Vitamin Excess and Deficiency
Diab, Krebs

Atopic Dermatitis
Waldman, Ahluwalia, Udkoff, Borok, Eichenfield

Clinical Presentation, Evaluation, and Management of Neuroblastoma
Sharma, Mer, Lion, Vik

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Visual Diagnosis: 7-year-old Girl with a Facial Rash
Le, O’Brien Jamison, Kirkorian
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The extent of their participation in the activity.

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BEXSERO is a vaccine indicated for active immunization to prevent invasive disease caused by Neisseria meningitidis serogroup B. BEXSERO is approved for use in individuals 10 through 25 years of age. Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed.

Important Safety Information for BEXSERO

• BEXSERO is contraindicated in cases of hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO.
• Appropriate observation and medical treatment should always be readily available in case of an anaphylactic event following the administration of the vaccine.
• The tip caps of the prefilled syringes contain natural rubber latex, which may cause allergic reactions in latex-sensitive individuals.
• Syncope (fainting) can occur in association with administration of BEXSERO. Ensure procedures are in place to avoid injury from falling associated with syncope.
• The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%).
• Vaccination with BEXSERO may not provide protection against all meningococcal serogroup B strains.
• Vaccination with BEXSERO may not result in protection in all vaccine recipients.

Please see accompanying brief summary of full Prescribing Information for BEXSERO.

References: 1. Prescribing Information for BEXSERO. 2. Prescribing Information for TRUMENBA.

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BEXSERO® (Meninogococcal Group B Vaccine) Suspender for intramuscular injection

The following is a brief summary only, see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

BEXSERO® is a vaccine indicated for active immunization to prevent invasive diseases caused by serum bactericidal activity for homologous serogroup B. BEXSERO is approved for use in individuals 10 through 25 years of age.

Approvals of BEXSERO® are based on demonstration of immune responses as measured by serum bactericidal activity for homologous serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO® against diverse serogroup B strains has not been confirmed.

4 CONTRAINDICATIONS

Hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO. [See Description (1) of all prescribing information]

5 WARNINGS AND PRECAUTIONS

5.1 Preventing and Managing Allogenic Reactions

Appropriate observation and medical treatment should always be readily available in case of an anaphylactic event following the administration of the vaccine.

5.2 Syncope

Syncope (fainting) can occur in association with administration of BEXSERO. Ensure procedures are in place to avoid injury from falling associated with syncope.

5.3 Latex

The tip caps of the pre-filled syringes contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

5.4 Limitation of Vaccine Effectiveness

BEXSERO may not protect all vaccine recipients. BEXSERO may not provide protection against serogroup B strains not included in BEXSERO. [See Clinical pharmacology (12) of all prescribing information]

5.5 Adopting Immunocompetence

Individuals with altered immunocompetence may have reduced immune responses to BEXSERO.

6 ADVERSE REACTIONS

The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥18%), myalgia (≥18%), headache (≥10%), injection site reaction (≥83%), induration (≥83%), fatigue (≥45%), erythema (≥45%), and arthralgia (≥13%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

Efficacy

In a randomized controlled study conducted in the UK and Poland, 120 participants 10 through 25 years of age received only BEXSERO, 1,622 participants received a second dose of BEXSERO 2 months apart, 97 participants received a placebo vaccine followed by Menviron [Meninogococcal Group B Vaccine]. Across groups, median age was 13 years, males comprised 49% and 51% were Hispanic, 4% were Black, <1% were Asian, and 2% were other.

In a randomized controlled study conducted in Chile, all subjects (n = 1,622) 11 through 17 years of age received at least one dose of BEXSERO. This study included a subset of 910 subjects who received 2 doses of BEXSERO 1 or 2 months apart. A control group of 128 subjects received at least 1 dose of placebo containing placebo containing purified chicken egg protein. Across groups, median age was 13 years, males comprised 50% and 51% were Hispanic, 4% were Black, <1% were Hispanic, and 2% were other.

In an uncontrolled study conducted in Canada and Australia, 343 participants 11 through 17 years of age received at least 1 dose of BEXSERO, including 338 participants who received 2 doses of BEXSERO 1 month apart. Across groups, median age was 13 years, males comprised 50%, and 56% were White, 10% were Asian, 4% were Black, 1% were Hispanic, and 4% were other.

Local and systemic reactogenicity data were collected from all participants in the studies conducted in Chile, US, Pakistan and Australia, and from a subset of participants in the study conducted in the UK. Reports of unsolicited adverse events were collected up to six months after the second vaccination.

5.6 Additional Pre-Clinical and Clinical Experience

In a randomized controlled study conducted in the UK, all subjects (n = 1,622) 11 through 17 years of age received at least one dose of BEXSERO. This study included a subset of 610 subjects who received 2 doses of BEXSERO 1 or 2 months apart. A control group of 128 subjects received at least 1 dose of placebo containing purified chicken egg protein. Across groups, median age was 13 years, males comprised 50% and 51% were Hispanic, 4% were Black, 1% were Hispanic, and 2% were other.

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DEDICATED TO THE HEALTH OF ALL CHILDREN®
Vitamin Excess and Deficiency

Liliane Diab, MD,* Nancy F. Krebs, MD, MS*

*Section of Nutrition, Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO

Education Gap

Vitamins are organic compounds that humans cannot synthesize but need in small amounts to sustain life. Pediatricians’ knowledge about vitamins is challenged daily. Pediatricians are faced not only with parents requesting supplements but also with parents refusing them when they are clinically indicated. In addition, pediatricians need to be familiar with the effect of maternal health and diet on human milk to counsel their patients on how to prevent potentially devastating health consequences for the breastfed infant.

Tables 1 and 2 provide the reader with a quick reference to who is at risk and when to consider a vitamin or mineral deficiency (minerals will be covered in the second part of this review). Table 3 summarizes the pharmaceutical and supplemental sources of vitamin D and Table 4 provides a quick reference for diagnostic tests and treatment doses for vitamin deficiencies.

Objectives

After completing this article, readers should be able to:

1. Discuss the risk factors for developing selected vitamin deficiencies.
2. Identify the role of natural foods, fortified foods, and supplements in meeting the Dietary Reference Intakes of various vitamins.
3. Discuss the biological functions of various vitamins and their role in disease prevention.
4. Describe the clinical symptoms of various vitamin deficiencies and the role of laboratory data in making the diagnosis.
5. Explain treatment and prevention strategies for various vitamin deficiencies.

Abstract

The published literature supports the high prevalence of supplement use in children and adolescents in the United States. Pediatricians today are faced with questions from parents and patients about the benefits, safety, efficacy, and correct dose of vitamins and minerals. In this article, we review 7 vitamins with the most clinical relevance as judged by abundance in food, risks and symptoms of deficiency, and potential for...
PREVALENCE OF SUPPLEMENT USE IN THE UNITED STATES

The published literature supports the high prevalence of supplement use in children and adolescents in the United States. According to the National Health and Nutrition Examination Survey (NHANES), 34% of US children and adolescents used supplements in the past month, and almost half of those took a supplement daily. Supplement use was high in underweight patients. (1) Supplement users were more likely to be Asian, white, or non-Hispanic; to belong to families with higher income and education; to be in good or excellent health; and to have access to healthcare. (2)

THE DIETARY REFERENCE INTAKES

According to the Institute of Medicine (IOM), the Dietary Reference Intakes (DRIs) include 4 nutrient-based reference values that are used to assess and plan the diet of healthy people:

- Estimated Average Requirement: the average daily nutrient intake level that is sufficient to meet the requirements of half of the healthy population of a particular age and sex
- Recommended Dietary Allowance (RDA): the average daily nutrient intake level that is sufficient to meet the requirements of nearly all (97%-98%) of the healthy individual of a particular age and sex
- Adequate intake: the recommended average daily intake level based on estimated intake of apparently healthy people; adequate intake is used when RDA cannot be determined
- Tolerable Upper Intake Level (UL): the highest average daily nutrient intake level that is unlikely to pose a risk of adverse effects to almost the whole general population (3)

VITAMIN A (RETINOL)

Introduction

Until the 1980s, the focus on vitamin A deficiency was limited to its ocular manifestations as the leading cause of blindness in developing countries. However, in the past 3 decades, international studies indicate that subclinical vitamin A deficiency has broader consequences regarding childhood morbidity and mortality in the developing world. Vitamin A deficiency accounts for 1.7% of all deaths in children younger than 5 years in developing countries. (4)

Case

J.H. is a 14-year-old with autism who presented to the emergency department for evaluation because he fell off the school bus. J.H.‘s mother reports that recently he has been keeping his eye closed and he has been walking with his arms outstretched. J.H. was born full-term and has no other health conditions except for autism. J.H.‘s diet consisted of crackers and chips only, and he was not taking any vitamins or supplements. On physical examination, J.H. looked underweight (body mass index, 13 [5th percentile for age and sex]) and was agitated. Results of a head computed tomographic (CT) scan and a lumbar puncture were negative, so J.H. was discharged. On follow-up with his primary care doctor, bilateral corneal lesions were noted, so J.H. was referred for an urgent ophthalmology evaluation. J.H. was diagnosed as having xerophthalmia and corneal ulcers secondary to vitamin A deficiency. J.H. was treated with high-dose vitamin A. Two years later, on ophthalmology follow-up he was noted to be able to see objects and ambulate without assistance, but he had complete opacification of his left cornea and a corneal scar in his right eye.

Sources and DRIs

Vitamin A is the collective name for a family of fat-soluble compounds referred to as retinoic acids. There are 2 forms of dietary vitamin A. Preformed vitamin A is found in supplements and food from animal sources, such as fortified dairy products and liver. Provitamin A carotenoids are dietary precursors of retinol. The most important provitamin A carotenoid is β-carotene, which is found in carrots, broccoli, squash, peas, spinach, and cantaloupe. (3)

The RDAs for vitamin A are given as micrograms of retinol activity equivalents (RAEs) to recognize the different bioactivities of retinol and β-carotene. However, food and supplement labels state vitamin A levels in International Units. (3)
When reading supplement labels it is important to note that 1 mg RAE = 1 mg retinol = 2 μg β-carotene (supplement) = 12 μg β-carotene (dietary) = 3.3 IU. (3)

Infants aged 0 to 1 year require 400 to 500 μg RAE/d of vitamin A, with a UL of 600 μg RAE. Children aged 1 to 3 years require 500 μg RAE/d of vitamin A, with a UL of 600 μg RAE. Children aged 3 to 8 years require 400 μg RAE/d of vitamin A, with a UL of 900 μg RAE. Children aged 9 to 18 years require 600 to 900 μg RAE/d of vitamin A, with a UL of 1,700 to 2,800 μg RAE. (3)

Functions

Vitamin A plays a critical role in vision, immunity, and cell differentiation and growth. In the vitamin A–dependent vision cycle, 11-cis-retinal, a derivative of vitamin A, combines with a membrane protein in the retina called opsin to form rhodopsin. Rhodopsin absorbs light and enables the transmission of its stimuli to the brain. Vitamin A is essential to the integrity of the cornea and conjunctiva as well as many other organs because of its importance for cell differentiation. (5)

Factors and Consequences of Vitamin A Deficiency

Xerophthalmia is the term used to describe the ocular manifestations of vitamin A deficiency. Night blindness is the earliest symptom and it is normally a sensitive and specific indicator for vitamin A deficiency. Patients with night blindness cannot see well at night or in dim light, and this can be difficult to recognize, especially among toddlers. Mild cases of night blindness can become apparent only after exposure to a bright light that depletes the limited stores of 11-cis-retinal in the affected patient. Night blindness responds to vitamin A therapy within 24 to 48 hours. If untreated, it leads to keratinization of the surface of the conjunctivae and, thus, is the histopathologic picture of conjunctival xerosis and Bitot spots that are characteristic for vitamin A deficiency. Bitot spots are generally whitish, foamy-appearing ovoid areas on the conjunctiva that result from a buildup of keratin. (6) Corneal xerosis and ulceration can develop in advanced eye disease and can subsequently lead to blindness. (7)

Before xerophthalmia is apparent, other serious consequences, including increased mortality, result from subclinical vitamin A deficiency. The protective effect of vitamin A against infant morbidity and mortality is due to its vital role in enhancing the host immune functions at different levels. Its protective effect against diarrheal diseases is due to its vital role in sustaining the integrity of the intestinal mucosa. The positive effect of vitamin A in human immunodeficiency virus–infected children is due to increased T-cell lymphopoiesis. The therapeutic effects of vitamin A against measles are well validated and are attributed to enhanced antibody production. (8)

Without supplementation, measles can induce a decompensation of vitamin A status and is known to precipitate 25% to 50% of blinding xerophthalmia in Asia. In many parts of Africa, measles is considered the leading cause of childhood blindness. (7)
The American Academy of Pediatrics (AAP) recommends vitamin A supplementation for children 6 months to 2 years old who are hospitalized for measles. The recommended oral supplement dose is 100,000 IU (30,000 mg) for children 6 to 12 months old and 200,000 IU (60,000 mg) for children older than 1 year. (9)

Measles is one example of how seemingly unrelated disease states can alter an individual’s vitamin A balance and lead to deficiency.

The role of vitamin A for maintenance of normal epithelial cell integrity in the lungs has been examined in relation to chronic lung disease of preterm infants. A recent systematic review concluded that vitamin A supplementation had a modest benefit on risk of death, oxygen requirement, and development of chronic lung disease. No benefit was found on neurodevelopment in the second year of life. Definitive recommendations were not supported by the data. (10)

In patients with protein energy malnutrition, vitamin A deficiency can develop not only secondary to low dietary intake but also due to the effect of malnutrition on the transport and storage of vitamin A. (7)

Young children in developing countries are especially vulnerable to and at risk for vitamin A deficiency due to their dependence on human milk, which can be deficient if the mother is deficient. Intestinal infections that impair vitamin A absorption and respiratory infections, such as tuberculosis, that increase metabolic demands make affected children the most vulnerable victims of xerophthalmia. The same factors can affect older individuals, such as refugees who experience unsanitary conditions and nutritional deprivation. (7)

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**TABLE 2. Examples of Micronutrient Deficiencies that Are Associated with Selected Clinical Conditions**

<table>
<thead>
<tr>
<th>CLINICAL SCENARIO</th>
<th>NUTRITIONAL DEFICIENCY</th>
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<tr>
<td>Vegetarian diet</td>
<td>Vitamin B₁₂</td>
</tr>
<tr>
<td>Obesity</td>
<td>Vitamin D (iron)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Vitamins A, D, E, K, B₁₂</td>
</tr>
<tr>
<td>Inflammatory bowel disease, short gut syndrome</td>
<td>Folate, vitamin B₁₂, fat soluble vitamins (iron)</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Folate, vitamin B₁₂, fat soluble vitamins (iron, zinc)</td>
</tr>
<tr>
<td>Prolonged diarrhea</td>
<td>(Zinc)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>• Antacids</td>
<td>Vitamin D (iron)</td>
</tr>
<tr>
<td>• Seizure medications</td>
<td>Vitamin D</td>
</tr>
<tr>
<td>• Corticosteroids</td>
<td>Vitamin D</td>
</tr>
<tr>
<td>• Methotrexate</td>
<td>Folate</td>
</tr>
<tr>
<td>• Sulfasalazine</td>
<td>Folate</td>
</tr>
<tr>
<td>• Trimethoprim</td>
<td>Folate</td>
</tr>
<tr>
<td>The breastfed toddler with limited complementary food</td>
<td>(Iron, zinc)</td>
</tr>
<tr>
<td>Predominantly breastfed infant or toddler, refusing to walk, growth plateau</td>
<td>Vitamin D</td>
</tr>
<tr>
<td>Exclusively breastfed newborn, symptoms of bleeding or altered mental status</td>
<td>Vitamin K</td>
</tr>
<tr>
<td>The use of unfortified goat milk in infants with limited complementary food</td>
<td>Folate</td>
</tr>
<tr>
<td>Highly restrictive diet (autism, developmental delay, food allergies)</td>
<td>Depends on the diet (\text{Vitamin A is vulnerable as in the case in the vignette; vitamin C})</td>
</tr>
<tr>
<td>Highly restrictive diet and refusal to walk</td>
<td>Vitamin C</td>
</tr>
<tr>
<td>Measles</td>
<td>Vitamin A</td>
</tr>
<tr>
<td>Severe protein-energy malnutrition</td>
<td>Vitamin A, vitamin D, (zinc, iron)</td>
</tr>
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Micronutrients in parentheses are not covered in this article.
Risk of Toxicity

Preformed vitamin A toxicity can be acute (a single or short-term doses of retinol ≥150,000 μg for adults and proportionally lower doses for children) or chronic (long-term exposure to daily doses ≥600 μg). The toxic effects are transient and are due to increased intracranial pressure (pseudotumor cerebri). Symptoms include headache, blurred vision, vertigo, and a bulging fontanelle in infants. This has led the IOM to apply a large safety margin in recommending the ULs for vitamin A. Specifically important for women of childbearing age whose intake of retinol should not exceed 2,800 to 3,000 μg/d due to the risk of teratogenicity.

Isotretinoin (13-cis-retinoic acid), a medication used to treat severe acne, is a teratogen that is associated with common birth defects. Since 2006, the Food and Drug Administration (FDA) established the iPLEDGE program by which the prescribing and dispensing of isotretinoin is more tightly controlled in an effort to reduce inappropriate drug use and exposure to women of childbearing age.

VITAMIN B₁₂ (CYANOCOBALAMIN)

Case

C.S. is a 7-month-old infant who presented with failure to thrive, progressive loss of milestones, and shaking movements (Fig 1). On physical examination on the day of admission she looked pale but was alert and had normal vital signs. Her length and weight were below the 5th percentile, and she appeared malnourished. She showed generalized hypotonia with constant tremors of her tongue and extremities. The remainder of her physical examination was normal, with no anomalies or organomegaly.

C.S. was exclusively breastfed. The mother was on a well-balanced diet with oral multivitamins, and she has previously breastfed C.S.’s 2 siblings, who were reportedly healthy. The mother’s medical history was significant for Graves disease.

Results of a CT scan of her head were normal. Laboratory evaluation was notable for macrocytic anemia. The findings of macrocytosis triggered further evaluation of vitamin B₁₂ and folate levels, and her level of vitamin B₁₂ was found to be significantly low. The mother’s level of vitamin B₁₂ was undetectable. The mother was found to have intrinsic factor (IF) antibodies secondary to an autoimmune process triggered by Graves disease.

C.S. was treated with vitamin B₁₂ and was reported to have a nearly normal developmental outcome at 2 years of age.

Sources and Homeostasis of Vitamin B₁₂

Animal source foods such as milk, eggs, and meat are the only natural sources of vitamin B₁₂. Absorption of the vitamin is distinctively complex, especially compared with other water-soluble vitamins. In the stomach, hydrochloric acid and pepsin release vitamin B₁₂ from dietary protein, and cyanocobalamin is then bound to IF secreted by the gastric parietal cells. The complex B₁₂-IF remains intact until its uptake is facilitated by a specific receptor in the distal ileum. Vitamin B₁₂ deficiency can result from low dietary intake of animal source food due to cost, low availability, or religious and cultural beliefs. Dysfunction in any part of the sophisticated gastrointestinal pathway of cyanocobalamin absorption—from stomach to ileum—can lead to non–dietary-induced vitamin B₁₂ deficiency.

The DRIs

The RDA for vitamin B₁₂ is 0.9 μg/d for infants and toddlers, 1.2 to 1.8 μg/d for 4- to 13-year-olds, and 2.4 μg/d thereafter.

No adverse effects have been reported with excess vitamin B₁₂ intake, and the risk of toxicity is very low; therefore, a UL is not established.

Maternal and Infant Vitamin B₁₂ Deficiency

Most adults can tolerate a low vitamin B₁₂ intake status for years without any clinical symptoms. Mothers of infants...
with vitamin B₁₂ deficiency often have unrecognized pernicious anemia due to impaired vitamin B₁₂ absorption, but other etiologies were reported, including gastric bypass surgery, short gut syndrome, or long-term vegetarian or vegan diet. (13) Newborn infants have limited endogenous stores and are at risk for vitamin B₁₂ deficiency if they are predominantly breastfed, with a poor maternal vitamin B₁₂ status and intake. (14) Typical manifestations usually start between 4 and 10 months of age and include growth faltering, developmental regression, tremors, hypotonia, lethargy, irritability, and feeding difficulties. (14) Megaloblastic anemia is not always present. (13)

Vitamin B₁₂ replacement (1 mg intramuscular for 2 to 7 days [15]) leads to rapid recovery, with documented reversal of apathy, hypotonia, anorexia, and tremors within days of initiating treatment. Brain atrophy and growth failure reversed within several months. Unfortunately, despite the dramatic rapid improvement, many infants with vitamin B₁₂ deficiency experience long-term cognitive and developmental delay. (14)

Similar symptoms are seen in infants with inborn errors of vitamin B₁₂ absorption and utilization. A full discussion of these conditions is beyond the scope of this article.

Vitamin B₁₂ Deficiency in Children and Adolescents
A study of serum B₁₂ levels in 3,766 US children (4–19 years old) identified 3 children with levels less than 100 pg/mL (<74 pmol/L) (1 of 1,255) and 18 with levels less than 200 pg/mL (<148 pmol/L) (1 of 200). The highest incidence of children with levels less than 200 pg/mL (<148 pmol/L) was reported in the 12- to 19-year-old category, with a rate of 1 in 112. (15) Because the cutoff value suggested to define vitamin B₁₂ deficiency is a level less than 203 pg/mL (<150 pmol/L), (11) these data indicate that B₁₂ deficiency in children and adolescents is more common than previously suggested.

Of note, a vitamin B₁₂ level greater than 300 pg/mL (>221 pmol/L) is tentatively considered as the cutoff value for B₁₂ repletion. (16)

The estimated vitamin B₁₂ intake in the United States is higher than the RDA, but dietary B₁₂ deficiency is increasing due to atypical diets, such as extreme vegetarianism. (17) Patients who undergo gastric bypass or other bariatric surgeries are at risk for vitamin B₁₂ deficiency due to the loss of gastric production of IF. (13) Pathologic disorders that disrupt the ileal length or surface, such as short gut syndrome, Crohn disease, and celiac disease, can affect B₁₂ absorption. (15) It is especially important to note that previous and current use of gastric acid inhibitors for 2 or more years was significantly associated with the occurrence of vitamin B₁₂ deficiency in adults. (18)

Neurologic changes secondary to B₁₂ deficiency can occur without hematologic abnormality, including loss of deep tendon reflexes, developmental regression, hypotonia, and neuropsychiatric changes (eg, depression). (15)

Laboratory Evaluation
Several feasible indicators to assess vitamin B₁₂ status are available, and the least expensive is a serum vitamin B₁₂ level. (11) However, serum B₁₂ level is not always reflective of tissue levels that can be depleted with a low normal or borderline serum cobalamin level. (15) Methylmalonic acid (MMA) and homocysteine are 2 precursors in the metabolic pathway and are affected by B₁₂ deficiency. Homocysteine is elevated in both B₁₂ and folate deficiencies, but an elevated MMA level is reasonably specific for B₁₂ deficiency; MMA levels can be measured in both serum and urine. (13)

Studies are needed to determine the optimum strategy for the diagnosis of vitamin B₁₂ deficiency in children. Several experts recommend B₁₂, MMA, and homocysteine levels when B₁₂ deficiency is suspected. (13)(15) Once B₁₂ deficiency is confirmed, subspecialty consultation, eg, a physician nutrition specialist, gastroenterologist, or hematologist, is recommended to guide further evaluation and treatment.

VITAMIN C (ASCORBIC ACID)

Introduction
In 1747, Dr James Lind, a surgeon in the British Navy, demonstrated that scurvy can be cured by consuming oranges and lemons. Since then, scurvy, or vitamin C deficiency, which used to debilitate sailors, has become a rare disease that warrants a case report. A recent one was published in the *New York Times* in July 2015. Although a clue to a disrupted eating pattern was clear on the initial presentation (the child has developmental delay and will eat only macaroni and cheese), a nutritional deficiency was not suspected. The patient had an extensive evaluation that included bone marrow biopsy and many subspecialist consults. This case is a testimony to the importance of physician knowledge about certain clues that should prompt a more detailed nutritional history.

Functions
Vitamin C is a water-soluble vitamin that acts as an antioxidant and free radical scavenger. Vitamin C is a cofactor for many enzymes and hormones and plays a major role in the
biosynthesis of many components of connective tissue, such as collagen. It also modulates the absorption, transport, and storage of iron. (3)

The DRIs
The DRIs for vitamin C are based on estimates of tissue levels that are deemed adequate to provide antioxidant protection with minimal urinary loss. Tobacco smoking or environmental exposure to nicotine increases the vitamin C requirement by 33% to 40% due to increased oxidative stress. Vitamin C absorption in the small intestine is dose dependent, and the kidney also regulates its body content. As a result, excessive intake of vitamin C is unlikely to cause adverse effects other than gastrointestinal upset and osmotic diarrhea occasionally reported with large doses.

The RDA for vitamin C is 15 to 45 mg/d for children aged 1 to 13 years and 65 to 75 mg/d for those aged 14 to 18 years. (3)

Sources
Fruits and vegetables provide 90% of the vitamin C found in the typical diet. The major contributors are potatoes and citrus fruits and juices. (3) A diet that is persistently limited to meat, bread and/or dairy presents a high risk for inadequate vitamin C intake and development of deficiency.

Deficiency
Scurvy is rare in the current era but should not be forgotten. According to NHANES, children aged 6 to 11 years old had the highest mean serum concentration of ascorbic acid but showed a linear decrease thereafter. (19) In the pediatric population there are many case reports of scurvy in patients with autism due to their severely restrictive diet. Adults at risk for vitamin C deficiency include smokers, alcoholics, and those on a very restricted diet due to social isolation. (20)(21)

Clinical symptoms can develop only after 30- to 40 days of consuming a diet that is void of vitamin C. (22) The earliest symptoms of vitamin C deficiency are fatigue and refusal to walk. (20) Dermatologic findings include petechiae centered on hair follicles with hyperkeratosis and coiled hair. Hematomas, ecchymosis, poor wound healing, and edema may also be noted. Oral manifestations occur only in patients with teeth and include bleeding and hypertrophic gums. Musculoskeletal findings include joint pain, hemarthrosis, and muscle pain. Anemia is a common finding in vitamin C deficiency, and it can be attributed to the hemorrhagic symptoms and the role of ascorbic acid in iron absorption. (23) Infantile scurvy is rarely seen because human milk (if the maternal diet is sufficient) and formula provide an adequate supply of vitamin C. Infantile scurvy presents with bone abnormalities, bleeding, and anemia. (3)

High-Dose Vitamin C for the Treatment of Upper Respiratory Tract Infections
Supplementation trials have shown that vitamin C reduces the duration of colds, but this effect was not replicated in therapeutic trials. Further randomized controlled trials are warranted to investigate the role of vitamin C in the treatment of upper respiratory tract infections. However, given its low cost and excellent safety profile, it may be worthwhile for patients with common cold to try a therapeutic dose of vitamin C. (24)

VITAMIN D (CHOLECALCIFEROL)

Introduction
Rickets has plagued children, especially in the northeastern United States, since the 1800s. However, the beneficial effect of sunlight was not elucidated until 1921 when Hess and Unger reported a dramatic improvement in rachitic children who were exposed to the sun. (25) Contemporaneously, investigators observed that ultraviolet irradiation of milk and various foods imparted antirachitic activity. With this discovery it was thought that rickets was conquered. (25) However, in the 19th century it became clear that vitamin D deficiency is a common problem in children and adults worldwide. In fact, the discovery that various cells and tissues express the vitamin D receptor has highlighted its many other nonskeletal functions. Now experts believe that rickets is simply only the “tip of the iceberg” of the consequences of vitamin D deficiency. (26)

Case
J.L. is a 15-month-old white boy who fell off his bed and refused to walk afterward. He had been walking for about a month before this episode. His dietary history showed that he was breastfed until 6 months of age and then was placed on a mostly liquid diet consisting of water, juice, and some milk. Solids in his diet consisted of some baby food without dairy products. No supplemental vitamins were given.

