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Answer Key for October Issue:
Rotavirus: 1. C; 2. A; 3. C; 4. C; 5. C
Developmental-Behavioral Screening Measures: 1. B; 2. C; 3. B; 4. D; 5. E
Metabolic Syndrome: 1. B; 2. D; 3. E; 4. B; 5. A

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Acute Gastroenteritis

Deise Granado-Villar, MD, MPH,* Beatriz Cunill-De Sautu, MD,† Andrea Granados, MD§

Author Disclosure
Drs Granado-Villar, Cunill-De Sautu, and Granados have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Educational Gap

In managing acute diarrhea in children, clinicians need to be aware that management based on "bowel rest" is outdated, and instead reinstitution of an appropriate diet has been associated with decreased stool volume and duration of diarrhea. In general, drug therapy is not indicated in managing diarrhea in children, although zinc supplementation and probiotic use show promise.

Objectives

After reading this article, readers should be able to:

1. **Recognize the electrolyte changes associated with isotonic dehydration.**
2. **Effectively manage a child who has isotonic dehydration.**
3. **Understand the importance of early feedings on the nutritional status of a child who has gastroenteritis.**
4. **Fully understand that antidiarrheal agents are not indicated nor recommended in the treatment of acute gastroenteritis in children.**
5. **Recognize the role of vomiting in the clinical presentation of acute gastroenteritis.**

Introduction

Acute gastroenteritis is an extremely common illness among infants and children worldwide. According to the Centers for Disease Control and Prevention (CDC), acute diarrhea among children in the United States accounts for more than 1.5 million outpatient visits, 200,000 hospitalizations, and approximately 300 deaths per year. In developing countries, diarrhea is a common cause of mortality among children younger than age 5 years, with an estimated 2 million deaths each year. American children younger than 5 years have an average of two episodes of gastroenteritis per year, leading to 2 million to 3 million office visits and 10% of all pediatric hospital admissions. Furthermore, approximately one third of all hospitalizations for diarrhea in children younger than 5 years are due to rotavirus, with an associated direct cost of $250 million annually. (1)(2)

Definitions

Diarrhea is defined as the passage of three or more loose or watery stools per day (or more frequent passage of stool than is normal for the individual). Stool patterns may vary among children; thus, it is important to note that diarrhea should represent a change from the norm. Frequent passage of formed stools is not diarrhea, nor is the passing of "pasty" stools by breastfed young infants. (2)(3)

There are three clinical classifications of diarrheal conditions:

- Acute diarrhea, lasting several hours or days
- Acute bloody diarrhea or dysentery
- Persistent diarrhea, lasting 14 days or longer

Abbreviations

CDC: Centers for Disease Control and Prevention
IV: intravenous
K+: potassium
Na+: sodium
NG: nasogastric
ORS: oral rehydration solution
WHO: World Health Organization

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Clinical Presentation

The clinical manifestations of acute gastroenteritis can include diarrhea, vomiting, fever, anorexia, and abdominal cramps. Vomiting followed by diarrhea may be the initial presentation in children, or vice versa. However, when emesis is the only presenting sign, the clinician must contemplate other diagnostic possibilities, such as diabetes, metabolic disorders, urinary tract infections, meningitis, gastrointestinal obstruction, and ingestion. The characteristics of the emesis, such as color, intensity, and frequency, as well as relationship to feedings, often lead to the most likely diagnoses. (1)(2)(4)

A complete history and physical examination always must be performed. The clinician should inquire about the duration of illness; the number of episodes of vomiting and diarrhea per day; urine output; the presence of blood in the stool; accompanying symptoms such as fever, abdominal pain, and urinary complaints; and recent fluid and food intake. Recent medications and the child's immunization history also should be reviewed. The physical examination should focus on identifying signs of dehydration such as level of alertness, presence of sunken eyes, dry mucous membranes, and skin turgor. (1)(3)

Viruses are the cause of the majority of cases of acute gastroenteritis in children worldwide. Viral infections usually are characterized by low-grade fever and watery diarrhea without blood. Bacterial infections may result in infiltration of the mucosal lining of the small and large intestines, which in turn causes inflammation. Children thus are more likely to present with high fever and the presence of blood and white blood cells in the stool. Table 1 lists the common causal pathogens of acute gastroenteritis in children. (2)

Table 1. Causes of Acute Gastroenteritis in Children (2)

Viruses
Rotaviruses
Noroviruses (Norwalk-like viruses)
Enteric adenoviruses
Caliciviruses
Astroviruses
Enteroviruses
Bacteria
Campylobacter jejuni
Nontyphoid *Salmonella* spp
Enteropathogenic *Escherichia coli*
Shigella spp
Yersinia enterocolitica
Shiga toxin producing *E coli*
Salmonella typhi and *S paratyphi*
Vibrio cholerae
Protozoa
Cryptosporidium
Giardia lamblia
Entamoeba histolytica
Helminths
Strongyloides stercoralis

Assessment of Dehydration

Dehydration related to acute gastroenteritis is a major concern in pediatric patients. Therefore, clinicians in primary care offices, emergency departments, and hospital settings must assess the circulatory volume status as part of the initial evaluation of children presenting with acute gastroenteritis. This assessment is essential in guiding the decision making regarding therapy and patient disposition.

In 1996, the CDC published recommendations on the assessment of dehydration, which were subsequently endorsed by the American Academy of Pediatrics (AAP). These guidelines classified patients into three groups based on their estimated fluid deficit: mild dehydration (3%–5% fluid deficit), moderate dehydration (6%–9% fluid deficit), and severe dehydration (>10% fluid deficit or shock). These classifications are similar to those delineated by the World Health Organization (WHO) in 1995, which also divided patients into three groups: no signs of dehydration (<3%–5%), some signs of dehydration (5%–10%), and severe dehydration (>10%).

The authors of studies have evaluated the correlation of clinical signs of dehydration with posttreatment weight gain and have demonstrated that the first signs of dehydration might not be evident until 3% to 4% dehydration. Furthermore, more obvious clinical signs of dehydration become apparent at 5% dehydration, and indications of severe dehydration become evident when the fluid loss reaches 9% to 10%. As a result, the CDC revised its recommendations in 2003 and combined the mild and moderate dehydration categories, acknowledging that the signs of dehydration might be apparent over a relatively wide range of fluid loss (Table 2). The ultimate goal of this assessment is to identify which patients can be sent home safely, which should remain under observation, and which are candidates for immediate, aggressive therapy. (1)

Laboratory Evaluation

Serum electrolytes are not indicated routinely in patients who have acute gastroenteritis. Authors of several studies have evaluated the utility of laboratory tests in assessing the degree of dehydration, and the evidence reveals that

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Table 2. **Symptoms Associated With Dehydration (1)**

Symptom	Minimal or No Dehydration (<3% Loss of Body Weight)	Mild to Moderate Dehydration (3%–9% Loss of Body Weight)	Severe Dehydration (>9% Loss of Body Weight)
Mental status	Well; alert	Normal, fatigued or restless, irritable	Apathetic, lethargic, unconscious
Thirst	Drinks normally; might refuse liquids	Thirsty; eager to drink	Drinks poorly; unable to drink
Heart rate	Normal	Normal to increased	Tachycardia, with bradycardia in most severe cases
Quality of pulses	Normal	Normal to decreased	Weak, thready, impalpable
Breathing	Normal	Normal; fast	Deep
Eyes	Normal	Slightly sunken	Deeply sunken
Tears	Present	Decreased	Absent
Mouth and tongue	Moist	Dry	Parched
Skin fold	Instant recoil	Recoil in <2 seconds	Recoil in >2 seconds
Capillary refill	Normal	Prolonged	Prolonged; minimal
Extremities	Warm	Cool	Cold; mottled; cyanotic
Urine output	Normal to decreased	Decreased	Minimal

such studies are imprecise and may distract clinicians from focusing on signs and symptoms that have proven diagnostic utility. Commonly obtained laboratory tests, such as blood urea nitrogen and bicarbonate concentrations, generally are helpful only when the results are markedly abnormal. Thus, these laboratory tests should not be considered definitive predictors of dehydration. (1)(5)(6)(7) Additionally, current evidence demonstrates that urinary indices, including specific gravity and the presence of ketones, also are not useful diagnostic tests for identifying the presence of dehydration. (8)(9) Therefore, measurement of electrolytes should be reserved for patients afflicted with severe dehydration who require intravenous (IV) fluid therapy upon initial clinical assessment and for those in whom hypernatremic dehydration is suspected (ie, ingestion of hypertonic solutions). (1)

Stool studies should be considered during outbreaks, especially in child care settings, schools, and hospitals, where there is a public health concern that mandates the identification of a pathogen and the identification of the source of disease. Other special circumstances that warrant the collection of stool samples for identification of enteric pathogens include the evaluation of children who have dysentery, a history of recent foreign travel, and managing young or immunocompromised children who present with high fever. (2)

The Evolution of Oral Rehydration Solutions

The introduction of oral rehydration solutions (ORSs) has decreased significantly the morbidity and mortality associated with acute gastroenteritis worldwide. (1) ORS is the cornerstone of therapy in managing uncomplicated cases of diarrhea.

