations associated with the sepsislike illness or TSS. For example, patients afflicted with sepsis and osteomyelitis will need to be treated for at least 4 weeks. In cases of tampon-associated TSS, the recommended length of therapy is 10 to 14 days.

Less Common Sites of Infection
Endocarditis is rare in children although cases caused by S. aureus, including MRSA have been reported. That being said, echocardiographic assessment to exclude endovascular disease is recommended in the child who has congenital heart disease, in those having multiple repeated positive blood cultures (>3 d), and in those children whose clinical manifestations are suggestive of endocarditis. Transthoracic echocardiography generally is acceptable unless the child is older than 10 years of age or has a thick chest wall. Although vancomycin generally is regarded as an essential drug in the empiric therapy for endocarditis, it is essential to recognize that vancomycin kills staphylococci slowly in comparison to beta lactams and beta lactam (nafcillin or oxacillin) therapy is preferred in cases of MSSA endocarditis.

Empirical therapy for the child with endocarditis should include vancomycin plus nafcillin or oxacillin (200 mg/kg per day divided into four doses). Once susceptibilities are known, a single agent can be utilized. The addition of an aminoglycoside is not recommended because these drugs do not add to efficacy but are associated with toxicity and resistance. Daptomycin is an alternative to vancomycin in the adult population, and higher dosing (10 mg/kg per day) is advised. Daptomycin would be considered in the child who has refractory disease. In general, linezolid, tigecycline, TMP-SMX, quinupristin-dalfopristin, and clindamycin are NOT considered for first-line therapy of endocarditis.

Central nervous system infection caused by S. aureus is not common, but when it occurs, infection often is difficult to treat because it can be difficult to achieve desired drug concentrations in cerebrospinal fluid (CSF) with many of the typically used antistaphylococcal antibiotics. Penetration across uninfamed meninges is 1% of serum concentrations, although higher concentrations are achievable in neurosurgical infections or in cases where the meninges are inflamed (up to 10%). For this reason, many experts add rifampin to vancomycin because penetration is excellent and bactericidal concentrations can be expected in CSF. Most commonly, central nervous system infection with MRSA is associated with a ventricular shunt or other neurosurgical foreign body. In all cases, clinical success depends on removal of the infected foreign body. Linezolid’s penetration into CSF in children is variable and overall limited efficacy data are available. To date, there are no good data on daptomycin concentrations in the CSF, although animal model data suggest that concentrations of 3 to 4 mcg/mL can be achieved with dosing of 15 mg/kg once daily.

Recurrent Skin Infections
The approach to treatment of the child who has current skin abscess (usually caused by MRSA) is not well researched. Based on recommendations from the IDSA/PIDS guideline for management of MRSA infection, the first step is enhanced hygiene and environmental cleaning. Concurrent with these basic steps is treatment for anyone in the family who has active disease. We have found that coexisting infection in the parent is common but often not revealed by the family except by explicit questioning; further, parents who have been identified as having recurrent skin infections often have not received effective therapy (drainage or MRSA-targeted antibiotic treatment). Nasal mupirocin and skin decolonization (chlorhexidine or bleach baths) also are recommended. At this time, routine nasal culturing of the child or family members is not recommended, and treatment with antibiotic-based decolonization regimens (usually rifampin plus an additional agent) should be reserved for patients with recalcitrant infection, utilizing infectious disease consultation, or those who have a planned surgical procedure where a foreign body is being implanted.

Other and Future Pediatric Drugs
Tigecycline, a derivative of tetracycline in the glycycline drug group, and quinupristin-dalfopristin, a streptogramin antibiotic, are not Food and Drug Administration (FDA)-approved for children, nor are they first-line drugs in the child who has MRSA infection, mainly because of their associated toxicities. Approximately 40% of patients experience nausea and vomiting with tigecycline, and myopathy and nearly uniform infusion
reactions (chills, myalgias) occur with quinupristin-dalfopristin.

Televancin, a new ipoglycopeptide, has bactericidal activity against MRSA and is FDA-approved in adults who have complicated skin and soft tissue infection. There are no published data on children as yet, but this drug holds promise.

Ceftibiprole, a fifth-generation beta lactam having MRSA activity, is still in pharmacokinetic trials in children in 2010, and has yet to obtain FDA approval for treatment in adults.

**Principles of Treatment**

The treatment of staphylococcal infections is based on the presentation, location, and severity of illness. Basic principles in treating children include draining abscesses (except pulmonary), utilizing culture and susceptibility data, knowing the local antimicrobial susceptibility patterns of *S. aureus*, and understanding the pharmacokinetic and pharmacodynamic properties of antistaphylococcal agents in various clinical conditions.

**Drainage**

Draining of abscesses has been demonstrated to be an effective method in the treatment of many infections. Importantly, antibiotics fail to penetrate abscesses adequately and uniformly, and the milieu in an abscess can be analogous to biofilm, with organisms not being metabolically active, so antibiotic targets are not available. Furthermore, drainage of abscesses without the addition of antibiotics may be sufficient in the treatment of certain infections. In skin and soft tissue infections, both a retrospective and a pediatric randomized, controlled trial showed that drainage alone of abscesses less than 5 cm in size was as effective as drainage plus antibiotics.

Drainage should not be limited to skin and soft tissue infections. This strategy also should be employed in the treatment of pyomyositis or subperiosteal abscesses because drainage will help eliminate a large burden of disease that will aid in a better treatment response. In cases in which tissue necrosis has occurred, debridement of the necrotic area is essential because tissue without blood supply will persist as a nidus of infection, in part due to failure of penetration of most antibiotics. For children with staphylococcal infection in whom persistent fever is noted, a search for a sequestered focus is essential (based on strong evidence and consensus).

**Susceptibility Patterns**

Treatment of staphylococcal infection invariably is driven by susceptibility information, and because the epidemiology and antimicrobial resistance of such infections has changed over the last 10 years, local or patient-specific data are essential in ensuring good outcome. With MRSA comprising from 20% to 70% of *S. aureus* isolates across the country, local data are essential to guide the clinician in the most appropriate empiric antibiotic choice. It is important to note that >90% of MRSA infections are uncomplicated skin or soft tissue infection. Also, in the setting of invasive disease, MSSA remains an important pathogen.

Clinicians need to be aware of *S. aureus* antibiotic resistance rates in their geographic locales. With the increase in MRSA in the past 15 years, many clinicians began to use clindamycin as their empiric antibiotic of choice. However, MSSA still causes serious infections. So choosing empiric antibiotics requires consideration of local resistance rates for both MRSA and MSSA. MRSA resistance to clindamycin may be as little as 5% or as high as 30%, and clindamycin resistance rates in MSSA may be as high as 25% in some areas. Additionally, with increased use of clindamycin, it is likely that this rate is only going to increase. Recent guidelines suggest that if local data demonstrate a >10% rate of MRSA or MSSA resistance to clindamycin, adding a second drug or altering the choice of empiric therapy should be considered, particularly in more than minimally ill children. In uncomplicated skin infections that require treatment, TMP-SMX is a reasonable alternative if GAS is not suspected as the main or copathogen (based on some research studies and consensus).

**Clinical Considerations**

The initial empiric antibiotic choice in patients with a suspected *S. aureus* infection is dependent also on the clinical presentation. In children who appear septic, are hemodynamically unstable, or have impending respiratory failure, vancomycin is the empiric antibiotic of choice. *S. aureus* fully resistant to vancomycin has not yet been reported in pediatrics. Addition of oxacillin or nafcillin (more rapidly bactericidal to MSSA) to the vancomycin regime is recommended because the combination decreases the length of bacteremia in MSSA infections. Finally, when evidence of toxin is present the addition of clindamycin provides an antibiotic that down-regulates the production of the toxin by the *S. aureus* bacteria. Children who are not severely ill can be treated initially with clindamycin unless endocarditis or a central nervous system infection is suspected, or if clindamycin resistance rates locally are greater than 10% (based on some research studies and consensus).
Summary

- Management of MRSA infection in the pediatric patient continues to rely on prompt diagnosis and localization of focus, and utilization of susceptibility data.
- Drainage or debridement of abscess or necrotic material as well as knowledge of pharmacokinetic and pharmacodynamic data should guide appropriate therapy for specific infections.
- Although vancomycin continues to be the cornerstone of therapy for MRSA infection in children, the increasing identification of strains having a vancomycin MIC at or beyond 1 mcg/mL may serve to change the scope of treatment for such infections in the future.