Physical examination was significant for underweight status (weight-for-length <5th percentile), length age of 9 months (his length was 70.6 cm), a prominent forehead, and swelling at the wrists. Radiographs of his leg revealed a distal left femur fracture, and wrist radiographs showed osteopenia with metaphyseal flaring.
Laboratory studies showed a low-normal serum calcium level of 8.2 mg/dL (2.05 mmol/L), a low serum phosphorus level of 3.4 mg/dL (1.1 mmol/L), but elevated alkaline phosphatase and parathyroid hormone (PTH) levels. The serum 25-hydroxyvitamin D (25(OH)D) level was low at 11 ng/mL (27 nmol/L).

J.L. was given stoss therapy with a high dose of vitamin D (100,000–600,000 IU given over 1–5 days). The appearance of his wrist at 1 and 5 months of age showed gradual healing of his rickets (Fig 2).

Definition of Vitamin D Deficiency

There continues to be much debate regarding what constitutes vitamin D deficiency, insufficiency, and sufficiency. Vitamin D status is defined by the level of serum circulating 25(OH)D. (27)(28)

The Endocrine Society proposed the following cutoff points (27):

- Vitamin D deficiency: 25(OH)D level ≤20 ng/mL (<50 nmol/L)
- Vitamin D insufficiency: 25(OH)D level of 21 to 29 ng/mL (52–72 nmol/L)
- Vitamin D sufficiency: 25(OH)D level of 30 to 100 ng/mL (75–250 nmol/L)

The Endocrine Society determined these cutoff points using many criteria that affect bone metabolism, such as PTH, bone mineralization, and intestinal calcium absorption.

However, to establish vitamin D requirements through the life cycle at a population level, the IOM prioritizes specific end points associated with health outcomes. Accordingly, the IOM has questioned the premise that a serum level of 25(OH)D greater than 30 ng/mL (>75 nmol/L) provides additional health benefits. (29) At present, the IOM, the AAP, and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition also suggest 20 ng/mL (50 nmol/L) as the cutoff value for deficiency, (30) but the controversy continues regarding the level of serum 25(OH)D that defines sufficiency.

Prevalence of Vitamin D Deficiency

Vitamin D deficiency is widespread around the world. (27) The NHANES studies examined thousands of American children and adolescents, which provides a reliable report of their vitamin D status. According to NHANES 2001–2004, 9% of US children and adolescents had vitamin D deficiency (25(OH)D levels <15 ng/mL [<37 nmol/L]), and 61% had vitamin D insufficiency (25(OH)D levels of 15–29 ng/mL [37–72 nmol/L]). (31)

Causes and Risk Factors for Vitamin D Deficiency

Limited Sunlight Exposure. When absorbed by the skin, UV-B converts 7-dehydrocholesterol to previtamin D3, which is isomerized to vitamin D3. There are many factors, such as skin pigment and use of sunscreen, that influence the cutaneous production of vitamin D3. Increased skin pigmentation causes the melanin to absorb most of the UV-B, resulting in much lower vitamin D3 production in African American individuals compared with white individuals for the same UV-B exposure. Sunscreen with a sun-protecting factor of 30 can reduce the skin’s ability to produce vitamin D by 95% to 99%. The influence of these factors is exacerbated by the season, latitude, and time of day. When the zenith angle of

Figure 2. J.L. wrist radiographs from left to right: at presentation and 1 and 5 months after treatment. Notice the swelling at the wrist.
the sun is more oblique during the winter season (especially far north and south) and for the daylight hours before 10 AM and after 3 PM, more UV-B radiation is absorbed by the ozone layer. Passage through glass or plastic and air pollution also dramatically reduces UV-B. (32)

**Limited Nutritional Intake in Infancy and Beyond.** Breastfed infants and toddlers are at risk for vitamin D deficiency. The content of vitamin D in human milk is greatly influenced by all the factors that affect maternal vitamin D status, such as sun exposure, skin pigmentation, season, latitude, and maternal vitamin D intake. The optimal vitamin D supplement dose for nursing mothers is not yet established. However, studies have shown that maternal supplementation of vitamin D at 4,000 IU/d was not enough to consistently yield at least 400 IU of vitamin D per liter of human milk. It is hypothesized that a supplemental dose of 6,000 IU/d may be needed to achieve this effect. This should not undermine the value of human milk as a vital source of nutrition for infants but highlights the basis for the recommendation to supplement all infants who are breastfeeding or taking less than 1 L of formula per day with 400 IU of vitamin D daily. (33)(34)

Beyond the first year of life, an intake of 32 oz of vitamin D–fortified milk provides 400 IU of vitamin D. Fatty fish and other vitamin D–rich foods tend to be absent in most infant and adolescent diets, and the content of vitamin D in fortified foods may be overestimated. For example, fortified cereal provides only 40 IU per serving. Thus, for children and adolescents who do not receive regular sunlight exposure, they may be at increased risk for nutritional vitamin D deficiency and insufficiency. (35)

**The Effect of Obesity.** The association between obesity and lower 25(OH)D serum concentration is well established. Possible mechanisms include lower dietary intake, sedentary behavior that tends to limit sunlight exposure, and sequestration of 25(OH)D in the adipose tissue. (36)

**Medications.** Antiepileptic drugs and systemic glucocorticoids have been shown to reduce 25(OH)D concentrations when dietary sources of vitamin D and sunlight exposure are limited. Of note, there is no evidence that inhaled corticosteroids at a conventional dose given for 2 to 3 years have a negative effect on bone mineral density and bone turnover biomarkers, including 25(OH)D. (37)

Orlistat and cholestyramine cause fat malabsorption and, thus, impair vitamin D absorption. (38)

**Diseases that Interfere with Vitamin D Absorption and Metabolism.** Vitamin D absorption is chylomicron dependent; thus, children with fat malabsorption are at increased risk for deficiency. Cystic fibrosis, Crohn disease, and celiac disease are known risk factors for nutritional rickets. (38) Food allergies and small-bowel resection can also lead to fat malabsorption and vitamin D deficiency. (35)

**Genetic Factors.** In a study published in the *New England Journal of Medicine*, Powe et al report that more than 90% of African American individuals have a genotype that is associated with a lower level of vitamin D–binding protein compared with white individuals. (39) The authors speculate that variation in vitamin D–binding protein levels may be responsible for observed racial differences in 25(OH)D levels and the clinical manifestations of vitamin D deficiency. (39) More research is needed to elucidate if genetic polymorphism plays a role in determining vitamin D requirements in different ethnic groups.

**Skeletal Consequences of Vitamin D Deficiency**

A vitamin D–deficient state is associated with reduction in intestinal calcium absorption from approximately 30% to 40% to 10% to 15%. The body responds to the reduction in serum calcium with hyperparathyroidism. (35)

Parathyroid hormone enhances calcium absorption in the renal tubules. It also causes phosphaturia, leading to a low serum phosphorus level that causes a maturation defect in the chondrocytes with cellular ballooning and disruption of the growth plate, leading to the widening at the end of the long bones that is characteristic of rickets. (35)

Rickets can be divided into 3 stages (Fig 3). The first stage is characterized by osteopenia and subclinical hypocalcemia. Bone pain and rachitic changes start in the second stage and become progressively worse in the third stage. (35)

Clinically, rickets in children ranges from an asymptomatic disease to varying degrees of poor growth, bone pain, irritability, and gross motor delay.

The signs of rickets include, but are not limited to, genu varum (bowing of the legs) or genu valgum (knock-knees), due to the lack of structural support as the child learns to walk. The widening at the end of the long bones is most commonly manifested in the wrist. The *rachitic rosary* is a term used to describe the beading along the anterior chest wall and is a result of the hypertrophy of the costochondral joints. (25)(35)

In rare cases of severe maternal vitamin D deficiency, rickets can develop in utero. (33)(34)

**Nonskeletal Consequences of Vitamin D Deficiency**

Every cell and tissue in the body has a vitamin D receptor. Therefore, vitamin D deficiency has been associated with a plethora of negative health consequences. (25)(40) Maternal vitamin D deficiency is associated with low birthweight (33) and is linked to increased risk of preeclampsia. (25)(40)
Vitamin D deficiency has also been linked to increased risk of infectious disease, types 1 and 2 diabetes, multiple sclerosis, cardiovascular disease, dementia, and cancer, but controlled trials to determine causality are not available.

**Laboratory Evaluation of Vitamin D Status**

Circulating 25(OH)D level measured by a reliable assay is the best indicator of vitamin D status and stores. Measurement of serum 1,25 dihydroxyvitamin D (1,25(OH)2D) is not recommended because 1,25(OH)2D does not reflect vitamin D reserves and can be normal or elevated in patients with vitamin D deficiency due to secondary hyperparathyroidism. Measurement of the 1,25(OH)2D level is useful in conjunction with the PTH level in disorders of 25(OH)D and phosphate metabolism, such as chronic kidney disorders and vitamin D-resistant rickets. In nutritional rickets, the classic biochemical profile includes the triad of hypocalcemia, hypophosphatemia, and elevated alkaline phosphatase levels.

Some experts recommend incorporating the measurement of vitamin D–binding protein for better assessment of vitamin D status in African American individuals and in diverse populations, but more research is needed.

**Screening**

Universal screening of all patients for vitamin D deficiency is not recommended and should be reserved and considered only for high-risk patients, including but not limited to:

- Patients with nonspecific symptoms, such as poor growth, irritability, and gross motor delay
- Dark-skinned patients, especially those who live in higher latitudes
- Children taking long-term glucocorticoids or seizure medications
- Children with chronic diseases that are associated with fat malabsorption, such as cystic fibrosis, inflammatory bowel disease, and post–bariatric surgery

![Figure 3. Stages and skeletal consequences of vitamin D deficiency. PTH=parathyroid hormone; 1,25(OH)2D=1,25 dihydroxyvitamin D.](image-url)
• Patients with frequent fractures and low bone density (35)
• Patients with chronic kidney disease (27)
• Obese patients (27)

Screening can also be considered for patients with low dietary intake and very limited sun exposure.

Sources and Forms of Vitamin D

There are 2 sources of vitamin D. Cholecalciferol (D₃) is synthesized in the skin and found in oily fish. Ergocalciferol (D₂) is synthesized by plants and produced from the irradiation of yeast. Both forms are used to fortify milk and are found in dietary supplements, but vitamin D₂ is the only prescription form available in the United States. (33)(42) Table 3 summarizes the pharmaceutical and supplemental sources of vitamin D.

Calcidiol (25[OH]D), the form that defines vitamin D status, is formed in the liver from vitamins D₂ and D₃ by the action of 25-hydroxylase. Calcitriol (1,25[OH]₂D), the active form of vitamin D, is created when a second hydroxylation occurs in the kidney and many other tissues in the body. (33)(42)

Treatment of Vitamin D Deficiency

There are many strategies to treat vitamin D deficiency. Based on studies that examine the effect of D₂ and D₃ administered in different doses on 25(OH)D serum level, experts estimate that 100 IU of vitamin D₂ or D₃ daily will raise the blood level of 25(OH)D by 1 ng/mL (25 nmol/L). (25)(26) Short-term administration of 2,000 IU of vitamin D₂ or D₃ daily yields an equivalent outcome to weekly 50,000 IU of vitamin D₂. (27)(43) Thus, pediatricians can individualize their treatment of vitamin D to meet the patients’ and families’ preferences and probability of compliance. When compliance is a major concern, stoss therapy (stoss in German means to push), with doses of 100,000 to 600,000 IU given over 1 to 5 days, can be administered to infants older than 1 month of age. (35) However, the recommendations of the stoss therapy, especially in outpatient settings, have been met with controversy due to the risk of hypercalcemia. (43)

In July 2011, the Endocrine Society published the following guidelines for the evaluation, treatment, and prevention of vitamin D deficiency (27):
• Infants 0 to 1 year old: 2,000 IU orally once daily or 50,000 IU orally once weekly for 6 weeks until the 25(OH)D blood level is greater than 30 ng/mL (>75 nmol/L), followed by maintenance therapy (400–1,000 IU/d)
• Children 1 to 18 years old: 2,000 IU orally once daily or 50,000 IU orally once weekly for 6 weeks until the blood level is greater than 30 ng/mL (>75 nmol/L), followed by maintenance therapy (600–1,000 IU/d)
• Use of a high dose (double or triple the 2 previously mentioned doses) is recommended for obese patients or patients taking medications or having conditions that affect vitamin D metabolism and/or absorption

Prevention of Vitamin D Deficiency: The DRIs and Other Recommendations

The AAP recommendations on vitamin D supplementation are in agreement with the IOM recommendations released in 2011. The IOM proposed that healthy infants younger than 1 year of age consume 400 IU/d of vitamin D, and older children (1–18 years old) consume 600 IU/d. (35)(44)

Dietary Sources of Vitamin D. Many children and adolescents in the United States do not consume most of the natural food sources of vitamin D in sufficient quantities. Furthermore, meeting the RDA of vitamin D would require an impractically large intake of fortified food. For example,

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### TABLE 3. Summary of Supplemental and Pharmaceutical Sources of Vitamin D (26)

<table>
<thead>
<tr>
<th>VITAMIN D SUPPLEMENT</th>
<th>DOSE</th>
<th>NOTES</th>
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<tbody>
<tr>
<td><strong>Prescription</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Vitamin D₂ (ergocalciferol, labeled calciferol)</td>
<td>Capsule: 50,000 IU Liquid: 8,000 IU/mL</td>
<td>For small children, the capsule can be soaked in water to soften it, then given intact with blended food such as apple sauce (35)</td>
</tr>
<tr>
<td><strong>Over the counter</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pediatric multivitamin (liquid or chewable)</td>
<td>300, 400, 600 IU D₂ or D₃</td>
<td>D₃ 400 IU/mL is the standard to use (1 mL/d) for prevention of vitamin D deficiency in newborns and toddlers who are breastfeeding or taking &lt;1,000 mL/d of formula/whole milk. It is available over the counter under many brand names.</td>
</tr>
<tr>
<td>• Vitamin D₃ (labeled cholecalciferol)</td>
<td>400, 800, 1,000, and 2,000 IU</td>
<td></td>
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Diagnostic Tests and Treatment Doses for Selected Vitamin Deficiencies

<table>
<thead>
<tr>
<th>VITAMIN</th>
<th>DIAGNOSTIC LABORATORY TEST</th>
<th>TREATMENT</th>
</tr>
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</table>
| Vitamin A | Serum retinol <20 μg/dL. Molar ratio of retinol to retinol binding protein <0.08 (calculated in μmol/L) (75) | ▪ Infants <6 mo old: 50,000 IU orally × 1  
▪ Infants 6–12 mo old: 100,000 IU orally × 1  
▪ Children >12 mo old: 200,000 IU orally × 1 (76)  
Additional doses can be given, as needed, every 4 weeks based on clinical response. |
| Vitamin B12 | Use serum B12 as the initial test; if the level is <271 pg/mL (<200 pmol/L), check for elevated methylmalonic acid level (>0.37 μmol) (16) | ▪ Dietary deficiency: Infants (breastfed by vitamin B12–deficient mothers): IM 250–1,000 μg once daily for 1–2 wk, then weekly until recovery  
▪ Malabsorption: Infants, children, and adolescents: IM 250–1,000 μg/d or every other day for 1 wk, then weekly for up to 8 wk, and then every 4 wk; oral administration of a high dose of 2,000 μg/d can also be considered (16) |
| Vitamin C | Plasma and leukocyte vitamin C level (77) | Scurvy: Oral, IM, IV, SC: Initial: 100 mg per dose 3 times daily for 1 wk (300 mg/d) followed by 100 mg once daily for 1–3 mo (47) |
| Vitamin E | Serum α-tocopherol and serum α-tocopherol to lipid ratio (47) | Fat malabsorption: Supplement with 25 IU/kg per day to prevent deficiency (47) |
| Folate | Serum homocysteine level elevated (also elevated in B12 and B6 deficiencies) (47) | Oral daily administration of 0.1 mg in infants and 1 mg in children followed by oral daily maintenance of 0.1–0.3 mg (47)  
Note that treatment for folate deficiency without assessment of vitamin B12 status can mask B12 deficiency |
| Vitamin K | Prothrombin time is elevated (4 times normal) and the presence of protein induced by vitamin K deficiency (73) | ▪ Prevention: A single 1-mg IM dose for the full-term infant and 0.3–0.5 mg for the preterm infant  
▪ Fat malabsorption: 2.5–7 mg/d 2–7 times per week (47) |

IM=intramuscular, IV=intravenous, SC=subcutaneous.

A 15-year-old must consume a pound of cheese or 6 glasses of milk per day to obtain the recommended 600 IU of vitamin D daily.

Good natural food sources of vitamin D include salmon (100–1,000 IU of vitamin D per 3.5 oz) and cod liver oil (400–1,000 IU of vitamin D per 1 tsp). (26)

Preventive Use of Supplementation Vitamin D. Taking into consideration the IOM and AAP recommendations for the general population and the Endocrine Society focus on high-risk patients, the following key points are proposed in guidelines and experts’ statements:

▪ Vitamin D supplementation is recommended for all young infants regardless of the type of feeding because it takes 1 L of formula to provide 400 IU of vitamin D (33)  
▪ Vitamin D supplementation should be started within the first days after birth (33)  
▪ Recommended vitamin D supplement intake for children and adolescents without risk factors for vitamin D deficiency are 400 IU/d during the first year and 600 IU/d for children 1 to 18 years old (33)(44)  
▪ Recommended vitamin D intakes for infants, children, and adolescents with risk factors for deficiency are 400 to 1,000 IU/d during the first year and 600 to 1,000 IU/d for children 1 to 18 years old (30)  
▪ For preterm infants the recommended vitamin D intake is 400 to 800 IU/d (30)  
▪ The optimal duration of vitamin D supplementation has not yet been established; it is reasonable to consider supplementing while the growth velocity is high, until age 2 years (30)  
▪ In children older than 2 years of age, vitamin D supplementation should be based on risk factors, dietary intake, and sun exposure; a supplemental dose of 400 IU/d is recommended for children and adolescents who do not obtain such a dose from fortified milk (33)  
▪ Children with limited summer sun exposure may be supplemented in the late fall and winter (30)  
▪ Obese children or patients taking anticonvulsants or glucocorticoids should receive at least 2 to 3 times more vitamin D than children without such risk factors (27)(10)  
▪ Pregnant and lactating women require 600 IU/d of vitamin D; a dose of 1,500 to 2,000 IU/d may be needed.
to maintain the 25(OH)D serum level greater than 30 ng/mL (>75 nmol/L) (27)

**Sensible Sunlight Exposure.** Human skin has a wonderful capacity to produce vitamin D, which is stored in the fat tissue and released during the winter months. Sensible sunlight exposure, defined by the exposure of the arms and legs without sunscreen for 5 to 30 minutes between 10 AM and 3 PM twice a week, is often adequate. (26)(45)

**Toxicity**

Excessive intake of vitamin D can cause hypervitaminosis D and results in hypercalcemia and hypercalciuria. (28) However, vitamin D intoxication is rare, and the cases reported were the result of inadvertent ingestion of extremely high doses of vitamin D for prolonged periods. (32) Sunlight exposure never causes vitamin D intoxication. (32) The UL of vitamin D intake should not exceed 1,000 IU for infants 0 to 12 months old and 2,000 IU for older children (28) unless deficiency has been documented and therapy is being monitored.

**VITAMIN E (TOCOPHEROL)**

Vitamin E is a fat-soluble antioxidant that protects the cells from the damaging effects of free radicals. Cell damage due to free radicals has been linked to the development of cardiovascular disease and cancer.

**Structure, Sources, and the DRIs**

Vitamin E is abundant in many food sources, such as fruits, vegetables, meats, grains, and vegetable oils. Vitamin E is also available as a dietary supplement. Naturally occurring vitamin E exists in 8 forms (α-, β-, γ-, and δ-tocopherols and tocotrienols). α-Tocopherol is the only form recognized to meet human requirements and is the form referred to in the DRIs as set by the IOM. (3)

Adequate intake of vitamin E in the first year of life is 4 to 5 mg/d of α-tocopherol. The RDA of vitamin E for children aged 1 to 8 years is 6 to 7 mg/d of α-tocopherol, with a UL of 200 to 300 mg. The RDA of vitamin E for children aged 9 to 13 years is 11 mg/d of α-tocopherol, with a UL of 600 mg. The RDA for age 14 years through adulthood is 15 mg/d of α-tocopherol, with a UL of 800 to 1,000 mg. (3)

**Vitamin E Deficiency**

Because of its abundance in natural sources, vitamin E deficiency is rare and generally occurs as a result of fat malabsorption syndromes or in the setting of protein energy malnutrition. The main clinical symptom of vitamin E deficiency is peripheral neuropathy with ataxia and hyporeflexia. (3)(46) Patients with malabsorption (cystic fibrosis, pancreatic insufficiency) and biliary tract disorders are at risk for vitamin E deficiency. Failure to supplement high-risk patients leads to a progressive neurologic disorder, including ataxia, peripheral neuropathy, proximal muscle weakness, and ophthalmoplegia. These effects may be irreversible if the deficiency is longstanding. (47)

**Risk of Toxicity**

Supplements of vitamin E provide α-tocopherol with amounts that are more than or equal to 100 IU. These amounts are significantly higher than the RDAs. The possible effects of a high supplemental level of α-tocopherol remain uncertain. However, some adult studies suggest that the use of high doses of vitamin E may increase all-cause mortality. (48)

Vitamin E supplement use is high in the US population. The most frequently reported motivation for use was to improve overall health. (49) The 1986 National Health Interview Survey reports that supplements containing vitamin E are used by 37% of young children in the United States. (3) Excess vitamin E intake in individuals who are deficient in vitamin K or receiving anticoagulant therapy can lead to hemorrhagic toxicity. (3)

There is no evidence of adverse effects from exposure to high levels of the vitamin E naturally occurring in foods. (3)

**Therapeutic and Preventive Use of Vitamin E**

Using pharmacologic doses of vitamin E as an antioxidant has been proposed for the treatment or prevention of many diseases. Vitamin E supplementation in preterm infants reduced the risk of intracranial hemorrhage (ICH), and in the very low-birthweight infant it also reduced the risk of severe retinopathy. (50) However, the current evidence does not support the routine use of vitamin E supplementation intravenously in high doses due to the increased risk of sepsis. (51)

Several studies investigated the role of vitamin E and the reduction of oxidative stress in the treatment of non-alcoholic steatohepatitis (NASH) and have led to variable results. (52)(53)(54)

One of the largest studies in adults (247 patients) concluded that vitamin E at a dose of 800 IU/d was superior to placebo in the treatment of NASH in nondiabetic adults. (55) The same dose is proved to offer histologic benefits to children with biopsy-proven NASH, but more studies are needed before its use can be recommended in pediatrics clinical practice. (56)

Vitamin E may have functions that are not related to its role as a free radical scavenger. Vitamin E has a positive
effect on the immune system and a possible protective effect against upper respiratory tract infection. Vitamin E also has anti-DNA mutagenic damage properties that may explain its protective effects against cardiovascular diseases, Alzheimer disease, and cancer. (5)

**FOLATE (PTEROYLGLUTAMATE)**

**Introduction**

In 1931, Dr Lucy Willis demonstrated that a factor in yeast, subsequently shown to be folate, cured megaloblastic anemia of pregnancy. (57) In the 87 years since that original discovery, the roles of folate in the pathogenesis of neural tube defects (NTDs), vascular disease, and certain types of cancer have been established.

**Sources and the DRIs**

The term *dietary folate* is used to denote folate that occurs naturally in food sources and the more active synthetic form of folic acid used in fortified food. *Total folate* is an umbrella term used to encompass all dietary and supplemental exposure to folate and folic acid. (58)

Rich food sources of folate include dark green vegetables, beans, and legumes. (3) However, the food retention of folate is highly dependent on the type of food and the method of cooking. Folate from animal sources is more stable than folate in green vegetables, and steaming is superior to boiling for folate retention. (59) This has led to public health efforts to increase folic acid intake on a population level, especially since the finding that folic acid supplementation in the preconception period unequivocally decreases the incidence of NTDs. (60) The FDA authorized the addition of folic acid to enriched grain products in March 1996, with compliance mandatory by January 1998. (61) This resulted in a dramatic decrease in folate deficiency and NTDs. (61)(62)

The RDA of folate is 150 μg/d for the first 3 years after birth, then 200 to 300 μg/d for 4 to 13 years old and 400 μg/d thereafter. The RDA for pregnant women is 600 μg/d. The UL applies to folic acid from fortified food and supplements and ranges from 300 to 1,000 μg/d. (3)

**Causes and Metabolic Indicators of Folate Deficiency**

Isolated folate deficiency is rare; it is often associated with conditions that affect other nutrients. Small-bowel disorders associated with malabsorption, such as inflammatory bowel disease and celiac disease, can cause folate deficiency. Pregnancy, lactation, and chronic hemolytic anemia increase folate requirements. Other populations at risk for folate deficiency include premature infants and alcoholics. (46) Infants consuming unfortified goat milk have classically been found to develop folate deficiency, manifesting as macrocytic anemia.

Several medications, such as methotrexate and trimethoprim, act as folate antagonists and produce a deficiency by inhibiting dihydrofolate reductase. Other medications that can lead to folate deficiency include anticonvulsants, antituberculosis drugs, and oral contraceptives, but the mechanism is unclear. (46)

Serum or erythrocyte concentrations of folate are reasonable indicators of this vitamin status. Serum levels reflect relatively recent intake and can respond quickly; erythrocyte levels may be preferred as an indicator of chronic intake. Both MMA and homocysteine assays obtained in the setting of megaloblastic anemia help differentiate between B12 and folate deficiency. Both are elevated in B12 deficiency, but only homocysteine is increased in folate deficiency. (11)

Correction of macrocytic anemia with folate can mask an underlying B12 deficiency and will allow progression of neurologic damage due to the latter. It is, thus, critical to distinguish folate vs B12 deficiency before initiating treatment.

**Health Consequences of Folate Deficiency**

A decline in serum folate level occurs in approximately 2 weeks of consumption of a folate-deficient diet, and megaloblastic anemia occurs within weeks if the deficiency continues. (11)

The effect of maternal folate status on pregnancy outcome is indisputable. There is a strong association between low maternal folate status and increased risk of NTDs. However, the association between folate status and the risk of other birth defects, such as cleft palate, is not as strongly established. (11)

There is also strong evidence of an inverse association between blood folate concentration and the risk of low birthweight. (11)

In adults, there is moderate evidence that low folate concentration is associated with a higher prevalence of depression, cognitive impairment, and dementia. The association between folate status and cognitive function is weaker in children. (11)

**Folate and Chronic Disease Prevention**

Folate plays an important role in DNA synthesis and repair, but the research about its effect on carcinogenesis and cancer prevention has been contradictory, and this has led to its being called a double-edged sword. Earlier studies suggested that the use of folate in adults can reduce the risk
of colon cancer in women and men. (63)(64) However, randomized controlled trials did not confirm this effect and raised the possibility of a cancer-promoting effect. (65) More research is needed from a public health perspective on the effect of folate on cancer risk and prognosis.

Folate was also postulated to play a protective role against cardiovascular disease because of its role in lowering the homocysteine level, (66) but randomized controlled trials did not provide any evidence to support this role. (67)

Risk of Toxicity
No adverse effects have been attributed to excessive consumption of folate from food. Excessive intake from supplemental folate may obscure and potentially delay the diagnosis and treatment of vitamin B12 deficiency, which can lead to neurologic damage. (3)

VITAMIN K (PHYTONADIONE)
In 1943, Dam and Doisy received the Nobel Prize in Medicine for elucidating the chemical structure of vitamin K. They named this fat-soluble compound K due to its role in “Koagulation.”

Structure and Sources
Vitamin K belongs to a family of molecules that share a 2-methyl-1, 4-napthoquinone ring but differ in the identity of the side chain at the 3-position. Vitamin K is present in plants as phylloquinone and is produced by bacteria in human and animal large intestine as menaquinone. The significance of the gut microbial production of vitamin K is not clear because most of the absorption occurs in the small intestine. The small intestinal absorption of this liposoluble vitamin is enhanced by dietary fat but also depends on the flow of bile and pancreatic enzymes. Vitamin K is stored in the liver. (3)(5)

Dietary sources of vitamin K include green leafy vegetables such as spinach and collard greens, soy and canola oils, and margarine.