ORSs began to evolve in the 1940s, as an initiative of Daniel Darrow at Yale and Harold Harrison at Baltimore City Hospital. Darrow performed studies in children who had acute diarrhea and identified the need for appropriate replacement of sodium (Na+), potassium (K+), and alkali to correct the metabolic acidosis. Subsequently, Harrison added glucose to a balanced electrolyte solution and established that such a solution could be used successfully for rehydration. In 1953, Chatterjee first demonstrated that ORSs could rehydrate patients who have cholera and avoid the need for IV fluids.

Studies evaluating the mechanism of intestinal solute transport have revealed that the absorption of water in the gastrointestinal tract is a passive process that depends on the osmotic gradient created by the transcellular transport of electrolytes and nutrients. Although there are alternate mechanisms that contribute to the absorption of Na+ in the enterocyte, it is the coupled transport of Na+ and glucose at the intestinal brush border that is responsible for the success of ORSs.

Sodium-solute-coupled cotransport is an energy-dependent process. The Na+ gradient within the cell is maintained by the Na+–K+ adenosine triphosphatase pump on the basolateral membrane of the enterocyte. Subsequent research has revealed that other solutes, such as amino acids, also were absorbed by active transport mechanisms involving Na+ ion coupling.

Clinical studies of ORSs in patients who have cholera in the Philippines and India have confirmed that oral

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replacement of water and electrolytes produced a sufficient osmotic gradient to rehydrate patients successfully, even in severe diarrheal disease. Solutions of lower osmolarity that maintain the 1:1 glucose to Na+ ratio function optimally as oral solutions for diarrhea management. Subsequent clinical studies have confirmed the dramatic effect that ORSs had on decreasing mortality in acute diarrheal disease; consequently, the WHO and the AAP have endorsed the implementation ORSs worldwide. (4)

Management

Most cases of acute gastroenteritis in children are self-limiting and do not require the use of medications. An initial critical step in the management of acute gastroenteritis usually begins at home with early fluid replacement. Families should be instructed to begin feeding a commercially available ORS product as soon as the diarrhea develops. Although producing a homemade solution with appropriate concentrations of glucose and Na+ is possible, serious errors can result in attempting to use a homemade solution. Thus, standard commercial oral rehydration preparations should be recommended where they are readily available. (4)

ORS is recommended by the WHO and the AAP as "the preferred treatment of fluid and electrolyte losses caused by diarrhea in children with mild to moderate dehydration." The basis of this endorsement is meta-analysis comparing ORSs with traditional IV rehydration. The evidence supports low overall treatment failures with ORSs (3.6%), defined as the need to revert to IV therapy, without an increased incidence of iatrogenic hyponatremia or hypernatremia. (10) Other advantages of ORS include its lower cost, the elimination of the need for intravascular line placement, and the involvement of the parents in providing oral fluid replacement in the home environment when tolerated.

Common household beverages such as fruit juices, sports drinks, tea, and soft drinks should be avoided in the management of acute gastroenteritis. Many of these beverages have a high osmolality due to their high sugar content and contain little Na+ and K+; consequently, use of these fluids may worsen the patient's condition by increasing the stool output and increasing the risk of hyponatremia. Table 3 provides a comparison of the carbohydrate load and electrolyte composition of

Table 3. Composition of Commercial Oral Rehydration Solutions (ORS) and Commonly Consumed Beverages

Solution	Carbohydrate (gm/L)	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Base* (mmol/L)	Osmolarity (mOsm/L)
ORS						
World Health Organization (WHO) (2002)	13.5	75	20	65	30	245
WHO (1975)	20	90	20	80	30	311
European Society of Paediatric Gastroenterology, Hepatology and Nutrition	16	60	20	60	30	240
Enfalyte®†	30	50	25	45	34	200
Pedialyte®§	25	45	20	35	30	250
Rehydralyte®¶	25	75	20	65	30	305
CeraLyte®**	40	50–90	20	NA††	30	220
Commonly used beverages (not appropriate for diarrhea treatment)						
Apple juice§§	120	0.4	44	45	N/A	730
Coca-Cola®¶¶ Classic	112	1.6	N/A	N/A	13.4	650

*Actual or potential bicarbonate (e.g., lactate, citrate, or acetate).
†Mead-Johnson Laboratories, Princeton, New Jersey. Additional information is available at http://www.meadjohnson.com/products/cons-infant/enfalyte.html.
§Ross Laboratories (Abbott Laboratories), Columbus, Ohio. Data regarding Flavored and Freezer Pop Pedialyte are identical. Additional information is available at http://www.pedialyte.com.
¶Ross Laboratories (Abbott Laboratories), Columbus, Ohio. Additional information is available at http://rpdcon40.ross.com/pn/PediatricProducts.NSF/web_Ross.com_XML_PediatricNutrition/96A5745B1183947385256A80007546E5?OpenDocument.
**Cera Products, L.L.C., Jessup, Maryland. Additional information is available at http://www.ceralyte.com/index.htm.
††Not applicable.
§§Meeting U.S. Department of Agriculture minimum requirements.
¶¶Coca-Cola Corporation, Atlanta, Georgia. Figures do not include electrolytes that might be present in local water used for bottling. Base=phosphate.
Source: Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR* 2003;52(No. RR-16):1–16.

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Table 4. **Summary of Treatment Based on the Degree of Dehydration (1)**

Degree of Dehydration	Rehydration Therapy	Replacement of Losses	Nutrition
Minimal or no dehydration	Not applicable	<10 kg body weight: 60–120 mL ORS for each diarrheal stool or vomiting episode >10 kg body weight: 120–240 mL ORS for each diarrheal stool or vomiting episode	Continue breastfeeding, or resume age-appropriate normal diet after initial hydration, including adequate caloric intake for maintenance
Mild to moderate dehydration	ORS, 50–100 mL/kg body weight over 3–4 hours	Same	Same
Severe dehydration	Lactated Ringer solution or normal saline in 20 mL/kg body weight intravenously until perfusion and mental status improve; then administer 100 mL/kg body weight ORS over 4 hours or 5% dextrose in ½ normal saline intravenously at twice maintenance fluid rates	Same; if unable to drink, administer through NG tube or administer 5% dextrose in ¼ normal saline with 20 mEq/L potassium chloride intravenously	Same

commercial ORSs with the content of commonly offered household drinks deemed inappropriate for oral rehydration therapy. (4)

Treatment of acute gastroenteritis should include two phases of therapy: rehydration and maintenance. In the rehydration phase, fluid should be replaced rapidly in a 3- to 4-hour period. In the maintenance phase, calories, in addition to fluids, are administered.

Rapid re-alimentation should follow rapid rehydration, having the goal of returning the patient quickly to an age-appropriate, unrestricted diet. During both phases, persistent fluid losses from vomiting and diarrhea should be replaced continuously. Table 4 summarizes the recommended rehydration and fluid loss replacement therapies based on the degree of dehydration. (1)

For more than 15 years, physicians have recognized the importance of early introduction of an age-appropriate diet, compared with the outdated practice of "bowel rest." Reinstitution of an appropriate diet has been associated with decreased stool volume and duration of diarrhea.

Breastfeeding should be continued during both the rehydration and maintenance phases. The diet should be advanced as tolerated to compensate for lost caloric intake during the acute illness. Lactose restriction ordinarily is not indicated, although such restriction might be helpful in cases of diarrhea in malnourished children or among children who have a severe enteropathy. In general, changes to a lactose-free formula should be made only if the stool output significantly increases on a milk-based diet. (1)(3)(4)

Minimal or No Dehydration

The ultimate goal for patients who have minimal or no dehydration is to provide adequate fluid intake while continuing an age-appropriate diet. Nutrition should not be restricted. (4) Patients who have diarrhea must have increased fluid intake to compensate for losses and cover maintenance needs; the use of ORSs containing at least 45 mEq Na+/L is preferable to other fluids for preventing and treating dehydration. In principle, 1 mL of fluid should be administered for each gram of stool output. In the hospital setting, soiled diapers can be weighed (without urine), and the estimated dry weight of the diaper can be subtracted. At home, 10 mL of fluid can be administered per kilogram body weight for each watery stool or 2 mL per kilogram for each episode of emesis. As an alternative, children weighing less than 10 kg should be administered 60 to 120 mL (2–4 ounces) of ORS for each episode of vomiting or diarrheal stool, and those weighing more than 10 kg should be fed 120 to 240 mL (4–8 ounces). (1)

Mild to Moderate Dehydration

Children who have mild to moderate dehydration should have their estimated fluid deficit replaced rapidly. Fifty to 100 mL of ORS per kilogram body weight should be administered over a period of 2 to 4 hours to replace the fluid deficit, with additional ORS administered to replace ongoing losses. By using a teaspoon, syringe, or medicine

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dropper, small volumes of fluid should be offered initially and increased gradually as tolerated. If a child appears to want more than the estimated amount of ORS, more can be offered. Nasogastric (NG) feeding allows continuous administration of ORS at a slow, steady rate for patients who have persistent vomiting or oral ulcerations. Clinical trials support using NG feedings as a well-tolerated, more cost-effective method associated with fewer complications when compared with IV hydration. This method is particularly useful in the emergency department, where hospital admissions can be avoided if oral rehydration efforts are successful. In addition, a meta-analysis of randomized controlled trials comparing ORS versus IV rehydration in dehydrated children demonstrated shorter hospital stays and improved parental satisfaction with oral rehydration. (1)(4)