Suggested Reading


PIR Quiz

Quiz also available online at: http://pedsinreview.aappublications.org.

NOTE: Beginning in January 2012, learners will be able to take Pediatrics in Review quizzes and claim credit online only. No paper answer form will be printed in the journal.

5. An otherwise healthy 4-year-old boy presents with his second community-acquired MRSA skin infection in the past year. The first involved scattered folliculitis on his right forearm; he cleared promptly with oral trimethoprim-sulfa. His current problem is a 3-cm abscess on the right leg that you have just incised and drained. Given the history, you should

A. Assume his host defense system is intact.
B. Evaluate for immune globulin deficiency.
C. Explore T cell function.
D. Obtain complement studies.
E. Suspect a disorder of chemotaxis.

6. A previously well 5-year-old girl has a 4-cm fluctuant abscess on her left buttock. She is afebrile. The remainder of her examination is normal. The best choice of initial therapy is incision and drainage accompanied by

A. Local wound care alone.
B. Oral cephalaxin.
C. Oral clindamycin.
D. Oral doxycycline.
E. Oral trimethoprim-sulfa.
7. A previously well 5-year-old girl has a 4-cm fluctuant abscess on her left buttock. Erythema and tenderness extends 4 cm beyond the area of fluctuation. She has a temperature of 38°C and appears mildly ill. The remainder of her examination is normal. The best choice of initial therapy is incision and drainage accompanied by

A. Local wound care alone.
B. Oral cephalexin.
C. Oral doxycycline.
D. Oral trimethoprim-sulfa (some might recommend clindamycin in this patient).
E. Parenteral vancomycin.

8. You practice in a community where 50% of staphylococcal infection is caused by MRSA and your local antibiogram shows 8% clindamycin resistance. Today a previously healthy 7-year-old boy presents to your office with fever and a right-sided limp for the past 3 days. On examination, there is point tenderness over the metaphysic of his right distal tibia. An MRI demonstrates characteristic changes of osteomyelitis and suggests the presence of necrotic bone. While awaiting a surgical procedure as well as blood culture and susceptibility results, the best choice of initial therapy is intravenous

A. Cefazolin.
B. Clindamycin.
C. Daptomycin.
D. Linezolid.
E. Nafcillin.

9. A previously healthy 10-year-old ill-appearing girl presents to the emergency department with a 4-day history of fever and a boil on her left shoulder. She is hypotensive and has a diffuse erythrodermatous rash. IV cefepime was given in the emergency department; additional antimicrobial coverage in this child should include

A. Daptomycin and cefazolin.
B. Linezolid and gentamicin.
C. Nafcillin and ceftriaxone.
D. Vancomycin and TMP-SMX.
E. Vancomycin and clindamycin.
Developmental Milestones 3: Social-Emotional Development

Objectives

After completing this article, readers should be able to:

1. Know the sequence through which social abilities develop in the infant and young child.
2. Understand the concept of joint attention.
3. Be aware of the ways in which infants and young children mature in their emotional development.
4. Recognize when a child is not achieving the appropriate social or emotional milestones and requires further evaluation.

This is the third and final article in a series on developmental milestones. Previous articles have focused on motor and cognitive aspects of development. As has been mentioned, developmental skills are interrelated and do not evolve in isolation. Problem-solving, language, and fine motor skills all are required for an infant to develop normal social-emotional skills.

Social Milestones

Most children are born with an inherent drive to connect with others and share feelings, thoughts, and actions. The earliest social milestone is the bonding of a caregiver with the infant, characterized by the caregiver’s feelings for the child. The infant learns to discriminate his mother’s voice during the first month after birth. He cries to express distress from hunger, fatigue, or a wet diaper. Attachment theory suggests that as the caregiver responds to these cries and other behaviors, the infant gains confidence in the caregiver’s accessibility and responsiveness. This behavior system promotes the parent–child relationship that some researchers believe facilitates parental protection, and thus infant survival. From this relationship comes the first measurable social milestone: the smile.

The infant smiles at first in response to high pitched vocalizations (“baby talk”) and a smile from his caregiver; but over time, less and less stimulation is required. Ultimately, just seeing the caregiver elicits a smile. The infant learns that he can manipulate the environment to satisfy personal needs by flashing a toothless grin or, alternatively, by crying. His interactions then begin to involve to-and-fro vocalizations by 4 months. Visual skills develop as well, and he can recognize his caregivers by sight at 5 months. Stranger anxiety, or the ability to distinguish between familiar and unfamiliar people, emerges by 6 months. Whereas the 4-month-old infant smiles at any adult, the slightly older infant cries and looks nervously between his caregiver and other adults.

Joint attention is the quintessential social milestone that develops towards the end of the first year after birth. Joint attention is the process whereby an infant and caregiver share an experience and recognize that the experience is being shared. The earliest demonstration of joint attention occurs around 8 months of age, when an infant follows a caregiver’s gaze and looks in the same direction. In a few months, the infant looks back at the caregiver as an indication of a shared interaction. The infant consistently turns her head to the speaker when her name is called by 10 months, further demonstrating a connectedness with her environment.

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Between 12 and 14 months, children begin to point to request something (proto-imperative pointing), and they usually integrate this pointing with eye contact directed between the object of interest and the caregiver, sometimes accompanied by a verbal utterance. Proto-imperative pointing then proceeds to proto-declarative pointing by 16 months of age, characterized by the child pointing at something merely to indicate interest. Again, the pointing is accompanied by eye contact directed between the object and the caregiver. By 18 months, he brings objects or toys to his caregivers to show them or to share the experience. The online version of this article has several video clips that demonstrate these core joint attention skills.

Play skills also follow a specific developmental course. Initially, an infant holds blocks and bangs them against each other or on the table, drops them, and eventually throws them. Object permanence allows her to realize that the blocks are still present, even if she cannot see them. She learns that dropping the blocks from her highchair will cause her caregiver to pick them up and return them to her; so she repeats this “game” over and over. As fine motor and cognitive skills develop, she starts to use objects for more specific purposes, such as using blocks to build a tower. By 18 months, she can dress the doll and put her to bed. She might use a toy phone to “talk” on it or “feed” a doll by using a toy spoon or bottle.

After his second birthday, the child begins to play with others his own age. A rule of thumb is that a child can play effectively only in groups of children in the same number as his age in years. Thus, a 2-year-old can play well only with one other child. Two-year-old play often is described as “parallel” because a child of this age often plays next to another child but not with him. However, the 2-year-old frequently looks at his playmate and imitates his actions. He has not yet mastered the skill of cooperation; so aggression often is the tool of choice to obtain a desired object.

By 30 months, the child uses complex pretend play, such as using generic items to represent other objects. A block may be used as a telephone in one scenario or used as a bottle to feed a doll in another. The scenarios themselves also increase in complexity, from merely feeding the doll to dressing the doll and putting her to “sleep.”

By age 3 years, a child has mastered her aggression to some extent, and she is able to initiate a cooperative play experience with one or two peers. Most of the time, they are able to have joint goals and take turns. She also moves into simple fantasy or imaginative play. She may pretend to be a dog or an airplane. However, she cannot yet distinguish between what is real and what it is make-believe; so fear of imaginary things is common at this time.

Four-year-olds usually have mastered the difference between real and imaginary. They become interested in tricking others and concerned about being tricked themselves. They are able to play effectively with up to three other children, although some may have a preferred friend. Imaginary scenarios increase in complexity: a cardboard box may become a sailboat, and toilet paper rolls may become binoculars.

By age 5, children have learned many adult social skills, such as giving a positive comment in response to another’s good fortune, apologizing for unintentional mistakes, and relating to a group of friends. Their imaginative play is increasingly more complex, and they love to dress up and act out their fantasies. Kindergarten classrooms usually are well-equipped with toys that promote this imaginative play.

**Emotional Milestones**

Coexisting with the development of social skills is a child’s emotional development. As early as birth, all children demonstrate individual characteristics and patterns of behavior that constitute that individual child’s temperament. Temperament influences how an infant responds to routine activities, such as feeding, dressing, playing, and going to sleep. There seems to be a biologic basis to these characteristics, although how a child learns to regulate her emotional state also depends on the interactions between child and caregiver. For a more detailed discussion of temperament, please see the Suggested Reading list.

Emotional development involves three specific elements: neural processes to relay information about the environment to the brain, mental processes that generate feelings, and motor actions that include facial expressions, speech, and purposeful movements. The limbic system is responsible primarily for receiving, processing, and interpreting environmental stimuli that produce emotional responses. During development, the repertoire of specific emotions remains constant, but the stimuli that produce them become more abstract.