The DRIs
The data were insufficient to recommend an Estimated Average Requirement and an RDA for vitamin K. Adequate intake of vitamin K intake is 2 to 2.5 μg/d for infants and 30 to 75 μg/d for 1- to 18-year-olds. Others have recommended 1 μg/kg per day. (68) No adverse effects were reported from high vitamin K intake from food or supplements in healthy individuals who are not receiving anticoagulant drug therapy. The data were insufficient to establish a UL. (3)

Functions and Consequences of Vitamin K Deficiency
Vitamin K is a cofactor for γ-glutamyl carboxylase, the enzyme responsible for the modification of the side chain of some proteins from glutamate to γ-carboxyglutamate. Most γ-carboxylated proteins are clotting factors such as factors II (prothrombin) VII, IX, and X. This underlies the essential role of vitamin K in the coagulation cascade.

Other carboxylated proteins play an important role in calcium homeostasis and, thus, are important for bone and cardiovascular health. There is also emerging evidence about the protective effects of vitamin K against oxidative stress, age-related decline in motor and cognitive functions, cancer, and hepatitis C. (5)

Clinically relevant vitamin K deficiency is rare and is usually limited to patients with lipid malabsorption syndromes or those who take certain medications (such as antibiotics, vitamin A, and vitamin E) that interfere with vitamin K metabolism. (3) In this review, we focus on the importance of recognizing the recrudescence of vitamin K deficiency bleeding (VKDB), formerly known as hemorrhagic disease of the newborn.

Cases
A 6-week-old infant presented to a tertiary care center emergency department with a 1-day history of poor breastfeeding, increased crying, pallor, and a “full and hard” anterior fontanelle. The medical history was relevant for exclusive breastfeeding and no vitamin K prophylaxis at birth. A full sepsis evaluation was initiated, and due to the bloody cerebrospinal fluid and the altered mental status, a head CT was obtained, which demonstrated a large ICH. The infant was treated with neurosurgical evacuation of the hematoma and administration of anticonvulsant agents. He remained seizure free with therapy but had a right hemiparesis and significant developmental deficit 3 months after ICH.

This infant was 1 of 5 cases of late VKDB presenting to a tertiary care center in Tennessee between February and September 2013, raising concerns about an increased occurrence of late VKDB due to parental refusal of vitamin K prophylaxis at birth. All 5 infants were exclusively breastfed and did not receive vitamin K prophylaxis at birth. Their age range was 6 weeks to 5 months, and 2 of the infants were born at home. One of the infants presented with a gastrointestinal bleed, and the other 4 had ICH. Of those who presented with ICH, 3 had varying degrees of developmental delay on follow-up. (69)
**Symptoms and Risk Factors for VKDB**

Recognition of VKDB is critical for prompt diagnosis and urgent therapy. Vitamin K deficiency bleeding can be classified as early (<24 hours after birth), classic (2–14 days), and late (2–12 weeks but can be seen in infants up to 6 months old). Symptoms of VKDB range from mild “warning bleeds” (umbilical cord, gastrointestinal, or circumcision bleeding) to severe (ICH). (5)(69) It is important to note that warning bleeds proceed ICH by days to weeks. (70)

Newborn infants are at increased risk for VKDB for several reasons. First, the placental transfer of vitamin K is poor, and its half-life in the liver stores is short. Second, the newborn gut flora is immature and unable to produce vitamin K, rendering the newborn infant dependent on dietary intake as the main source of vitamin K. The exclusively breastfed infant is especially at risk for late VKDB because the human milk content of vitamin K is low; standard fortification of infant formulas provides adequate intake. (5)(69)

**Incidence**

Early VKDB is rare and is almost exclusively related to maternal medications, especially antiseizure drugs, that increase the degradation of vitamin K (ICH occurs in 20%–25% of such infants) (71).

Classic VKDB often presents with mild symptoms such as gastrointestinal and umbilicus blood loss and rarely ICH; however, VKDB incidence without vitamin K prophylaxis is estimated to be 0.25% to 1.7%. (72)

Late VKDB incidence in exclusively breastfed infants with no vitamin K prophylaxis is 4.4 of 100,000 to 7.2 of 100,000. Infants with fat malabsorption syndromes (cystic fibrosis, cholestatic jaundice, etc) are especially at risk, and sometimes VKDB is the presenting symptom. (72) Late VKDB often presents with ICH. (73)

**Diagnosis**

In vitamin K–deficient individuals, uncarboxylated vitamin K–dependent proteins, normally called “proteins induced by vitamin K absence” (PIVKA), are present in the blood and can be measured. PIVKA II, or uncarboxylated prothrombin, is a marker of subclinical vitamin K deficiency and is usually present before the development of abnormal coagulation test results. (68)(73)

A confirmed case of VKDB should fulfill the diagnostic criteria of prothrombin time that is 4 times the control value, and at least 1 of the following:

- Normal or elevated platelet count, normal fibrinogen level, and absent fibrin degradation products
- Normalization of prothrombin time after vitamin K administration
- PIVKA (usually PIVKA II) level greater than that of healthy controls

The prompt diagnosis of late VKDB can have important legal consequences in cases of suspected nonaccidental brain injury. Retinal hemorrhage, a signature of nonaccidental brain injury, was recently documented in 2 confirmed cases of VKDB. PIVKA II has a long half-life and can be of major value in retrospective diagnosis of VKDB even weeks after the event. (73)

**Vitamin K Prophylaxis**

The AAP recommends that vitamin K be given to all newborns as a single intramuscular (IM) dose of 0.5 to 1 mg. The AAP concludes that additional research is needed regarding the oral administration of vitamin K to prevent late VKDB. (72)

Oral administration of vitamin K for the prevention of VKDB was promoted due to concerns regarding a possible causal association between parenteral vitamin K and childhood cancer, a claim that was subsequently and definitively debunked. Orally administered vitamin K prophylaxis, even with multiple-dose regimens, is associated with a resurgence of late VKDB in several countries. (68)(72)

Some oral regimens have proven efficacy in the prevention of late VKDB and are used in Europe, such as the weekly administration of 1 mg of vitamin K for 12 weeks or 2 mg at weeks 1 and 4. However, oral vitamin K is not effective in the prevention of late VKDB in patients with liver disease or malabsorption. (68) Currently, the Canadian Paediatric Society suggests that oral vitamin K should be given to newborns whose parents decline IM vitamin K as a 2-mg dose at birth and at weeks 1 and 6. (74)

**Talking Points for the Clinician when Parents Decline Vitamin K Prophylaxis**

After the recent increase of infants presenting with late VKDB, the Centers for Disease Control and Prevention (CDC) conducted an investigation and determined that 28% of the parents for children born at local private birthing centers in Tennessee declined vitamin K prophylaxis. Some reasons for parental refusal include concern about an increased risk of leukemia, concern about the use of a synthetic medication, and the impression that giving medications at birth is neither natural nor necessary for healthy term infants. There was a remarkable lack of awareness among the Tennessee families about the potentially life-threatening nature of late VKDB. (69)
When faced with vitamin K refusal, the clinician should respectfully elicit the parents’ concerns and attempt to educate and correct any misinformation. The clinician can discuss the recent cases of late VKDB in Nashville, Tennessee, and point out that in all cases the parents had refused the vitamin K prophylaxis at birth.

There is no expert consensus on whether circumcision should be refused or deferred in infants whose parents refuse vitamin K prophylaxis. When confronted with this request there are many considerations. First, there is no available data on the optimal timing of the procedure. Second, the medical provider and the nursing staff comfort with this decision must be taken into analysis because they have to practically manage the bleeding should it occur.

In contemplating the idea of suggesting oral vitamin K to parents who refused the IM injection, it is important to note that oral vitamin K preparations used in Europe with proven efficacy are not available in the United States. The phytonadione 5-mg tablet is the only oral formulation of vitamin K currently approved by the FDA. However, because giving a tablet to a newborn can be challenging and requires crushing or compounding, the injectable phytonadine (1 mg/0.5 mL) is sometimes given orally. Unlike the European vitamin K preparations, US formulations have not been studied for efficacy. (74)

One can argue that delivery of some vitamin K is better than none, but when parents are offered oral vitamin K they seem to perceive it as equally effective as the IM injection. Some parents may consider the IM route if the oral form is not an option. There is also the ethical aspect of prescribing an unproven formulation for the prevention of a potentially life-threatening disease when a treatment of proven efficacy exists. (74)

Summary

- Thirty-four percent of US children and adolescents used vitamin supplements in the past month, and almost half of those children took a supplement daily. (1) Supplement users were more likely to be Asian, white, or non-Hispanic; to belong to families with higher income and education; to be in good or excellent health; and to have access to health care. (2) (Evidence Quality B)

- Vitamin A deficiency is prevalent, especially in the developing world. In fact, vitamin A deficiency accounts for 1.7% of child mortality. (4) (Evidence Quality B)

- The American Academy of Pediatrics recommends a vitamin A supplement for children 6 months to 2 years old who are hospitalized for measles. (9) (Evidence Quality D)

- The recognition and treatment of vitamin B12 deficiency is critical, especially in infants, because with early diagnosis it is a reversible cause of developmental regression and cognitive delay. (13)(14) (Evidence Quality D)

- In the exclusively breastfed infant, the most common cause of B12 deficiency is undiagnosed maternal pernicious anemia. Other etiologies include maternal gastric bypass surgery and vegetarian diet. (13) (Evidence Quality D)

- Neurologic symptoms secondary to B12 deficiency can occur without hematologic abnormalities. (13) (Evidence Quality D)

- It is reasonable to suspect B12 deficiency in any infant with failure to thrive and developmental regression. (14) (Evidence Quality D)

- Symptoms of vitamin C deficiency can develop after 30 to 40 days of consuming a diet that is void of vitamin C. (22) Scurvy should be considered in the differential diagnosis of an at-risk child (especially in the setting of a developmental disorder and a restrictive diet) who presents with refusal to walk. (21)(22) (Evidence Quality D)

- Infants and children aged 0 to 1 year need at least 400 IU/d of vitamin D. Children 1 year and older need at least 600 IU/d of vitamin D. (27) (Evidence Quality A)

- Infants and children aged 0 to 18 years who are vitamin D deficient can be treated with 2,000 IU/d of vitamin D2 or D3, or with 50,000 IU of vitamin D2 or D3 once a week for 6 weeks to achieve a blood level of 25(OH)D greater than 30 ng/mL (>75 nmol/L). (27) (Evidence Quality B)

- Universal screening of all patients for vitamin D deficiency is not recommended and should be reserved and considered only for high-risk patients. (27) (Evidence Quality D)

- Vitamin E at a dose of 800 IU/d is beneficial for the treatment of nonalcoholic steatohepatitis in adults. More studies are needed before its use can be recommended in children. (55)(56) (Evidence Quality D)

- Since the Food and Drug Administration authorized the addition of folic acid to enriched grain products in 1996 there has been a dramatic decrease in folate deficiency and neural tube defects. (61) (Evidence Quality C)

- Recognition of vitamin K deficiency bleeding (VKDB) is critical for prompt diagnosis and urgent therapy. Warning bleeds (umbilical cord, gastrointestinal, or circumcision bleeding) precede ICH by days to weeks. (70) (Evidence Quality C)

- The American Academy of Pediatrics (AAP) recommends that vitamin K be given to all newborns as a single intramuscular dose of 0.5 to 1.0 mg. The AAP concludes that additional research is needed regarding the oral administration of vitamin K to prevent late VKDB. (72) (Evidence Quality C)

References for this article are at http://pedsinreview.aappublications.org/content/39/4/161.
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1. A 20-month-old boy is brought to the pediatrician’s office for a well-child checkup. He has recently immigrated to the United States from East Africa. The mother reports that he has trouble seeing at night and stumbles repeatedly. On physical examination, his cornea is normal. You diagnose the patient as having night blindness. Deficiency of which of the following vitamins is most likely responsible for this condition in this patient?
   A. Vitamin A.
   B. Vitamin B₁₂.
   C. Vitamin C.
   D. Vitamin D.
   E. Vitamin E.

2. You are part of the Global Health Brigade and are taking care of a hospitalized infant with measles in rural Uganda. According to the American Academy of Pediatrics, which of the following is the recommended dose of vitamin A supplementation in this patient?
   A. 10,000 IU.
   B. 50,000 IU.
   C. 100,000 IU.
   D. 200,000 IU.
   E. 300,000 IU.

3. In your office you are seeing a 4-month-old girl for failure to thrive. The child was born at term, and the mother had an uneventful pregnancy. You notice that since the last time you saw her, she has been having some trembling movements and has lost her deep tendon reflexes. The child is exclusively breastfed, and the mother is strictly vegan. You decide to send the patient to the hospital for direct admission. In addition to a complete blood cell count, which of the following vitamin serum levels will you most likely order in this patient?
   A. Vitamin A.
   B. Vitamin B₁₂.
   C. Vitamin C.
   D. Vitamin D.
   E. Vitamin E.

4. You practice in a small clinic in the Northeastern United States and are seeing an African American toddler who does not play outside because of the cold weather. He was exclusively breastfed until 6 months of age. He mostly eats pureed foods and does not like eating any dairy foods. You notice that he walks with bowed legs and has widening of wrists on physical examination. Based on the history and physical examination findings, which of the following is the most likely diagnosis in this patient?
   A. Langerhans cell histiocytosis.
   B. Megaloblastic anemia.
   C. Osteogenesis imperfecta.
   D. Rickets.
   E. Scurvy.
5. You are a pediatrician practicing in rural Tennessee and are seeing a 6-week-old girl who was born at home. Per the parents, there were no problems at birth, and she has been exclusively breastfed. She has not been previously seen by a medical provider. She now presents with poor feeding, irritability, and a bulging fontanelle. Which of the following is the most likely underlying vitamin deficiency to explain the presumed diagnosis of intracranial hemorrhage?

A. Hypervitaminosis A.
B. Hypervitaminosis D.
C. Vitamin B6 deficiency.
D. Vitamin K deficiency.
E. Vitamin E deficiency.
Atopic Dermatitis

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Education Gap

Clinicians are often challenged in the primary care setting with children who present with moderate-severe recalcitrant atopic dermatitis. Many patients present at the subspecialist level grossly undertreated with topical medications and emollients. Recently, numerous clinical investigations have evolved our understanding of the pathogenesis of atopic dermatitis, and the American Academy of Dermatology released new atopic dermatitis guidelines in 2014. Understanding the groundbreaking discoveries in disease pathogenesis and implementing up-to-date management guidelines in clinical practice are critical for pediatricians.

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

1. List the age-specific clinical features of atopic dermatitis (AD).
2. Understand the essential, important, and associated diagnostic criteria of AD.
3. Recognize the atopic and nonatopic clinical comorbidities associated with AD.
4. Understand the cutaneous infectious complications associated with AD.
5. Understand the disease pathogenesis and its relationship to therapeutic management.
6. Understand the state-of-the-art treatment guidelines, including the recent “proactive” maintenance therapy recommendations.
7. Recognize the importance of multidisciplinary management and clinical indications for subspecialty referral.
8. Understand effective strategies of therapeutic patient education and implement them into clinical practice.

INTRODUCTION

Atopic dermatitis (AD) is a chronic pruritic inflammatory skin disease with a frequently remitting and relapsing course. It is postulated as the first manifestation of the “atopic march”—often preceding the later development of food allergies, allergic rhinitis, and asthma. The terms atopic dermatitis and eczema are

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ABBREVIATIONS

AD atopic dermatitis
ADHD attention-deficit/hyperactivity disorder
AE adverse effect
FDA Food and Drug Administration
FLG filaggrin
IgE immunoglobulin E
IL interleukin
TCI topical calcineurin inhibitor
TCS topical corticosteroid
Th T helper
WWT wet wrap therapy
commonly used interchangeably to describe eczematous dermatitis, although technically there are eczemas other than AD, including allergic contact dermatitis and irritant dermatitis. The cardinal features of AD include xerosis, pruritus, eczematous lesions in the typical morphology and distribution, and a personal or family history of atopy.

The personal, social, emotional, and financial resources of patients, their caregivers, and the health-care system are largely burdened by AD. Not including the lost opportunity costs and productivity, such as missed work or school days, or the loss of individual quality of life, annual US economic burdens are conservatively estimated to be approximately $5 billion. (1) An estimated two-thirds of patients with AD initially present with mild disease and may be managed by their primary medical care provider. (2) Pediatricians are nearly always a child’s first line of management, and the purpose of this review is to provide up-to-date information regarding AD pathophysiology, clinical presentation, and state-of-the-art treatment guidelines.

**EPIDEMIOLOGY**

Atopic dermatitis is the most common chronic inflammatory dermatologic disorder in children, affecting an estimated 12.5% of children in the United States. (3) Sixty percent of children with AD present in the first year after birth, and 90% present by 5 years of age. (3) Numerous studies suggest that AD affects both sexes nearly equally. (4) Most children with AD present with mild disease (67%), and the remaining 33% present with moderate-to-severe AD. (3)

Multiple investigations have analyzed the demographic and geographic associations with AD. A study published in 2011 by Shaw et al (5) using National Survey of Children’s Health data reported an increased disease prevalence in individuals of African American race. In addition, higher educational level (greater than high school) is associated with higher rates of AD. (5)(6) Domestically, the regions with highest disease prevalence in the United States include numerous northeastern states as well as Idaho, Nevada, and Utah. (5) The prevalence of AD has risen dramatically during the past 50 years in developed countries, especially in the United States, Europe, and Japan. (6) In addition, the incidence of pediatric AD in developing countries seems to be rising, with a maximum prevalence of nearly 30% in some populations. (7) The causes of the increasing prevalence of pediatric AD are unknown, but several systematic large-scale studies point to numerous genetic and environmental factors as potential contributors. (7)

**PATHOGENESIS**

A major debate has existed as to whether AD is primarily driven by immune abnormalities (inside-out theory) or epidermal barrier dysfunction (outside-in theory). It is clear that AD pathogenesis is multifactorial, resulting from a complex interplay among epidermal barrier dysfunction, immune dysregulation, and environment. Numerous studies have suggested genetic susceptibilities for AD. (8) Preceding classification of the human genome, concordance in monozygotic twin studies and case reports detailing transfer of AD after bone marrow transplant supported a genetic basis for the disorder. (9) Most recently, groundbreaking research worldwide has positively associated 46 genes with AD. (8) Of these investigations, the most steadily replicated findings involve variations in genes encoding filaggrin (FLG), which is also implicated in the etiology of ichthyosis vulgaris. Ichthyosis vulgaris presents with xerotic skin, especially on the extensor surfaces of the legs, is associated with hyperlinear creases on the palms and feet and is due to homozygous or heterozygous deficiencies in the FLG genes.

In the superficial epidermis, FLG influences epidermal differentiation, affects barrier function (preventing water loss and blocking the entry of foreign substances), promotes skin hydration, and modulates immune function. (10) It may be that more porous skin is more easily sensitized by skin contactants. Studies have shown that FLG gene mutations are associated with higher rates of AD development, more common in certain populations than others, and that variation in FLG gene copy numbers (influencing FLG protein expression) influence the development of AD.

Environmental factors undoubtedly interact with genetic susceptibilities, resulting in the clinical expression of AD. Mechanical injury, allergens, and microbes activate the skin’s innate immune system, leading to increased expression of specific cytokines that incite inflammation, notably thymic stromal lipoprotein, interleukin (IL)-25, and IL-33. These cytokines trigger type 2 innate lymphoid cells to activate T helper (Th) 2 cells. Increased Th2 cell activity promotes specific cytokine-associated inflammation, eosinophilia, and immunoglobulin E (IgE) production while suppressing epidermal barrier proteins and antimicrobial peptides (IL-4, IL-5, IL-13). The Th2 response also contributes to pruritus by promoting IL-31 production along with several other mediators, including thymic stromal lipoprotein, histamine, tryptase, and neuropeptides. Interleukin-17, a cytokine implicated in the etiology of psoriasis, is also increased in AD, but this association is poorly understood. In addition, barrier function is markedly impaired due to a decline in expression of the structural proteins and lipids.
that play a role in water retention and barrier protection. Also of importance, Th1 and Th22 cytokines are significantly increased in chronic AD, in addition to Th2 cytokines. The novel Th22 cytokine IL-22 has recently been linked to lichenification through impairing epidermal differentiation and promoting epidermal hyperplasia. These factors contribute to the acute and chronic clinical presentation of AD. (3)(11)(12)

RISK FACTORS FOR DISEASE DEVELOPMENT

Of the numerous risk factors linked with AD, 2 are greatly associated—FLG gene mutations and a family history of atopic disease. More than two-thirds of children with AD have an immediate family member with atopic disease. The chances of developing AD increase exponentially with parental atopy. The risk of developing AD is 2 to 3 times more likely with 1 atopic parent and 3 to 5 times more likely with 2 atopic parents. (13) Furthermore, a robust quantity of literature has acknowledged the association between FLG mutations and AD. Sixty percent of individuals with FLG mutations ultimately develop AD—more than 3-fold higher than the occurrence in the general population. (10) This association is reinforced by numerous studies showing a positive correlation between FLG mutations and severe AD.

Further investigations highlighted the higher incidence of eczema herpeticum and asthma in patients with AD with FLG mutations (10)(14). Conversely, 40% of children with FLG mutations do not develop AD, and these mutations are uncommon in specific populations. A recent genomic study of 100 South African children with severe AD and ichthyosis vulgaris showed no FLG mutations in this population, and an analogous study of 75 Ethiopian children revealed an FLG mutation incidence of 1.3%, much lower than the 10% prevalence documented in individuals of European ancestry. (15)(16) Loss-of-function mutations are also uncommon in African American individuals. (17)

Other environmental exposures in genetically susceptible children may increase the risk of AD, but this is highly controversial. Two clinical investigations of independent birth cohorts revealed a correlation between cat ownership at birth and the development of AD in individuals with FLG loss-of-function mutations. (18)(19) Another investigation suggested that dog ownership from birth may reduce the incidence of AD. (20)

Multiple studies suggest a positive correlation between urban environment and atopic disease prevalence. (21) These findings support the hygiene hypothesis, which speculates that early exposure to pathogens may serve as protective in the development of atopy, and in the absence of such exposure, atopic conditions become more prevalent. Several different rural pathogens have been proposed to safeguard individuals from the development of atopic disease, including farm animals, unpasteurized milk, and helminthes. (22)

CLINICAL FINDINGS

Hallmark clinical findings of AD include xerosis (dry skin), pruritus, and eczematous lesions in an age-specific distribution. Morphologically, erythema, lichenification, crusting, exudation, and excoriation characterize the lesions. Skin involvement varies from mild and localized to severe and widespread. The skin of AD is termed by some to be sensitive, with lower thresholds for irritation and pruritus. Pruritus is the most bothersome symptom to children and caregivers, which often significantly worsens quality of life. The resulting “itch-scratch” cycle is a major root of morbidity leading to complications such as secondary infection and poor sleep quality. Pruritus may be exacerbated by factors such as xerosis, coarse clothing (eg, wool), environmental irritants (temperature extremes, harsh soaps or detergents), and allergens.

Classically, AD lesions are characterized as poorly demarcated eczematous plaques; however, the presentation often varies according to age and race. Three distinct age-associated phases—infantile, childhood, and adult—define the usual distribution of AD lesions. The infantile phase typically evolves in the first few years of life, and the childhood and adult phases are distinguished by the initiation of puberty. Noteworthy, the symptoms of individuals occasionally fall outside their age-specific phase.

Characteristic infantile eczema is typically on the scalp, cheeks, and forehead. Lesions progressively extend to involve the trunk and extensor surfaces of extremities. The diaper region is typically shielded from involvement as a result of protection from transepidermal water loss and external irritation. Flexural surface involvement is common in childhood AD. Most frequently, lesions arise in the antecubital and popliteal fossa. Other well-established sites of involvement include the perioral region, wrists/ankles, and neck. Parents often voice concerns about the pigmentary changes, although these typically resolve without long-term scarring. From puberty forward, major areas of involvement consist of the face (periorbital and perioral regions), dorsal feet, hands, and upper back.

The expressed phenotype of AD may vary according to race. African American children often present with more papular or follicular AD. Furthermore, increased pigmentedary changes, both hypopigmentation and hyperpigmentation, may be noted in darker skin-type patients, especially in lichenified or resolving areas. Other classic
cutaneous conditions associated with AD include keratosis pilaris, ichthyosis vulgaris, and pityriasis alba. Keratosis pilaris is characterized by follicular hyperkeratosis of the extensor surfaces of the upper arms and legs and the face. These rough-feeling keratotic papules are highly associated with ichthyosis vulgaris, an autosomal dominant disorder defined by generalized xerosis and hyperkeratosis. Pityriasis alba is a common concurrent condition, often presenting with blotchy hypopigmentation of the face. More common in patients with AD, it is thought to be due to the hyperkeratosis of the epidermis, which decreases UV penetration. Pityriasis alba and postinflammatory hypopigmentation may overlap, although pityriasis alba can be seen in individuals without underlying AD. Parents may be reassured that these hypopigmented patches gradually improve with time and sun protection.

CLINICAL COMORBIDITIES

Numerous investigations have supported the relationship between AD and other atopic disorders, including asthma, allergic rhinitis, and food allergies. (23) Noteworthy, patients with AD with FLG mutations have an additional risk of developing other atopic disorders, especially asthma and peanut allergy. (24)

Additional associations between AD and nonatopic comorbidities have recently been highlighted in the literature. Sleep disruption is the most prevalent comorbidity, affecting up to 60% of children with AD. (25) Pruritus during AD exacerbations causes increases in sleep disturbance, which may lead to neurocognitive impairment, affecting school performance, peer relations, and familial interactions. (25) Studies have also linked neurobehavioral disorders with AD. Several studies of children with AD found a significantly increased prevalence of comorbid attention-deficit/hyperactivity disorder (ADHD) and additional psychiatric disorders, including anxiety, conduct disorder, and depression. (26)

Finally, emerging evidence for comorbidities, including cancer, hypertension, and obesity, is controversial, requiring further investigation. (27) The prospect of these associated comorbidities highlights the importance of obtaining a complete review of systems when evaluating patients with AD and implementing a multidisciplinary approach in their management.

MAKING THE DIAGNOSIS

The diagnosis of AD is primarily clinical, based on a constellation of essential, important, and associated features listed in Table 1. A task force of AD experts updated diagnostic guidelines at a 2013 consensus conference organized by the American Academy of Dermatology. Essential features in the diagnosis of AD include pruritus, chronic relapsing eczematous dermatitis, and age-specific distribution. Other compelling associations include personal or family history of atopy and IgE reactivity; however, these are not essential for diagnosis. Table 1 lists additional clinical findings that are commonly associated. Finally, a diagnosis of AD is contingent on ruling out a variety of additional conditions, including seborrheic dermatitis, scabies, contact dermatitis, psoriasis, and others, as well as other less common conditions that may present with eczematous-appearing rashes (Table 1). (23)

The severity of AD may be delineated through several methods. Numerous scoring systems have been used for clinical trials, such as the Eczema Area and Severity Index, the Investigator Global Assessment, and the Scoring Atopic Dermatitis, but they are not generally used in clinical practice. Generally, milder disease will involve less body surface area and have skin lesions with less erythema, papules, edema, excoriations, lichenification, and intensity of itch. Disease persistence, frequency of flares, effect on quality of life, and comorbidities may influence severity classification. More severe disease may require more aggressive treatment and consideration for referral to a specialist. (23)

DIFFERENTIAL DIAGNOSIS

Table 2 lists the core differential diagnosis of AD. Less common diagnoses are also listed in Table 2, which should be considered in individuals presenting with atypical rash, poor response to therapy, unusual infections, and/or failure to thrive. This differential diagnosis includes infectious, neoplastic, genetic, immunodeficiency, and inflammatory etiologies. When considering a diagnosis of AD, these clinical disorders must first be excluded. (23)

INFECTION COMPICATIONS

It is commonly recognized that individuals with AD have a high frequency of infectious complications. This stems largely from the increased occurrence of Staphylococcus aureus colonization in the AD population. (28) Recent studies involving patients with AD document S aureus colonization in up to 90% of actively affected skin and 76% of nonaffected skin. (29)(30) This sharply contrasts with the 2% to 25% prevalence of colonization in controls. (29)(30) The increased adherence of S aureus to superficial skin cells, impaired epidermal barrier function, and insufficient production of antimicrobial peptides promote
colonization and, ultimately, cutaneous and/or systemic infection. (31)(32) The cutaneous manifestations of *S aureus* superinfection are characterized by honey-colored crusting, weeping, and pyoderma. Several case reports document severe systemic complications likely resulting from *S aureus* colonization in patients with AD, including bacteremia, sepsis, endocarditis, and osteomyelitis. (33)(34)

Group A *Streptococcus* also accounts for a significant number of AD superinfections. A retrospective review of children with AD with skin cultures revealed colonization with group A *Streptococcus* in 16%. (35) Furthermore, children with group A *Streptococcus* superinfection had a greater frequency of fever, facial involvement, and hospitalization than patients with staphylococcal etiology. (35)

Patients with AD may have an increased risk of developing disseminated viral infections. Eczema herpeticum may present as umbilicated vesicopustules resulting from herpes simplex virus. The hallmark of this condition is grouped vesicles in a “cluster of grapes” appearance overlying diffuse eczematous papules and plaques. Patients can manifest with severe pruritus, pain, and systemic illness, often requiring hospitalization. Molluscum contagiosum, a common ailment of childhood, tends to be more prevalent and can be more severe in children with AD, in addition to inducing eczematous rashes. Molluscum is characterized as a dome-shaped papule with a central white core and/or umbilication. Recently defined in the literature, eczema coxsackium characterizes the atypical clinical presentation of coxsackie virus (CVA6) in children with AD. Mathes et al (36) first described a vesicular pattern with erosions, morphologically similar to eczema herpeticum, localized to areas previously or currently affected by AD. This published constellation of findings suggests that eczema coxsackium should be considered in the differential diagnosis of patients with AD presenting with vesicular lesions. (36)

### MANAGEMENT

Figure 1 summarizes the American Academy of Dermatology recommendations for AD therapeutic management for pediatric providers. These guidelines are further detailed throughout this section.