Hydration status should be evaluated on a regular basis in the clinical setting to objectively assess the response to therapy and to evaluate the correction of the dehydration. Upon return to the home setting, caregivers must be provided with and must understand fully the instructions containing specific indications prompting their return for re-evaluation and further medical care. (1)

Severe Dehydration

Severe dehydration is characterized by a state of hypovolemic shock requiring rapid treatment. Initial management includes placement of an IV or intraosseous line and rapid administration of 20 mL/kg of an isotonic crystalloid (eg, lactated Ringer solution, 0.9% sodium chloride). Hypotonic solutions should not be used for acute parenteral rehydration. The patient should be observed closely and monitored on a regular and frequent basis. Serum electrolytes, bicarbonate, urea nitrogen, creatinine, and glucose levels should be obtained, although commencing rehydration therapy without these results is safe. A poor response to the initial, immediate treatment should raise the suspicion of an alternative diagnosis, including septic shock as well as neurologic or metabolic disorders. Therapy may be switched to an oral or NG route as soon as hemodynamic stability is accomplished and the patient's level of consciousness is restored. (1)(4)

Indications for Admission

The majority of children who experience acute gastroenteritis can be managed on an outpatient basis.

The decision to admit patients who have acute gastroenteritis must take into account risk factors predisposing to unfavorable outcomes, such as prematurity, young maternal age, lack of immediate and follow-up access to a health-care facility, and other socio-economic stressors. Clinical indications for the management of acute gastroenteritis in a hospital setting are described in the following scenarios (1):

- Intractable emesis, poor ORS tolerance, or ORS refusal.
- Severe dehydration defined as loss of more than 9% body weight.
- Young age (<1 year old), irritability, lethargy, or an uncertain diagnosis that may require close observation.
- Underlying illness that may complicate the course of the disease.
- ORS treatment failure, including worsening of diarrhea and dehydration despite appropriate administration of ORS.
- Concerns regarding adequate care at home by caretakers.

Limitations of ORS Therapy

There are several clinical settings in which oral rehydration therapy is contraindicated. These conditions include the care of children who have hemodynamic instability, altered mental status, and shock in which the use of ORSs can increase the risk of aspiration because of the loss of airway protective reflexes. Likewise, ORSs should not be used in cases of abdominal ileus until bowel sounds are present. In cases of suspected intestinal intussusception, which might present with diarrhea or dysentery, the need for radiologic studies and surgical evaluation may be warranted before considering the use of ORSs. (1)(10)

If the stool output exceeds 10 mL/kg body weight per hour, the rate of ORS treatment failure is higher. However, ORSs should continue to be offered because the majority of patients will respond well if adequate fluid replacement is administered. (1)

For children presenting with persistent emesis, physicians should instruct parents to offer small amounts of ORS; for example, 5 mL with a spoon or syringe every 5 minutes, with a gradual increase in the fluid amount consumed. This technique frequently results in successful fluid replacement and often a decrease in the frequency of vomiting as well. (1)(10)

Pharmacologic Therapy

Antimicrobial Agents

Antibiotics are not indicated in cases of uncomplicated or viral acute gastroenteritis and may actually cause harm. Antimicrobial agents may increase the risk of prolonged carrier stage and relapses in nontyphoid *Salmonella*

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infections. Furthermore, treating gastroenteritis due to Shiga toxin producing *Escherichia coli* with antibiotics may increase the risk of hemolytic-uremic syndrome. The use of antibiotics is reserved for the treatment of acute enteritis complicated by septicemia and in cases of cholera, shigellosis, amebiasis, giardiasis, and enteric fever. (1)(2)(3)

Antidiarrheal Agents

Antidiarrheal drugs are not recommended for routine use because of the risk of their adverse effects. Antimotility agents, such as loperamide, are known to cause opiate-induced ileus, drowsiness, and nausea in children younger than age 3 years. Conversely, agents such as bismuth subsalicylate have demonstrated limited efficacy in treating acute gastroenteritis in children. Racecadotril, an enkephalinase inhibitor that decreases the intestinal secretion of water and electrolytes without effects on intestinal motility, has been studied in children in the inpatient setting with promising effects; however, the drug is not yet approved for use in the United States. Further well-designed prospective studies of its efficacy and safety are needed. (1)(2)(3)(10)

Antiemetic Agents

The desire to alleviate vomiting arises from the need to prevent further dehydration and to avoid the need for IV therapy and subsequent hospital admission. Ondansetron, a selective serotonergic 5HT3 receptor antagonist, has shown to be an effective antiemetic agent, decreasing the rate of admissions in patients treated with a single dose in the emergency department with few adverse effects reported. (11)(12)

Older generation antiemetics such as promethazine, a phenothiazine derivate with antihistamine and anticholinergic activity, have been found to be less effective in reducing emesis. Promethazine is approved by the Food and Drug Administration only for children older than age 2 years and is associated commonly with adverse effects such as sedation and extrapyramidal effects, which may interfere with the rehydration process.

Metoclopramide, a procainamide derivate that is a dopamine receptor antagonist, has been proven to be more effective than placebo, but the rate of extrapyramidal reactions reported in association with its use is up to 25% in children. The use of these medications is not recommended routinely by the AAP or the CDC. None of these drugs addresses the causes of diarrhea, and the use of pharmacotherapy may distract the general care physician away from the mainstay therapy: appropriate fluid and electrolyte replacement and early nutrition therapy. (1)(10)

Supplemental Zinc Therapy

Zinc is an essential micronutrient that protects cells from oxidative injury. In cases of acute or chronic diarrhea, there is a significant loss of zinc due to increased intestinal output. Some clinical trials done in developing countries in which the prevalence of zinc deficiency is high have revealed a potential benefit from zinc therapy in conjunction with ORS therapy. The theory postulates that zinc may improve the absorption of water and electrolytes, although the exact mechanism of action is not understood completely. Studies comparing zinc supplementation with placebo have revealed a reduction in stool frequency and shortening of the duration of diarrhea. The addition of zinc to ORSs is now recommended by the WHO and the United Nation's Children's Fund worldwide for the treatment of diarrheal diseases of children. (2)(13)

Functional Foods

Probiotics are live microorganisms in fermented foods that potentially benefit the host by promoting a balance in the intestinal flora. *Lactobacillus rhamnosus* GG, *Bifidobacterium lactis*, and *Streptococcus thermophilus* are the most common probiotic bacteria studied. Randomized controlled trials have particularly supported the efficacy of *L rhamnosus* GG in the treatment of acute infectious diarrhea, reducing the duration of the diarrhea by 1 day.

When analyzing the different causes of diarrhea, *Lactobacillus* was more effective in treating gastroenteritis caused by rotavirus, with a reduction in duration of diarrhea of 2 days. Probiotics seem to be more helpful when the therapy is started early in the presentation of illness in otherwise healthy patients who have viral gastroenteritis. Prebiotics, on the other hand, are oligosaccharides, rather than microorganisms, that stimulate the growth of intestinal flora. Randomized controlled trials studying prebiotics have failed to demonstrate a reduction in the duration of diarrhea in children; therefore, prebiotics are not recommended routinely. (14)

Summary

- Based on epidemiologic evidence, most episodes of acute gastroenteritis are self-limited, and laboratory investigations should be performed only if the results will influence the management and outcome of a specific patient.
- Based on strong evidence, an adequate history and physical examination allow the clinician to classify the acute diarrheal illness, assess the severity of dehydration, determine whether investigations are needed, and begin the appropriate management.

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- Based on strong evidence, administration of ORSs is the preferred method for replacing fluid and electrolyte deficits resulting from intestinal tract losses in children who have acute gastroenteritis.
- Based on strong evidence, rapid reinstitution of an unrestricted age-appropriate diet should be introduced as part of the maintenance phase of treatment.
- Strong evidence suggests that pharmacologic therapy generally is not indicated in cases of acute gastroenteritis, and the use of drugs may complicate the natural course of the disease.

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PIR Quiz

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New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for *AMA PRA Category 1 Credit™*. In order to successfully complete 2012 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

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1. A previously healthy 3-year-old boy presents with a 1-day history of a fever up to 39˚C accompanied by bloody diarrhea. The most likely explanation of his problem is an infection with

   A. Enteric adenovirus.
   B. *Giardia lamblia.*
   C. Norovirus.
   D. Rotavirus.
   E. *Shigella dysenteriae.*

2. A previously healthy 15-month-old girl vomited twice this morning. She has not vomited since but has now experienced three episodes of profuse watery diarrhea. She has been afebrile. On examination, she refuses fluids but is alert. The following are normal: bowel sounds, capillary refill, heart rate, and respiratory rate and effort. If the clinician draws a blood sample to check a basic metabolic panel, he would expect to find:

   A. A normal profile.
   B. Significantly elevated blood urea nitrogen.
   C. Significantly elevated serum potassium.
   D. Very low serum bicarbonate.
   E. Very low serum potassium.