Studies have demonstrated that three distinct emotions are present from birth: anger, joy, and fear. All infants demonstrate universal facial expressions that reveal these emotions, although they do not use these
expressions discriminately before the age of 3 months. Cognitive input is not a requirement; anencephalic infants may show disgust with sour flavors and pleasure with sweet flavors, just as normocephalic infants do.

Eventually, however, cognitive skills play a role as emotional expressions become connected to specific occurrences. For example, an 8-month-old infant can let his parents know that he is upset about being left alone in his crib or happy about playing with a toy. Because he now has object permanence, he demonstrates fear in new situations due to the ability to shift attention and recognize “familiar” from “unfamiliar.”

Emotional development continues as the toddler learns to identify different emotions in other people. At 15 months, a child demonstrates empathy by looking sad when she sees someone else cry. She also develops self-conscious emotions (embarrassment, shame, pride) as she evaluates her own behavior in the context of the social environment. Having once performed cute tricks on demand, she suddenly seems embarrassed and refuses to perform when she realizes that others are watching. She may hide behind a chair to have a bowel movement and become upset if someone catches her in the act.

As language skills develop, the child can label different emotional states in others and even associate language with emotions and memory. For example, if he had a tantrum when he didn’t get a toy from the store, he may have an identical emotional outburst when he hears a verbal reminder of the situation. By age 2 years, he starts to mask emotions for social etiquette.

During the preschool years, children learn more and more behavioral strategies to manage their emotions, depending on a given situation. They begin to understand that their expressed emotion—whether a facial, vocal, or behavioral expression—does not necessarily need to match their subjective emotional experience. They demonstrate an increased understanding and use of “display rules.” These are “culturally defined rules that guide a person’s decision to alter emotional behavior consistent with the demands of the social context.” (1)

Children learn to substitute their expressions (smile and say “thank you” even though they are disappointed in the birthday present), amplify expressions (exaggerate a painful response to get sympathy), neutralize expression (put on a “poker face” to hide true feelings), or minimize emotion (look mildly upset when feeling extremely angry). By the time they enter kindergarten, children have started to master many of the emotional nuances of social interactions.

### Developmental Red Flags

As in other streams of development, failure to achieve specific milestones in the social-emotional domain should prompt the pediatrician to evaluate a child more thoroughly. The Table lists the developmental red flags specific to the social-emotional domain, although there is some overlap with language and cognitive skills. A lack of age-appropriate joint-attention skills or any loss of previously gained skills warrants screening by using a validated instrument. If abnormal, simultaneous referral to early intervention services as well as to a developmental specialist for a thorough evaluation should be the next step.

The Suggested Reading list includes several references to specific autism screening tools, as well as several websites with video clips highlighting the differences in children with autism.

In addition, pediatricians need to be aware of behavioral abnormalities that may stem from temperament and psychosocial factors or may signal the early stages of a behavior disorder. A discussion of these behavior problems is beyond the scope of this article. Please see the Suggested Reading list for more information.

A comprehensive table (Table 2) of developmental milestones in all domains is printed in the first of these three articles (Pediatr Rev. Jul 2010; 31: 267–277) and as a data supplement to this article in the online edition.

### Table: Social-Emotional Red Flags

<table>
<thead>
<tr>
<th>Age</th>
<th>Red Flag</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mo</td>
<td>Lack of smiles or other joyful expressions</td>
</tr>
<tr>
<td>9 mo</td>
<td>Lack of reciprocal (back-and-forth sharing of) vocalizations, smiles, or other facial expressions</td>
</tr>
<tr>
<td>12 mo</td>
<td>Failure to respond to name when called</td>
</tr>
<tr>
<td></td>
<td>Absence of babbling</td>
</tr>
<tr>
<td>15 mo</td>
<td>Lack of reciprocal gestures (showing, reaching, waving)</td>
</tr>
<tr>
<td>18 mo</td>
<td>Lack of proto-declarative pointing or other showing gestures</td>
</tr>
<tr>
<td>18 mo</td>
<td>Lack of single words</td>
</tr>
<tr>
<td>24 mo</td>
<td>Lack of two-word pretend play</td>
</tr>
<tr>
<td></td>
<td>Lack of spoken language/gesture combinations</td>
</tr>
<tr>
<td>Any age</td>
<td>Loss of two-word meaningful phrases (without imitating or repeating)</td>
</tr>
<tr>
<td>Any age</td>
<td>Loss of previously acquired babbling, speech, or social skills</td>
</tr>
</tbody>
</table>

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*Table.* Social-Emotional Red Flags

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Summary

- The development of a child from infancy to preschool years is truly remarkable. As with physical growth, neurodevelopment proceeds in a sequential and predictable fashion that can be observed, measured, and followed over time.
- In a few short years, human beings change from completely helpless creatures who depend entirely on their caregivers, to small beings with independent movement, complex language and problem-solving skills, as well as the ability to interact in positive and productive ways with others.
- Children thus become well-suited for the next phase of development, characterized by academic achievement and more complex problem-solving and thinking skills.
- Developmental milestones provide a valuable framework with which the pediatrician can appropriately evaluate and observe children over time.

References


Suggested Reading


Suggested Websites

www.firstsigns.org
www.autismspeaks.org

Thank You!

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Congenital Infections (TORCH)

Jeannine Del Pizzo, MD*

Introduction
TORCH is an acronym for a group of congenitally acquired infections that may cause significant morbidity and mortality in neonates. TORCH stands for the following:

Toxoplasmosis
Other: syphilis, hepatitis B, varicella-zoster virus (VZV), human immunodeficiency virus (HIV), parvovirus B19, enteroviruses, lymphocytic choriomeningitic virus
Rubella
Cytomegalovirus (CMV)
Herpes simplex virus (HSV)

Some experts consider the acronym TORCH outdated, largely due to the growing number of infections listed in the “other” category. However, use of the acronym may aid in remembering the causative organisms.

While each of the congenital infections possesses distinct clinical manifestations and sequelae, some of these infections share characteristics. It is important to think of one or more of these infections when a neonate presents with microcephaly, intracranial calcifications, rash, intrauterine growth restriction (IUGR), jaundice, hepatosplenomegaly, elevated transaminase concentrations, and thrombocytopenia. However, many congenital infections may be silent at birth, with symptoms manifesting years later.

Also, some agents, such as VZV, are associated with infection in utero as well as infection during or after delivery, with differing effects depending on the time of infection. This article includes discussion of true congenital infections that are present at the time of delivery as well as some transmitted during or after delivery.

When a congenital infection is suspected, a thorough maternal history should be obtained, including immunization status, past and recent infections, and exposures. A careful physical examination of the neonate is vital because different clinical findings may indicate a specific diagnosis. Diagnostic testing should be directed only toward those infections that fit the clinical and historical picture. The sometimes employed TORCH titers should never be used as a single test to diagnose or rule out a congenital infection.

Toxoplasmosis
The causative agent in toxoplasmosis is the protozoan and obligate intracellular parasite *Toxoplasma gondii*.

**ROUTE OF INFECTION.** *T. gondii* is spread via the fecal–oral route. Oocysts of *T. gondii* are excreted via cat feces and ingested by humans through inadequately cooked meat, contaminated water and soil, and unpasteurized goat milk. Oocysts remain infectious for variable amounts of time, and after excretion can endure in damp soil for as long as 18 months.

**CLINICAL MANIFESTATIONS.** Toxoplasmosis is transmitted to the fetus during a mother’s primary infection or if the mother is immunocompromised and has chronic infection. The risk of fetal transmission during a maternal infection increases with gestational age. However, the earlier in pregnancy the fetal infection occurs,
the more likely it is to be severe. Transmission during the first trimester may result in death, or if the fetus survives, frequently it will demonstrate ophthalmologic and central nervous system (CNS) sequelae. Transmission in the second trimester causes multiple effects, including the "classic" triad of hydrocephalus, intracranial calcifications, and chorioretinitis, as well as jaundice, hepatosplenomegaly, anemia, lymphadenopathy, microcephaly, developmental delay, visual problems, hearing loss, and seizures. Fetuses infected in the third trimester often are asymptomatic at birth.