#### Basic Management

The cornerstone of successful AD management is the implementation of basic management strategies, including good bathing practices and adequate skin hydration. Individuals with AD have baseline xerosis due to barrier function deficits and an unfavorable balance of transepidermal water loss and water retention. Bathing may hydrate skin

#### TABLE 1. Essential, Important, and Associated Features Used for the Clinical Diagnosis of Atopic Dermatitis

<table>
<thead>
<tr>
<th>ESSENTIAL FEATURES</th>
<th>IMPORTANT FEATURES</th>
<th>ASSOCIATED FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both must be present:</td>
<td>Add support to the diagnosis, observed in most cases of AD:</td>
<td>Suggestive of AD, but too nonspecific to be used for defining or detecting AD in research or epidemiologic studies:</td>
</tr>
<tr>
<td>1. Pruritus</td>
<td>1. Early age at onset</td>
<td>1. Atypical vascular responses (eg, facial pallor, white dermographism, delayed blanch response)</td>
</tr>
<tr>
<td>2. Eczema (acute, subacute, chronic)</td>
<td>2. Atopy</td>
<td>2. Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis</td>
</tr>
<tr>
<td>A. Typical morphology and age-specific patterns:</td>
<td>A. Personal and/or family history</td>
<td>3. Ocular/periorbital changes</td>
</tr>
<tr>
<td>a. Infants/children: facial, neck, and extensor involvement</td>
<td>B. Immunoglobulin E reactivity</td>
<td>4. Other regional findings (eg, periocular changes/periocular lesions)</td>
</tr>
<tr>
<td>b. Any age group: current or previous flexural lesions</td>
<td>3. Xerosis</td>
<td>5. Perifollicular accentuation/lichenification/prurigo lesions</td>
</tr>
<tr>
<td>c. Sparing of the groin and axillary regions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Chronic or relapsing history</td>
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</tbody>
</table>

*AD*=atopic dermatitis

and reduce irritants, bacteria, and crusts. Expert consensus recommends bathing in lukewarm water followed by application of moisturizer or topical prescription medications. The use of mild or nonsoap cleansers is preferred to avoid irritation and detrimental barrier effects. Transepidermal water loss may result from water evaporation after bathing if moisturizer is not applied. Thus, application of emollients after bathing is encouraged to retard evaporation of water. Applying emollients generously at least twice daily is additionally recommended to boost cutaneous hydration and provide symptomatic relief. (37) Emollient choice is highly dependent on provider and patient predilection. Thicker occlusive agents, such as ointments, may be more effective, but moisturizers vary in formulation and water content and can include ointments, creams, oils, gels, and lotions. Recently, several studies documented anti-inflammatory benefits and enhanced efficacy of emollients with physiologic concentrations of lipids and ceramides. (38)(39)(40) These formulations are more expensive, and the cost-benefit ratio is yet to be established. A variety of studies exploring the efficacy and microbiome effects of specific oils have emphasized that oils are not substitutable. Coconut oil was superior to olive oil in several head-to-head studies in decreasing S aureus colonization and AD severity. (41)(42)

### Acute Treatment of Exacerbations

Topical corticosteroids (TCSs) have long been established as the first-line therapy for acute flares due to their remarkable anti-inflammatory properties. During the past 60 years, efficacy has been demonstrated in more than 100 clinical investigations. (37) Topical corticosteroids are formulated in a variety of strengths, ranging from lowest potency (group VII) to highest potency (group I). Examples of alternatives in each class are shown in Table 3. Often, TCSs are prescribed

#### TABLE 2. Core Differential Diagnosis and Less Common Diagnoses of Atopic Dermatitis

<table>
<thead>
<tr>
<th>Core Differential Diagnosis</th>
<th>Primary Immunodeficiency Disorders</th>
<th>Other Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scabies</td>
<td></td>
<td></td>
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<tr>
<td>Psoriasis</td>
<td></td>
<td></td>
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<tr>
<td>Ichthyoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seborrheic dermatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact dermatitis (irritant or allergic)</td>
<td></td>
<td></td>
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<tr>
<td>Cutaneous T-cell lymphoma</td>
<td></td>
<td></td>
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<tr>
<td>Photosensitivity dermatoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunodeficiency diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythroderma of other causes</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nutritional and Metabolic Disorders</th>
<th>Primary Immunodeficiency Disorders</th>
<th>Other Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrodermatitis enteropathica</td>
<td>Agammaglobulinemia</td>
<td>Ataxia-telangiectasia</td>
</tr>
<tr>
<td>Biotin deficiency</td>
<td>Hyperimmunoglobulin E syndrome</td>
<td>Langerhans cell histiocytosis</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Omenn syndrome</td>
<td></td>
</tr>
<tr>
<td>Essential fatty acid deficiency</td>
<td>Severe combined immunodeficiency disorder</td>
<td></td>
</tr>
<tr>
<td>Hartnup disease</td>
<td>Wiskott-Aldrich syndrome</td>
<td></td>
</tr>
<tr>
<td>Hurler syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td></td>
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</tr>
<tr>
<td>Prolidase deficiency</td>
<td></td>
<td></td>
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<tr>
<td>Zinc deficiency</td>
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</tr>
<tr>
<td>Acrodermatitis enteropathica</td>
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<tr>
<td>Zinc deficiency</td>
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for varying durations of a few days to several weeks to manage AD refractory to basic good skin care and emollient use alone. Low-potency (ie, 1%–2.5% hydrocortisone) and medium-potency (ie, 0.1% triamcinolone) TCSs are recommended as first-line management for flares of mild and moderate-to-severe AD, respectively, especially in infants and young children. (37) Facial and intertriginous areas are very penetrable and should be treated with low-potency corticosteroids to avoid adverse reactions. Recommendations for TCS therapy duration are numerous and largely based on expert consensus. Recently published guidelines for primary care providers endorse continued application of TCS twice daily for up to 3 days beyond flare resolution, (43) but there are data to support sufficient therapeutic response with once daily application. (44) Adequate quantities of mild- to moderate-strength TCS should be described proportionate to age and body surface area involvement. For instance, acute treatment of a 4-year-old with 50% body surface area involvement with a topical corticosteroid ointment applied twice daily should use 62 to 125 g of TCS per week based on “fingertip unit dosing.” (45) Patient non-compliance, cutaneous superinfection, and/or misdiagnosis must be considered if the exacerbation fails to improve within 10 to 14 days of therapy. Referral to a dermatologic specialist is recommended for unresponsive dermatitis with appropriate medication use. (43)

To enhance TCS therapy efficacy, wet wrap therapy (WWT) is often used in the management of refractory moderate-severe AD. (46) Health-care providers in the clinical setting may demonstrate this technique to patients with AD and caregivers. The WWT involves the application of TCSs or emollients followed by 2 successive layers of cotton pajamas, gauze, or tubular bandages (first layer wetted with warm water; second layer dry). The occlusive properties of WWT enhance penetration of the topical agent(s), improving treatment success. (46) Wet wrap application for up to 24 hours is acceptable and may be repeated for several days to 2 weeks, permitting patient tolerance. Cautious use of mid-higher potency TCSs in WWT is advised because greater absorption may cause adverse effects (AEs) and/or infection. The WWT should be performed as directed by a practitioner trained in its use. (47)

Rarely, AD worsened by TCSs or other topical therapy may result from allergic sensitization to specific components in topical formulations, including preservatives, vehicle, or active ingredients. (48) Specialist referral for patch testing is recommended if contact dermatitis is suspected. (43)
The AEs reported from TCS utilization are infrequent and primarily cutaneous, but disproportionate fears of their use are many, with corticosteroid phobia being common. Much “recalcitrant” AD is due to insufficient use of prescribed topical therapy. Therapy noncompliance may result from parental fear of AEs. The true frequency of AEs is unknown, but they are rare in studies and clinical practice. Counseling patients and caregivers on clinical signs and reversibility of AEs, including skin atrophy, telangiectasias, acneiform lesions, and hypertrichosis, is critical to treatment adherence. Systemic AE incidence is extremely rare but increases with prolonged duration of therapy. Rare reports of hypothalamic-pituitary axis suppression, hyperglycemia, and hypertension are documented in the literature. (49) Predisposing factors to systemic AEs include long-term utilization, large body surface area, and high-potency formulation. Providers should be aware of TCS AEs and monitor for associated clinical signs. Specific laboratory

| TABLE 3. Topical Corticosteroids Ranked by Potency (from Most Potent to Least Potent) |
|---|---|---|
| GROUP | GENERIC NAME (BRAND NAME) | VEHICLE | CONCENTRATION, % |
| I | • Betamethasone dipropionate (Diprolene) | Ointment | 0.05 |
| | • Clobetasol propionate (Temovate) | Cream, ointment, lotion | 0.05 |
| | • Diflorasone diacetate (Psorcon) | Ointment | 0.05 |
| | • Halobetasol propionate (Ultravate) | Cream, ointment | 0.05 |
| II | • Acmcinonide (Cyclocort) | Ointment | 0.1 |
| | • Betamethasone dipropionate (Diprosone/Maxivate) | Ointment | 0.05 |
| | • Desoximetasone (Topicort) | Cream, ointment | 0.25 |
| | • Fluocinonide (Lidex) | Gel | 0.5 |
| | • Mometasone furoate (Elocon) | Cream, ointment, gel, solution | 0.05 |
| | • Triamcinolone (Aristocort) | Ointment | 0.1 |
| III | • Acmcinonide (Cyclocort) | Cream, lotion | 0.1 |
| | • Betamethasone dipropionate (Diprosone) | Cream | 0.05 |
| | • Betamethasone valerate (Valisone) | Ointment | 0.1 |
| | • Diflorasone diacetate (Psorcon) | Cream | 0.05 |
| | • Fluticasone propionate (Cultivate) | Ointment | 0.005 |
| | • Triamcinolone acetonide (Aristocort) | Ointment | 0.1 |
| IV | • Fluocinolone acetonide (Synalar) | Ointment | 0.025 |
| | • Hydrocortisone valerate (Westcor) | Ointment | 0.2 |
| | • Mometasone furoate (Elecon) | Cream, lotion | 0.1 |
| | • Triamcinolone acetonide (Kenalog, Aristocort) | Cream | 0.1 |
| V | • Betamethasone dipropionate | Lotion | 0.05 |
| | • Betamethasone valerate (Valisone) | Cream | 0.1 |
| | • Fluticasone acetonide (Synalar) | Cream | 0.025 |
| | • Hydrocortisone butyrate (Locril) | Cream, ointment, lotion | 0.2 |
| | • Hydrocortisone valerate (Westcor) | Cream | 0.2 |
| | • Prednicarbate (Dermatop) | Cream | 0.1 |
| VI | • Alclometasone dipropionate (Aclovate) | Cream, ointment | 0.05 |
| | • Betamethasone valerate | Lotion | 0.1 |
| | • Desonide (DesOwen/Tridesilon) | Cream, ointment | 0.05 |
| | • Fluocinolone acetonide (Synalar) | Oil | 0.01 |
| | • Triamcinolone acetonide (Aristocort, Kenalog) | Solution | 0.01 |
| | • Triamcinolone acetonide (Aristocort, Kenalog) | Cream | 0.025 |
| VII | • Hydrocortisone acetate | Cream | 1 |
| | • Methylprednisolone acetate | Cream | 0.25 |
| | • Dexamethasone sodium phosphate | Cream | 0.05 |

monitoring for systemic AEs is not routinely suggested. (57) Pediatricians should feel comfortable prescribing specific quantities of TCS to be used over time, counseling about safe TCS use rather than fueling inappropriate corticosteroid phobia that may contribute to inadequate disease control.

The topical calcineurin inhibitors (TCIs) 0.1% pimecrolimus cream and 0.03% tacrolimus ointment are Food and Drug Administration (FDA) approved for children older than 2 and 15 years, respectively. These topical medications are indicated as “second line therapy for the short term and noncontinuous chronic treatment of moderate to severe atopic dermatitis in nonimmunocompromised children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis or when those treatments are not advisable.” (50)

Contrasting with TCS therapy, TCI therapy has fewer cutaneous risks and may be more suitable for thin-skinned areas, such as the face and intertriginous regions. Caregivers and providers often have concerns about TCI treatment in light of the FDA-issued black box warning in 2006. (50) A lack of long-term safety data at the time and concerns of hypothetical risk of skin malignancy and lymphoma led to the issuance of this warning. Since that time, numerous studies involving more than 17,000 infants and children have displayed drug safety with minimal evidence of immunocompromise or malignancies with their use. (51)

Recently, topical phosphodiesterase-4 inhibitors have been studied, and crisaborole 2% topical ointment is FDA approved for AD in children 2 years and older. A nonsteroidal anti-inflammatory agent, it is not associated with skin atrophy. Although it may be incorporated into regimens of care similar to other topical anti-inflammatory medications, it was studied as monotherapy in mild-to-moderate AD applied 2 times a day for 28 days. (52)

“Proactive” Maintenance Therapy

After resolution of disease flare, maintenance therapy largely depends on AD persistence and severity. Control with basic management is typically sufficient for patients with mild disease that is intermittent. Basic management principles include appropriate skin care (detailed previously herein) and irritant avoidance. Emollients constitute an integral part of maintenance and preventive therapy given their cost-effectiveness and capacity to enhance skin hydration. Noteworthy, a recent randomized controlled trial of 124 neonates at risk for atopic disease suggested an inverse correlation between emollient application from birth and subsequent AD development by 6 months of age. (53) Larger-scale investigations are necessary to confirm these encouraging results.

Multiple specialty group guidelines have recommended the use of TCIs and TCSs in proactive maintenance regimens of care. A proactive approach for maintenance therapy is advised to use regularly scheduled topical application of anti-inflammatory medications to frequently flaring skin areas, as contrasted to reactive flare management. Both TCSs and TCIs may be useful on disease-prone areas, applied on a routine periodic basis. Multiple clinical investigations reveal significant flare reduction with proactive consistent application of moderate or lower-potency TCSs, and/or TCIs, with varying application frequencies. (51)(54) Current recommendations allow flexibility, endorsing TCI application 2 to 3 times weekly, or once to twice daily in recalcitrant cases. (55) Similarly, TCSs are recommended once to twice weekly (medium potency; excluding face and intertriginous regions) and/or once to twice daily (low potency; including face and intertriginous regions). (55)

**OTHER THERAPEUTIC CONSIDERATIONS**

**Irritants, Allergy, and Environmental Modifications**

Irritants include chemicals, course fabrics (ie, wool), lanolin, soaps/detergents, fragrances, acidic foods, tobacco smoke, and temperature extremes. Avoidance of irritants and known allergens may lessen disease severity and lead to more disease-free days.

Children with AD have higher rates of IgE sensitization, which may be evaluated through specific IgE or skin prick testing. However, IgE sensitization is not the same as clinical food allergy, which is defined as “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.” (56) The incidence of IgE-mediated food allergy development in 2 large US-based investigations of infants with mild-to-moderate AD, 1 retrospective and 1 prospective, was approximately 15%. (57) Food allergy rates increased to approximately 30% to 40% in patients with moderate-to-severe disease. (57) The most common food allergens in patients with AD include egg, milk, peanut, soy, and wheat. Food allergens may be a more significant issue in younger children with AD. However, both skin prick and specific IgE tests have high false-positive rates and are not necessarily predictive of clinically relevant reactions. (56)

Food allergy reactions in patients with AD can include elicitation of eczematous changes or urticarial skin findings or systemic symptoms such as wheezing, vomiting, diarrhea, and/or proctocolitis. Suspected food allergy may need to be evaluated with oral food challenges. It is not recommended for children without documented or proven food allergy to avoid potentially allergenic foods as a means of
managing AD. An expert panel recommended that children younger than 5 years with moderate-severe AD should undergo food allergy testing if “1) the child has persistent atopic dermatitis in spite of optimized management and topical therapy; and/or 2) the child has reliable history of an immediate reaction after ingesting specific foods.” (56) If they do have documented food allergy and AD it is reasonable to avoid the specific food allergens. Regular growth monitoring and nutritional management may be an important part of intervention.

Recently, young children with AD have been identified as a group that may benefit from the early introduction of specific foods, decreasing subsequent development of food allergy. The novel “Learning Early about Peanut Allergy” (LEAP) trial, published in 2015, was the first large-scale randomized trial investigating allergy prevention by early allergen introduction. Children with severe eczema and/or egg allergy were shown to have a decreased rate of development of peanut allergy with early peanut consumption, beginning at 4 to 11 months of age and continuing until 5 years of age. (57) Prevention was shown in children with negative skin prick test results for peanut, as well as those with positive skin prick test results, although individuals with larger wheal size (5 mm) were excluded from the trial. Expert recommendations are advising the identification of children with severe AD in the first year of life as a cohort that should be evaluated with specific IgE to peanut, with early feeding with a negative serum test result and referral to allergy for skin prick testing for positive specific IgE peanut blood test results, or direct referral before serum screening, for skin prick evaluation for determination of the safety of early peanut feeding. (58)(59)

Reactivity to aeroallergens predominates over food allergen sensitization in older children and adolescents with AD. Sensitization to aeroallergens occurs more frequently in patients with moderate-to-severe AD. Common aeroallergens include animal dander, dust mites, fungi, and pollen. Similar to food allergen sensitization, clinical relevance of aeroallergen sensitization is variable, worsening eczema severity in some individuals but not others. Eczematous dermatitis predominantly on exposed cutaneous surfaces, including the arms, face, neck, and V area of the chest, may be a clue to aeroallergen involvement. Avoidance of aeroallergens through environmental modifications has not consistently decreased cutaneous involvement. Numerous investigations have focused on minimizing house dust mite exposure to improve AD severity. Although cleaning measures and mattress covers may reduce house dust mite sensitization, investigations, although few, have shown clinical improvement in patients with AD who undergo these interventions. Current American Academy of Dermatology guidelines advise that pillow and mattress covers may be considered in children with house dust mite sensitization and refractory AD, on the basis of limited evidence. (55)

Microbial Management

Antimicrobial therapy should be reserved for the management of patients with clinical signs of infection. Localized impetigo may be treated topically with antistaphylococcal antibiotics (ie, mupirocin), whereas widespread involvement often requires more aggressive therapy with systemic antibiotics. First-generation cephalosporins provide broad antibacterial coverage against staphylococcal and streptococcal agents except methicillin-resistant S. aureus. Poor clinical response should prompt culture of affected skin to assess for methicillin-resistant S. aureus and to guide antibiotic selection based on sensitivity and resistance patterns. Topical or systemic antibiotic treatment of AD that is not clinically infected is not advised. (60)

Hospitalization and intravenous antimicrobials are occasionally required for extensive infections, especially eczema herpeticum. Once a dermatologic emergency, mortality from this potentially lethal condition is virtually prevented with prompt intravenous systemic acyclovir administration. A multicenter retrospective cohort study recently showed an inverse correlation between hospital length of stay and delay in acyclovir initiation, providing further evidence for the efficacy of therapy. (61) Outpatient oral antiviral management is often sufficient for localized outbreaks and should be considered in mild cases.

In children prone to cutaneous bacterial infections, proactive antiseptic bleach baths may reduce AD severity by decreasing inflammation and cutaneous microbial colonization. (62) One randomized placebo-controlled investigation revealed a significant decrease in eczema severity in children 6 to 17 years of age with clinical signs of bacterial infection who received daily 0.005% sodium hypochlorite (bleach) baths for 3 months. (29) The American Academy of Dermatology currently recommends bleach baths (0.005% sodium hypochlorite) twice weekly to daily in patients prone to bacterial superinfections on the basis of this evidence. Instructions for appropriately mixing a therapeutic bleach bath are listed in Table 4.

Pruritus and Sleep Disturbance

The use of topical antihistamines for the symptomatic relief of pruritus in patients with AD is not recommended due to the risk of cutaneous absorption. (37) Short-term treatment with sedating systemic antihistamines is often used to improve sleep quality during flares, although the evidence supporting this is limited. The first-generation
antihistamines (ie, diphenhydramine and hydroxyzine) with sedative properties are favorable. Nonsedating antihistamines are not suggested in the absence of other atopic disorders but may be useful for concurrent atopic conditions (ie, allergic rhinitis). (60)

**REFRACTORY THERAPEUTICS**

Immunosuppressive agents or narrow-band UV-B phototherapy is frequently used at the specialist level for moderate-severe refractory AD that is persistent or frequently flaring despite the use of topical medications. UV radiation is postulated to have immunosuppressive, antibacterial, and barrier-enhancing properties beneficial in AD management. (63) Systemic immunomodulatory agents (ie, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil) are sparingly recommended for children recalcitrant to first-line therapies and/or phototherapy. (60) Oral corticosteroids are occasionally used for severe AD flares but are not recommended due to only transient effects and a poor AE profile. Newly established understanding of the immunologic dynamics underlying AD has triggered recent investigations into novel therapeutics, including biological agents and small molecules (eg, IL-4 receptor alpha antibodies (dupilumab), JAK inhibitors, and others. Initial results are encouraging, and further investigations are currently underway.

**TABLE 4. BLEACH BATH INSTRUCTIONS FOR CAREGIVERS**

1. Add common 6% household bleach to a bathtub full of water (8.75% bleach is one-third more concentrated; use one-third more water or one-third less bleach)
2. Measure the amount of bleach before adding it to the bathwater
3. For a full tub of water, use ½ cup; for a half-full tub of water, add ¼ cup of bleach
4. While the tub is filling, pour the bleach into the water
5. Wait until the bath is fully drawn before placing the child in the tub
6. Never apply bleach directly on a child’s skin
7. Soak for 10 min
8. Pat the child’s skin dry after the bath
9. If the child uses eczema medication, apply it immediately after the bath, then moisturize the child’s skin
10. As an alternative to bleach baths, comparable dilute bleach solutions can be made using 1 tsp of bleach per gallon of water. This may be useful in spray bottles for use in showers (eg, for adolescents) or for smaller baby bathtubs. Alternatively, commercial sodium hypochlorite products that seem to have similar effects as bleach baths are available.

**THERAPEUTIC PATIENT EDUCATION**

Educating caregivers and patients on disease course, prognosis, and effective implementation of therapeutic interventions is critical to AD management success. Comprehensive education may improve treatment compliance and minimize caregiver misunderstandings and reservations. Teaching should begin with implementation of an initial management plan and continue through each subsequent visit, ensuring continued patient understanding as therapy is continued and/or adapted. Educational methods vary significantly and can be conveyed individually or through group sessions. Numerous different educational interventions have been investigated during the past decade. Evidence strongly supports intensive formal training programs, showing significant improvements in patient disease severity and quality of life. These interventions are often less feasible in clinical practice due to substantial physician and personnel time constraints. (64) Other more practicable educational strategies include written action plans, PowerPoint or video instruction modules, and nurse instructional sessions.

Written action plans have been successful in improving treatment compliance in asthmatic and diabetic children. (64) Numerous clinical providers have used an analogous action plan for patients with AD detailing proper skin care and specific indications for systemic and topical medications. (64) Further studies must be performed on their educational effectiveness, but these written action plans are promising. (64)(65)

Physicians should be cognizant of additional management resources for patients with AD, including information provided by the American Academy of Dermatology (http://www.aad.org), the National Eczema Association (http://nationaleczema.org), and The Eczema Center at UCSD/Rady Children’s Hospital, San Diego (http://www.eczemacenter.org).

**Summary**

- On the basis of recent epidemiologic evidence, atopic dermatitis (AD) is the most common chronic inflammatory dermatologic disorder, affecting approximately 12.5% of children in the United States (60% by age 1 year and 90% by age 5 years).
- On the basis of recent epidemiologic evidence, disease prevalence is highest in African American children and increases in direct association with parental educational level.
- On the basis of strong evidence, loss-of-function mutations in the FLG gene and familial atopy increase the genetic susceptibility to AD development.
On the basis of expert consensus, AD may be diagnosed clinically based on a constellation of essential, important, and associated features (Table 1).

On the basis of expert consensus and some research evidence, physicians should be conscious of and evaluate for AD comorbidities, including allergic rhinitis, asthma, food allergies, sleep disturbance, attention-deficit/hyperactivity disorder, anxiety, and depression.

On the basis of strong evidence, individuals with AD have baseline xerosis for which emollient use is a critical component of management.

On the basis of some evidence and expert consensus, bathing in lukewarm water for a limited duration using a mild or nonsoap cleanser is recommended to hydrate skin and eliminate residual irritants, bacteria, and crusting.

On the basis of strong evidence, lowest- to moderate-potency topical corticosteroid (TCS) application for up to 3 days beyond flare resolution is recommended.

On the basis of some evidence and expert consensus, wet wrap therapy enhances the penetration of topical agents, improving treatment success.

On the basis of some evidence and expert consensus, antiseptic 0.005% bleach baths may help AD in those with frequent infection.

On the basis of strong evidence, “proactive” maintenance therapy with TCSs once or twice weekly or topical calcineurin inhibitors (TCIs) twice weekly to daily is efficacious in decreasing flare frequency.

On the basis of strong evidence, TCIs may be safely used off label in children younger than 2 years.

On the basis of some evidence and expert consensus, educating caregivers and patients on disease course, prognosis, and effective implementation of therapeutic interventions is critical to AD management success.

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/4/180.supplemental.

Atopic Dermatitis
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1. A 10-month-old girl is brought to you for evaluation of a skin rash. Both parents have a history of eczema. On physical examination, her skin is dry, with poorly demarcated plaques. Given this child’s age, the presence of plaques over which of the following locations of her body is most likely consistent with eczematous plaques?
   A. Diaper region.
   B. Dorsum of the feet.
   C. Flexural skin surfaces.
   D. Scalp, cheeks, and forehead.
   E. Upper back.

2. A 5-year-old boy has a history of eczema since infancy. He has been treated with daily emollients and intermittent topical corticosteroids with good response. He is now in kindergarten, and he is brought to you by his parents for evaluation of honey-colored crusted lesions in the antecubital skin regions bilaterally with similar lesions in the popliteal fossae. He has had no fever. You are concerned that his skin lesions are infected. Which of the following pathogens is the most likely cause of the skin infection in this patient?
   A. Coxsackie virus.
   B. Group A Streptococcus.
   C. Herpes simplex virus.
   D. Staphylococcus aureus.
   E. Staphylococcus epidermidis.

3. A 7-year-old girl has had eczema treated with increasing strength of topical corticosteroids. On a routine physical examination she is found to have eczematous plaques on the flexural surfaces of her wrists, elbows, and knees. You are concerned that she is not responding to increasing strength of prescribed therapies. Which of the following is the most likely etiology of poor response to therapy that must be considered first in this patient?
   A. Allergy to emollient therapy.
   B. Bacterial infection of skin lesions.
   C. Hypothalamic-pituitary axis suppression.
   D. Missed diagnosis of pityriasis alba.
   E. Noncompliance due to parental fear of corticosteroid adverse effects.