3. Optimal *initial* management of the 15-month-old girl described above requires

   A. Ad lib sports drink with electrolytes.
   B. An intravenous bolus of normal saline.
   C. As much dilute apple juice as tolerated.
   D. Oral ondansetron every 4 hours.
   E. 6 ounces of commercial oral rehydration solution for each diarrheal stool.

4. This same patient does not vomit again; hence, small frequent feedings of oral rehydration solution are not required, although her watery diarrhea continues. Optimal nutritional management of the diarrhea now requires

   A. Avoidance of breastfeeding.
   B. Complete bowel rest.
   C. Limitation of protein intake.
   D. Resumption of an unrestricted regular diet as tolerated.
   E. Routine use of a special lactose-free formula.

5. Aside from appropriate fluids and nutrition, the BEST way one can shorten the course of diarrhea and promote recovery of this child is by giving her oral

   A. *Lactobacillus rhamnosus.*
   B. Loperamide.
   C. Metoclopramide.
   D. Ondansetron.
   E. Trimethoprim-sulfamethoxazole.

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The Pediatric Role in the Care of Children in Foster and Kinship Care

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Dr Szilagyi has 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.

Educational Gap

In September 2010, 408,425 children and adolescents resided in foster care. Recent legislation highlights an increasing focus on involving pediatricians in supporting children in foster care and defines specific requirements relevant to the role of pediatricians.

Objectives

After completing this article, readers should be able to:

1. **Understand the purposes of foster care and the problems associated with preplacement childhood trauma and foster care placement.**
2. **Know the basics of how foster care systems work.**
3. **Recognize that children in foster care are by definition children with special healthcare needs.**
4. **Understand that many children in foster care have behavioral problems that can lead to placement instability that, in turn, can exacerbate those problems.**
5. **Understand the physician's role in foster care.**

Foster care is intended to provide a temporary haven for children during a time of family crisis when children are at imminent risk for harm. The goals of foster care are to promote child health, safety, permanency, and well-being. Foster care also has the mission of building on family strengths and providing birth parents with the services they need to reconnect (reunify) with their children. Because children fare best in stable and nurturing families, there has been an increased emphasis in the past decade on shortening the time to permanency through reunification, placement with relatives, and adoption. Foster care also has the obligation to prepare youth for independent living when none of these permanency options is possible.

The Impact of Kinship Care on Foster Care

In some states, more than one third of children in foster care are in court-ordered (formal) kinship placements, arrangements in which the related (kin) caregiver may or may not be a certified foster parent. Even outside the child welfare system, somewhere between 4% and 8% of children reside with members of their extended family, neighbors, or friends for a variety of reasons.

During the past decade, several studies were published reporting that children experience greater placement stability in kinship care than in nonrelative foster care, and that kin caregivers report fewer child behavior problems. Other data indicate that children in kinship care have as many issues as children in foster care, and that kinship caregivers are older, are less healthy, and have less access to services than nonrelative foster parents. However, recognizing that maintaining a child's ties to his or her family of origin holds advantages for the child, relatively more children are being placed in kinship care as a result of child protective investigation.

Other children are spending brief amounts of time in foster care while child welfare attempts to identify and investigate kinship resources. The definition of kin has expanded to include nonrelatives, such as family friends, acquaintances, and neighbors. There is little information about the outcomes of reunification with parents or kinship care, including child health and mental health outcomes and the percentage of kinship homes that undergo disruption. The vast majority of kinship placements are without oversight or subsidy,

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although recent federal legislation was intended to improve financial support for this group of caregivers.

Health Issues of Children in Foster Care

Children in foster care are classified as children who have special health-care needs by the American Academy of Pediatrics (AAP) because of their high prevalence of medical, emotional, behavioral, developmental, educational, and dental health-care problems. Most pediatric practitioners will encounter children and adolescents in foster or kinship care in their practices. It is important that pediatricians be familiar with the effects of childhood trauma and adversity, separation from family, and ongoing uncertainty on child behavior, mental health, and development.

Pediatricians are in a unique position to identify problems, make appropriate referrals, and offer support and advice to caregivers. Foster care ideally should be developmentally appropriate and child-centered, and pediatricians can play a crucial role in offering developmentally sound advice and emotional support to caregivers about parenting traumatized children and children who have significant behavior problems. Pediatricians also should suggest ways to promote placement stability and successful permanency.

Most maltreated children are not removed from their birth parents, but they appear to have the same health issues as children in foster and kinship care. The knowledge and skills that pediatricians bring to the care of children in foster and kinship care also apply to the larger population of children whose families are involved with child welfare agencies.

Epidemiology

Of 3.3 million child abuse and neglect reports in 2010, 436,321 (22%) were substantiated, and 254,000 children were removed to foster care. Over the past decade, the increasing trend toward keeping children with their birth parents or with kin caregivers after child protective investigation has reduced the total number of children in foster care. In the United States, on September 30, 2010, 408,425 children and adolescents resided in foster care, 26% in a relative (kinship) foster home, 48% in a nonrelative foster home, and 9% in either a group home or residential care setting. Of the remainder, 4% lived with a preadoptive family, 5% were on a trial discharge with their parents, and 2% were listed as "run-away."

Estimates suggest that more than 700,000 individual children have spent some time in foster care during the preceding 12 months. Census data indicate that approximately four to eight times as many children and teenagers live in informal, unregulated kinship care without child welfare involvement. Approximately 40% of those in foster care are teenagers, whereas 30% are children under age 5 years. Children in foster care range in age from birth to 21 years, although 47 states still emancipate adolescents at age 18 years.

Minorities are represented prominently in foster care. In 2010, 29% of children were of African American heritage, 21% Hispanic, 41% white, and 5% of two or more races. Significant concern exists that the overrepresentation of minority children reflects bias in child protective referrals, investigation, and removal, as well as a lower likelihood of reunification after removal.

Discrete subpopulations in foster care that present with unique health needs include children who have multiple handicaps, teenagers involved with juvenile justice, pregnant and parenting teenagers, and unaccompanied refugee minors from countries ravaged by war or severe internal strife.

The average length of stay in foster care in 2010 was 25 months, with a median of 14.5 months. The lower median is attributed to more intensive permanency planning, resulting in shorter times to reunification or placement with extended family. However, the higher mean is affected by the 25% of children who remain in care for years.

Length of stay is affected by several factors: the biological family's cooperation with the individualized case plan for their family; the availability of appropriate extended family to care for the child; diligence in permanency planning by child welfare; and the challenges of finding adoptive resources for older children, minority children, large sibling groups, and children who have significant behavioral and developmental problems.

Longer stays in foster care are associated with a reduced likelihood of reunification and an increased number of placements. Approximately 50% of children and teenagers will experience more than one foster care placement, with approximately 25% having three or more placements.

In 2010, of the 254,114 children who exited foster care, 51% returned to their parents and 14% went to a relative or guardian, whereas 21% were adopted and 11% aged out of foster care. The vast majority of the 27,854 individuals who aged out were emancipated at age 18 years.

Childhood Trauma and Risk Factors for Placement

Because the long-term benefit of foster care placement is uncertain, admission to foster care is and should be difficult.

Almost all children entering foster care are placed involuntarily by court order after child protective investigation.

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Child neglect, including lack of supervision or neglect of basic nutritional, educational, and medical needs, is the most commonly cited reason for placement. Overall, approximately 70% of admissions are for maltreatment. Teenagers tend to be placed for disruptive behaviors through either the juvenile justice system or as persons in need of supervision. Voluntary placements constitute less than 1% of admissions and often are made by families as a means of accessing treatment services for a child or teenager who has complex mental health or medical problems.

Families whose children reside in foster care come from all walks of life, but financial poverty remains a pervasive common factor underlying foster care placement (>50% of children live with impoverished families before foster care). Poverty, however, extends beyond the financial to the lack of the normal, predictable, nurturing environment that promotes good developmental and emotional health. Most children have experienced childhood adversities beyond maltreatment, including exposure to significant violence in their homes (84%) or communities (48%).

At placement, investigators report that 84% of caregivers have significantly impaired parenting skills, coupled with mental health problems (46%), substance abuse (48%), criminal involvement, or cognitive impairment (12%). Parents often lack social supports, have limited education and high unemployment, and are single.

Approximately one third of birth parents admit to being abused or neglected as children, and about the same percentage spent time in foster care. Children often have had multiple caregivers even before placement in foster care. Removal of a child often follows prolonged involvement with child welfare agencies, with the removal occurring after preventive strategies have been exhausted, when the child's health and safety are at imminent risk.

The Impact of Childhood Trauma

Mounting evidence indicates that early childhood trauma or multiple adverse childhood experiences, and chronic stress are associated with poor short- and long-term mental health, developmental, and physical health outcomes. Trauma exposure and chronic stress, especially in the absence of ameliorating protective factors, alter the neurobiology of the brain, especially in a very young child. Chronic stress predominantly alters those areas of the brain involved in cognition, rational thought, emotional regulation, activity level, and attention.

Thus, children entering foster care with their cumulative early life traumas and adversities are children who have immense emotional, developmental, and physical health needs. Studies on resiliency and recovery are just now accumulating, but early data indicate that stability in a nurturing and responsive family promotes healing after childhood traumatic experiences.