**DIAGNOSIS.** Definitive diagnosis of toxoplasmosis is made by organism isolation from the placenta, serum, and cerebrospinal fluid (CSF); however, organism isolation can be challenging and is not generally available. A positive maternal enzyme-linked immunosorbent assay suggests the diagnosis but does not clinch it. Other studies that can build a case for congenital toxoplasmosis are ophthalmologic examination evaluating for chorioretinitis, a computed tomography scan of the head looking for calcifications, and CSF studies demonstrating elevated protein and pleocytosis. An infant’s toxoplasmosis immunoglobulin G (IgG) titer will be positive if the mother was infected; however, this finding does not prove the infant’s infection. If the infant is infected, the IgG concentration will continue to be elevated after maternal-derived antibody concentration decreases, at approximately 6 months to 1 year of age.

**TREATMENT.** Congenital toxoplasmosis is treated with pyrimethamine, sulfadiazine, and leucovorin for 1 year. Infants who receive treatment have improved hearing loss, although they remain at risk for recurrent chorioretinitis.

**Syphilis**

Syphilis is caused by infection with the gram-negative spirochete *Treponema pallidum.*

**ROUTE OF INFECTION.** *T pallidum* is spread through direct contact with a spirochete-containing lesion, sexually, or transplacentally.

**CLINICAL MANIFESTATIONS.** The majority of infants born with congenital syphilis are asymptomatic at birth. The time of onset of clinical manifestations is used to classify early congenital syphilis and late congenital syphilis. The former presents at 1 to 2 months of age with development of one or more of the following: maculopapular rash, snuffles, generalized lymphadenopathy, hepatomegaly, thrombocytopenia, anemia, meningitis, chorioretinitis, pneumonia alba, and osteochondritis. Late congenital syphilis presents after 2 years of age with signs such as Hutchinson teeth (small teeth with an abnormal central groove), mulberry molars (bulbous protrusions on the molar teeth resembling mulberries), hard palate perforation, eighth nerve deafness, interstitial keratitis, bony lesions, and saber shins (due to chronic periostitis).

**DIAGNOSIS.** The definitive diagnosis of congenital syphilis is demonstration of spirochetes under dark-field examination or direct fluorescent antibody in fluid from a lesion, the placenta, or the umbilical cord. However, because this testing is not always available, a presumptive diagnosis is made using nontreponemal and treponemal tests. Nontreponemal tests such as the venereal disease research laboratory test and rapid plasma reagin are used for screening and monitoring treatment of the disease. Treponemal tests such as the fluorescent treponemal antibody absorption test or *T pallidum* particle agglutination are used to confirm diagnosis. Treponemal tests are not used alone due to false positives that may occur with other infections such as Lyme disease, yaws, pinta, and leptospirosis. A false-negative result also may occur because of an overwhelming quantity of antibodies, which is called the prozone effect.

The recommendations for screening mothers and infants are established in the United States by the Centers for Disease Control and Prevention (CDC). The best way to determine an infant’s risk for congenital syphilis is to know the mother’s status. The CDC recommends that all pregnant women be screened for syphilis with a nontreponemal test and, if positive, receive a confirmatory treponemal test. Infected pregnant women should be treated with penicillin G and followed up with both a nontreponemal test and treponemal test 4 weeks after treatment and then monthly.

An infant should be tested with the same nontreponemal test as the mother if the mother has a nontreponemal titer that increased fourfold; had a positive treponemal test without documented treatment; had a positive treponemal test not treated with penicillin; had a positive treponemal test and was treated less than 1 month before delivery; or if the infant has signs of congenital syphilis. If the infant’s nontreponemal titer is more than fourfold higher than the mother’s or if there is any clinical finding consistent with congenital syphilis, the infant must be treated and undergo a venereal disease research laboratory test of CSF, liver function tests, complete blood count, and long bone radiographs.
**TREATMENT.** The treatment of choice for *T. pallidum* infection at any age is penicillin G.

**Hepatitis B**

Hepatitis B virus (HBV) is a DNA virus that hails from the hepadnavirus family.

**ROUTE OF INFECTION.** Transmission of HBV occurs after exposure to contaminated blood or body fluids. Transplacental transmission is a rare occurrence. Most neonates are infected during delivery through exposure to maternal blood during delivery.

**CLINICAL MANIFESTATIONS.** The majority of neonates who acquire perinatal HBV infection are asymptomatic. Rarely they may demonstrate signs consistent with hepatitis including jaundice, thrombocytopenia, elevated transaminase concentrations, and rash.

**COMPLICATIONS.** The risk of morbidity of HBV is inversely proportional to the gestational age at the time of initial infection. Children infected at a younger gestational age have a higher risk of progressing to chronic infection and disease. As the gestational age at the time of acute infection increases, the risk of chronic infection decreases. Progression of HBV infection to chronic disease is worsens because 25% of children chronically infected with HBV will develop hepatocellular carcinoma or cirrhosis.

**DIAGNOSIS.** It is essential to know the mother’s status to determine if an infant has been exposed to HBV. In the United States, pregnant women are screened for HBV surface antigen (HBsAg). The presence of this antigen signifies that the mother has an acute or chronic infection. Infants born to mothers with a positive HBsAg should receive HBV vaccine and hepatitis B immune globulin within 12 hours of birth. These infants should then complete the HBV vaccine series with two more additional immunizations per the CDC’s recommended schedule, as well as undergo HBsAg and anti-HBs testing after 9 months of age. If the mother’s HBV status is unknown at the time of delivery, she should be tested for HBsAg immediately. The infant should receive the HBV vaccine while awaiting the mother’s results. If the mother’s HBsAg is negative, no further treatment is required. However, if it is positive, the infant should receive hepatitis B immunoglobulin within 7 days of birth. Preterm infants exposed to HBV and weighing less than 2 kg should be treated as outlined above with one exception: the dose of HBV vaccine received within 12 hours of birth should not be counted toward completion of the vaccine series. They should begin the usual three-dose vaccine series at 1 month of age.

**TREATMENT.** There is no treatment for acute HBV. Lamivudine is approved for treating chronic HBV infection in children 2 years of age and older.

**Varicella-Zoster Virus**

VZV is a member of the herpesvirus family.

**ROUTE OF INFECTION.** VZV is transmitted through contact with fluid from vesicles or through airborne contact with respiratory secretions. Congenital varicella is acquired transplacentally.

**CLINICAL MANIFESTATIONS.** A maternal varicella infection transmitted to the fetus under 20 weeks’ gestation results in fetal demise or development of anomalies, including ophthalmologic malformations, cutaneous scarring, limb hypoplasia, and damage to the CNS. If maternal infection and subsequent fetal transmission occur later in gestation, the infant may develop the typical signs of varicella after birth or may be asymptomatic but have a risk of developing zoster later on. Perinatal infection occurring several days before or after birth may result in neonatal death.

**DIAGNOSIS.** Varicella should be suspected in a mother who demonstrates the classic signs of varicella: a prodromal illness with dewdrop lesions developing in crops that form crusts. In an infant who presents with typical vesicular lesions, a polymerase chain reaction (PCR) or direct fluorescent antibody of the fluid can be performed. Acute and convalescent immunoglobulin M (IgM) titers can diagnose in hindsight but will not identify acute disease.

**TREATMENT.** Pregnant women who acquire varicella may be treated with acyclovir. Pregnant women who are exposed to varicella can be given prophylactic varicella-zoster immunoglobulin or immunoglobulin intravenous. Infants born with congenital varicella should be treated with acyclovir and varicella-zoster immunoglobulin.

**Human Immunodeficiency Virus**

HIV is an RNA virus belonging to the Retroviridae family. There are two types of HIV: HIV-1 and HIV-2, with HIV-1 being the predominant virus found in the United States. Humans are the only known hosts of HIV-1 and HIV-2.

**ROUTE OF INFECTION.** HIV is spread parenterally through exposure...
to infected blood, semen, vaginal and cervical secretions, contaminated needles or sharp objects, contaminated blood transfusions, and vertically. HIV can be transmitted to the infant at any time during pregnancy: transplacentally, during labor and delivery, or after birth through breastfeeding. The highest risk of neonatal infection occurs during delivery with exposure to maternal blood.

**CLINICAL MANIFESTATIONS.** Neonates suspected of having perinatally acquired HIV will be asymptomatic and have normal-for-age lymphocyte counts. As the infection evolves, T-cell function declines. Depending on T-cell counts, various opportunistic infections can take hold, such as encapsulated bacteria, *Pneumocystis jiroveci*, VZV, CMV, and HSV, among others.