4. A 4-month-old boy is brought to you for a health supervision visit. Family history is strongly positive for atopy. He has 2 older siblings who have eczema, and 1 of his siblings has asthma. There is also a strong family history of food allergies that include allergies to nuts, eggs, corn, and wheat. The family would like to discuss the introduction of foods into their son’s diet over the next few months. Which of the following is the most appropriate recommendation to give regarding solid food introduction in this patient?
   A. Avoidance of all bread products.
   B. Avoidance of eggs until 2 years of age.
   C. Early introduction of peanut.
   D. Prolonged rice-based diet.
   E. Soy-based diet until 3 years of age.
5. You care for a 12-year-old girl who has been hospitalized several times with bacterial skin infections related to her atopic dermatitis. She and her family are well-educated regarding the use of emollients and topical corticosteroids, but she continues to have recurrent bacterial skin infections. To decrease the frequency of skin superinfections, which of the following is the most appropriate preventive measure to recommend for this patient?

A. Daily 0.005% sodium hypochlorite (bleach) baths for 3 months.
B. Intramuscular ceftriaxone 100 mg/kg monthly for 3 months.
C. Intravenous solumedrol 2 mg/kg infusion.
D. Oral prednisone 1 mg/kg corticosteroid burst for 1 week.
E. Oral cephalexin 50 mg/kg for 1 month.
Clinical Presentation, Evaluation, and Management of Neuroblastoma

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Education Gap

Pediatricians play a pivotal role in the diagnosis of neuroblastoma and as such should be aware of the elusive signs and symptoms to provide clinical surveillance, appropriate referral, and medical support as part of the patient’s multidisciplinary team.

Objectives

After completing this article, readers should be able to:

1. Identify signs and symptoms of neuroblastoma.
2. Identify patients who require emergency care for a life-threatening presentation.
3. Discuss the basics of clinical presentation, diagnostics, and management of neuroblastoma.

INTRODUCTION

Pediatric cancers occur in 171 per 1 million children in the United States each year and are the leading cause of disease-associated death in children. (1) Neuroblastoma is not only the most common cancer in infancy but also the most prevalent solid tumor outside the cranium, (2) and it sometimes requires the most aggressive treatment plan in pediatric oncology. Therefore, pediatricians should be familiar with clinical presentations that should prompt appropriate and timely referral. In this review, we present neuroblastoma, which exemplifies several principles of pediatric oncology, including its multidisciplinary treatment approach.

EPIDEMIOLOGY

The annual incidence of neuroblastoma is approximately 700 cases in North America. (1) In a review of national cancer registries from 2001 through 2009, a diagnosis of neuroblastoma or ganglioneuroblastoma was found in approximately 6% of the cases. (1) Neuroblastoma is more common in the white population (9.7 per 1 million) than in the African American population (6.8 per 1 million) (2) and more common in males (8.5 per 1 million) than in females (7.6 per 1 million).

AUTHOR DISCLOSURE

Drs Sharma, Mer, Lion, and Vik 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.

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CBC</td>
<td>complete blood cell</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>HVA</td>
<td>homovanillic acid</td>
</tr>
<tr>
<td>IHC</td>
<td>immunohistochemical</td>
</tr>
<tr>
<td>IL-2</td>
<td>interleukin-2</td>
</tr>
<tr>
<td>mIBG I-123</td>
<td>metaiodobenzylguanidine</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>OMS</td>
<td>opsoclonus myoclonus syndrome</td>
</tr>
<tr>
<td>VMA</td>
<td>vanillylmandelic acid</td>
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<td>WBC</td>
<td>white blood cell</td>
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Although the median age at diagnosis of neuroblastoma is 18 months, (4) there is a wide age range, from in utero diagnosis to individuals in their 20s. (5) Research studies have interrogated several exposures, including viruses, chemicals, radiation, and drugs. No strong causality has been found to support a role of environmental risk factors in the pathogenesis of neuroblastoma.

**PATHOPHYSIOLOGY**

Neuroblastoma arises from abnormal growth of embryonic neural crest cells that normally make up the sympathetic ganglia and the adrenal medulla. (6) As in all cancers, this aberrant growth is caused by gene mutations. Serving as a starting point, the gene mutation may be germline (occurring in sperm or eggs, thereby hereditary) or somatic (in other cells of the body, which become a tumor).

In some cases, hereditary gene mutations predispose to neuroblastoma. A germline mutation in the ALK oncogene accounts for less than 2% of all neuroblastoma cases and is known as familial neuroblastoma. Familial neuroblastoma often presents with severe clinical features, such as younger age at diagnosis, bilateral adrenal tumors, and multifocal primary neuroblastoma. (7) A PHOX2B loss-of-function mutation can result in neuroblastoma as one feature of congenital central hypoventilation syndrome. (8)(9) A neurocristopathy syndrome is a rare, heritable group of conditions that result from abnormal neural crest cell development and must be considered when seeing a child with simultaneous occurrence of Hirschsprung disease, congenital hypoventilation syndrome, and congenital neuroblastoma.

In contrast, somatic mutations account for more than 98% of neuroblastoma cases. (10) Several genetic alterations have been identified, including gene amplification, chromosomal alterations, and gene polymorphisms. The most important biomarker in neuroblastomas, the MYCN gene, is amplified in approximately 20% of cases. (11) The ALK oncogene has also been shown to have gain-of-function somatic mutation in approximately 14% of neuroblastomas. (12) Both MYCN and ALK amplifications are associated with aggressive tumor phenotype and poor prognosis. Recurrent gain or loss of specific chromosomal segments is found in almost all high-risk neuroblastomas. The most important alterations include gain of 17q and loss of 11q and 1p. (6) Ongoing research efforts are underway to better understand genes that are housed in the aforementioned chromosomal regions, which are associated with aggressive neuroblastomas. Finally, the number of whole chromosomes in a cell, also known as ploidy, is another prognostic marker. Tumor cells can have more (hyperploidy) or less (hypoploidy) than the normal number of copies of whole chromosomes. As with neuroblastomas and most other pediatric cancers, hyperploidy is a more favorable prognostic sign than hypoploidy. (13) Conclusively, there is a great variety of genetic alterations possible, leading to a wide spectrum of clinical behavior of neuroblastomas. The following cases show the dramatic extremes of presentation.

**CLINICAL PRESENTATION**

**Case 1**

Katie is a 4-month-old healthy girl who is brought to her pediatrician by her mother with a concern of “projectile vomiting” for 3 days. Katie’s mother is worried that she may have pyloric stenosis just as her older brother did when he was an infant. The mother denies sick contacts. Urinary output has been adequate, and Katie is gaining weight adequately. Katie’s vital signs and physical examination findings are normal. A complete abdominal ultrasound is negative for pyloric stenosis. However, it is positive for an incidental finding of a 2-cm heterogeneous mass in the right retroperitoneal space. The mass may be arising from the adrenal gland, and it contains areas of calcification, with partial vascularity on Doppler, and is not causing mass effect. On consultation, a pediatric oncologist would like to see Katie in her clinic today, with plans to obtain a complete blood cell (CBC) count, basic metabolic panel, liver enzyme levels, coagulation profile, and random urinary catecholamine levels.

This case demonstrates 1 side of the clinical spectrum, in which a neuroblastoma may be discovered as an incidental radiologic finding. The symptoms, which brought her to the pediatrician, may very well be unrelated to the neuroblastoma. In addition, a small neuroblastoma may not be palpable on physical examination. The location of the mass on imaging gives a clue to the diagnosis. Although Katie’s tumor is located in the most common site, the adrenal gland, a neuroblastoma can occur anywhere along the sympathetic nervous system. These sites include the adrenal glands (>50%), the abdominal paraspinal ganglia (24%), the thoracic paraspinal ganglia (20%), the neck (3%), and the brain (rarely).

The CBC count shows a white blood cell (WBC) count of 10,200/μL (10.2 × 10⁹/L), with 58% neutrophils and 44% lymphocytes. The hemoglobin level is 12 g/dL (120 g/L), and the platelet count is 250 × 10⁹/μL (250 × 10⁹/L). Her electrolyte, liver enzyme, and fibrinogen levels and coagulation profile are all normal. Her urinary vanillylmandelic acid (VMA) level is 722 mg/g creatinine (reference range, <25.0 mg/g creatinine) and urinary homovanillic acid (HVA) level is 960 mg/g creatinine (reference range, <35.0 mg/g creatinine). The oncologist explains the laboratory values to the mother and states that the increase
in urinary catecholamine levels combined with the ultrasonography findings raise concern for a neuroblastoma.

A diagnosis of neuroblastoma is suggested by laboratory, radiologic, and histologic findings (Table 1). Katie’s CBC count is normal, without findings of neutropenia, anemia, or thrombocytopenia, which most likely excludes bone marrow involvement. Abnormal liver enzyme levels and coagulation panel values are generally secondary to liver metastasis, which is not the case for Katie. Both VMA and HVA are catecholamine metabolites that are secreted by neuroblastoma cells and are elevated in 90% to 95% of patients with neuroblastomas. Of note, spot or random urinary catecholamine levels are sufficient to make the diagnosis, and a 24-hour urine collection for catecholamine levels is not needed. Although radiologic studies such as ultrasonography or chest radiography are initially used, magnetic resonance imaging (MRI) (preferred) or computed tomography (CT) is required to better evaluate disease burden (Fig 1).

An abdominal MRI demonstrates a 2-cm heterogeneous mass with calcifications arising from the right adrenal medulla. No lymph node or perivascular involvement is noted.

Although Katie’s laboratory and MRI findings are favorable for localized disease, a metastatic evaluation is necessary for the management of a neuroblastoma. Indeed, metastatic disease to the bone marrow, liver, and skin is found in approximately 50% of patients during the initial presentation. These patients often present with constitutional symptoms such as fever, malaise, pallor, and fussiness. In addition, there may be refusal to walk/crawl, localized pain, and abdominal distention. A “blueberry muffin rash” is a cutaneous manifestation of a neuroblastoma in infants, representing tumor spread to subcutaneous tissue. These cutaneous nodules are purpuric lesions that blanch on palpation. When examining purpuric subcutaneous nodules, leukemic infiltrates and extramedullary hematopoietic centers must be included in the differential diagnosis because the location and appearance are similar. Orbital findings, including heterochromia irides and periorbital ecchymosis, or “raccoon eyes,” are secondary to metastatic spread to the retrobulbar region and are rare but suggestive findings for a neuroblastoma.

An I-123 metaiodobenzylguanidine (mIBG) scan is used to look for metastatic disease (Table 1). It uses a radiolabeled molecule that possesses structural similarity to noradrenaline and is taken up by neuroblastoma cells. Although mIBG is 99% specific for metastatic neuroblastomas, 10% of neuroblastomas are not mIBG-avid, which can then be detected using positron emission tomography and CT scan. (14)

An I-123 mIBG scan showed uptake in the tumor but was negative for metastatic disease. The oncologist explains that a right-sided abdominal mass in an infant, such as Katie, with elevated urinary catecholamine levels without systemic findings evident on laboratory evaluation is most likely to be a neuroblastoma. Fortunately, Katie is in the favorable age range (<18 months) where she is highly likely to have spontaneous regression of her neuroblastoma. After detailing Katie’s low-risk features, the oncologist converses with the mother and recommends monitoring as the best option for Katie.

Approximately half of all neuroblastomas found in infants spontaneously regress. (4)(6) In infants younger than 6 months, there are a few factors that ensure 98% event-free survival with observation alone. These factors include location (primary adrenal location, without metastases), size (<5 cm), clinical aggressiveness (<50% increase in tumor size during the screening phase), and laboratory evidence (<2-fold increase in urinary catecholamine levels starting from the time of diagnosis through the entire observation period). (15) Observation consists of sequential abdominal ultrasonography and urinary catecholamine levels at 6 and 12 weeks, followed by serial screening every 3 months for the first year and every 6 months for the second year. Surgical evaluation and histologic assessment are necessary if the tumor grows during the screening

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**TABLE 1. Laboratory, Radiology, and Pathology Evaluation for Neuroblastoma (6)**

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Complete blood cell count with peripheral smear</th>
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<tr>
<td></td>
<td>Complete metabolic panel, uric acid</td>
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<tr>
<td></td>
<td>Coagulation panel</td>
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<tr>
<td></td>
<td>Ferritin and lactate dehydrogenase levels</td>
</tr>
<tr>
<td></td>
<td>(nonspecific)</td>
</tr>
<tr>
<td></td>
<td>Urine vanillylmandelic acid and homovanillic acid</td>
</tr>
<tr>
<td>Radiology</td>
<td>Initial: chest radiograph or ultrasonography</td>
</tr>
<tr>
<td></td>
<td>Urgent/emergency: CT scan</td>
</tr>
<tr>
<td></td>
<td>Preferred: MRI of primary site AND chest, abdomen, and pelvis</td>
</tr>
<tr>
<td></td>
<td>Metastatic: I-123 metaiodobenzylguanidine scan</td>
</tr>
<tr>
<td>Pathology</td>
<td>Bilateral bone marrow aspirate and biopsy with IHC analysis</td>
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<tr>
<td></td>
<td>Tumor biopsy with IHC analysis</td>
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<tr>
<td></td>
<td>DNA ploidy</td>
</tr>
<tr>
<td></td>
<td>Fluorescence in situ hybridization for MYCN</td>
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<td></td>
<td>Segmental chromosomal alteration analysis</td>
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CT, computed tomographic; IHC, immunohistochemical; MRI, magnetic resonance imaging.
period. This mild presentation is contrasted by the opposite side of the clinical spectrum, as seen in the following 2 cases.

**Case 2**

Chase is a 3-year-old boy who presents to the pediatrician’s office with worsening hip pain, leg pain, and back pain for 3 weeks. He has numbness in both legs, and his mother has noted shortness of breath when he is active. Vital signs are normal in the office. Significant physical examination findings include decreased breath sounds over the right lung, a large nontender abdominal mass, and 1+ Achilles reflex bilaterally. Chase’s gait is weak and altered, with dragging of his right leg and frequent falls when taking a few steps. Laboratory results include a WBC count of 9,200/μL (9.2×10^9/L) with a normal differential count, a hemoglobin level of 13.4 g/dL (134 g/L), and a platelet count of 420×10^3/μL (0.42×10^10/L). Electrolyte levels are normal aside from an elevated creatinine level of 1.2 mg/dL (106 μmol/L). Liver enzyme levels and results of coagulation studies are normal. Emergency transport is arranged to take Chase to a pediatric hospital emergency department because of concern for spinal cord compression.

Figure 1. A. Chest radiograph shows a soft tissue mass at the right lung base. B. Computed tomographic scan shows a large right paraspinal mass with partial enhancement, large areas of necrosis, and scattered calcifications. C. Growth of tumor through interpedicular spaces. D. T2-weighted magnetic resonance image demonstrates tumor neuroforaminal invasion in a classic “dumbbell” pattern.
As in this case, a neuroblastoma may present with a clinical sign specific to the location of tumor invasion. Neuroblastoma is one of the most common neoplastic causes of spinal cord compression in children. Common features of spinal cord compression include pain, numbness, and limb weakness. Given that all these signs and symptoms can be subtle in a child, a high index of suspicion is necessary. Sphincter dysfunction, presenting as loss of bowel or bladder function, and loss of deep tendon reflexes are relatively uncommon but ominous signs of spinal cord compression requiring immediate neurosurgical evaluation. An MRI is the most sensitive modality for identifying spinal cord pathology.

A chest radiograph is obtained and demonstrates a large soft tissue mass displacing the right lung (Fig 1A). A contrast abdominal CT scan shows a large lobulated partially enhancing mass with calcifications (Fig 1B). The tumor has displaced nearby structures and collapsed the right lung, with bony destruction of adjacent ribs and the vertebral column (Fig 1C). Spinal MRI depicts the tumor growing through the neuroforamina of the lower thoracic spine and compressing the spinal cord (Fig 1D).

Imaging studies can confirm spinal cord compression. A multidisciplinary approach, involving pediatric oncology and neurosurgery, is required to manage spinal cord compression secondary to a solid tumor. (16) When spinal cord compression is identified, dexamethasone is given with the intent to reduce spinal cord edema while helping the patient live each day to the fullest. Palliative care often starts with the pediatrician, who has the deepest relationship with the patient and family. The pediatrician not only starts the palliation process, which involves quality of life discussions, establishing advance care goals, and providing social, physical, and spiritual support for the patient and family, but also provides an important link to the palliative care specialist.

**Case 3**

Kurt is a 5-year-old boy who presents to the clinic with fever, fussiness, and decreased activity for 2 weeks. Kurt has lost 2.2 lb (1 kg) since his last visit 4 months ago. On physical examination Kurt is febrile (102.7°F [39.3°C]) and tachycardic. He appears pale and listless. He has bilateral cervical lymphadenopathy, abdominal distention with some tenderness, and petechiae on his extremities. Kurt refuses to stand and starts crying. The CBC count shows a WBC count of 3000/µL (3×10^9/L), with an absolute neutrophil count of 800/µL (0.80×10^9/L), a hemoglobin level of 6 g/dL (60 g/L), and a platelet count of 13×10^9/µL (0.013×10^12/L).

The constellation of pancytopenia, fever, and weight loss raises a concern for a malignancy involving the bone marrow. Because a neuroblastoma commonly metastasizes to the bone marrow, it can present similarly to acute leukemia. A word of caution regarding the abdominal examination is warranted. The presence of ascites may make it difficult to palpate the margins of an abdominal mass. The other frequent abdominal tumor in children is a Wilms tumor. Due to concern for rupture of a Wilms tumor, (17) it is recommended that the abdominal examination not entail deep palpation. In this case, it is sufficient to know that there is no concern for a surgical abdomen and that follow-up imaging to rule out an abdominal mass is needed.

A CT scan of the chest, abdomen, and pelvis shows a large right adrenal mass with widespread lymphadenopathy notably in the right iliac chain, as well as with the right inguinal lymph nodes. The spleen is enlarged. The mIBG scan shows extensive axial and appendicular skeletal uptake (Fig 2). The oncologist performs bilateral bone marrow aspirations and biopsies, which show small clusters of round blue cells, separated by a fibrillar matrix (Homer-Wright rosettes). The small round blue cells are atypical mononuclear cells with irregular nuclei, clumped chromatin, and mostly indistinct nucleoli. Molecular studies from the tumor biopsy show MYCN amplification, gain of 17q, and hypoploidy. Histopathologic review of the tumor and lymph node biopsy samples demonstrate a stroma-poor, poorly differentiated neuroblastoma.

Given the wide variance in neuroblastoma behavior, from spontaneous regression (case 1) to metastatic disease (case 3), a rational treatment plan requires risk stratification. Prognostic variables taken into account for stratification are 1) age at diagnosis, 2) stage of disease, 3) molecular alterations, and 4) histopathologic analysis of the tumor. In case 3, Kurt’s age at presentation already places him as a
high-risk case. Genetic alterations, including MYCN amplification, hypoploidy, and the presence of chromosomal alterations, are poor prognostic features. The unfavorable histologic appearance of the tissue biopsy is in concordance with these molecular findings. Given these features, Kurt’s case presents as a classic example of a high-risk neuroblastoma, which will require the most aggressive therapy. A detailed discussion of staging and risk stratification of neuroblastoma is beyond the scope of this review, but a brief stratification scheme is provided in Table 2, and excellent reviews have recently been published elsewhere. (6)(18)(19)

NEUROBLASTOMA TREATMENT

A discussion of treatment for high-risk neuroblastoma encompasses all modalities currently in use for pediatric cancer, which include surgery, chemotherapy, radiotherapy, autologous stem cell transplant, and immunotherapy/biological therapy.

Surgery
Surgery was the only treatment available for solid tumors, such as neuroblastomas, before radiotherapy and chemotherapy were used. Because surgery was felt to be definitive treatment, and some neuroblastomas were not able to be surgically resected at the time of diagnosis, the first chemotherapy regimens were designed with an intent to make these tumors operable. (20) Most patients with low-risk neuroblastoma, such as a child with localized disease, favorable histologic findings, nonamplification of MYCN, and age younger than 12 months, are, indeed, cured with observation or surgery, when appropriate. (21)(22) However, with high-risk neuroblastoma behavior now elucidated, surgery is an ancillary part of the multimodal treatment. For example, after chemotherapy results in shrinking of the tumor, a second-look surgery is often performed for resection of the tumor. Of note, in a patient with MYCN amplification, micrometastases precipitate local recurrence and distant relapse, thereby making surgery alone insufficient for these patients.

Radiotherapy
A neuroblastoma is sensitive to radiotherapy, which has been used in combination with chemotherapy in many earlier neuroblastoma treatment plans. (23) However, radiotherapy carries a risk of late effects, including diabetes mellitus (24) and decreased height potential. (25) More importantly, radiotherapy carries an increased risk of secondary malignancy in
neuroblastoma survivors. (26) This has led to stem cell preparative regimens, which avoid total body irradiation by giving larger doses of chemotherapy. Given the discovery of intermediate-risk neuroblastoma being cured with chemotherapy and/or surgery alone, radiotherapy now is mostly reserved for high-risk neuroblastoma. (27)

Chemotherapy
Chemotherapy remains essential for patients with intermediate- and high-risk neuroblastoma. As with most cancers, to reduce the risk of selecting out cancer populations that become resistant to a single drug, multiagent regimens are used. Common chemotherapeutic agents considered include cyclophosphamide or ifosamide, cisplatin or carboplatin, vincristine, doxorubicin or adriamycin, etoposide, topotecan, and busulfan. The length of treatment has been reduced, and more moderate chemotherapy can be used for intermediate-risk patients. (28) Higher-dose chemotherapy with increased risk of toxicity is prescribed for children with high-risk neuroblastomas. The advent of stem cell transplant has enabled further intensification of chemotherapy for high-risk patients.

Autologous Stem Cell Transplant
Stem cell rescue is accomplished with the patient’s own peripheral blood stem cells, infused after a preparative regimen that suppresses the bone marrow. The myeloablative regimen continues to evolve, with variations involving the chemotherapeutic agents used, the number of sequential transplants performed, and perhaps most important for long-term adverse effects, whether radiation is used. In randomized controlled trials, autologous stem cell transplant decreases the risk of relapse by approximately 10%. (27)(29)

Immunotherapy
Fifty percent of children treated for high-risk neuroblastomas, despite achieving initial remission, will relapse. (30) To this end, a maintenance phase was developed involving isotretinoin, anti-GD2 antibody therapy, and cytokines, including granulocyte-macrophage colony-stimulating factor (sargramostim) and interleukin-2 (IL-2). Most familiar to pediatricians in its use for severe acne, isotretinoin is a vitamin A derivative. Also known as 13-cis-retinoic acid, isotretinoin acts on neuroblastomas by decreasing tumor cell proliferation and causing differentiation into nonmalignant cells. The attractive aspects of this drug are its ease of administration (given orally) and its relative tolerability. In fact, it can be given for an extended period, even for years. (31) In randomized controlled trials, isotretinoin alone reduces relapse risk at least by 10%, presumably by reducing minimal residual disease, an index used to describe the lowest residual disease burden after chemotherapy that is compatible with a cure, in addition to being used to define relapse.

Given its tolerability, isotretinoin can be combined with more intense maintenance therapy, namely, anti-GD2 antibody therapy. GD2 is one of the few disialoganglioside

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**TABLE 2. International Neuroblastoma Risk Group (INRG) Staging Classifications (19)**

<table>
<thead>
<tr>
<th>INRG STAGE</th>
<th>AGE, MO</th>
<th>MYCN</th>
<th>11q ABERRATION</th>
<th>PLOIDY</th>
<th>PRETREATMENT RISK GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td></td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Very low</td>
</tr>
<tr>
<td>L2</td>
<td>&lt;18</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Low</td>
</tr>
<tr>
<td>L2</td>
<td>≥18</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Intermediate</td>
</tr>
<tr>
<td>L2</td>
<td>≥18</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>Intermediate</td>
</tr>
<tr>
<td>M</td>
<td>&lt;18</td>
<td>–</td>
<td>–</td>
<td>Hyperdiploid</td>
<td>Low</td>
</tr>
<tr>
<td>M</td>
<td>&lt;12</td>
<td>–</td>
<td>–</td>
<td>Diploid</td>
<td>Intermediate</td>
</tr>
<tr>
<td>M</td>
<td>12 to &lt;18</td>
<td>–</td>
<td>–</td>
<td>Diploid</td>
<td>High</td>
</tr>
<tr>
<td>M</td>
<td>&lt;18</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Very low</td>
</tr>
<tr>
<td>M</td>
<td>≥18</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>High</td>
</tr>
<tr>
<td>MS</td>
<td>&lt;18</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>High</td>
</tr>
</tbody>
</table>

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antigens expressed by most high-risk neuroblastoma cells. (32) The chimeric monoclonal antibody ch14.18 targets the GD2 protein, killing residual neuroblastoma cells via antibody-dependent immune activity. (33) This immune activity is augmented by giving the patient injections of granulocyte-macrophage colony-stimulating factor and by coupling the GD2 antibody with an infusion of IL-2. Given that GD2 is also expressed by peripheral nerve fibers, aggressive pain control is required during its infusion. In addition, the patient must be monitored during the infusion for capillary leak syndrome, which is a severe adverse effect of IL-2. Despite its severe potential adverse effects, the addition of anti-GD2 antibody and IL-2 to isotretinoin has reduced early relapse by approximately 20%, earning its place as part of the current standard therapy for high-risk neuroblastomas.

CONCLUSIONS

Neuroblastoma is a complex disease with diversity of presentation, clinical course, and treatment. Few other diseases may be treated with either intense multimodality treatment or mere observation. When signs and symptoms are recognized early, the pediatrician can help improve outcomes by making a timely referral to the oncologist. Although low-risk groups are highly likely to be cured, the pursuit to improve outcomes for high-risk patients continues. Despite multimodality therapy, cure rates for children with high-risk neuroblastomas remain approximately 50%. More research is needed to delineate treatment targets and new modalities of therapy.

ACKNOWLEDGMENT

We are indebted to the patients and families treated at Riley Children’s Hospital.

Summary

- On the basis of strong evidence, (2) a neuroblastoma is the most common extracranial solid tumor that requires multifaceted treatment, including observation, surgery, chemotherapy, radiotherapy, autologous stem cell transplant, and immunotherapy.
- Based on strong evidence, (10) neuroblastoma is mostly due to somatic mutations that cause abnormal growth of neural crest cells of the adrenal medulla and sympathetic ganglia.
- On the basis of consensus, pediatricians play a pivotal role in the diagnosis of neuroblastoma. A high index of suspicion is required given the wide spectrum of clinical presentation by neuroblastoma. Neuroblastoma should be considered in children with findings of abnormal breathing, especially when associated with Hirschsprung disease, an abdominal mass, ambulating difficulties, bowel/bladder dysfunction, fever, malaise, bone pain, or abnormal skin findings.
- Based on strong evidence, (6) increased urinary catecholamine levels are highly sensitive for detecting a neuroblastoma, and further evaluation, including laboratory, radiographic, and histologic analyses, are necessary to confirm the diagnosis of a neuroblastoma and to guide medical therapy.
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1. A 15-month-old girl presents to your office with a 3-week history of pain in both legs and refusing to stand, intermittent fever, and bruising. She has a decreased appetite and has lost 3 lb (1.4 kg) in the past 2 to 3 weeks. Vital signs show a temperature of 100.9°F (38.3°C), a pulse of 135 beats/min, a respiratory rate of 20 breaths/min, and blood pressure of 100/52 mm Hg. Physical examination shows an ill-appearing girl with scattered ecchymoses of the extremities and around the eyes. An abdominal mass is palpated in the right flank. Abdominal ultrasonography shows the right kidney to be displaced downward by a suprarenal mass. Which of the following is the most likely diagnosis in this patient?
   A. Hepatoblastoma.
   B. Lymphoma.
   C. Neuroblastoma.
   D. Ovarian germ cell tumor.
   E. Wilms tumor.

2. Further evaluation with I-123 metaiodobenzylguanidine (mIBG) scan shows enhancement of the right suprarenal mass with an enhancing mass in the central portion of the abdomen. Multiple areas of osseous uptake are seen in the arms, legs, vertebral bodies, and skull. Which of the following biomarkers is most likely to be elevated in this patient?
   A. Serum \( \alpha \)-fetoprotein.
   B. Serum \( \beta \)-human chorionic gonadotropin.
   C. Serum carcinoembryonic antigen.
   D. Urine 5-hydroxyindole acetic acid.
   E. Urine vanillylmandelic acid (VMA).