Entry into foster care is fraught with uncertainty, upheaval, and losses for children. Despite high levels of family dysfunction, removal from the family of origin and all that is familiar is another emotionally traumatizing experience for many children, whereas, for other children, placement in foster care may be the first time they have felt truly safe. Although stable placement in a quality foster home can promote healing, the ongoing uncertainties and losses endemic to foster care may erode a child's sense of well-being over time.

Recent Foster Care Legislation

Recent legislative activity highlights an increasing focus on involving pediatricians in supporting children in foster care. The Fostering Connections to Success and Increasing Adoptions Act of 2008 (www.fosteringconnections.org) requires foster care agencies to identify kinship resources at entry to foster care, promote and support kinship care, maintain children in their schools of origin, support Native American tribes in keeping children within tribal foster care systems, and enhance resources for youth, with a goal of independent living.

Most significantly for pediatric health professionals, Fostering Connections requires states to develop health systems for children in foster care, involve pediatricians in the development of such health systems, improve health-care coordination, promote the use of medical homes, monitor psychotropic medication use, and measure health outcomes.

The Foster Care System: Important Roles in Caring for Children in Foster Care

The foster care system is simple in its concept of providing needy children with nurturing families, but also complex in practice. Federal legislation determines patterns of funding and regulatory guidelines, but responsibility for the implementation of foster care programs resides with state social service agencies, which may, in turn, delegate daily management to county or private child welfare agencies. Despite Herculean efforts by dedicated professionals, the foster care system remains burdened by huge caseloads, limited funding, birth parents who have multiple intractable problems, and bureaucratic, legal, and ethical demands that sometimes appear to be in conflict with each other.

ROLE OF CASEWORKERS. Each child welfare agency is responsible for hiring and training caseworkers for what is

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a complex job, requiring multiple skills commensurate with masters' level social work. Most casework positions are, however, entry-level jobs requiring no more than 2 years of college education in many agencies. As case managers for the biological family, caseworkers must engage parents around the care of their children while making *diligent efforts* to assist them with securing whatever educational or service resources are necessary (eg, housing, mental health, parenting education, medical care, and drug and alcohol rehabilitation) to promote reunification.

Meanwhile, caseworkers also must coordinate educational, developmental, medical, and mental health services for children, and support the foster parents in their care. When birth parents are noncompliant or unable to undertake the work necessary for reunification, caseworkers have the delicate task of supporting them through the process of alternate permanency planning. Caseworkers also are expected to help children develop secure attachments and a sense of belonging to a different family than their family of origin.

Caseworkers also recruit, train, monitor, and annually recertify foster parents. They must have a working familiarity with the legal system in their state, particularly family court and the juvenile justice systems. Within 72 hours of removing a child from a family, the caseworker must prepare a court petition documenting the reasons for removal. For the child or adolescent remaining in foster care, the caseworker must return to court at designated intervals to provide ongoing documentation for the continuation of placement and to detail their own efforts on behalf of parents and children toward reunification.

THE LEGAL SYSTEM. Every child in foster care is represented in court by a law guardian (guardian ad litem), who may or may not be an attorney, depending on the state. In some states, in particularly difficult cases, the court also may designate a court-appointed special advocate on behalf of the child. As trained volunteers who are not attorneys, court-appointed special advocates devote many hours to investigating the child's circumstances for presentation to the court.

Ultimate oversight resides with the judicial system. Family court judges have the compelling task of deciding, based on information presented to them in court, whether a child remains in out-of-home placement after removal or not; ordering services for biological parents; and rehearing at set intervals the case for a child in out-of-home care to determine whether continued placement or an alternative permanency arrangement is warranted. Ultimately, the court decides the permanency outcome, with the hope that such a decision is based on the input from attorneys, all caregivers, child welfare agencies, mental health and other professionals, and the youth who is of sufficient age and developmental capacity to speak on his or her own behalf. Education for the legal profession regarding child development, parenting, and early childhood trauma remains limited.

FOSTER PARENTS. Foster parents are the heart and soul of the foster care system, and foster parenting is the major therapeutic intervention. Foster parents come from all walks of life, but, on average, tend to be married, be of lower middle income, have at least a high school education, be employed, and have children of their own. Many have strong religious affiliations, and most are driven by a desire to do something positive for children. Some people become foster parents with the hope of eventually adopting. A small percentage of foster parents are same-sex couples, and laws are evolving to ensure that same-sex couples can both foster and adopt children.

Approximately 5% of foster families undergo specialized training to act as resources for severely emotionally disturbed or medically fragile children. However, most foster parents receive very little education about parenting children who have significant trauma histories and attachment issues. There are some elegant studies demonstrating that specific education and supports for foster parents and birth parents (such as Treatment Foster Care, and evidence-based parenting education for foster parents) improve outcomes for children, but these programs have not achieved widespread use.

Reimbursement for foster parenting varies widely. Families are paid a daily board subsidy for each child in their care that is set by individual states. The rate is determined by the child's age, health needs, and the complexity of the parenting tasks. The board subsidy is expected to cover food, shelter, personal needs, recreation, and most transportation and educational costs. A recent study shows that board subsidies cover only approximately two thirds of the cost of parenting a child in foster care.

Recruitment, education, and retention of suitable foster families are some of the most compelling tasks facing child welfare agencies. Boundaries are blurred in the foster care system in terms of authority, responsibility, and accountability. Foster families retain the bulk of the daily responsibility for children and teenagers, but are accountable to caseworkers, the legal system, and the birth family for the child's care. Legal custody remains with the birth parent until a child is freed for adoption, but the foster care agency is responsible for ensuring that a child's needs are met and the child is well cared for.

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GROUP CARE. Approximately 20% of youth in foster care, mostly adolescents, reside in residential or group home placements, which can cost upward of $100,000 per child annually. Mental health services usually are available on-site, but staff turnover is high. The outcomes of group care have not been well studied, and there appears to be wide variability in the quality of such care.

Important Processes in Foster Care

VISITATION. Although consistent visitation of a child with his or her biological parent is the best predictor for reunification, visits may be difficult for the parents and child. The tenor of the parent-child relationship is variable. Children who have been abused or severely neglected by their parents may not feel safe even in a supervised visitation setting. Birth parents may not understand the need to focus on the child during visitation and instead focus on their own issues or problems with child welfare. Birth parents may attempt to sabotage the relationship of the child with the current caregivers, and vice versa. Parents may visit inconsistently, which is confusing and frightening for children, and parental no-shows reinforce rejection and abandonment. When the parent does come, the visit ends with separation that may be challenging for both parent and child.

Visitation usually progresses through stages, beginning with visits supervised by caseworkers in a neutral setting. Visits then transition to a community setting or the parent's home, where the visit is monitored before eventually becoming unsupervised. Kinship placement may allow for more frequent contact with the birth parent, but kin caregivers also may face unique challenges if they harbor resentment toward the birth parent, are conflicted about visitation, or have to enforce court-ordered restrictions to which the parent and other relatives object.

Evidence is mounting for models of visitation in which a mental health professional helps parents identify their child's cues, understand their child's developmental capacities, practice parenting skills learned in parenting education classes, and respond to their child in an appropriate manner. Evidence-based models, such as child-parent psychotherapy or child-parent interactive therapy, still are not widely used, because such models are time- and labor-intensive and require specialized training. Another promising model is Visitation Coaching, in which trained visitation specialists prepare birth parents for visits, help the parent stay on track during the visit, and debrief with them afterward.

CRITICAL JUNCTURES IN FOSTER CARE. In addition to the challenges associated with visitation, children may encounter other adversities in foster care. Disruptions in foster care placement, disruptions in school or child care placement, separation from siblings, the presence of other children entering or leaving their foster home, unkept promises by birth parents, a poor relationship with their foster caregiver, being teased or bullied, and court dates are but some of the potential difficulties children may face. For an already stressed child, even one additional seemingly minor transition can be sufficient to overwhelm coping skills.

RECIDIVISM. Recidivism is defined as the return of a child to foster care after reunification, placement with extended family or guardian, or adoption. Depending on the locality, 20% to 30% of children return to foster care, mostly as a result of a disruption of reunification with their birth parents. An unknown but small percentage of adoptions undergo disruption, usually during an adoptee's adolescence.

TERMINATION OF PARENTAL RIGHTS. Legally, parents retain guardianship of their children residing in *the care and custody* of the state or county commissioner of social services. Guardianship can be terminated only as part of a legal process, in which the commissioner becomes the child's legal guardian until the child either reaches the age of majority or is adopted. Biological parents sometimes choose to surrender their children for adoption; but, more often, termination of parental rights (TPR) occurs involuntarily after diligent efforts at reunification have failed. The TPR process can take years, during which time concurrent, but conflicting, efforts at reunification and alternative permanency planning occur.

Time constraints imposed by federal legislation in 1997 require states to begin TPR once a child has been in foster care for 15 of the past 22 months and when there is no compelling reason not to start the process. States and localities vary in the rigor with which they follow this federal mandate. Although child welfare, as a result of the growing body of scientific studies on childhood trauma, early brain development, and placement stability, has moved toward a child-centered approach to foster care, the judiciary is not required to decide permanency based on the "best interests of the child."