**DIAGNOSIS.** The American Academy of Pediatrics and CDC recommend routine HIV-1 testing for all pregnant women in the United States. Knowledge of the maternal infection can prompt measures to decrease transmission, including HIV drug prophylaxis, cesarean section before rupture of membranes for women with a viral load of greater than 1,000 copies/mL at full term delivery, avoidance of breastfeeding, and early detection in the infant. HIV serum DNA and RNA assays have low sensitivity shortly after birth. Either HIV-1 DNA or RNA PCR should be analyzed in the infant born to an HIV-infected mother at the following times: 14 to 21 days after birth, 1 to 2 months of age, and 4 to 6 months of age. An infant is considered uninfected if he or she meets either of the following laboratory criteria: 1) two negative HIV-1 DNA or RNA assays, one obtained after 1 month of age and the other at 4 months of age or older, or 2) two negative HIV-1 antibody tests from separate specimens obtained at 6 months of age or older. Some practitioners may follow antibodies until after 18 months of age because maternally derived antibodies rarely persist beyond this age.

**TREATMENT.** Infants suspected of having HIV infection are started on zidovudine until 6 weeks of age. Infants with confirmed HIV infection are started on further antiretroviral treatment.

**Parvovirus B19**

Parvovirus is a single stranded DNA virus.

**ROUTE OF INFECTION.** Parvovirus is spread through respiratory tract secretions, exposure to contaminated blood, and transplacentally.

**CLINICAL MANIFESTATIONS.** Infants who are infected with parvovirus are at risk for hydrops, pleural and pericardial effusions, IUGR, and death. Infection during the first half of pregnancy confers the greatest risk to the fetus. Infected infants demonstrate the extremes of outcomes with almost no middle ground: either life-threatening infection or no residua.

**DIAGNOSIS.** If congenital parvovirus is suspected, an IgM titer should be obtained from infant serum.

**TREATMENT.** Treatment is limited to supportive care. There is evidence that intravenous immunoglobulin may be beneficial.

**Rubella**

Rubella, also known as German measles, is a member of the Togaviridae family.

**ROUTE OF INFECTION.** Rubella is spread through contact with respiratory secretions (both direct and droplet) and transplacentally.

**CLINICAL MANIFESTATIONS.** Signs at birth of congenital rubella include “blueberry muffin” rash (dermal erythropoiesis), lymphadenopathy, hepatosplenomegaly, thrombocytopenia, interstitial pneumonitis, radiosclerotic bone disease, and IUGR.

**COMPLICATIONS.** As with toxoplasmosis, the earlier during gestation infection occurs, the more severe the disease will be. Fetal transmission during the first trimester often results in readily apparent sequelae at birth, such as congenital defects. In contrast, infection after 12 weeks may have no clinical manifestations but is more likely to result in future hearing loss and visual problems. Congenital rubella can affect multiple systems. Eye problems associated with congenital rubella include microphthalmos, pigmented retinopathy, cataracts, and congenital glaucoma. Cardiac manifestations include peripheral pulmonic stenosis and patent ductus arteriosus. Endocrinopathies can occur, the most common being diabetes mellitus. Neurologic sequelae include developmental delay, encephalitis, and sensorineural hearing loss.

**DIAGNOSIS.** A positive infant rubella IgM titer is indicative of recent infection; however, this test can be complicated by both false positives and false negatives. The virus can be isolated in culture from certain body fluids, including blood, urine, CSF, and oral and nasal secretions. The diagnosis of congenital rubella can be established by persistently elevated or rising IgG titers over time.
TREATMENT. Treatment is limited to supportive care.

Cytomegalovirus
CMV is classified as part of the herpesvirus family and is the most common congenital infection in the United States. The prevalence of congenital CMV infection in live-born infants in industrialized nations is estimated to be 0.5% to 1%.

ROUTE OF INFECTION. CMV can be transmitted to an infant during pregnancy (transplacental transmission), during delivery (via contact with infected genital tract secretions), or postnatally (via ingestion of contaminated human milk or direct contact with other body fluids such as urine and saliva). Mothers who have been exposed to CMV before pregnancy are still at risk for transmitting the infection to the fetus by way of reactivation or infection with a new strain. However, maternal infection before pregnancy and subsequent development of immunity significantly decrease the risk of congenital CMV.

CLINICAL MANIFESTATIONS. The majority of neonates born with congenital CMV are asymptomatic at birth. Symptomatic infants with CMV may have IUGR, microcephaly, periventricular calcifications, hepatosplenomegaly, jaundice, thrombocytopenia, and retinitis. Some infants may demonstrate hypotonia, lethargy, and poor suck. It is important to note that preterm infants may present as if they have sepsis (apnea, bradycardia, intestinal distention, and poor color). The risk of fetal morbidity is increased when the mother has a primary infection during pregnancy, especially during the first trimester. Postnatal infection via ingestion of human milk causes no clinical sequelae, likely due to protection from maternal antibody.

COMPLICATIONS. Whether an infant is symptomatic at birth can help predict future morbidity. Approximately one half or more of symptomatic neonates will develop CNS sequelae, including retinitis, sensorineural deafness, and developmental delay. This incidence is in contrast to asymptomatic infants, fewer than 20% of whom will develop CNS sequelae. There is an increased likelihood of developmental delay when infants manifest chorioretinitis, microcephaly, and intracranial calcifications.

DIAGNOSIS. Congenital CMV is diagnosed by demonstration of the virus in body fluids such as urine or pharyngeal secretions in the first 3 weeks after birth. After 3 weeks of age, it is difficult to determine whether the infection was congenital or postnatal. Virus can be detected in body fluids by culture, rapid centrifugation-enhanced culture (requires 24 h incubation), or PCR. Antibodies are not useful in diagnosing congenital CMV because neonatal IgG indicates maternal infection but does specify when it occurred, and assays for IgM have poor sensitivity and specificity.

TREATMENT. There is no approved agent for the treatment of congenital CMV. Treatment with ganciclovir has been shown to improve both hearing loss and neurodevelopmental outcomes.

Herpes Simplex Virus
HSV 1 and 2 are double-stranded DNA viruses from the Herpesviridae family.

ROUTE OF INFECTION. HSV is transmitted primarily through direct contact with infected lesions or mucosa. Neonates most often acquire the infection while passing through an infected vaginal canal during birth or from the virus ascending after rupture of membranes. Fetal transmission via the placenta occurs only rarely and can result in congenital anomalies and death. Primary maternal infection during pregnancy, especially in the third trimester, imparts the greatest risk to the fetus. Postnatal infection can occur from infected caregivers kissing or touching the infant.

CLINICAL MANIFESTATION. Infants with congenitally acquired HSV infection usually will present in the first 6 weeks after birth. Early signs may be vague and include irritability, poor feeding, lethargy, skin vesicles, fever, and seizures. There may be no signs at all. It is essential to have a high degree of suspicion, because there is a known maternal history of herpes in only 12.5% of infants diagnosed with congenital HSV. The manifestations of neonatal herpes can be classified in three ways: primarily skin, eyes, and mucosal involvement (SEM disease); primarily CNS disease; and disseminated disease with multiple organ involvement. However, these categories are not exclusive of each other and infants can have signs from more than one. Infants given a diagnosis of SEM disease also may have occult CNS infection.

COMPLICATIONS. Untreated, neonatal HSV infection causes high morbidity and mortality. If treated, the infants with SEM disease have the best prognosis with respect to both survival and neurologic development; however, about one half will suffer recurrent skin outbreaks. Treated infants who have CNS disease have a good prognosis for sur-
vival but suffer significant neurologic sequelae.

**DIAGNOSIS.** An infant is considered infected with herpes if any of the following tests are positive: serum HSV IgM, HSV PCR of the CSF, or HSV culture of a lesion or any other mucosal surface. Because of its high sensitivity (ranging 75% to 100%), HSV PCR is the test of choice for evaluation of the CSF. It is important to note that the CSF PCR may be negative the first 5 days of illness. If HSV remains strongly suspected, despite an initial negative result, the CSF PCR should be repeated. For SEM disease, HSV culture of a cutaneous or mucosal lesion is the test of choice. Neither PCR nor culture of the blood has a particularly high sensitivity. HSV serologies may be helpful; however, not all patients seroconvert initially and false negatives may persist up to 2 weeks into the illness. Maternal HSV IgG antibodies also may be present in the infant.

**TREATMENT.** The preferred treatment for neonatal herpes infection is intravenous acyclovir. Treatment with acyclovir improves mortality rates for all infants who have neonatal herpes and neurologic development in those who have SEM and disseminated disease.

**Suggested Reading**


**Acknowledgment**

Thank you to David Berman, DO, for his editing contribution to this article.
The reader is encouraged to write possible diagnoses for each case before turning to the discussion.