3. The child is taken for biopsy of the abdominal mass and bone marrow aspirate and biopsy. Pathology shows neuroblastoma. Which of the following gene amplifications is most associated with neuroblastoma and is associated with aggressive tumor phenotype and poor prognosis?
   A. \textit{BRAF}.
   B. \textit{BCR-ABL}.
   C. \textit{MDR1}.
   D. \textit{MYCN}.
   E. \textit{P53}.

4. A 1-week-old full-term infant is brought to your office for follow-up evaluation. He was found on prenatal ultrasonography to have an abdominal mass in the left suprarenal region. At the time of birth, a magnetic resonance image (MRI) of the abdomen showed a 2.5-cm mass in the left adrenal gland with no other abnormalities seen. An mIBG scan performed while he was in the nursery showed enhancement of the left adrenal mass but no other abnormal enhancement. A complete blood cell count and a comprehensive metabolic panel were normal. Urine for homovanillic acid (HVA) and VMA obtained in the nursery are reviewed and found to be elevated. Which of the following is the most appropriate next step in the management of this infant?
   A. Immunotherapy with anti-GD2 antibody.
   B. Isotretinoin.
   C. Observation with close follow-up.
   D. Radiotherapy to the mass.
   E. Surgical resection of the mass.

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5. A 6-week-old infant presents with a 1-week history of vomiting and abdominal swelling. The mother has noted blue to purple nodules on his skin during the past few days. Physical examination shows a well-appearing infant with a temperature of 98°F (36.7°C), a pulse of 110 beats/min, and a respiratory rate of 24 breaths/min. There are several purple, blanching nodules on the skin. The lungs are clear to auscultation. The abdomen is protuberant, with the liver palpated 3 cm below the costal margin. He is moving all extremities. A complete blood cell count shows a white blood cell count of 2,500/μL (2.5 × 10^9/L), a hemoglobin level of 9 g/dL (90 g/L), and a platelet count of 110,000/μL, with 30% neutrophils, 65% lymphocytes, and 5% monocytes. An MRI with contrast of the abdomen shows a 3-cm mass in the right adrenal gland and an enlarged liver with numerous enhancing nodules. An mIBG scan shows disease localized to the liver and right adrenal gland but without bony involvement. Urine for VMA and HVA showed elevated levels. A biopsy of the skin lesion confirms the diagnosis of neuroblastoma. MYCN and chromosomes 1p and 11q are normal. Which of the following represents the stage of neuroblastoma in this infant?

A. L1.
B. L2.
C. Metastatic.
D. Metastatic special.
E. Not enough clinical information to assign a stage.
INTRODUCTION

The complete blood cell (CBC) count is a widely available and commonly used inexpensive laboratory test used in clinical practice. Information contained therein includes the white blood cell count and differential count, red blood cell (RBC) count, RBC indices, hemoglobin level, hematocrit concentration, and platelet count. The RBC indices include the mean cell volume (MCV), mean cell hemoglobin, mean cell hemoglobin concentration, and RBC distribution width (RDW). (1) Traditionally, the clinical use of RDW has been limited to helping differentiate certain types of anemias (eg, β-thalassemia minor and iron deficiency anemia, which can both have decreased MCV and decreased mean cell hemoglobin but will differ in their RDW). (2) During the past decade, this quick and inexpensive test has been the subject of several studies attempting to evaluate its use as, among other things, an inflammatory marker, (3)(4)(5)(6)(7)(8) a predictor of all-cause mortality, (9)(10) and a prognostic tool for morbidity and mortality associated with sepsis and cardiovascular disease. (4)(11)(12)(13)(14)(15)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25) This article focuses on discussing the RDW as a diagnostic and prognostic tool in various medical conditions.

DEFINITION

What Is the RDW?

Each RBC is shaped as a biconcave disk with a depressed center, its volume ranging from 80 to 100 femtoliters (fL; 1 fL = 10^-15 L) in adults (represented by the MCV in the CBC count). The RBC membrane is extremely flexible and, in certain conditions, is able to change shape (eg, in hereditary spherocytosis or sickle cell disease) and to decrease or increase in size (eg, microcytosis in the thalassemias, macrocytosis in folate deficiency) without significant cell injury or loss in function. Differences in cell volume among the RBCs, or anisocytosis, is reflected in the CBC count by the RDW. It is calculated by dividing the standard deviation of RBC volumes by the MCV and multiplying the result by 100. (2)

Determinants of the RDW

Erythropoietin, a hormone produced in the kidneys, is primarily responsible for RBC production and maturation in the bone marrow and is a major determinant of the RDW. (2) Abnormal production of erythropoietin (eg, in renal disease) and decreased responsiveness to the hormone (eg, in chronic inflammatory conditions and critical illness) can thus lead to an increase in RDW values. (2)(26)(27)(28)(29) Jelkmann (28)
noted that the proinflammatory cytokines interleukin-1 and tumor necrosis factor-α suppress erythropoietin gene expression. Many of the conditions for which an increase in RDW was correlated with systemic inflammation and critical illness, but the exact pathophysiologic mechanisms underlying the association of increase in RDW with morbidity and mortality remains unclear. (14) Given that erythropoietin is a key determinant of the RDW, it could perhaps be postulated that any condition affecting erythropoietin activity (eg, inflammation, primary renal disease, heart failure, bone marrow failure) could potentially lead to increased RDW values.

Studies in adults by Miyamoto et al (23) and Rodriguez-Carrio et al (30) have found a significant association between RDW increase and elevated levels of proinflammatory cytokines. Miyamoto et al studied 144 patients with adult congenital heart disease and found that elevated RDW of greater than 15% was significantly associated with elevated serum interleukin-6 levels. (23) Rodriguez-Carrio et al found a positive correlation in patients with rheumatoid arthritis between RDW and serum levels of interferon-α, interleukin-8, vascular endothelial growth factor, and neutrophil to lymphocyte ratio. These support the association of RDW increase with not only systemic inflammation but also vascular remodeling. (30)

Another consideration could be poor nutritional status, often present in patients with chronic diseases or critical illness, or nutrient deficiencies (eg, iron, vitamin B₁₂, or folate deficiency) that are associated with anisocytosis. Other physiologic determinants that have been found to be associated with RDW changes include aging, black ethnicity, and physical exercise. (2)

Note that the use of different hematologic analyzers in different laboratories may result in discrepancies in the measurement of RBC size and in the calculation of the standard deviation of RBC volumes, potentially limiting the use of universal reference ranges and thresholds for RDW values. (2) In 1987, Dr Robert Novak reported normal values of RDW in children (Table 1). (31)

**CLINICAL USES OF THE RDW**

Table 2 lists the conditions in children where RDW was found to be elevated.

**Anemia**
The RDW has traditionally been used, along with the MCV, to evaluate anemias based on morphology. (1)(2) Anemias are typically classified as normocytic, microcytic, or macrocytic, depending on their MCV values. Evaluation of the RDW can further narrow down the potential underlying cause of the anemia. Anemias secondary to nutrient deficiencies (eg, iron deficiency, vitamin B₁₂ deficiency, or folate deficiency) are typically associated with marked anisocytosis compared with anemias secondary to genetic defects or primary bone marrow disorders, although significant overlap may occur. (2) Sousa et al, (3) for example, studied 34 pediatric patients with Fanconi anemia, a genetic bone marrow failure syndrome, and found a significant increase in RDW in 68% of patients, noting a correlation with anemia, neutropenia, and thrombocytopenia, concluding that significantly increased RDW is associated with progression of Fanconi anemia disease.

Hemolytic anemias, except in acute hemolysis, is associated with anisocytosis (eg, in microangiopathic hemolytic anemia). (1)(2) Sazawal et al (32) studied 1,026 children with iron deficiency anemia, finding that the sensitivity of a combined hemoglobin level of 10 g/dL or less (≤80 g/L) and RDW greater than 15% in diagnosing the disease was 99%, with specificity of 90%. Thus, simply getting a hemoglobin level and evaluating the RDW is a cost-effective way to diagnose iron deficiency anemia in children without the need for further and more expensive testing of iron status markers. (32)

**Autoimmune Diseases**
Increased RDW has been reported to reflect systemic inflammation. (33) Studies in adults(34)(35)(36) have found a correlation between increased RDW and disease activity in rheumatoid arthritis, proposing that RDW could be used as an inflammatory marker, similar to the more traditionally used erythrocyte sedimentation rate (ESR) and C-reactive

---

**TABLE 1. Age-Appropriate Values for RDW**

<table>
<thead>
<tr>
<th>AGE</th>
<th>NO. OF PATIENTS</th>
<th>RDW (MEAN ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–6 mo</td>
<td>68</td>
<td>13.0 ± 1.5</td>
</tr>
<tr>
<td>7–12 mo</td>
<td>84</td>
<td>13.7 ± 0.9</td>
</tr>
<tr>
<td>13–24 mo</td>
<td>108</td>
<td>13.4 ± 1.0</td>
</tr>
<tr>
<td>2–3 y</td>
<td>119</td>
<td>13.2 ± 0.8</td>
</tr>
<tr>
<td>4–5 y</td>
<td>151</td>
<td>12.7 ± 0.9</td>
</tr>
<tr>
<td>6–8 y</td>
<td>106</td>
<td>12.6 ± 0.8</td>
</tr>
<tr>
<td>9–11 y</td>
<td>98</td>
<td>12.8 ± 1.0</td>
</tr>
</tbody>
</table>

RDW = red blood cell distribution width.
protein (CRP). As mentioned earlier, positive correlations have been reported between increased RDW and levels of certain proinflammatory cytokines. (23)(30)

Ozer et al studied 153 children with familial Mediterranean fever (FMF) to investigate potential markers of subclinical inflammation in these patients. They found that mean ± SD RDW was significantly higher in symptom-free patients with FMF (14.89 ± 2.56) compared with a control group of 90 volunteers (13.68 ± 2.35). (5) A study by Yildirim et al (6) conducted in adults with FMF yielded similar results, with significantly higher RDW levels in symptom-free patients with FMF compared with a control group.

Hu et al (7) noted increased RDW in adult patients with systemic lupus erythematosus, and glucocorticoid treatment decreased RDW values. Zou et al (8) reported significantly increased RDW in patients with active systemic lupus erythematosus disease, irrespective of anemia status, with significantly greater flare-free survival within a year in those with normal RDW. These studies have found various degrees of positive correlation between RDW and ESR, (6)(7) between RDW and CRP, (5)(7) and between RDW and high-sensitivity CRP. (8)

Significantly higher RDW has also been reported in adults with active inflammatory bowel disease compared with those without active disease and controls. (37)(38) Similar observations have been found between increased RDW and disease activity in other autoimmune disorders, including ankylosing spondylitis, (39)(40) primary Sjogren syndrome, (41) polymyositis, (42) and multiple sclerosis. (43)(44)

**Sepsis**

Elevated RDW has been associated with increased morbidity and mortality in patients with severe sepsis and septic shock. Several adult studies have proposed it as a potentially useful prognostic marker in this population. (13)(14) (15)(33) However, there are few pediatric studies that have evaluated RDW in sepsis, and results have been conflicting.

Chen et al (11) retrospectively studied the relationship of RDW with disease severity and prognosis in 97 newborns admitted for sepsis to a hospital in China. Patients were divided into 3 groups depending on sepsis severity (sepsis group, severe sepsis group, and septic shock group). Significant differences in RDW were found among the 3 groups: mean ± SD RDW in the sepsis group was 16.59 ± 1.71, in the severe sepsis group was 18.88 ± 1.78, and in the septic shock group 19.71 ± 1.97. The mortality rate was higher in those with elevated RDW (defined as RDW >18%) compared with those with normal RDW (91.76% versus 49.32%). Further statistical analysis found a significant positive correlation between RDW values and mortality (Table 3). (11)

In contrast, a cross-sectional Indonesian study by Devina et al (12) found no significant differences in mortality rates between those with elevated RDW (defined as RDW >14.5%) and those with normal RDW in a population of 40 pediatric patients with sepsis (age range, 2 months to 17 years; median age, 34 months) (Table 3). They also did not find a significant association between increased RDW and length of stay in the ICU. (12)

Ramby et al (16) retrospectively studied 596 patients (age range, 1.5–12.9 years; median age, 4.4 years) admitted to the PICU and found that RDW was independently associated with overall PICU mortality (odds ratio, 1.25; 95% confidence interval, 1.09–1.43). An association with sepsis-specific mortality was not studied, but RDW was not

<table>
<thead>
<tr>
<th>TABLE 2. Pediatric Conditions Associated with Elevated RDW</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANEMIAS</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Anemia associated with nutritional deficiencies (iron, vitamin B12, folate)</td>
</tr>
<tr>
<td>Hemolytic anemia (except acute hemolysis)</td>
</tr>
<tr>
<td>Fanconi anemia</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Conflicting studies, see Table 3.

RDW = red blood cell distribution width.
found to be associated with a prolonged (>48 hours) PICU stay in patients with sepsis. (16) (Table 3)

Cardiac Conditions

Congenital Heart Disease. There are several studies on the association of RDW with surgical outcomes in children with congenital heart disease. Massin (21) studied 688 children undergoing surgery for congenital heart disease and found that RDW was a strong predictor of adverse outcomes in these children, correlating with ICU stay and postoperative death. The mean ± SD preoperative RDW of those who died during their postoperative hospital stay was 18.34 ± 4.68, which was significantly higher than the RDW of those who survived (16.12 ± 2.84). Postoperative death risk was 5 times higher for patients with an RDW of 16% or more. (21) A study by Polat et al (24) had similar results, concluding that RDW could be used as a significant predictor of morbidity and mortality in postoperative patients with congenital heart disease.

Similarly, Kumar et al (20) found that elevated RDW was associated with delayed postoperative recovery in children with tetralogy of Fallot. Those with an RDW greater than 17.8% had significantly longer ICU stays, hospital stays, and ventilation time and more surgical site infections.

Kojima et al, (19) in a study of 38 patients with a Fontan circulation who underwent routine cardiac catheterization, found a strong positive correlation between RDW and central venous pressure and a strong negative correlation between RDW and mixed venous oxygen saturation. In fact, the brain natriuretic peptide (BNP) level, which is a common marker used to monitor heart failure in the pediatric population, was not found to have a significant relation with central venous pressure or mixed venous oxygen saturation, whereas the RDW was found to be a significant independent predictor of these. This highlights the potential of RDW as a convenient and inexpensive marker to detect heart failure in patients with a Fontan circulation.

Acquired Heart Disease. Multiple studies have supported the association of elevated RDW with cardiovascular diseases in adults, including acute coronary syndrome, stroke, peripheral artery disease, atrial fibrillation, heart failure, and hypertension. (17)(45)(46) The lower incidence of cardiovascular diseases in children perhaps explains the relative lack of pediatric studies, but Kucuk et al (4) evaluated RDW in pediatric patients with acute rheumatic carditis. The mean ± SD age of patients in their study was 11.6 ± 2.5 years; RDW was found to be significantly higher in those with acute rheumatic carditis compared with a control group, and significantly decreased (along with CRP level, ESR, and platelet count) after 8 weeks of anti-inflammatory treatment. There was also a significantly positive correlation between RDW and the severity of mitral regurgitation in the patient group. The authors concluded that elevated RDW after initial treatment could indicate ongoing subclinical inflammation, which could lead to subsequent valvular stenosis. (4)

Heart Failure. Forhecz et al (47) found that RDW was an independent predictor of all-cause mortality in adult patients with heart failure. Correlations were found between RDW and levels of serum iron, ferritin, soluble transferrin receptor, interleukin-6, soluble tumor necrosis

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>POPULATION</th>
<th>FINDINGS</th>
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<tbody>
<tr>
<td>Chen et al (11)</td>
<td>97 newborns admitted for sepsis to a hospital in China</td>
<td>Increased mortality rate in those with elevated RDW &gt;18%</td>
</tr>
<tr>
<td>Devina et al (12)</td>
<td>40 pediatric patients admitted for sepsis (age range, 2 mo to 17 y; median age, 34 mo) in a hospital in Indonesia</td>
<td>No significant difference in mortality rates between those with elevated RDW &gt;14.5% and those with normal RDW No significant association between increased RDW and ICU stay</td>
</tr>
<tr>
<td>Ramby et al (16)</td>
<td>596 pediatric patients (age range, 1.5–12.9 y; median age, 4.4 y) admitted to the ICU in a US hospital; 111 with sepsis</td>
<td>No significant association between increased RDW and prolonged ICU stay in patients with sepsis</td>
</tr>
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</table>

RDW=red blood cell distribution width.
factor receptors I and II, CRP, prealbumin, total cholesterol, albumin, and renal function, indicating the association of RDW with inflammation, undernutrition, ineffective erythropoiesis, and impaired renal function. (47)

Mawlana et al (22) studied 31 pediatric patients with heart failure (mean ± SD age, 16.16 ± 14.97 months; 58.1% with congenital heart disease with left-to-right shunts, 41.9% with dilated cardiomyopathy) and found that RDW greater than 16.4% was significantly correlated with certain echocardiographic markers of left ventricular function, such as fractional shortening and E/A ratio, although the same relationship was not present with left ventricular end-diastolic dimension, left ventricular end-systolic dimension, and E/E ratio. (22)

The results of a 2014 systematic review reinforced the value of RDW as a prognostic indicator in patients with heart failure. (18)

Pulmonary Disease
Ozgul et al (48) studied 175 adult patients with chronic obstructive pulmonary disease (COPD) and found that mean ± SD RDW was significantly higher in these patients compared with a control group (15% ± 2.3% versus 13.8% ± 2.5%). In the patients with COPD, RDW was found to correlate positively with CRP, albumin, right ventricular dysfunction, pulmonary hypertension, and the presence of cardiovascular disease. Elevated RDW was independently associated with right ventricular dysfunction. (48)

Although COPD is not a pediatric disease, research delving into the potential use of RDW as an inexpensive prognostic marker in pediatric pulmonary hypertension could be helpful. N-terminal proBNP is a commonly used marker to monitor right ventricular dysfunction and heart failure in neonates with pulmonary hypertension, but it is a very expensive laboratory test and is not typically available in smaller hospitals. The previously mentioned study by Kojima et al (19) found RDW to be a significant predictor of central venous pressure independent of the BNP, so further studies into its use in pediatric pulmonary hypertension could be of value.

Other Illnesses
A retrospective study by Ramby et al (16) of 596 critically ill pediatric patients found an association between RDW and prolonged PICU stay in those without sepsis, with a 1.17 increased odds for each 1% increase in RDW. Patients with an RDW less than 13.4% had a 53% risk of a PICU stay greater than 48 hours and a 3.3% risk of mortality, whereas those with an RDW greater than 15.7% had a 78% risk of mortality. (16)

In a study by Garofoli et al, (49) preterm newborns with patent ductus arteriosus, late-onset sepsis, and bronchopulmonary dysplasia were all associated with significantly higher RDW levels compared with preterm newborns without these pathologies. Elevated RDW in preterm newborns and infants with intrauterine growth restriction was also found to be significantly associated with early mortality. (49)

A study by Yilmaz et al (50) found significantly higher RDW levels in adults with preeclampsia compared with controls. The RDW was also significantly higher in those with severe preeclampsia compared with those with mild preeclampsia. Given the increased rates of pregnancy-associated hypertension and eclampsia in teenage pregnancies, monitoring the CBC count and RDW in this population may be useful.

Bozlu et al (51) studied the diagnostic utility of RDW in children with acute appendicitis, retrospectively evaluating 344 children who underwent appendectomy. Children with simple or perforated appendicitis had significantly higher white blood cell counts, CRP levels, and RDW levels than those with a normal appendix, but there was no significant difference in RDW values between those with simple versus perforated appendicitis. The diagnostic utility of RDW in pediatric patients with acute appendicitis was thus concluded to be low because it was not found to be superior to white blood cell count, which is also included in a CBC count; nor was it of value in predicting perforated appendicitis.

Other conditions that have been found to have an association with elevated RDW in adult studies include cancer, diabetes mellitus, kidney disease, liver disease, and complicated community-acquired pneumonia. (2)

CONCLUSIONS
The RDW, as part of the CBC count, is routinely assessed when evaluating anemias. However, as evidenced by recent studies, it may also be an inexpensive method to assess the prognosis and clinical status of critically ill patients, those with inflammatory disorders (eg, FMF), and those with cardiac disease (eg, heart failure,
acute rheumatic carditis, postoperative patients with congenital heart disease), particularly in resource-limited settings. Several studies in adults, and a few in children, have supported the role of an elevated RDW in these conditions. Although the prognostic utility of an elevated RDW in adult patients with sepsis has been substantiated by multiple studies, those performed in children have had conflicting results. Other adult studies have found an association between elevated RDW and cancer, diabetes mellitus, kidney disease, liver disease, and complicated community-acquired pneumonia. Pediatric studies in these areas are currently lacking. Further studies on the diagnostic and prognostic uses of the RDW in different pediatric conditions, particularly those involving infection, inflammation, cardiac, and perhaps cardiopulmonary disease, would be of great benefit.

References for this article are at http://pedsinreview.aappublications.org/content/39/4/204.
A 10-day-old boy presents with discharge from the left eye. It started at 3 days of age as a continuous, clear discharge and became copious and mucopurulent at 7 days of age. The mother reports swelling over the left eye, which started 2 days ago, and it worsened gradually so that he is not able to open his left eye today. The mother denies fever, trauma, sick contacts, recent travel, or rash. The patient was born at term via cesarean delivery. Maternal history is significant for a *Trichomonas vaginalis* infection during the second trimester, which was adequately treated. All other prenatal test results were negative. Review of the nursery records revealed that the patient received erythromycin prophylaxis for conjunctivitis.

On admission, he is afebrile and his vitals are stable. Physical examination shows a fussy neonate with eyelid swelling and erythematous conjunctiva with mucopurulent discharge from the left eye. The remaining physical examination findings are normal.

Initial laboratory evaluation shows a normal complete blood cell count and serum electrolyte levels. His human immunodeficiency virus (HIV) antibody test as well as rapid plasma reagin test results are negative. The cerebrospinal fluid (CSF) analysis results are normal. Additional evaluation leads to the diagnosis.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/4/210.
DISCUSSION

The differential diagnosis of injected conjunctiva with eye discharge (conjunctivitis) in the neonatal period includes chemical conjunctivitis, chlamydia conjunctivitis, gonococcal conjunctivitis, and trauma. Gram-stain of the discharge from the left eye of our patient showed gram-negative diplococci, which were confirmed to be Neisseria gonorrhoeae on culture. Chlamydia polymerase chain reaction was negative. Blood, urine, and CSF cultures were sterile.

The patient was initially started on intravenous ampicillin and cefotaxime pending culture results. The antibiotics were discontinued after 48 hours when the blood, urine, and CSF cultures were reported to be negative. However, after the culture result from the left eye was confirmed to be N gonorrhoeae, the patient was treated with a single dose of ceftriaxone and underwent scheduled irrigation of both eyes. The patient was evaluated by a pediatric ophthalmologist to ensure that he has not developed the complications of gonococcal conjunctivitis, and none were identified. The patient responded well, with complete resolution of the swelling and mucopurulent discharge. The mother and her partner were requested to get evaluated and treated for sexually transmitted infections (STIs).

The Condition

Ophthalmia neonatorum (ON), also called neonatal conjunctivitis, is a broad term and includes all forms of acute, mucopurulent infection of the eyes in the first 4 weeks of life. Up to 12% of newborns are affected by ON. In the past (before the 1880s), the term ON was used only for cases of conjunctivitis caused by infection with N gonorrhoeae and was the primary cause of neonatal blindness. (Table)

Epidemiology

Chlamydial infections are the most common bacterial cause of conjunctivitis in neonates, accounting for up to 40% of cases of neonatal conjunctivitis. Streptococcus pneumoniae and nontypeable Haemophilus influenzae have been estimated to account for 30% to 50% of cases of ON, whereas N gonorrhea accounts for less than 1% of cases of ON in the developed world. In the United States, perinatal transmission occurs in 30% to 40% of patients with maternal cervical infection. (2) Intrauterine transmission is also possible after the rupture of membranes.

Gonococcal infection in neonates born by cesarean delivery is rare. The first case of gonococcal conjunctivitis after cesarean delivery was described by Thompson et al in a case series of 7 patients in 1974. (3)

A variety of mechanisms have been proposed to explain the transmission of gonococcal infection in newborns born via cesarean delivery, as discussed. (4) One of the suggested modes of transmission is spread of infection from the infected birth canal to the amniotic fluid during a period between rupture of membranes and birth of the neonate. It is also possible to have postnatal transmission of infection from maternal genitalia to neonatal eyes by person-to-person transmission. (4) In another study, Handsfield et al found neonatal orogastric contamination with N gonorrhoeae, suggesting intrauterine infection. (5)

Prophylaxis

Historically, the introduction of postnatal prophylaxis with 2% silver nitrate decreased the incidence of neonatal gonococcal conjunctivitis from 10% to 0.3%. (1) A need for prophylaxis is under debate because of the decreasing incidence of STIs, effective treatment for conjunctivitis, and risk of developing resistance to antibiotic agents. Currently, the standard of care in the United States is the use of topical erythromycin ointment for prophylaxis. However, although the use of postnatal prophylaxis decreases the incidence of transmission, it does not completely eliminate it. (1)

Microbiology and Pathogenesis

Neisseria gonorrhoeae is an intracellular gram-negative diplococci. The outer membrane of N gonorrhoeae contains lipooligosaccharide, phospholipid, and a variety of proteins, including the porin (PorB) protein. PorB is essential for bacterial viability because it mediates ion exchange between N gonorrhoeae and the environment. PorB has also

**TABLE. Causes of ophthalmia neonatorum**

<table>
<thead>
<tr>
<th>CHEMICAL</th>
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<tr>
<td>Chemical</td>
<td>Bacterial</td>
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<td></td>
<td>Adenovirus</td>
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<tr>
<td>Chemical</td>
<td>Chlamydia trachomatis</td>
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<td>Chemical</td>
<td>Herpes simplex virus</td>
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<tr>
<td>Chemical</td>
<td>Neisseria gonorrhoeae</td>
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<td>Haemophilus species</td>
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<td>Staphylococcus aureus</td>
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<td>Streptococcus viridans</td>
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<td>Escherichia coli</td>
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<tr>
<td>Chemical</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Chemical</td>
<td>Other</td>
</tr>
</tbody>
</table>
been implicated in being crucial for the pathogen to evade both the innate and adaptive immune systems. There are 2 alleles for PorB, known as PIA and PIB, that are associated with different phenotypes. The PIA strains are associated with disseminated disease because these strains are resistant to the bactericidal effects of human serum, and the PIB strains are associated with localized urogenital infections. (6)(7)(8) Initial attachment of gonococci to the surface of columnar epithelial cells is mediated by type IV pili. After attaching to mucosal cells, gonococci are engulfed in a process known as parasite-directed endocytosis, and the gonococci proceed to replicating intracellularly. The bacteria can then extend through lymphatics or can cause bacteremia, leading to disseminated disease.

Clinical Features
Infection usually is manifested 2 to 5 days after birth. It causes purulent conjunctivitis, with profuse exudate and swelling of the eyelids. If untreated, severe complications such as corneal scarring, blindness, and septicemia can occur.

Diagnosis
Gonococcal conjunctivitis is diagnosed by prenatal and perinatal history, physical examination, and microbiologic examination of conjunctival exudate. A Gram-stain of the conjunctival exudate should be examined for the presence of typical gram-negative intracellular kidney bean–shaped diplococci. For identifying N gonorrhoeae from nongenital sites, culture is the most widely used test. The patient should also be evaluated for chlamydia trachomatis, congenital syphilis, and HIV infections because of an increased incidence of coinfections with these pathogens. The mother’s hepatitis B status should also be investigated. In addition, the patient’s mother and her sexual partner should be evaluated for gonococcal and other STIs. (9)

Treatment
Infants suspected of having gonococcal ophthalmic disease should be hospitalized and observed for response to therapy and for disseminated disease (sepsis, arthritis, meningitis). After obtaining cultures (from eye, blood, urine, and CSF), empirical treatment should be started in patients in whom organisms are seen on Gram-stain or in those with negative Gram-stain but who are considered to be at high risk (eg, a mother with no prenatal care, history of STIs, or substance abuse). The current guidelines recommend treatment of neonatal gonococcal conjunctivitis with a single dose of ceftriaxone 25 to 50 mg/kg, with a maximum of 125 mg given intravenously or intramuscularly. (9) Furthermore, patients require frequent irrigation of the eye with saline until resolution of discharge from the affected eye. (9) Topical antimicrobial therapy alone is not adequate to treat gonococcal conjunctivitis. Treatment of ON should be continued beyond the single treatment dose until all bacterial cultures are negative and systemic infection has been excluded, typically after 48 to 72 hours of therapy.