ADOPTION OUT OF FOSTER CARE. Adoptions out of foster care (public adoption) peaked several years ago. Over 60% of children adopted out of care are adopted by their foster parents, and 30% are adopted by kinship caregivers. According to the most recent available data, there were 107,011 children awaiting adoption out of foster care in 2010, of whom 64,084 were freed for adoption and

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13,603 resided in preadoptive homes. Fostered children without an identified adoptive resource tend to be older, minority children, to be part of large sibling groups, or to have significant disabilities, especially emotional and behavioral problems, that continue to be great impediments to achieving permanency.

Birth Parents

Birth parents most often view child welfare efforts as an intrusion into their lives and the reason for the disruption of their family. Although some parents cooperate with child welfare agencies, others either fail repeatedly to complete rehabilitation programs, remain with a violent partner, or engage in criminal acts that delay reunification. Some blame the child for the removal, whereas others express great remorse over the disruption of their family and express appreciation for the resources that child welfare helps them access. Many birth parents have trauma and loss histories extending back into their own childhoods that have remained unspoken and untreated. Many lack the most basic of parenting skills, and removal of their children may reinforce their feelings of failure and inadequacy.

Experiences of Children in Foster Care

Child welfare agencies may initially place children in a shelter, an emergency foster home, or the home of a relative, pending the outcome of the initial court hearing after child protective investigation. Placement with kin caregivers is assumed to be less traumatic if the child already has a meaningful relationship with them. The first few days in foster care may be filled with a host of strangers, from child protective personnel to police officers, health providers, and members of the foster home.

Children new to foster care often are wary for the first several weeks, a stage viewed by most child welfare professionals as a time of emotional withdrawal for the overwhelmed and confused child. Children who have severe trauma histories may begin to display behaviors that were adaptive in their previous environments, but dysfunctional in the new setting. The majority of children are simply overwhelmed by feelings they do not understand and cannot control or express in healthier ways.

Children in foster care often deny awareness about why they are in foster care, and children may even blame themselves for the disruption of their families. They worry about the well-being of their parents and siblings. Uncertainty, powerlessness, and guilt pervade their lives. They rarely know how long they will be in care, whether or when their parents will come for visits, or when a parent will get out of jail or rehabilitation. Birth parents may make promises they do not or cannot keep. Other children tease them about being in foster care, contributing to their already poor self-regard and sense of alienation.

Younger children and infants quickly form attachments to foster parents and may view their less frequently seen birth parent as a stranger. Differences in parenting styles, or outright conflict between caregivers, create confusion for children and teenagers. Children may not be adequately prepared for discharge from foster care or transition to a new placement.

Changes in foster care placement almost always are traumatic for children, given that each transition involves a loss that reinforces feelings of rejection and worthlessness. Reasons for disrupted placements vary but include child behavior problems, limited foster parent skills, conflict between birth and foster parents, and agency administrative decisions. Rarely, a foster home may be abusive or neglect a child's needs, resulting in removal.

When foster care goes well, it is because the care is truly child-centered. A responsive and nurturing foster parent creates a zone of comfort and safety for the child, allowing the child to grieve the loss of family and adjust to the new home. The foster care placement is stable during the child's time in care. The foster and birth parent minimize conflict and work together on behalf of the child. The birth parent appears consistently for visits, behaves appropriately at them, and takes advantage of the services offered by child welfare. Child welfare helps the birth parent identify and build on the family's strengths, and the crisis that led to the family's disruption is ameliorated. Children receive appropriate trauma-informed mental health services, and their parents participate in those services as needed. Unfortunately, the foster care experience usually does not go this well.

Adolescents in Foster Care

Adolescents in foster care are a varied group. Some have grown up in foster care, whereas others enter foster care through the juvenile justice system or are placed by a parent unable to manage their behaviors or to access appropriate mental health-care services. Adolescents tend to have the greatest placement instability; they experience a variety of foster care settings over time (foster family homes, group homes, residential care) or move back and forth between foster care, home, and/or juvenile justice. A small percentage of teenagers are intellectually disabled and have significant behavior issues. Intellectually competent teenagers may lack the educational background to succeed in school.

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Pregnant or parenting teenagers are another small group who may be living with their children or placed separately from them if they have significant mental health issues or constitute a risk to their offspring. Some teenagers enter foster care as unaccompanied refugee minors, having immigrated to the United States from a variety of countries after surviving war, rape, injury, slavery, or the death of their families.

The majority of adolescents in foster care reside in group-care settings, where their activities are restricted, education is structured, and they receive mental health services and substance-abuse treatment, if needed.

In general, adolescents in foster care have experienced similar childhood traumas, including maltreatment, as younger children in foster care. They have accumulated losses and transitions; but their high-risk behaviors, including substance abuse, risky sexual activity, school truancy, and petty criminal mischief, may be challenging enough that the reasons underlying them remain unattended.

Adolescents in foster care are less likely to find permanency, either through reunification or adoption. Some return to parents or relatives, but many age out at age 18 years, run away, or are moved to another agency or placement setting (residential care or group home care). Exposure to normalizing activities and preparation for independent living is largely inadequate. After-care resources are essentially nonexistent. Foster or kin families who remain invested in youth are their best resource, and youth who identify and remain connected to foster parents, kin, or other adult mentors appear to fare better.

What is known about the outcomes of youth who have aged out is discouraging. Within a year of aging out, most youth have spent at least one night homeless, and many young women have had an unintended pregnancy. Young adults who are a decade removed from foster care are underemployed, undereducated, have difficulty with trust in intimate relationships, and have high rates of mental health problems, including posttraumatic stress disorder and substance abuse. Prevalence studies indicate that adults with a history of foster care are overrepresented among the homeless and incarcerated populations.

Adolescence is the time during which the individual is supposed to form a stable identity rooted in self-esteem, a sense of autonomy rooted in self-efficacy, and a larger sense of commitment and comfort in relatedness to peers. For young people in foster care, especially minority youth, negative self-concept, lack of self-esteem, and a lack of self-efficacy are likely outcomes of early adverse experiences, the accrual of multiple losses over time, and a sense of helpless dependence is developed from living in the uncertain world of foster care.

Early abuse and neglect, coupled with impaired caregiving, repeated separation and losses, unpredictability, and a lack of role models for healthy relationships result in a high prevalence of young adults who are isolated, alienated, dependent, and prone to distrust.

Less well studied are those former foster youth who are resilient and create a meaningful life despite multiple childhood adversities.

Health-Care Issues of Children in Foster and Kinship Care

The health issues of children in foster care are rooted in their histories of trauma, neglect, and loss. Chronic and multiple adverse childhood experiences and early childhood trauma, coupled with the lack of protective factors, underlie the poor health status of children in foster care. The AAP defines children in foster care as *children with special health-care needs* because of their high prevalence of chronic medical illness, developmental disabilities, educational disorders, dental problems, and behavioral, emotional, and mental health problems (Table 1). In addition, almost 100% of children in foster care have issues related to family functioning.

Studies about the health status of the foster care population have yielded fairly bleak results. At entry to care, 30% to 45% have at least one chronic medical condition,

Table 1. Health Issues of Children and Adolescents at Entry to Foster Care

Health Problem	Percentage of Population
Chronic medical problems	30%–45%
Complex medical/developmental[a]	10%
Mental health	48%–80%
Developmental delay	60% of children <6 y old
Educational issues[a]	45% in special education or with individualized educational plan
Dental problems[a]	35%
Family dysfunction	100%

[a]Unpublished data from Starlight Pediatrics, Rochester, NY. Other data from a variety of sources.

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and approximately 10% have complex chronic health problems. The reasons for the high prevalence of physical health conditions include medical neglect or lack of access to health services before foster care; genetic susceptibility; inability of the parent to cope with child's health needs, resulting in placement; and the impact of untreated childhood adversities on health. Neurologic and developmental conditions are particularly prevalent and may be the direct result of trauma, the sequelae of psychosocial deprivation and childhood trauma, or the result of substance exposures.

Multiple studies report that the major ongoing health problems of children in foster care are mental health and developmental problems. Sixty percent of children under age 6 years enter foster care with developmental delays in at least one domain, and up to 70% of children over age 5 years have a mental health or behavioral problem. These problems are rooted in the adversities and trauma children have experienced before foster care. Behaviors that may have been adaptive in a neglectful or abusive environment become maladaptive in a more normative setting. Evidence indicates that significant behavioral problems (aggression, stealing, defiance, prolonged tantrums, destruction of property, substance abuse), especially if accompanied by developmental problems, lead to placement disruptions that, in turn, exacerbate emotional and mental health problems.

Barriers to Health-Care

Once children enter foster care, their overall health does not appear to improve significantly. The transient nature of the population dramatically increases the likelihood that they will continue to have poor access to health-care. Health information on admission into foster care is almost universally lacking. Neither caseworkers nor foster parents have the level of knowledge necessary to serve as the health-care manager, yet the foster system relies on them to perform this complex task.