Case 1: Pallor, Screaming, Sweating, and Breathing Difficulty Associated With Feeding in a 2-month-old Infant

Case 2: Swelling, Redness, Warmth, Tenderness, and Purulent Drainage Under the Nail in an Adolescent Girl

Case 3: Urticarial Rash, Fatigue, Achiness, and Dark Urine in an Adolescent Girl

Case 1 Presentation
A 2-month-old term girl presents to an ED with a 3-week history of episodic difficulty in breathing together with screaming during and after feeding. The episodes are described as rapid breathing and shortness of breath that happen only with feeds and are associated with sweating and pallor, occurring multiple times a day. The patient has no other signs, including fever, runny nose, nasal congestion, drooling, noisy breathing, difficulty swallowing, or arching of the back with feeds. Her weight gain is appropriate for age. The patient has been evaluated for these complaints and felt to have colic or gastroesophageal reflux disease, for which ranitidine was prescribed. Her birth and perinatal histories are unremarkable.

On physical examination, the following are found: temperature, 37.2°C; heart rate, 160 beats/min; respiratory rate, 52 breaths/min; pulse oximetry, 96% in room air; and blood pressure, 92/52 mm Hg. She is alert and has moderate respiratory distress with tachypnea and subcostal retractions. Her precordium is hyperdynamic. On auscultation, there is a gallop rhythm but no murmurs. Pulses are palpable but weak in four limbs, and capillary refill is prolonged at 4 seconds. There is no hepatomegaly. The findings on the rest of the examination are within normal limits.

Laboratory findings include a normal CBC, capillary blood gas, and serum concentrations of lactic acid and electrolytes. Liver function tests, including serum albumin, prothrombin time, and partial thromboplastin time, also yield normal results. Cardiac enzymes are normal except for a mildly elevated serum troponin concentration at 0.43 ng/mL (normal 0 to 0.4 ng/mL). Additional evaluation leads to the diagnosis.

Case 2 Presentation
A 15-year-old girl is hospitalized for progressive right thumb redness and swelling, redness, warmth, tenderness, and purulent drainage under the nail. Her past medical history is significant for a boil on her right hand that was treated with antibiotics 10 days prior to admission. She has a history of skin infections and acne. Her family history is significant for a brother with a history of acne. She has no history of hand injuries or surgeries.

On physical examination, the following are found: temperature, 37.6°C; heart rate, 80 beats/min; respiratory rate, 18 breaths/min; and blood pressure, 120/80 mm Hg. She is in no acute distress. Her right thumb is swollen, red, and warm with purulent drainage under the nail. There is no evidence of cellulitis or lymphangitis. The rest of her examination is unremarkable.

Laboratory findings include a normal CBC, capillary blood gas, and serum concentrations of lactic acid and electrolytes. Liver function tests, including serum albumin, prothrombin time, and partial thromboplastin time, also yield normal results. Cardiac enzymes are normal except for a mildly elevated serum troponin concentration at 0.43 ng/mL (normal 0 to 0.4 ng/mL). Additional evaluation leads to the diagnosis.

Frequently Used Abbreviations

- ALT: alanine aminotransferase
- AST: aspartate aminotransferase
- BUN: blood urea nitrogen
- CBC: complete blood count
- CNS: central nervous system
- CSF: cerebrospinal fluid
- CT: computed tomography
- ECG: electrocardiography
- ED: emergency department
- EEG: electroencephalography
- ESR: erythrocyte sedimentation rate
- GI: gastrointestinal
- GU: genitourinary
- Hct: hematocrit
- Hgb: hemoglobin
- MRI: magnetic resonance imaging
- WBC: white blood cell
swelling. She reports tactile fevers and chills. She has pain with movement of the thumb and tenderness over the affected area, but no limitation of motion or paresthesia. She was evaluated 2 days earlier and started on an oral antibiotic. Her WBC count at that time was normal. She did not tolerate the oral antibiotic due to gastrointestinal side effects and failed to show any clinical improvement; therefore, she was hospitalized.

On physical examination, the girl is afebrile with normal vital signs for age. Examination of the right thumb reveals circumferential swelling, erythema, and warmth of the distal phalanx and a hypopigmented macular lesion with central necrosis on the volar surface. The affected thumb is twice the size of her other thumb. Spontaneous drainage of pus is noted under the fingernail. Slight tenderness to palpation is present. She has full range of motion of the thumb. Circulation and sensation are normal.

Laboratory studies reveal a C-reactive protein concentration of 0.5 mg/dL (normal <0.8 mg/dL) and an ESR of 26 mm/h (normal 10 to 20 mm/h). Culture of the nail drainage grows methicillin susceptible Staphylococcus aureus (MSSA) with inducible clindamycin resistance.

A MRI with gadolinium contrast shows changes consistent with distal phalanx osteomyelitis and a wide sinus tract extending from the volar skin surface to the bone. Additional history reveals the initiating event.

Case 1 Discussion
The chest radiograph showed cardio-megaly with increased pulmonary venous markings (Figs. 1 and 2). ECG showed inverted T waves in leads I and aVL, Q waves in lead aVL, and deep S waves in lead V1 (Fig. 3) consistent with anterior wall ischemia with left ventricular hypertrophy and strain. Echocardiography showed normal cardiac anatomy with left ventricular dilation. There was decreased systolic function along with reversal of flow in the left coronary artery that entered the main pulmonary artery (Fig. 4). A diagnosis of anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) was established.

Differential Diagnosis
The differential diagnosis for infants presenting with respiratory distress, unexplained tachycardia, and signs of poor perfusion is broad and includes sepsis, anemia, and cardiogenic shock secondary to cardiac diseases such as structural cardiac anomalies, myocarditis, and dilated cardiomyopathy. Other considerations include airway abnormalities such as choanal atresia and tracheo-esophageal fistula. However, these conditions usually present at a much earlier age and...
are not associated with poor perfusion.

The Condition

ALCAPA is a life-threatening condition first described by Bland et al (Bland-White-Garland syndrome), having an incidence of 1/300,000 live births and mortality rate of 90% during the first year after birth if uncorrected. (1) The disorder has a male predilection (male to female, 2:1).

As the pulmonary arterial resistance falls at and after birth, perfusion pressure in the left coronary artery becomes inadequate, which leads to myocardial ischemia, infarction, and fibrosis, causing cardiogenic shock. Myocardial steal syndrome develops as collaterals connect the right coronary to the left coronary artery, with reversal of the abnormal flow from the left coronary to the pulmonary artery, which contributes to survival beyond 1 year after birth.

ALCAPA usually presents as heart failure within the first few months after birth, with recurrent attacks of discomfort, restlessness, irritability, respiratory distress, diaphoresis, and pallor, with or without mild cyanosis. These episodes occur during periods of increased myocardial demands such as during feeding or defecation. Physical examination usually demonstrates a gallop rhythm. Cardiac murmurs may be nonspecific; a holosystolic murmur due to mitral insufficiency may be heard. Patients with severe congestive heart failure can present with hepatomegaly and cardiogenic shock.

Diagnosis

Laboratory tests seldom are diagnostic of ALCAPA. Chest radiograph usually shows cardiomegaly with or without pulmonary vascular congestion. The ECG may show evidence of lateral wall ischemia. Echocardiography is useful in identifying the anomalous origin of the coronary artery from the pulmonary artery, with color Doppler flow demonstrating the abnormal retrograde flow into the pulmonary artery. Cardiac catheterization and angiography often are diagnostic and are indicated in patients who have a history strongly suggestive of ALCAPA despite negative echocardiography.

Treatment and Prognosis

Medical treatment of heart failure using diuretics, digoxin, and afterload reducing agents usually is a temporary stabilizing measure. Surgery is imperative to establish revascularization of the left coronary artery. This
goal is achieved either by detaching and re-implantation of the anomalous coronary artery to the aorta or by cardiac transplantation in patients with a severely damaged myocardium. Prognosis is excellent if treated early in the process of the disease with surgical correction.

This patient underwent coronary re-implantation. The immediate post-operative period was complicated by cardio-respiratory failure, necessitating extracorporeal membranous oxygenation. The patient was discharged from the hospital 6 weeks after surgery. The child was asymptomatic at 1-year follow up, demonstrating normal growth and development. Echo-cardiography showed normal cardiac function with mild mitral regurgitation that is treated with afterload reduction using enalapril.