Lessons for the Clinician
- Clinicians should have a high index of suspicion for serious bacterial infections, such as infections with Neisseria gonorrhoeae, as the cause of neonatal conjunctivitis even in neonates born via cesarean delivery.
- Clinicians should start with systemic antibiotic drug treatment when gonococcal conjunctivitis is suspected.
- One should closely monitor neonates for ophthalmologic and systemic complications of gonococcal conjunctivitis.
- All newborns should be provided topical antibiotic drug prophylaxis at birth.

References
PRESENTATION

An 18-year-old boy presents with right-sided jaw pain, migratory body pains, decreased appetite, pain on deep inspiration, severe odynophagia, and dark urine. He had no history of sick contacts or international travel. He was evaluated a week earlier for a sore throat, moderate dysphagia, fever, and decreased energy. On physical examination at that time he was found to have an erythematous posterior pharynx, moderately enlarged tonsils, and cervical lymphadenopathy. His streptococcal antigen and Monospot test results were negative. He was prescribed corticosteroids and naproxen for pain and severe tonsillar enlargement.

Physical examination shows an erythematous posterior pharynx without exudates, severely enlarged tonsils, pleuritic chest pain on deep inspiration, and right mid-thoracic paraspinal tenderness. Vitals on presentation are a

Figure 1. Axial computed tomographic scan of the thorax demonstrates an ovoid nodule (red arrow) in the right middle lobe with a small focus of central cavitation suspicious for a septic embolus.
temperature of 102.4°F (39.1°C) and a heart rate of 90 beats/min. The remaining physical examination results are normal.

He is hospitalized for further evaluation and treatment with ceftriaxone for concern for peritonsillar abscess.

Laboratory evaluation shows a white blood cell count of $2.4 \times 10^3/\mu L$ with 60% neutrophils and 25% bands, a platelet count of $115 \times 10^3/\mu L$ ($115 \times 10^9/L$), a blood urea nitrogen level of 30 mg/dL (10.7 mmol/L), and a creatinine concentration of 1.1 mg/dL (97.2 μmol/L). Urinalysis shows trace ketones, 5 to 9 red blood cells per high-power field, a urobilinogen level of 8 mg/dL, 2+ bilirubin, and 1+ protein. A chest computed tomographic (CT) scan is performed because of pleuritic chest pain and shows interstitial pneumonia with possible septic emboli along with mediastinal and hilar lymphadenopathy (Fig 1). After 3 days, blood cultures are negative.

Given continued symptoms 3 days later, he is transferred to a tertiary care center, where additional imaging studies revealed the final diagnosis.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/4/211.
DISCUSSION

At the tertiary care center he developed acute respiratory distress, inability to turn or lift his head, and reduced leftward neck rotation and extension, with pain near the sternocleidomastoid in the region of the internal jugular vein. Pulmonary examination showed shallow tachypnea with decreased inspiratory effort and scant expiratory wheezes over the left lower lobe.

A CT of the neck with intravenous (IV) contrast showed a thrombosis of the middle segment of the right internal jugular and right parapharyngeal veins with surrounding edema and inflammation (Fig 2). With the jaw tenderness, internal jugular and parapharyngeal vein thrombophlebitis, and fever, the patient was diagnosed as having Lemierre syndrome and was transitioned to IV clindamycin from ceftriaxone. The patient’s blood cultures grew *Fusobacterium necrophorum*. After 2 days he did not show much improvement so his antibiotics were changed to IV meropenem. He was discharged 2 days later in fair condition. The patient went home on IV meropenem 1 g every 8 hours for 6 weeks, enoxaparin 80 mg/0.8 mL subcutaneously every 12 hours, and *Lactobacillus rhamnosus* as a probiotic 2 times a day. The decision was made to send the patient home on enoxaparin to reduce his risk of further thrombosis and to allow for his current clot burden to dissipate.

THE CONDITION

Lemierre syndrome was first described in 1936 by French microbiologist Andre Lemierre, who came across 20 patients who had sepsis, metastatic pulmonary lesions, and *Bacillus funduliformis* (now known as *F necrophorum*). (1) This rare infectious syndrome is most commonly caused by *F necrophorum*, a gram-negative anaerobic bacillus that is part of the normal human oral flora. (1) The pathophysiology of this syndrome is unclear, and it is not known why *F necrophorum* becomes invasive. (2)

Lemierre syndrome was once a more common disease until the advent of antibiotics. Before the wide use of penicillin, Lemierre syndrome carried with it mortality of close to 90%. (1) Once the advent of penicillin occurred, this disease became virtually extinct. Between 1974 and 1995 there were only 100 published cases of Lemierre syndrome. (4) However, in the late 1990s the disease began a resurgence, and its incidence has near doubled and has continued to rise. There are 2 hypotheses as to why Lemierre syndrome is reemerging, the first of which is that clinicians are trying to avoid unnecessary antibiotic drug use in pharyngitis that follows a typical viral pattern or in patients with a negative rapid streptococcal antigen test result. (1)(5) The second hypothesis is simply that the reporting of Lemierre syndrome increased and that the incidence of the disease was at its current level. (1)
In 2010, it was estimated that pharyngitis caused by *F. necrophorum* may be as common as that caused by group A streptococcus. (5) Furthermore, 1 in 400 cases of *F. necrophorum* infection lead to complications, which include abscess, septicemia with pulmonary emboli, and Lemierre syndrome. (5) Case series have shown mortality associated with *F. necrophorum* of 3% to 5% and morbidity of 10%. (5) Although the incidence of the disease has been increasing, it still remains a rare cause of pharyngitis. At this juncture it does not warrant treating all streptococcal antigen test–negative pharyngitis with antibiotic agents. This disease most commonly affects healthy adolescents and young adults, with a higher incidence in the winter and spring. (1) However, as demonstrated by the present case, the disease does not follow a strict seasonal pattern. The most common presenting symptom is pharyngitis, which usually precludes all other symptoms for 4 to 5 days. (1) On physical examination patients usually have a fever and may have a peritonsillar abscess. Symptoms typically progress over the next 5 to 12 days, with the development of neck pain, pleuritic chest pain, dyspnea, night sweats, and possible arthralgia. (1) Patients rapidly develop signs of endovascular sepsis, with tachycardia, fever, and leukocytosis. (2) The differential diagnosis includes infectious and malignant etiologies (Table 1). Lemierre syndrome is a clinical diagnosis based on the findings of gram-negative anaerobic bacteremia, metastatic septic pulmonary emboli, and thrombophlebitis of the internal jugular vein. Various imaging modalities are important to use to identify disease-defining pathology. Commonly, a chest CT scan is helpful in differentiating causes of pleuritic chest pain such as infection and malignancy. Ultrasonography of the neck can help identify any thrombosis in the jugular venous system. Other diagnostic imaging can be helpful in identifying and treating other manifestations of this disease, such as meningitis and septic arthritis.

### MANAGEMENT

Treatment of Lemierre syndrome requires 4 to 6 weeks of antibiotic drug therapy. (1) The antibiotic of choice is penicillin for Lemierre syndrome. (1)(5) It is important to note that *F. necrophorum* is not sensitive to macrolides, which is the typical treatment for a penicillin-allergic patient with pharyngitis. (5) Therefore, if neck swelling occurs or there is progression of the symptoms the patient should be treated with clindamycin, metronidazole, imipenem, amoxicillin-clavulanate, or cefoxitin. (6) Surgical treatment for the removal of thrombosis is controversial, but abscesses may need to be drained. (1) Anticoagulation therapy is also controversial and not widely used. (1)

### Lessons for the Clinician

- Pharyngitis caused by *Fusobacterium necrophorum* is thought to be as common as that caused by group A streptococci and carries with it a different set of complications, which can lead to significant mortality and morbidity. However, at this time, Lemierre syndrome remains rare and does not warrant prophylactic treatment.
- It is important to consider this diagnosis when pharyngitis does not follow the typical course seen with group A streptococcal infection.
- The typical patient with Lemierre syndrome is a young healthy adolescent or young adult with fever, pharyngitis, and a progressive clinical course that includes septicemia, metastatic septic pulmonary emboli, and thrombophlebitis of the internal jugular vein.
- The treatment for penicillin-allergic patients includes clindamycin and not macrolide if infection with *Fusobacterium* is suspected.

### References


### TABLE 1. Differential diagnosis based the presentation and progression of the signs and symptoms of Lemierre’s Disease.

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
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<tbody>
<tr>
<td>Pyelonephritis</td>
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<td>Pharyngitis</td>
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<td>Viral URI</td>
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<td>Torticollis</td>
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<td>Uro-Sepsis</td>
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<td>Mononucleosis</td>
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<td>Pharyngeal/Tonsillar Abscess</td>
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<td>Lymphoma</td>
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<td>Tuberculosis</td>
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PRESENTATION

A 14-year-old girl is admitted to the hospital with a 3-week history of sore throat leading to significantly decreased oral intake. She reports progressive worsening of a painful sore throat resulting in avoidance of nearly all oral intake and an associated 22-lb weight loss. She has presented to care twice, 2 weeks and 2 days earlier. During each of those visits, rapid group A streptococcal (GAS) antigen testing and follow-up GAS culture were negative. She was discharged with symptomatic care for presumed viral pharyngitis. She vomited twice but has not had fevers, cough, rash, or diarrhea. Her medical history is noncontributory. Her immunizations are up to date. She reports one lifetime sexual partner and reports condom use with every encounter.

On examination the patient is tachycardic to 150 beats/min, afebrile, and other vital signs are normal. Her mucous membranes are dry. She has posterior and anterior cervical lymphadenopathy, palatal petechiae, and erythematous enlarged tonsils with mild exudates. Results of cardiac, pulmonary, abdominal, and complete neurologic examinations are normal.

Initial laboratory tests are notable for an elevated white blood cell count of 20,500/μL (20.5 x 10^9/L), a sodium level of 154 mEq/L (154 mmol/L), a blood urea nitrogen level of 32 mg/dL (11.4 mmol/L), and a creatinine level of 1.03 mg/dL (91 μmol/L) (her baseline creatinine level is 0.4 mg/dL [35 μmol/L]). Further laboratory testing reveals the diagnosis.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/4/213.
DISCUSSION

Clinical Course and Management
The patient’s fractional excretion of sodium was 0.2%, and, therefore, her acute kidney injury and hypernatremia were thought to be consistent with dehydration and a prerenal state. Both resolved with appropriate fluid resuscitation. An otorhinolaryngologist performed a bedside nasal endoscopy and laryngoscopy, which revealed thick yellow mucus in the posterior oropharynx. Repeated GAS rapid testing as well as serum Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus serologies were within normal limits. A multipathogen throat culture and specific cultures for gonorrhea and chlamydia were sent to the laboratory. Thayer-Martin culture grew gram-negative diplococci consistent with Neisseria gonorrhoeae. On repeated sexual history the patient disclosed having unprotected receptive oral sex with a 15-year-old male partner 4 weeks earlier. She received appropriate treatment with ceftriaxone and azithromycin and experienced a full recovery.

The Condition
Neisseria gonorrhoeae is a gram-negative diplococci more commonly known to cause cervicitis in females and urethritis in males as well as disseminated disease in both sexes characterized by fever, arthritis, tenosynovitis, and dermatitis. Neisseria gonorrhoeae is a rare (1%–2%) cause of pharyngitis that should be considered in a patient with pharyngitis after receptive oral sex. Changes in sexual practices and age of sexual debut are likely to make this diagnosis increasing relevant to frontline pediatric providers.

Most patients with pharyngeal N gonorrhoeae are asymptomatic. In fact, in the sentinel study of pharyngeal gonococcal infection conducted in a very high-risk population, pharyngeal N gonorrhoeae was not significantly more prevalent in those with sore throat compared with asymptomatic peers. (3) These data raise the question of whether N gonorrhoeae is pathologic or simply an incidental finding in patients with pharyngitis of a different etiology. Our patient’s presentation and improvement with appropriate treatment suggest that it is in fact pathologic; however, additional research is needed to clarify the relationship between N gonorrhoeae and sore throat. Based primarily on case reports, when symptomatic, the clinical presentation of N gonorrhoeae pharyngitis varies widely, ranging from acute suppurative tonsillitis, to subacute mild pharyngitis, often with adenopathy, and usually without fever. (3)(4)(5)

Diagnosis
Given the variability in clinical presentation, suspicion based on symptoms alone is difficult, and epidemiologic clues should be used. The practice of receptive oral sex is the method of infection. Historically, rates are highest in men who have sex with men, followed by females, and lowest in men who do not have sex with men. (3)(6)(7) In addition, patients with urogenital gonorrhea are at increased risk for concurrent pharyngeal infection. (7) The percentage of youth reporting to have had sexual intercourse is decreasing. (8) However, younger birth cohorts are more likely to report oral sex during adolescence, indicating that the rate of oral sex during adolescence is rising. (9)

Risk stratification is limited by the ability to accurately ascertain sexual practices. Studies have found that patients underreport oral sexual exposures to health-care providers. (10) In addition, a minority of adolescent patients (20%) consider oral-genital contact to be sex and, therefore, many may not disclose such practices when asked generally about sexual history. (11) This was the case for this patient and likely contributed to her delay in diagnosis. Therefore, relevant sexual exposures should be explicitly discussed.

Standard throat culture will not identify N gonorrhoeae. When gonococcal pharyngitis is suspected, clinicians should contact their laboratory such that specific testing can be pursued. Traditionally, culture on Thayer-Martin medium has been used to diagnose gonococcal pharyngitis. However, nucleic acid amplification testing is more sensitive than culture on Thayer-Martin medium (95% versus 47%), with similar specificity (98% versus 100%). (12)

Treatment
Pharyngeal gonococcus is more likely to fail therapy than urogenital disease. Decreased antibiotic penetration into the pharynx and horizontal gene transfer of resistance genes from commensal oral Neisseria species have been proposed as possible explanations. (13) The Centers for Disease Control and Prevention (CDC) recommends single doses of intramuscular ceftriaxone (250 mg) and oral azithromycin (1 g) for treatment of gonococcal pharyngitis. (14) Azithromycin serves to prevent the emergence of cephalosporin-resistant N gonorrhoeae and to treat possible Chlamydia trachomatis coinfection. (14)

Lessons for the Clinician
• Neisseria gonorrhoeae is a rare but not insignificant cause of pharyngitis.
Clinicians should consider the diagnosis in high-risk populations or cases of pharyngitis in which other common causes have been excluded. Diagnosis can be made by nucleic acid amplification testing of a pharyngeal swab. Recommended treatment is 1 dose of intramuscular ceftriaxone (250 mg) and 1 dose of oral azithromycin (1 g).

References
A former 32-week-gestation, now 8-week-old girl presents to her primary care clinic with a diffuse rash. The rash started at 4 weeks of age as a single lesion on her right thigh. The rash subsequently spread throughout her lower extremities. The mother brought the patient to the clinic at 6 weeks of age for the rash, which had crusted over. The patient was diagnosed as having bullous impetigo and was prescribed oral cephalexin and topical mupirocin. A wound culture from that visit grew normal skin flora. Her rash continued to worsen. The patient presents today for her 2-month well-child check with persistent rash.

On physical examination, the patient’s vital signs are within normal limits. Her rash is most prominent on the trunk and lower extremities. The rash appears as scattered, well-defined erythematous papules and pustules with overlying scale and several erythematous nodules. It involves the palms and soles and spares the diaper region (Fig 1). Other than the rash, she is doing well, with no fevers, fussiness, lethargy, or abnormal movements. She is growing appropriately and meeting her developmental milestones. Her mother denies anyone else at home with a rash. Of note, her mother’s prenatal infectious laboratory test results were negative, including syphilis.

Preliminary laboratory evaluation reveals a negative treponemal immunoglobulin G/M, a negative human immunodeficiency virus antigen/antibody

Figure 1. A. Erythematous papules, pustules, and nodules with overlying scale. Rash is most prominent on the lower extremities, with the diaper region spared. B. Crusted lesion on the plantar surface of the right foot.
screen, and a normal complete blood cell count. A telephone call with her mother the following day helps make the diagnosis.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/4/214.
DISCUSSION

While discussing the reassuring laboratory results, the patient’s mother disclosed that although no one else at home currently had a rash, the family had an outbreak of scabies 3 months earlier for which the patient’s 6 siblings and parents were all appropriately treated. Our patient was prescribed permethrin 5%. At a follow-up examination 1 week later, her rash was dramatically improved (Fig 2).

The Condition
Scabies is a parasitic skin infection caused by the *Sarcoptes scabiei* mite, common in overcrowded living situations. Mites can live both on and off the human host, including in clothing, bedding, furniture, and carpeting. It classically presents with a pruritic, papular rash involving interdigital webs on the hands, the flexor surface of the wrists, the extensor surface of the elbows, the abdomen, the axilla, and the genitalia. The rash is secondary to inflammatory and hypersensitivity reactions to the mite. The presence of burrows, serpiginous lines that are formed from the breakdown of mite digestive products, can be pathognomonic for this diagnosis. (1)

Neonatal scabies often has a markedly different presentation than scabies in older children or adults. It typically presents with diffuse vesicles, papules, and pustules; lacks burrows; and does not involve the interdigital web spaces. In addition, scabies in neonates rarely presents with obvious pruritus due to the patient’s age. It has a similar presentation to other disease processes, which can lead to a delay in diagnosis or misdiagnosis altogether. (a) The differential diagnosis includes impetigo, folliculitis, congenital infections including syphilis and herpes simplex virus, papular urticaria, infantile acropustulosis, eczema, and Langerhans cell histiocytosis. (1)(2)(3)(4)

Congenital syphilis was a concern in this case owing to the location and appearance of the rash. Newborns with congenital syphilis are usually asymptomatic at birth and begin showing signs by 5 weeks of age. The first sign is typically rhinitis (“snuffles”), followed by a diffuse, desquamating maculopapular rash involving the palms and soles. Syphilitic pemphigus is a common finding that is manifested by a vesiculobullous rash that crusts over after 1 to 3 weeks and can mimic neonatal scabies. (5)(6)(7) A key differentiating factor is rash distribution, with congenital syphilis often including the diaper region and neonatal scabies often sparing it.

Diagnosis
Neonatal scabies can be diagnosed using a variety of methods. Most commonly, it is a clinical diagnosis that requires a high index of suspicion. Close contacts diagnosed as having scabies or with severe pruritus often aid in making the diagnosis. The gold standard for diagnosis is direct visualization of the scabies mite or eggs, which can be done via potassium hydroxide scraping of a burrow (if present) or skin biopsy. (1)(8)

![Figure 2. Appearance of the rash at follow-up 1 week after treatment with permethrin 5%](image-url)
Complications
A diagnosis of scabies can cause significant psychological and emotional distress for families, which should be addressed by providers. (1) The most common serious complication from scabies is a secondary bacterial infection, often caused by group A Streptococcus (GAS) or Staphylococcus aureus. Secondary infections caused by GAS have led to outbreaks of glomerulonephritis and rheumatic heart disease. (1)(4)(8) Postscabies pruritus, which can last for weeks to months, is another common complication. It is the result of a hypersensitivity reaction that can lead to excoriations causing dyspigmentation. Postscabies nodules are similarly caused by a hypersensitivity reaction and can persist for weeks. Families should be counseled and reassured about these common complications because they are often misinterpreted as reinfestation. (1)(2)(8)

Management
The standard treatment for scabies in adults and children aged 2 months and older is permethrin 5% cream applied once at bedtime for 8 hours, with an additional application as needed 1 week later. (1)(2)(8) A recent Cochrane review confirmed permethrin 5% as the most effective topical treatment for scabies. (8) Serious adverse effects to permethrin 5% are extremely rare. (1)

For children younger than 2 months, the recommended treatment is 10% topical sulfur in petroleum. (2)(4) However, this product must be compounded and can be difficult for some families to access. Due to the minimal risks associated with its use, some providers choose to use permethrin 5% in children younger than 2 months. (2)

There are additional topical and oral treatment options for scabies that are generally less preferred due to inferior efficacy and significantly worse adverse effect profiles compared with permethrin 5%. (8) To prevent recurrence, all family members should be treated with at least 1 application of permethrin 5%. In addition, all bedding, clothing, and towels should be washed in hot water, and furniture and carpeting should be vacuumed. (1)(2)(8)

Lessons for the Clinician
- Neonatal scabies is characterized by diffuse vesicles, papules, and pustules and, unlike scabies in older children and adults, often lacks burrows or involvement of the interdigital web spaces.
- Neonatal scabies often spares the diaper region, which can differentiate it from the rash associated with congenital syphilis.
- Mites can live both on and off the human host, including in clothing, bedding, furniture, and carpeting, necessitating inquiry about remote infestations when scabies is on the differential diagnosis.
- In children aged 2 months and older, permethrin 5% is the most effective topical treatment for scabies.

References
A 1-year-old previously healthy white girl presents to the emergency department with worsening genital and perianal rash. The rash started on her perineum 5 days before presentation and spread quickly to her pudental cleft. Her mother applied an over-the-counter diaper rash ointment with no relief. The toddler is playful but becomes fussy during diaper changes. She had a runny nose and 2 episodes of watery diarrhea in the past week. She has had no vomiting; a decrease in urine output; no oral, ocular, or nasal mucosal involvement; and no vaginal discharge. The older sibling had a red painful blister under her nose 2 weeks ago. The infant has a normal birth history, and her medical history is significant for atopic dermatitis. She has worn the same brand of diapers since her birth. Both her mother and sister help change her diapers at home.

Physical examination reveals a nontoxic-appearing infant with a temperature of 101°F (38.3°C). Other vital signs are within normal parameters. She has diffusely dry skin. Examination of the diaper area reveals multiple punched out...

Figure 1. Ulcerated genital rash.
ulcerated lesions measuring 1.5 cm wide with erythematous bases and tiny blisters with serous fluid in the genital and perianal regions (Fig 1). The rash is foul smelling and tender to palpation. There is no lymphadenopathy.

Laboratory evaluation reveals the complete blood cell count and serum electrolyte levels to be within the reference range. Cultures of the blood and lesions are sent to the laboratory. The Gram-stain is negative. The culture and direct fluorescent antibody (DFA) results confirm our diagnosis.

The Case Discussion and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/4/216.
DISCUSSION

The patient’s DFA test result was reported to be positive for herpes simplex virus (HSV) 1 in 24 hours, and her HSV culture results came back positive in 3 days. The tests confirmed our suspicion of a primary herpetic infection based on the history of a sibling with a recent cold sore that had frequent physical contact with the child. The patient also had atopic dermatitis diffusely and scratched herself, which may have led to breaks in the skin and provided opportunity for inoculation. The child abuse medical team was consulted on this patient. After a thorough investigation of the family and of the evidence, they concluded that there had not been any evidence of abuse given the probable route of transmission from the sibling and the infant having no current or past injuries. She was treated with a 10-day course of oral acyclovir.

Differential Diagnosis

Diaper dermatitis is a common skin condition in infants and is usually caused by irritation from excessive moisture, yeast infection, or an allergic reaction to substances such as diaper dyes. Other possible diagnoses for rashes in the diaper region include seborrhea, atopic dermatitis, impetigo, scabies, psoriasis, and infections with cytomegalovirus, herpes virus, pinworm, and varicella virus. Seborrhea causes greasy patches of scaly skin in the inguinal region and is often found in other areas as well. Atopic dermatitis rarely occurs in the diaper region because the diaper tends to trap moisture in. Impetigo can develop when there is a break in the skin and can appear as tiny raised yellow fluid-filled vesicles and honey-colored crusted lesions. An autoimmune process such as psoriasis can present as reddened patches primarily in the diaper region without the distinctive silver scale and can cause concern for nonaccidental trauma. Other systemic autoimmune processes to consider when evaluating perianal ulceration are conditions such as Kawasaki disease and Crohn disease. Scabies can present in the diaper region with a widespread red, raised, itchy rash where the mites have burrowed in the skin, and it often affects multiple family members at the same time. Jaquet dermatitis is a severe form of contact diaper dermatitis that presents as pruritic nodules and ulcers in the genitalia of children with chronic diarrhea and incontinence and can be difficult to treat.

The Condition

After the neonatal period, infants usually acquire HSV (1 or 2) from direct skin-to-skin contact with someone with an active lesion, either a caregiver or from abuse. Most primary HSV infections during the period of childhood are asymptomatic, and shedding can occur in saliva without clinical disease. In childhood, gingivostomatitis is the most common presentation of HSV and can be accompanied by the characteristic painful ulcerative or clustered oral and perioral vesicles on an erythematous base, fever, irritability, poor appetite, and adenopathy. Primary herpes is usually more severe than recurrent herpes. Blisters or ulcers can occur on any part of the body, and autoinoculation can happen anywhere. Children often contract herpetic whitlow by autoinoculation from finger sucking when they have orofacial herpetic infection. Children with eczema are more prone to acquiring herpes due to breaks in the skin. Eczema herpeticum is a rare but severe infection that occurs when HSV vesicles become concentrated at the sites of skin damage usually in patients with atopic dermatitis. Rarely, HSV can lead to Stevens-Johnson syndrome. The incubation period of HSV is usually 2 days to 2 weeks, and the sores of a primary infection last 1 to 3 weeks.

Diagnosis and Treatment

Gram-stain and culture can identify secondary bacterial infections. Potassium hydroxide testing of scrapings from the rash can identify a fungal infection. To diagnose HSV, viral testing is standard. The vesicle must be unroofed, and the lesion’s base must be swabbed. The sensitivity of viral culture is low and declines rapidly as lesions crust and heal. Polymerase chain reaction assays for HSV DNA are more sensitive than cultures. The DFA staining of vesicular scraping is a rapid diagnostic test to accompany viral culture but is less sensitive than viral culture.

Treatment is primarily supportive. Despite painful oral lesions, children should be encouraged to drink fluids to prevent dehydration. In immunocompetent patients, there are limited data available on the efficacy of antiviral agents on the course of primary mucocutaneous HSV infection. However, our patient was treated with an antiviral agent in an attempt to decrease the duration of her symptoms. Exposed lesions can be covered with a dressing to prevent infection risk to others. Oral HSV infection is common in children, and they should not be prevented from attending school. Contact with newborns or those with eczema or immunosuppression should be avoided until the sores are healed. The prognosis is good, with lesions healing in 2 to 4 weeks.

Lessons for the Clinician

• Infants and toddlers usually acquire herpes simplex virus (HSV) from direct contact with someone with an active lesion.
• Treatment with antiviral agents is typically not warranted in immunocompetent hosts who acquire primary mucocutaneous HSV.
• Children who are not sufficiently mature to engage in consensual sexual activity who present with genital HSV
warrant a multidisciplinary child protection investigation to assess for sexual assault.

**Suggested Readings**


A 17-year-old previously healthy girl with no chronic medical conditions presents to the clinic with a rash on her face. Three days before presentation, she awoke with the painful red rash. The day before onset she had pruritus of her chin without any other signs or symptoms and no other changes to the skin per her report. She has no history of eczema or allergies. She uses foundation for makeup and has not changed brands in more than a year. She notes no changes in soap or skin care products. There is no new exposure to detergents, plants, latex, nickel, or jewelry. No family members have similar skin lesions. She has not applied any other creams/lotions to the rash. Over the next 2 days the rash became more erythematous and painful but less pruritic. On presentation to the clinic the rash is erythematous and patchlike, with central ulcerations, well-demarcated borders, and overlying healing bullae along the chin and lower face (Fig). Vitals are all within normal limits. No other rashes are present on physical examination, and there are no other abnormal findings on examination.

On further questioning, a probable diagnosis emerges.

Figure. Clinical images of the chin and face with the described rash on presentation to our clinic, obtained via secure methods.
DISCUSSION

The patient admits that she performed an Internet search for home remedies to treat pruritus. She followed a recommendation to apply garlic, ground into a paste, to her face. No other chemicals or components were added to the mixture. She applied the paste in the evening and left it on overnight and awoke with the previously described rash.

This case highlights 2 important lessons: first is the importance of understanding the rare but possible chemical burn–like reaction that can be induced by garlic components and second is the importance of developing open lines of communication and a strong rapport with our adolescent patients to reduce the risk of harmful treatment strategies arising from seemingly benign “natural” home remedies.