Although most children in foster care have health insurance in the form of Medicaid, this circumstance also limits access to health-care because of inadequate reimbursement, delays in payment, and limited numbers of medical subspecialists willing to participate in Medicaid. Medicaid-managed care may increase access to medical subspecialty care, but it reduces significantly mental health access for children in foster care. Failure to support and educate foster parents about a child's medical, developmental, and mental health needs and failure to secure appropriate treatment can lead to disruptions in placement when foster parents become overwhelmed.

Complex consent and confidentiality requirements may delay evaluations and treatment and confound communication among professionals. Emergency care can be provided even if consent is not available. However, each state has specific regulations about who can consent for health-care on behalf of a child in foster care. Many states, for example, require written consent of the legal guardian, who is usually the birth parent, for any procedure requiring informed consent, including administration of psychotropic medication. In general, child welfare agencies have protocols in place for obtaining consent, and health-care providers should address consent issues with their local child welfare agency.

Although the health clause of the Fostering Connections legislation now requires states to develop health systems for children in foster care, enactment is in its infancy in most states. Health systems with intensive care coordination are essential because inadequate health-care management underlies the pattern of inadequate, fragmented, and, occasionally, redundant care children receive.

Health-Care Recommendations

The Medical Home

Ideally, children in foster care will receive their health-care as children who have special health-care needs in the context of a pediatric medical home. The AAP has a number of resources (http://www.aap.org/fostercare) to assist pediatric professionals, but the major guiding principles of the medical home for the child in foster care are as follows:

- Pediatric care is accessible and continuous over the child's time in foster care, regardless of placement.
- Health-care coordination exists that ensures that all of a child's health-care needs, including mental health, dental, and developmental/educational needs, are identified and addressed.
- Compassionate care is given that includes an understanding of the impact of childhood trauma and loss on children and families.
- Care is culturally competent and includes an understanding of the microculture of foster care and its impact on children and families.
- Communication exists that includes the willingness to collaborate with child welfare and includes all of a child's caregivers, when appropriate and safe, in planning for a child's health needs.
- Comprehensive high-quality pediatric care is provided in accordance with AAP health-care standards for children in foster care.

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Health-Care Standards

The medical home should follow the health-care standards for children and teenagers in foster care defined by the AAP Task Force on Foster Care adapted from AAP District II: New York State, *Fostering Health: Health-Care Standards for Children and Adolescents in Foster Care*. The standards are now available on the AAP's Healthy Foster Care America website (www.aap.org/fostercare).

This website was designed for use by interdisciplinary professionals (legal, child welfare, judicial, mental health, and health), caregivers, and youth in foster care. These resources and detailed standards may also be helpful to pediatricians in advocating with states and foster care agencies for improved health services. A brief summary of the AAP health-care standards for children in foster care are listed in Table 2 and further described here.

ADMISSION HEALTH SERIES. Pediatric professionals should see children "early and often" after entry to foster/kinship care, because serial encounters often reveal more health needs than one isolated evaluation, and they nurture a trusting relationship between the professional and patient. The recommended admission series includes:

- An initial health screen ideally performed within 72 hours of removal and placement to document growth parameters, signs and symptoms of abuse or neglect, and details of acute or chronic conditions, including mental health problems, in need of acute care or foster/kinship caregiver education.
- A comprehensive health evaluation within 30 days of placement, including a review of available health records, developmental and mental health assessments and referrals, assessment of adjustment to the foster care placement, appropriate screening, and continued caregiver education and support.
- A follow-up health visit within 60 to 90 days of placement to ensure that recommended evaluations are in process or complete, to continue monitoring the

Table 2. Foster Care–Specific Health Visits

Age of Child	Timing or Frequency	Rationale for Visit
Admission health screen	Ideally within 72 h of placement	Obtain growth parameters; document signs of abuse/neglect; diagnose and treat acute/chronic medical and mental health problems; ensure child has necessary medications and equipment; support and educate caregivers and youth through transition period
Comprehensive health assessment	Within 30 d of entry to foster care	Review all available health information. Monitor growth, adjustment to placement, and for signs of maltreatment; comprehensive physical examination; conduct recommended screening; mental health and developmental assessment and referral; caregiver and youth health education and foster care–specific anticipatory guidance
Follow-up health visit	60–90 d after entry to foster care	Review health, mental health, and developmental assessments. Review any new health information; monitor growth and development and care in foster home; monitor for signs of abuse and neglect; ensure all needs being met; ongoing anticipatory guidance and education
Infants to 6 mo	Monthly (between preventive health-care visits)	Monitoring of growth and development, especially if premature, substance-exposed in utero, or having complex health issues; support and education of caregivers
21 mo	Extra visit at age 21 mo	Monitor development and behavior closely; support and education for caregivers
2 to 21 y	Semiannual (between annual preventive health-care visits)	Monitor growth and development; assess adjustment to placement; monitor for emerging behavioral, emotional, and developmental problems and make appropriate referrals; support and education of caregivers and youth

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adjustment to foster care, and to reassess the "goodness of fit" in the placement.
- Health information gathering is a process that starts at entry to foster care and may continue throughout the child's time in foster care depending upon the complexity of issues.
- Communication with child welfare personnel around the child's health, which should occur after every health encounter and include a health-care plan.

FOSTER CARE HEALTH VISITS AND PREVENTIVE HEALTH-CARE. Periodicity underlies quality health-care for all children, but especially for those with special health-care needs. Children in foster care should have health-care visits over and above those recommended for all children to monitor all aspects of their health (medical, developmental, educational, emotional and behavioral, and dental; see http://brightfutures.aap.org/). Every health-care encounter should include monitoring for child abuse and neglect in the current placement. Foster care–specific visits (Table 2) that should be considered in addition to the AAP's Periodic Preventive Health-Care Schedule include:

- Monthly health visits for infants from birth to age 6 months, especially in the case of infants who were premature, or who have a developmental or growth problem, difficult sleep or other behaviors, or a chronic illness.
- An additional health visit at age 21 months to monitor development and behavior through a critical period for toddlers in care.
- Semiannual visits from age 2 to 21 years in this highly mobile population to monitor developmental, educational, emotional, and physical health and to provide ongoing anticipatory guidance.

For children who have complex medical, developmental, or mental health problems, the pediatrician may consider even more frequent health visits if indicated.

MENTAL HEALTH-CARE. Mental health is the single most important health-care need of children in foster care. Children need early screening and assessment of mental health status and timely referral to pediatric mental health professionals. Components of mental health-care include:

- Mental Health Screening in the Pediatric Office. Ideally, all children in foster care would receive a full mental health evaluation, but, in communities with limited resources, the periodic administration of a validated mental health assessment (beginning in infancy) can help the clinician determine which children need referral.
- The Medical Home and Positive Parenting Strategies. The medical home can be a source of support and education for foster parents and children through a focus on children's strengths and reinforcement of positive parenting strategies.
- Evidence-based Mental Health Services. Children in foster care have significant trauma histories and universal experience with family disruption. Over the past decade, a number of mental health interventions have demonstrated efficacy in improving outcomes in this population. Unfortunately, these evidence-based services are not available in every community. A list of evidence-based and promising mental health services appropriate for children involved with child welfare is available through the California Evidence-Based Clearinghouse for Child Welfare Practice (www.cebc4cw.org).
- Psychotropic Medication. Studies show that children and teenagers in foster care are more likely to be on psychotropic medications than peers not in foster care; they are also more likely to be on multiple medications, sometimes from the same class of drugs. In addition, the psychotropic medications prescribed may not match the major symptom or diagnosis of concern. Although some adolescents and children undoubtedly benefit from psychotropic medications, there is concern that medications are overused. Several states have developed comprehensive guidelines regarding the prescription and management of psychotropic medications in the foster care population. The reader is directed to guidelines available on the Healthy Foster Care America website (http://www.aap.org/fostercare) for further information. In general, psychotropic medications should be prescribed when needed as part of a comprehensive mental health treatment plan by a qualified pediatric mental health professional. A detailed health history, including mental health, behavior, development, trauma, medication use, social and family history, and a full mental health evaluation should be obtained before beginning medication.

Several basic principles should be kept in mind when using psychotropic medication:

- Therapy should be initiated with a single agent at the lowest dose.
- Dosage increases should be gradual and the patient closely monitored for efficacy and adverse effects.
- Single-agent therapy should be the goal, whenever possible.
- Pediatric professionals should be aware that not every child in foster care who presents with concerns of

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hyperactivity and inattention has a true attentional disorder, because such behaviors may be a manifestation of early childhood trauma experiences, depression, or anxiety. Caution should be exercised before instituting any psychotropic medication.

- Referral to mental health professionals for evidence-based, mental health evaluation and services is the ideal initial assessment for the child or teenager in foster care.

DEVELOPMENTAL AND EDUCATIONAL HEALTH NEEDS. Developmental and educational problems are two other major health needs of children in foster care. Trauma experiences and losses may result in learning difficulties and impaired development across multiple domains. Cognition, communication, and personal/social development are the most likely areas to be affected. If full developmental evaluation for all children in foster care is not possible, the pediatric clinician should at least use a validated developmental assessment tool to identify children in need of a full evaluation. Although some children show improved developmental skills and school achievement in foster care, any child who has behavioral or learning problems in school should receive an educational evaluation. It is recommended that the pediatrician work closely with the child's school to ensure that educational needs are identified and addressed.