Lessons for the Clinician

- Respiratory distress with feeding in infants with or without sweating should be considered an early sign of cardiac failure.
- Symptoms suggestive of colic may actually be caused by angina.
- ALCAPA is a rare but life-threatening condition that is treatable with an excellent prognosis if identified early.

Case 2 Discussion

One week before developing symptoms, the patient used an over-the-counter (OTC) cryotherapy product to treat a wart on her thumb. Cryotherapy involves freezing a wart with application of a cryogen. In medical facilities, liquid nitrogen is used most commonly. The therapeutic effect is due either to necrotic destruction of infected skin cells or induction of local inflammation. In the past, freezing agents were available only in a licensed medical facility; but now OTC preparations are available. Although freezing with OTC preparations occurs at a lower temperature and a slower rate than liquid nitrogen, cold thermal burns have been reported due to failure to follow instructions properly. Package instructions advise against spraying directly onto normal skin and warn about resulting injuries. Clinicians must be careful in their use of these devices because of the potential for injury from misuse. Infectious complications are rare and usually localized. To our knowledge, this is the first case report of cryotherapy-associated osteomyelitis. The proposed mechanism of infection is direct inoculation as a result of cryotherapy-induced trauma.

The Condition

Acute osteomyelitis is a serious infection of the bone and bone marrow, most commonly of bacterial origin, that results in bone destruction. Pathogenesis is by way of hematogenous seeding in most cases but rarely may occur due to the spread of contiguous infection or direct inoculation as a result of trauma or surgery. In long bones, the metaphysis is involved most frequently. Often infection is preceded by blunt trauma at the site, although the pathologic role of trauma in osteomyelitis remains unclear.

S aureus is the most common pathogen in all age groups because of its expression of adhesion molecules that adhere to bone matrix and its ability to survive intracellularly within osteoblasts. Other organisms cause osteomyelitis, the agent being related to the age of the patient, underlying medical conditions, and the mechanisms of infection. Group B Streptococcus and gram-negative enteric organisms cause osteomyelitis in neonates. Group A Streptococcus, Streptococcus pneumoniae, and Kingella kingae are pathogens that infect infants and children, along with S aureus. Salmonella species are common in patients with hemoglobinopathies, and Pseudomonas aeruginosa osteochondritis is associated with puncture wounds through tennis shoes. Mycobacteria, fungi, and Bartonella henselae are atypical causes of osteomyelitis. In 50% of cases, no specific organism is identified, but improvement after empiric treatment for S aureus is usual.

The clinical presentation varies with the age of patient, location of infection, and acuity of infection. Acute osteomyelitis may present with fever, bone pain, irritability, pseudoparalysis, refusal to bear weight, and overlying skin changes.

Diagnosis begins with clinical suspicion followed by confirmatory laboratory and imaging studies. Typically, the WBC count and serum inflammatory markers are elevated. Blood cultures are positive in about 50% of cases. With the increasing prevalence of community-acquired methicillin-resistant S aureus (CA-MRSA), bone aspirate for culture is becoming increasingly important and useful especially when the blood cultures are negative or there is a lack of response to empiric therapy. Plain radiographs do not show bone changes until 10 to 21 days after the onset of infection. Radionuclide
bone scan is useful for identifying multifocal or poorly localized disease, but abnormal results are not specific for osteomyelitis. MRI is highly sensitive, detects early changes, delineates the extent of surrounding soft tissue involvement, aids in surgical planning, and identifies abscesses when performed with intravenous gadolinium contrast. Limitations of MRI include cost, need for sedation in young patients, and inability to detect multifocal disease.

Management
Children with presumed osteomyelitis commonly are hospitalized for administration of parenteral antibiotics as well as surgical intervention if required. Empiric antibiotic therapy should cover most likely organisms as well as CA-MRSA in areas where there is greater than 10% resistance. When empirically treating for CA-MRSA, the local prevalence of inducible clindamycin resistance must be taken into consideration. Minimum treatment length should be 3 weeks because shorter courses are associated with treatment failure. However, most experts recommend antibiotic therapy for 4 to 6 weeks. Several studies have shown good outcomes with early transition to oral antibiotics based on clinical improvement, including resolution of fever and declining serum inflammatory markers. However, the success depends on treatment compliance and availability of an appropriate oral agent.

Recent reports show a sharp increase in osteomyelitis caused by CA-MRSA, with an increased severity of infection linked to the expression of the Panton-Valentine leukocidin gene encoding for an exotoxin. Multifocal disease, overwhelming sepsis, deep vein thrombosis, septic pulmonary emboli, myositis, pyomyositis, and subperiosteal or intraosseous abscess are complications observed more commonly in cases of infection with S aureus expressing Panton-Valentine leukocidin gene.

Prognosis
With early and proper treatment, most children do not develop long-term sequelae. Permanent morbidities include disruption of bone growth, limb length discrepancies, abnormal gait, arthritis, and pathologic fractures. If untreated or improperly treated, chronic osteomyelitis can occur, with the development of necrotic bone. Necrotic cortical bone may separate, forming a sequestrum, and get encased by a sheath of new bone, forming what is known as an involucrum. Sequestra harbor bacteria despite antibiotic therapy and the infection may extend through the cortical bone, resulting in sinus tract formation with rupture through the skin.

Lessons for the Clinician
● Early diagnosis of osteomyelitis with appropriate surgical and medical treatment is imperative to prevent long-term musculoskeletal damage resulting in permanent disability.
● Empiric therapy should include an anti-staphylococcal antibiotic, with attention to local prevalence of CA-MRSA.

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Case 3 Discussion
Urinalysis yielded normal results, ruling out urinary tract infection, hematuria, and hyperbilirubinemia as causes for her dark-colored urine. Administration of diphenhydramine led to rapid improvement of her rash, confirming that this was an urticarial hypersensitivity reaction. After discontinuing metronidazole therapy, her urticaria resolved completely over the next few days, and the color of her urine returned to normal.

Metronidazole ingestion has been reported to cause dark urine. This phenomenon is thought to result from excretion of a pigmented drug metabolite. Hypersensitivity reactions and urticaria also have been reported with metronidazole therapy. Thus, although the patient’s dermatologic and urinary symptoms occurred through distinct pathologic mechanisms, they resulted from the same trigger: her treatment with metronidazole.

Differential Diagnosis for Dark Urine
The list of potential causes of dark urine is broad and includes a variety of pathogenic processes. Consideration of history, physical findings, and laboratory data are important in achieving an accurate diagnosis. Gross hematuria is the most common cause of dark urine, and blood can enter the urinary tract anywhere from the kidneys down to the urethral meatus. Infection is the most common cause of bleeding within the urinary system, but trauma, urolithiasis, malignancy, and other processes also can cause hematuria.

Glomerulonephritis often results in gross hematuria and typically causes dark or “cola-colored” urine. Glomerulonephritis can be distinguished from lower urinary tract bleeding by the presence of red blood cell casts on urine microscopy. Renal insufficiency, nephritic syndrome, and nephrotic syndrome can occur in the presence of nephritis; thus, an accurate and timely diagnosis of glomerulonephritis is particularly important.

Abnormalities in urine color can also be caused by extrarenal pro-
cesses. Rhabdomyolysis can result in myoglobinuria, and hemolysis can result in hemoglobinuria, both of which can cause dark urine. Both hemoglobin and myoglobin are detectable on urinalysis, although both are detected via the same reagent and will be reported as positive for “blood.” Urinary bilirubin also can darken urine and is detectable by urinalysis. A positive urinalysis for bilirubin indicates the presence of conjugated bilirubin. Unconjugated bilirubin, which is water-insoluble, cannot be excreted in urine.

Certain inborn errors of metabolism can result in dark urine. Disorders of tyrosine metabolism can lead to the excretion of colorless metabolites, which turn dark on oxidation. This color change typically occurs after the urine is left standing. In some types of porphyria, precursors of heme molecule accumulate in urine and lead to a red, brown, or even purple coloration.

Ingestion of foods and medications containing pigmented molecules can alter urinary color. Beets are a well-known cause of dark urine when consumed in sufficient quantities. Certain medications are known to be associated with urinary excretion of pigments or pigmented metabolites. Rifampin, pyridium, and metronidazole are well known examples.

The Condition

Urticaria is an immunoglobulin E mediated hypersensitivity reaction. Urticaria is common in children and often is idiopathic. Infection, food, and drugs account for most identifiable triggers. Viruses causing acute respiratory and gastrointestinal infections, hepatitis viruses, Epstein-Barr Virus, and herpes simplex virus are all associated with urticaria. Mycoplasma pneumoniae and Streptococcus pyogenes are known bacterial causes of urticaria. Parasitic infections can cause urticaria as well. Fish, shellfish, tree nuts, eggs, cow milk, and peanuts are common dietary causes of urticaria.