The Condition
Garlic is a member of the Alliaceae plant family and has long been used in alternative medicine strategies as well as for culinary purposes. (1)(2) Some studies have shown benefit in adjunctive topical garlic application, when the garlic is extracted and prepared into a solution, for dermatologic conditions such as tinea infection or alopecia areata. (3)(4) Adverse effects of garlic ingestion may include nausea, vomiting, diarrhea, bronchospasm, anaphylaxis, hypoglycemia, and dermatitis, the latter of which can be seen with topical application. (5)(6)(7) The oxidative by-products in garlic have been known in some instances to cause a type IV hypersensitivity contact dermatitis and to involve the epidermis alone. (1)(8) Reports of acute chemical burn reactions are even more rare in the literature, (9)(10)(11)(12)(13)(14) and the cases that are reported often have a history of occlusive dressing application over the garlic paste. (15) In vitro studies have shown that allicin, the oxidative derivative of dialyl disulfide in garlic, is able to induce acantholysis to cause the chemical burn reaction. (16) The present case shows that the less common chemical burn occurrence is possible even without occlusive dressings. Risk of scarring when involvement occurs into the dermis is considered in these cases, and the location and cosmetic/psychological implications are taken into consideration as well.

Management
The concern for dermal involvement and the thin epidermis of the face made for challenging treatment in this patient. She was referred to the burn clinic given the concern for dermal involvement, and there she was prescribed topical antibiotic cream for 6 weeks, consistent with recommended guidelines. She was seen by psychology and occupational therapy while in the burn clinic and has been continuing with routine occupational therapy visits to prevent contractures. She was referred to dermatology for follow-up care and has been gradually improving. Current problems include postinflammatory hyperpigmentation and scarring from the dermal involvement of her burn, and she is working with dermatology for an optimal long-term cosmetic outcome. Often, if contact dermatitis is a concern, patch testing may be performed to assess for a hypersensitivity reaction. Patch testing was not performed in this patient because the pattern and sequence of her burns in addition to the lack of previous exposure to topical garlic paste was believed, on review of the literature, to be more consistent with acute chemical burn rather than contact dermatitis.

Implications
In addition to informing about a rare adverse effect of topical garlic application, this case also raises awareness of the importance of establishing clear, available, and open lines of communication between physicians and patients. An Internet search performed with the terms itch of face treatment returned 493,000 results, and 2 of the top 25 hits suggested garlic paste as one of the treatment options. With the ease of access to information via the Internet and the prevalent use of technology in younger generations, it is critical that practices attempt to grow in parallel with their patients. Clinicians may not be the first or only source of health-care information that our patients use. In addition, the growing number of Internet health resources makes it all the more important that our patients are aware of appropriate and inappropriate resources and the differences between the two. The problem is complicated further in that some remedies, as previously stated, are, in fact, based on supportive data, and trying to delineate when to use a given remedy can become quite challenging for the general public. This is a great opportunity for the pediatrician to provide sound recommendations. The ideal setting is likely one in which patients and parents seek to ask their physician questions regarding symptoms and management rather than an Internet search and before application of compounds that can potentially cause chemical burns. Several resources are available for providers and patients/parents to help facilitate these lines of communication, such as the Natural Medicines Comprehensive Database, the Medicine and the Media initiative from the American Academy of Pediatrics, and others. (17) This case shows a setting where adolescent-specific strategies as well as developing a strong rapport are especially critical.

Lessons for the Clinician
• Garlic can cause a variety of adverse effects, including nausea, vomiting, diarrhea, bronchospasm, anaphylaxis,
and hypoglycemia. In addition, contact dermatitis and chemical burns have been seen in cases of topical garlic application.

- Contact dermatitis is seen more often than chemical burn with garlic application, but it is possible and should be kept in mind with cases of topical garlic application.
- Management of acute chemical burn from garlic application may include topical antibiotic cream and referral to a specialty clinic. Involvement into the dermis, scarring, and associated sequelae should be considered.
- Adequate lines of communication and appropriate use of technology and Internet resources with our patients should be kept in mind as the trend of technology use continues to evolve. Discussing these points and having open communication should questions arise will be important for pediatricians going forward.

References
Toxic ingestions represent a small but potentially life-threatening category of pediatric concerns. The peak age group for a toxic ingestion is 1 to 2 years, although the distribution in the pediatric population is bimodal, with a second peak in adolescence. Because toddlers tend to explore with their mouths, they are especially susceptible to unintentional ingestions of inappropriately stored household substances or medications. In contrast, adolescents may willfully ingest substances in an attempt to achieve a high or cause self-harm. Intentional ingestions are disproportionately more likely to have serious outcomes, including death. Therefore, all pediatricians should be familiar with the initial steps in assessment and treatment of potentially toxic ingestions.

Parents or health-care providers encountering a child with a known or suspected ingestion should always contact the Poison Control Center (PCC). This 24-hour hotline (1-800-222-1222) is staffed by toxicologists who provide expert medical advice to parents regarding whether the ingestion necessitates immediate medical assessment. The PCC will also assist physicians in the initial evaluation and management of an ingestion and provide recommendations about appropriate disposition. Note that the PCC hotline routes the call to the nearest center based on the telephone’s area code, so calls made from mobile phones with long-distance area codes will be routed to the corresponding region’s PCC.

The physician’s first steps in management must include a rapid assessment of the ABCDs (airway, breathing, circulation, and disability/decontamination) and vital signs. Heart rate and blood pressure are not only essential in assessing the patient’s overall clinical status and stability but may also provide clues to an unidentified ingestant. Depressed respiratory effort requires respiratory support and possibly intubation. Blood pressure should be monitored closely and fluid administered promptly in the case of hypotension. For the patient with profoundly depressed mental status, a point-of-care glucose determination and an empirical dose of naloxone are recommended. Finally, in cases of topical exposures, consider the need for decontamination by removing the child’s clothes and washing or irrigating all affected areas.

Once the ABCDs are assessed, the physician should proceed with a focused history and physical examination. The history should include an attempt to identify the substance(s) that the child might have consumed (including the dosage strength of the pills/liquid medications when applicable), amount and timing of the ingestion, and subsequent symptoms or complaints. Always consider the possibility of a coingestion because the clinical picture may be nebulous when several substances are taken simultaneously. Caregivers who contact the physician before arrival in the clinic or ED should be instructed to bring whatever substance(s) the child might have ingested as well as the chemical’s bottle or container. If the family arrives without the possible...
intoxicants, request that they contact someone “on the scene” to text a photograph of the product or bottle. When a container is available for inspection, the amount ingested can be estimated by noting how much is missing. Next, the physician should examine the patient purposefully, focusing on vital signs, neurologic and mental status, mucous membranes, pupils, and skin. Certain clinical examination findings may suggest specific toxidromes and aid in diagnosis when the ingested substance is unknown (Table 1).

Immediate steps in management include placing the patient on a cardiac monitor, establishing intravenous access, and collecting blood samples for laboratory tests, including a point-of-care blood glucose level. In most cases, obtaining acetaminophen, salicylate, and ethanol levels; a urine toxicology screen; and a complete metabolic panel is appropriate. These laboratory values can detect ingestions for which there is a known antidote (eg, N-acetylcysteine for acetaminophen) and identify treatable abnormalities (eg, hypoglycemia in β-blocker ingestions). Obtain a serum osmolarity and/or blood gas level if there is concern for ingestion of toxic alcohols (eg, methanol, ethanol) or substances causing acidosis (eg, salicylates). An electrocardiogram should be obtained to establish a baseline and screen for rhythm disturbances or conduction delays (such as QT prolongation), which may require immediate intervention.

Subsequent steps in management most often involve supportive care and close observation. Reexamine the patient frequently to assess for new or evolving symptoms. Correct blood glucose and serum electrolyte levels as indicated, and maintain hydration with intravenous fluids. Special attention should be given to urine output as a measure of hydration but also as a clue to an anticholinergic ingestion with urinary retention or to altered mental status with incontinence. If the patient is highly anxious or agitated, a weight-based dose of a benzodiazepine may be considered. It is imperative to recognize the subset of ingestions for which antidotes can be lifesaving (Table 2). Administer antidotes as early as possible and in consultation with a toxicologist.

In addition, the physician should carefully consider administration of activated charcoal, which minimizes absorption of drugs in the gastrointestinal tract by adsorbing the substance to the fine pores of the charcoal. Activated charcoal is prepared as an aqueous solution by mixing charcoal powder with sufficient tap water (eg, 30 g of charcoal in 240 mL of water). A single pediatric dose is 0.5 to 1 g/kg, up to 25 to 100 g. Activated charcoal is most effective when administered within the first hour after the ingestion and is ineffective for some substances (Table 3). Repeated doses may be indicated in large-quantity, highly toxic, or delayed-release ingestions. Of note, activated charcoal is contraindicated in patients with depressed mental status or risk of aspiration. If aspirated, charcoal may cause respiratory distress and chemical pneumonitis. For this reason, charcoal should only be administered orally in cooperative patients with normal mental status. Administration by nasogastric or

**TABLE 1. Toxidromes**

<table>
<thead>
<tr>
<th>TOXIDROME</th>
<th>HR/BP</th>
<th>RR</th>
<th>TEMPERATURE</th>
<th>NEUROLOGIC/MENTAL STATUS</th>
<th>PUPILS</th>
<th>SKIN</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic (antihistamines, atropine)</td>
<td>↑</td>
<td></td>
<td>↑</td>
<td>Agitated, delirium</td>
<td>Large</td>
<td>Dry, flushed</td>
<td>Urinary retention</td>
</tr>
<tr>
<td>Cholinergic (organophosphates)</td>
<td>↓</td>
<td>↑</td>
<td></td>
<td>Lethargy, seizures, coma, weakness</td>
<td>Small</td>
<td>Diaphoretic</td>
<td>Diarrhea, emesis, salivation</td>
</tr>
<tr>
<td>Opiates (morphine, heroin)</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Euphoria, somnolence, coma</td>
<td>Pinpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedative/hypnotic (benzodiazepine, EtOH)</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Confused, somnolent, coma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sympathomimetic (cocaine, amphetamine)</td>
<td>↑</td>
<td></td>
<td>↑</td>
<td>Agitation, paranoia, hyperactivity</td>
<td>Large, reactive</td>
<td>Diaphoretic</td>
<td></td>
</tr>
</tbody>
</table>

*BP=blood pressure; EtOH=ethyl alcohol, HR=heart rate, RR=respiratory rate.*
orogastric tube may be considered in select patients, so long as their airway is secured and protected.

Toxic ingestions represent an important clinical problem in the pediatric population. Whether an ingestion is suspected or confirmed, the physician should consult the PCC immediately and recontact the toxicologist as questions arise or the patient’s status changes. Although pediatricians play a significant role in the management of toxic ingestions, the importance of parental education and guidance on prevention cannot be overstated. Primary care physicians should discuss safe storage of medications and household chemicals using the principles of “Up, High, and Out of Sight” and should instruct parents to have quick and easy access to the PCC hotline number. Caregivers can also be encouraged to download the mobile app webPoisonControl, an online tool that helps determine whether an ingestion is dangerous and requires medical attention. When an ingestion is suspected despite preventive measures, the astute physician should have a high index of suspicion, perform a focused history and physical examination, and contact the PCC promptly to successfully manage a possible ingestion.

COMMENT: Yes, the importance of prevention cannot be overstated—it is truly the first step in the management of poisonings, and public health initiatives have been a fundamental support to our individual efforts. From the 1970 Poison Prevention Packaging Act to the 1971 Lead-Based Paint Poisoning Prevention Act to the 2016 Child Nicotine Poisoning Prevention Act, regulatory measures have played a major role in improving the safety of our children. However, in an environment where regulation has become a dirty word, with the federal guidelines protecting the integrity of our water and our air actively being dismantled, more and more the burden of promoting prevention will fall to us in our offices. With facts put into question and science put on the defensive, virtually every pediatrician has already been confronted with the rise of vaccine refusal, having to devote precious time to what should not be an issue. Unfortunately, we can likely expect more of the same, but we can take comfort at least in knowing that time devoted to prevention is well spent.

– Henry M. Adam, MD
Associate Editor, In Brief
Brucellosis

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Brucellosis is one of the most frequently encountered zoonotic diseases, with approximately 500,000 cases identified annually worldwide. Brucella are small, gram-negative, nonmotile, non–spore-forming, aerobic coccobacilli that can reproduce intracellularly only. Historically, human disease was thought to be caused by several different species, including Brucella melitensis, Brucella abortus, Brucella suis, and Brucella canis. However, these are now thought to be closely related organisms in a single species. The bacteria can survive for many days to weeks in dairy products but are killed by boiling, pasteurization, and souring or lactic acid fermentation of milk.

Brucellosis was first described in 1859 by British Royal Army Medical Corps (BRAMC) physician J.A. Marston among troops in Malta during the Crimean war. In 1886, David Bruce, another BRAMC physician, isolated the bacteria, later named for him, from the spleen of an affected patient in Malta. Approximately 10 years later, a Danish veterinarian, Bernhard Bang, isolated Brucella species (B abortus) from cattle with contagious abortions.

Disease is most commonly acquired from contaminated, unpasteurized sheep, cow, goat, and camel milk, and less frequently from direct contact with infected animals among farmers, veterinarians, and abattoir workers. Brucellosis is found worldwide but especially in developing countries, with the highest incidence in the Mediterranean basin, Arabian Peninsula, Indian subcontinent, Mexico, and South and Central America. The illness has also reemerged in Eastern Europe since the collapse of the Soviet Union. Historically, human brucellosis was found in the United States, but rates have declined with the eradication of bovine brucellosis by cattle immunization programs and test-and-slaughter techniques. Currently, in the United States there are fewer than 0.5 cases per 100,000 people, with the highest concentration of cases found along the US-Mexico border.

Brucella can be transmitted via inhalation, and this route has been the cause of laboratory-associated outbreaks, making it essential to inform the clinical microbiology laboratory whenever brucellosis is suspected. For safety reasons, serologic diagnosis is preferred at the local laboratory level, and if bacterial culture is to be performed, appropriate biosafety level 3 precautions need to be followed. Human-to-human transmission is rare, but congenital, sexual, and human milk transmissions have all been reported. Although once considered uncommon in younger age groups, disease is now more frequently recognized in children; they are at particular risk given their diet rich in milk (especially when unpasteurized) and in settings where animals share human living spaces.

Organisms enter the host via ingestion or inhalation or through mucous membranes or nonintact skin. The organisms are then taken up by polymorphonuclear cells or macrophages, where they can survive and replicate, evading the immune system. They are then transported to local lymph nodes, where bacterial replication continues, before spreading to reticuloendothelial organs, including the liver, spleen, and bone marrow.
Incubation of disease is typically 2 to 4 weeks but can be several months. Infection can remain subclinical or can result in an acute febrile illness, an insidious illness, or a chronic illness. The clinical picture is often marked by nonspecific symptoms, including fever, arthralgia, and fatigue. Fever often waxes and wanes, which is why the disease is also known as undulant fever. Young children can present with low energy, refusal to bear weight, or failure to thrive. In endemic areas, brucellosis can be the cause of fever of unknown origin.

Focal or localized infection complicates more than half of all cases, and almost any organ system can be involved:
- Osteoarticular infection occurs in 50% of cases of brucellosis. Children typically have large peripheral joint involvement, which can present similarly to other types of septic arthritis, and adults can present with sacroiliitis or spondylodiskitis. Osteomyelitis can also occur.
- Neurologic involvement occurs in 10% of patients. Direct central nervous system invasion is rare; more common are headache, inattention, and depression.
- Gastrointestinal involvement is frequent in children, with two-thirds of pediatric cases accompanied by nausea, vomiting, anorexia, weight loss, and abdominal pain.
- The liver is likely always involved in brucellosis, although liver transaminase levels can be normal or only mildly elevated. Granulomas and liver abscesses can also occur.
- Cardiovascular disease is rare but can present with a range of disease, including endocarditis, myocarditis, pericarditis, endarteritis, thrombophlebitis, or mycotic aneurysms. Endocarditis causes much of the morbidity associated with brucellosis.
- Orchitis or epididymitis complicates 2% to 20% of cases of brucellosis.
- Respiratory complications are relatively rare, found in only approximately 1% of cases, but can present as a range of disease from bronchitis and pneumonia to pulmonary granulomas, nodules, and abscesses. Nodular disease can be confused with pulmonary tuberculosis. Laboratory workers exposed to Brucella via the airborne route can develop pneumonia.
- Bone marrow suppression is commonly encountered. The spleen is also often involved, given its role in the reticuloendothelial system, and hypersplenism can exacerbate hematologic abnormalities.
- A range of cutaneous or mucosal lesions has been reported and may represent hypersensitivity response, immune complex deposition, or direct bacterial invasion.
- Ocular involvement is also encountered, most commonly as anterior uveitis or chorioretinitis.
- Of women affected with brucellosis during pregnancy, one-half to one-third develop complications, which include intrauterine infection, fetal death, spontaneous abortion, premature delivery, and low birthweight. Neonates born to mothers with brucellosis may have congenital infection and malformations. Maternal treatment can help improve outcomes.

As with other intracellular pathogens, cell-mediated immunity is important for controlling established infection. Antibodies play a limited role in fighting infection but are helpful for diagnosis. Immunoglobulin (Ig) M levels increase in the first week of infection, followed by increased IgG levels in the second week. High or rising antibody titers can help establish the diagnosis. After treatment, IgG and IgM levels decline, but IgG decreases more quickly and IgM can persist at low titers for months to years. Persistently elevated IgG and IgA levels beyond 6 months indicate chronic infection or relapse. However, serology should be interpreted with caution because negative test results cannot exclude a recent infection, and antibodies (particularly IgM) can persist after recovery. The IgG avidity test can be useful because high avidity suggests immune memory (indicating old infection) and low avidity suggests more recent infection. B canis is not detected on standard serologic testing because of differences in the antigens it presents.

The diagnosis of brucellosis can also be made by isolating the bacteria from blood, bone marrow, or tissue cultures provided that biosafety level 3 precautions are followed to protect laboratory personnel from infection. In vitro, Brucella have slow growth, so cultures should be monitored for up to 28 days. Newer continuously monitored blood culture systems can detect growth within 7 to 10 days. Polymerase chain reaction–based testing can provide a more rapid diagnosis and can detect bacteria within 10 days of inoculation.

Treatment of brucellosis demands a multidrug regimen because there is a high rate of relapse with monotherapy. In vitro, many drugs show activity against Brucella but clinically are less effective. The cornerstone of treatment for uncomplicated disease in adults and children older than 8 years is doxycycline, with the addition of an aminoglycoside (streptomycin or gentamicin) or rifampin. In younger children
and pregnant women, for whom tetracyclines are contraindi-
cated, trimethoprim-sulfamethoxazole can be used as an
alternative, with the addition of rifampin. Treatment of uncom-
licated disease is usually for 6 weeks. Neurobrucellosis and
endocarditis typically require longer treatment courses of 4 to
6 months with doxycycline or trimethoprim-sulfamethoxazole
plus rifampin. Unfortunately, relapses are common (5%–15%
cases) and frequently result from poor compliance with a
prolonged course of therapy, inappropriate antibiotic drugs,
or inadequately treated focal infection. Primary drug resis-
tance to tetracyclines and aminoglycosides has not occurred,
so these medications can be used to treat relapsed disease.

COMMENT: I must admit I’d never heard, as far as I can
remember, of David Bruce before reading this In Brief by
Drs Harrison and Posada. His story, it turns out, is inter-
esting on several counts. Born in Australia to Scottish
parents, Bruce and his family returned to their homeland
when he was a young child, and he eventually earned his
medical degree at the University of Edinburgh. Early in his
career he joined the BRAMC and was posted to Malta,
where he led the investigatory commission that eventually
identified the cause of a serious outbreak of fever among
British soldiers stationed on the island: So-called Malta fever
turned out to be an infection caused by a bacterium initially
named Micrococcus melitensis, later renamed in honor of
Bruce. Shortly afterward, Bruce was sent to South Africa,
where he studied an outbreak of cattle disease that he de-
termined to result from a trypanosome transmitted by the
tsetse fly. African trypanosomiasis, of course, causes not
only the animal disease known as nagana but also sleeping
sickness in humans, and the protozoan agent is named
Trypanosoma brucei.

To his credit, on another front, Bruce insisted that his wife,
Mary, who assisted him in all his work as a microbiologist,
share credit for his accomplishments, and her name appears
as coauthor on many of his published papers. His name is 1 of
23 that decorate the façade of the London School of Hygiene &
Tropical Medicine as a leading founder in public health.

– Henry M. Adam, MD
Associate Editor, In Brief

Correction
An error appeared in the print version of the January 2018 In Brief “Contiguous Gene Syndromes” (Pereira E, Marion R. Pediatrics in Review. 2018;39(1):46-49, DOI: 10.1542/pir.2016-0073). In the Table, the description of 22q11.2 deletion syndrome should include “hypocalcemia” instead of “hypercalcemia.” The online version of the article has been corrected, and a correction notice has been posted with the online version of the article. The journal regrets the error.

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7-year-old Girl with a Facial Rash

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PRESENTATION

A previously healthy, fully immunized 7-year-old girl presents to the dermatology clinic for evaluation of a rash on her left eyelid, forehead, and scalp. Her symptoms started 1 week earlier, first with pain of the left eyelid and subsequently, 2 days later, with scattered red papules around her left eye. She was evaluated by her pediatrician and treated with prednisolone for presumed allergic contact dermatitis to poison ivy. The rash evolved into vesicles distributed on the left eyelid and then spread to her forehead and scalp, prompting an emergency department visit. She was diagnosed as having cellulitis and was treated with oral clindamycin. Despite this therapy, she developed progressive edema of her left eyelid associated with eyelid pain. Her pediatrician urgently referred her to an ophthalmologist, who notes significant left periorbital edema but otherwise normal ophthalmic examination findings, including normal visual acuity and normal corneal examination without evidence of keratitis or ulceration. She is referred to a dermatologist on the same day, 9 days after her initial symptoms developed.

The patient has no fevers, nasal congestion, sore throat, cough, vomiting, diarrhea, headaches, or changes in mental status. The rash is associated with pruritus. She has not taken any new medications other than the antibiotics and corticosteroids prescribed for this eruption, and she has had no exposures to plants, new foods, or toxins. She has no known sick contacts. She has no significant medical history, and her immunizations are up to date.

On physical examination, she is well appearing but uncomfortable. She is unable to open her eye fully due to significant periorbital edema and associated discomfort. There is no conjunctival injection or discharge. There are numerous grouped vesicles, pustules, and crustated papules overlying an erythematous patch along the ophthalmic division of the trigeminal nerve, affecting the left upper eyelid, left forehead, and left scalp (Fig 1). There are no skin lesions at the tip or side of her nose to indicate nasociliary nerve involvement (negative Hutchinson sign). The rest of the examination results are normal.

DIAGNOSIS

A clinical diagnosis of herpes zoster (HZ) was made based on the acute onset of erythema and herpetiform vesiculopustules restricted to the ophthalmic (V1)
dermatome of the trigeminal nerve. The lack of involvement on the patient’s nose suggested that there was no nasociliary nerve involvement, making ocular inflammation or corneal injury an unlikely complication. (i) To confirm the diagnosis, varicella zoster virus (VZV) polymerase chain reaction (PCR) was performed on fluid obtained from an intact vesicle. The sample was submitted to the Centers for Disease Control and Prevention (CDC) for specific evaluation for wild-type VZV versus vaccine-type VZV. The sample was positive for wild-type VZV, confirming the diagnosis of HZ. Herpes simplex virus (HSV) PCR and bacterial cultures were negative. Neither direct fluorescent antibody assay nor viral culture was performed because PCR is a more sensitive test and can distinguish wild-type versus vaccine-strain VZV. (i)

Discussion

Varicella zoster virus causes 2 distinct clinical presentations, including varicella (chicken pox) and HZ (shingles). The latter is an acute vesicular eruption characterized by the presence of erythema and grouped vesicles in a dermatomal distribution of 1 or more sensory nerves. Herpes zoster is caused by reactivation of a latent VZV infection in the sensory ganglia. (i)

In vaccinated children, HZ can occur due to reactivation of vaccine-related live attenuated varicella (Oka strain) or reactivation of wild-type virus. In our case, the patient’s vesicular swabs were positive for wild-type VZV, implying that she either had a subclinical wild-type primary varicella infection before vaccination or had vaccine failure and acquired wild-type VZV after vaccination. Herpes zoster caused by wild-type VZV cannot be clinically distinguished from vaccine-strain VZV. A recent epidemiologic study found that patients with vaccine-strain HZ were more likely to have lumbar and cervical dermatomal involvement, whereas vaccinated and unvaccinated patients with wild-type HZ mostly had thoracic involvement. (ii) Notably, the occurrence of HZ in a healthy child does not imply immunodeficiency. (iii)

The accurate diagnosis of HZ can typically be made based on the distinctive clinical presentation, and laboratory tests are usually not necessary. (iv) The differential diagnosis for grouped vesicles or pustules also includes herpes simplex virus infection, contact dermatitis, and impetigo. If testing is pursued, the diagnostic test of choice is a VZV PCR. (i) The PCR swabs may be sent to the CDC for delineation of wild-type or vaccine-related virus. This serves an important epidemiologic purpose by helping to determine whether the clinical course and outcomes of HZ from wild-type and Oka strain virus are similar and whether HZ is occurring more frequently in children in the era of varicella vaccination.

In children with HZ, the decision to treat with antiviral therapy depends on several factors, including patient characteristics that may increase the risk of severe infection, extent of infection, and timeline of infection. (i) In immunocompetent children, the presentation and clinical course is typically mild, with viral replication typically complete 72 hours after the rash develops. (i) Treatment with antiviral therapy within 24 hours after onset of rash in healthy, immunocompetent hosts results in only mild symptom reduction, and, thus, routine antiviral therapy is not necessarily recommended in otherwise healthy patients. (i) Antiviral treatment with oral antiviral medications should be considered in unvaccinated children older than 12 years, children with chronic cutaneous or pulmonary disease, and children treated with intermittent corticosteroids or salicylate therapy. (i) Intravenous acyclovir is recommended in patients at risk for severe VZV infection and disseminated zoster, including those with congenital T-lymphocyte defects or acquired immunodeficiency syndrome, chronic severe systemic disease, and patients receiving long-term corticosteroids or other long-term immunosuppressive therapy. (i) Prompt diagnosis is especially important in these high-risk patients because antiviral treatment within 24 hours of rash onset is optimal. (ii) Delay in diagnosis in immunocompromised patients can result in rare, but serious complications, including meningoencephalitis, pneumonitis, hepatitis, or other disseminated visceral involvement. (iii) Postherpetic neuralgia is less common in children but can be a significant complication in those with ophthalmic HZ. (iv) A delay in diagnosis of HZ involving the ophthalmic branch (V1) of the trigeminal nerve can result in keratitis and even permanent corneal scarring. (v) When HZ ophthalmicus is suspected, prompt referral to ophthalmology is critical. Antiviral
medications such as acyclovir, valacyclovir, or famciclovir are the preferred therapy and are most effective when started within 72 hours of symptom onset. Early initiation may reduce the risk of postherpetic neuralgia and result in a decreased incidence of keratitis and uveitis. (7) Although these severe complications are more likely to develop in immunocompromised children, they can rarely occur in the absence of immunodeficiency and in vaccinated children. (8)(9) Pediatricians should be familiar with the presentation of HZ and suspect this entity in a child presenting with an acute erythematous and vesicular eruption in a dermatomal distribution regardless of the patient’s age, vaccination status, or lack of immunodeficiency.

Patient Course
Because the ophthalmic dermatome was involved, the patient was treated with acyclovir at the recommended dose of 80 mg/kg per day divided 4 times daily for a 7-day course. She returned to the clinic 1 week later and showed dramatic improvement, with crusting of all skin lesions and complete resolution of the periorbital edema, eyelid pain, and blurry vision (Fig 2). She experienced no neurologic, ophthalmic, or visceral sequelae from HZ.

Summary
• The diagnosis of herpes zoster (HZ) can be made clinically based on the characteristic presence of grouped vesicles on an erythematous base arranged in a dermatomal distribution of 1 or more sensory nerves.

• Laboratory testing is not needed for diagnosis, but if confirmation is pursued, the test of choice is varicella zoster virus polymerase chain reaction.

• Although HZ and its complications are more common in adults and immunocompromised patients, HZ can occur in immunocompetent and vaccinated children. In this population, HZ in usually self-limited and usually resolves without serious sequelae.

Suggested Readings

References