The drugs most often associated with urticaria are the penicillins, cephalosporins, sulfonamides, and aspirin. Notably, only 10% to 20% of patients who report penicillin allergy are truly allergic. This discrepancy is likely due to the frequent misdiagnosis of viral exanthem as hypersensitivity reaction. Urticarial lesions can develop within a few minutes to a few days after exposure to the causative agent. Individual urticarial lesions rarely last longer than 24 hours. Lesions can be extensive or localized, and they can coalesce to form large areas of involvement.

For patients with suspected cutaneous hypersensitivity drug reaction, the differential diagnosis includes erythema multiforme minor, Stevens-Johnson syndrome, toxic epidermal necrolysis, serum sickness-like reaction, the hypersensitivity syndrome, annular urticaria syndrome, and drug-induced vasculitis. These disorders often can be distinguished from urticaria by their distinct clinical characteristics, laboratory findings, and well-known associations with specific triggers (eg, anti-epileptic drugs and their well described association with the hypersensitivity syndrome).

Management and Prognosis

Most cases of drug-induced urticaria resolve soon after discontinuation of the causative drug. Treatment with histamine 1 (H1) blocking antihistamines often is effective. Nonsedating, second generation H1 blockers may be preferred for daytime use. Corticosteroid treatment is not routinely recommended for treating urticaria and usually is not necessary unless symptoms are unresponsive to antihistamines.

Lessons for the Clinician

- Cutaneous hypersensitivity reactions are common and can be serious and potentially life-threatening.
- Any patient who develops a new rash during drug treatment must be evaluated carefully.
- There are many causes for “dark” urine. A thorough history and careful physical examination as well as judicious use of laboratory tests can identify the cause in the majority of cases.

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To view Suggested Reading lists for these cases, visit pedsinreview.aappublications.org and click on Index of Suspicion.
The following Suggested Reading lists are included online only for the Index of Suspicion.

**Case 1 Suggested Reading**

**Case 2 Suggested Reading**

**Case 3 Suggested Reading**
Bruce TA. Dark urine related to metronidazole therapy. *JAMA.* 1971;218:1832
Methanol Ingestion

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In Brief

Methanol Ingestion

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Methanol, readily absorbed from the gastrointestinal tract and predominantly metabolized in the liver, is converted by the enzyme alcohol dehydrogenase to formaldehyde, which is further metabolized by aldehyde dehydrogenase to formic acid, the primary toxic metabolite of methanol. Both of these enzymatic reactions employ the reductant nicotinamide adenine dinucleotide (NADH) as cofactors. Ultimately, in a folate-dependent rate-limiting reaction, formic acid is broken down to carbon dioxide and water. Elimination half-lives for methanol are reported variably as 15 to 30 hours.

The toxicity of methanol results primarily from its metabolites. Formic acid is itself an organic acid that produces a profound anion gap metabolic acidosis. In addition, formic acid inhibits mitochondrial cytochrome oxidase, inhibiting oxidative phosphorylation. This arrest of aerobic metabolism contributes to the accumulation of NADH, driving the anaerobic conversion of pyruvate to lactate, thereby further exacerbating the metabolic acidosis.

In addition to its metabolic effects, methanol produces central nervous system and ocular toxicity. The initial central nervous system symptoms of methanol intoxication last only several hours and are similar to those of ethanol intoxication, although to a lesser degree: inebriation, disinhibition, and drowsiness. More ominous central effects, such as seizures, coma, and cerebral edema, are delayed by 12 to 24 hours and result from the accumulation of formic acid and ensuing severe metabolic derangements. The basal ganglia are especially vulnerable to the toxic effects of methanol. Parkinsonian-like sequelae have been reported, including dementia, tremor, rigidity, and bradykinesia. Computed tomography scan of the brain may reveal cerebral edema or bilateral necrosis of the putamen.

The optic nerve and pigmented cells of the retina are especially vulnerable to direct toxic effects of formic acid, and visual symptoms are the hallmark of methanol ingestion. Complaints include color changes, blurred vision, the characteristic “snowfield vision,” and complete blindness. Physical examination reveals hyperemia or pallor of the optic discs, loss of pupillary response and, in severe cases, optic atrophy and permanent loss of vision.

In addition, massive ingestions of methanol may result in pulmonary edema, dysrhythmias, and circulatory collapse. Pancreatitis and acute renal failure are rare but have been reported. Concomitant ethanol intoxication competitively inhibits metabolism of methanol by alcohol dehydrogenase and further delays the manifestations of its toxic metabolites.
A methanol concentration of 25 mg/dL is accepted conventionally as requiring action, although this value is not well based on supporting evidence. The lack of rapidly available methanol levels in most medical centers decreases their diagnostic utility. Two indirect laboratory markers that may be useful in the evaluation of methanol toxicity are the anion gap and the osmol gap (Table). Methanol is an osmotically active compound that manifests as an elevated osmol gap shortly following ingestion. However, an elevated osmol gap is neither sensitive nor specific for methanol ingestion.

As methanol is metabolized to formic acid, the osmol gap falls, while an anion gap metabolic acidosis develops. Because of the reciprocal relationship between the osmol and anion gaps, absence of an elevated anion gap does not exclude methanol toxicity early in the course of poisoning. Ethanol levels, by inhibiting the toxic conversion of methanol, serve to explain a delay in clinical toxicity. In addition, ethanol contributes to the overall osmol gap. Arterial blood gas determination, serum electrolytes, and lactate level are also useful in the assessment and management of methanol poisoning.

The initial management of methanol poisoning should focus on support of cardio-respiratory function and decontamination. Gastric evacuation via nasogastric tube may be attempted early in the course of massive ingestions. The poor adsorption of alcohols to activated charcoal precludes the utility of the sorbent for decontamination in methanol ingestion. However, activated charcoal should be considered, given the common occurrence of coingested substances.

Secondary efforts are aimed at minimizing the toxic conversion of methanol to formic acid. Traditionally, ethanol, with its comparatively greater avidity for alcohol dehydrogenase, was administered either intravenously or orally for this purpose. Given the inherent adverse effects of ethanol (inebriation, respiratory depression, metabolic disturbances, and fluid overload) and the difficulty in maintaining stable serum concentrations, its use has been all but abandoned in favor of a safer and effective alternative, fomepizole (4-methylpyrazole). Fomepizole is an intravenously administered competitive antagonist of alcohol dehydrogenase which, unlike ethanol, is essentially devoid of adverse effects and does not require monitoring of serum concentrations. Its primary disadvantage is that it is very expensive.

Deprived of its primary route of biotransformation, unmetabolized methanol has a half-life of about 54 hours and is eliminated minimally via the kidneys and lungs. Hemodialysis is a useful adjunct to alcohol dehydrogenase blockade because it not only clears the parent compound and its metabolites but also corrects acidosis and fluid overload. Patients who develop end-organ toxicity, renal failure, or severe metabolic acidosis, or who have a serum methanol concentration greater than 50 mg/dL, should be hemodialysed. Folic acid, a necessary cofactor for the final conversion of formic acid to carbon dioxide and water, should be administered. Careful monitoring of acid-base status and fluid balance along with meticulous respiratory support help optimize outcomes.

Methanol intoxication has a high morbidity and mortality. Poor prognostic factors include severe acidosis, coma, or seizures at presentation, acute renal failure, and hypotension. Approximately one third of patients suffer long-term visual or neurologic sequelae. Maintaining a high degree of suspicion for methanol intoxication, especially in the face of an elevated osmol gap or an anion gap metabolic acidosis, is of the utmost importance because rapid identification and early intervention offer the best hope for a favorable outcome.

Comment: Methanol ingestion is only one cause of a high anion gap metabolic acidosis, and thankfully not one of the more common ones. By far, dehydration with a resulting lactic acidemia is what pediatricians see most often in association with a high anion gap. A widely used mnemonic for remembering the causes of high anion gap metabolic acidosis is MUDPILES:


The mnemonic has evolved over the years, with the passing of agents such as paraldehyde and phenformin, the original Ps. If you have a sweeter tooth, forget the liberty taken with spelling and remember KARMEL:

Ketoacidosis, Aspirin, Renal failure, Methanol, Ethanol/Ethylene glycol, Lactic acidosis.

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