DENTAL HEALTH. Foster parents in most communities report that children in foster care have limited access to dental care, despite a high prevalence of significant dental disease. Pediatric clinicians are encouraged to collaborate with their local health department and dental organizations to address access issues for children in foster care.

ANTICIPATORY GUIDANCE. Anticipatory guidance is a time-consuming and challenging process in foster care. Many foster families have a wealth of child-rearing experience, but the clinician should not presume that they have expertise in parenting children and teenagers who have attachment issues, past trauma, and ongoing bereavement around losses. In addition to the usual advice, anticipatory guidance should address issues specific to foster care, such as focusing on the child's strengths; positive parenting strategies; the impact of trauma on child behavior; supporting children through transitions (visitation, permanency planning, changes in placement, etc); significant sleep disorders; confused loyalties; attachment issues; the need for normalizing activities; and working with birth parents to reduce conflict and coercion.

Adolescents and school-age children should be counseled about safe behaviors, healthy activities, planning for their futures, and developing relationships with adult mentors. Many teenagers in foster care, fearing yet another disappointment, have exhausted their capacity to attach to a parental figure; pediatric professionals can help foster parents understand the teenager's emotional world

Table 3. Health-Care Management

Health-care management is the ultimate responsibility of the foster care agency, but requires health expertise, as well. These are several key components.

1. Consent and confidentiality. Child welfare should obtain appropriate medical consents and releases of information from the birth family, provide copies to the pediatrician, and educate health providers about the foster care agency's guidelines regarding consent and confidentiality. Psychotropic medication administration and adolescent health issues, such as pregnancy, sexually transmitted infections, birth control, and substance abuse, are governed by separate confidentiality laws in most states.
2. Obtaining health information. The gathering of health information often is a time-consuming, difficult task that occurs over time. Both the child welfare agency and the pediatric professional have a role in attempting to access health records from previous health-care providers, schools, child care settings, and immunization registries.
3. Health-care standards. Health providers and child welfare should attempt to provide health-care services in accordance with health-care standards set forth by the American Academy of Pediatrics for this special needs population.
4. Care in the context of a medical home. The primary care pediatric professional may serve as the point of access to mental health, dental, developmental, and subspecialty care. Timely referrals and care coordination, including communication with child welfare agencies, are crucial to ensuring that children in foster care receive adequate health-care. The pediatric professional should have some knowledge about child abuse and neglect and the impact of trauma, losses, transitions, and foster care on the child and caregivers.
5. Education of caregivers, youth, and child welfare personnel. Pediatric professionals are in a unique position to counsel foster, kin, and birth parents; other professionals; and youth about the child's health needs and the impact of early trauma on child behavior and development.
6. Health-care plan. Health information should be shared with child welfare personnel in language that ensures that the health-care plan for the child is incorporated into the child welfare permanency plan.

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while supporting an authoritative parenting style. Support for foster families and youth in foster care around transitions and other stressors can stabilize a foster care placement for a child. Ideally, the pediatrician also engages the birth parent and the child's caseworker in these discussions.

Health-Care Management

Health-care management ultimately is the responsibility of the foster care agency, with the caseworker as the ultimate case manager. However, the pediatric medical home has an important role to play in ensuring that a child in foster care receives all necessary health-care in a timely manner, and that caseworkers, caregivers, and youth in care all understand and participate in the health-care plan. This coordination requires that health professionals partner closely with child welfare to ensure adequate communication and information exchange. Specific health-care management tasks are outlined in Table 3.

The Pediatrician as Child Advocate

Pediatricians are in a unique position to advocate for changes in systems of care for children in foster care, especially in light of the health clause in the Fostering Connections legislation. Pediatric professionals can collaborate with their local AAP chapter to:

- Work with states to ensure that child welfare agencies are aware of and promote health-care standards for children in foster care.
- Partner with state and local child welfare agencies, departments of public health, and mental health organizations to develop evidence-based mental health-care resources in their community.
- Partner with state and local child welfare agencies, departments of public health, and dental organizations to increase access to dental care for children in foster care.
- Partner with state and local early intervention and school/preschool special education programs to develop strategies to assess the needs of children in foster care and to ensure access to needed services.

Summary

- There is compelling research evidence that children and adolescents placed in foster care for reasons of safety enter foster or kinship care after experiencing multiple, synergistic adversities that affect their health and well-being negatively.
- Consequently, children and adolescents in foster care are children who have special health-care needs because they have a high prevalence of medical, mental health, developmental, educational, and dental health problems.
- Evidence also indicates strongly that behavioral problems are associated with placement instability, and that instability, in turn, exacerbates behavioral and developmental problems.
- Foster care should be considered a window of opportunity in which the child or teenager can heal from past trauma.
- Expert consensus contends that child health, mental health, and developmental outcomes will be improved by child-centered medical home care while the child or teenager is in foster care.
- In addition, it is recommended that the pediatrician be proactive in engaging child welfare agencies to ensure that the health plan is an integral part of the child's permanency plan.
- Pediatric professionals also have a role in educating child welfare professionals, foster and kinship parents, birth parents, and youth about health and foster care–specific issues, and in advocating for appropriate health-care for this vulnerable population.

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To view the Suggested Reading list, other suggested resources, and a glossary, visit http://pedsinreview.aappublications.org and click on "The Pediatric Role in the Care of Children in Foster and Kinship Care" link.

PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Since January 2012, learners can take *Pediatrics in Review* quizzes and claim credit online *only*. No paper answer form will be printed in the journal.

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Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for *AMA PRA Category 1 Credit™*. In order to successfully complete 2012 *Pediatrics in Review* articles for

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Starting with the 2012 issues of *Pediatrics in Review*, *AMA PRA Category 1 Credit™* may be claimed only if 60% or more of the questions are answered correctly. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

You are the pediatrician in your community who contracts with the local Department of Social Services to provide health-care to the approximately 200 children in the Foster Care and Kinship Care Program, age birth to 18 years. Your program follows the AAP standards for children in foster care.

1. A 14-month-old child is being placed in a foster care home this afternoon. You ask the caseworker to arrange for you to do an admission health screen on the child within the next
   A. 24 hours.
   B. 48 hours.
   C. 72 hours.
   D. 96 hours.
   E. 7 days.

2. You ask the caseworker also to arrange for you to perform a comprehensive health assessment on the child within the next
   A. 10 days.
   B. 15 days.
   C. 30 days.
   D. 45 days.
   E. 60 days.

3. The child has been neglected and a court hearing will be held about where she should be placed. You understand that every child is represented in court by a
   A. Caseworker.
   B. Court-appointed attorney.
   C. Court-appointed special advocate.
   D. Family court prosecutor.
   E. Law guardian who may or may not be an attorney.

4. You recognize that the primary goal of the foster care program is
   A. Foster care for 1 to 3 years.
   B. Out-of-family adoption.
   C. Placement with a family member.
   D. Termination of parental rights.
   E. Timely permanency, ideally with the birth family when that is a safe option.

5. Your admission screen reveals a malnourished 14-month-old white girl who has an extensive candidal rash. You also learn that she has 2- and 3-year-old brothers who were found abandoned in another apartment in the house. They had been whimpering her name. The factor most likely to be problematic in finding a placement for this child is her
   A. Age.
   B. Gender.
   C. Medical problems.
   D. Race.
   E. Sibling group size.

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Chronic Recurrent Abdominal Pain

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Educational Gap

Chronic abdominal pain in childhood accounts for 2% to 4% of office visits to primary care clinicians and 50% to pediatric gastroenterologists. Differentiation among organic gastrointestinal, organic non-gastrointestinal, and functional gastrointestinal disorders can be difficult, but specific criteria are available.

Objectives

After completing this article, readers should be able to:

1. **Develop a differential diagnosis of chronic abdominal pain in children.**
2. **Be aware of alarming signs and symptoms that could indicate organic disease.**
3. **Differentiate the four abdominal pain–associated functional gastrointestinal disorders in children as outlined by the Rome III criteria.**
4. **Discuss the role of acid peptic disorders as it pertains to chronic abdominal pain in children.**
5. **Discuss the role of lactase deficiency as it pertains to chronic abdominal pain in children.**
6. **Determine when referral to a pediatric specialist is warranted.**

Introduction

Chronic abdominal pain in childhood is encountered frequently by primary care physicians, subspecialists, and surgical specialists alike. This symptom accounts for 2% to 4% of office visits to primary care clinicians and 50% of office visits to pediatric gastroenterologists. (1)(2) Chronic abdominal pain is defined by the American Academy of Pediatrics' 2005 clinical report as "long-lasting intermittent or constant abdominal pain that is functional or organic." (3) Chronic abdominal pain in children ignites significant anxiety in both patients and their families. In addition, the economic impact on health care is substantial. Furthermore, the short- and long-term effects on school attendance, academic performance, and peer interaction cannot be understated. The exact prevalence of chronic abdominal pain is not known. However, it has been suggested that 13% to 17% of the pediatric population experience chronic abdominal pain. (1) Of note, there are many organic gastrointestinal (GI) conditions that can lead to chronic abdominal pain (ie, inflammatory bowel disease, esophagitis, chronic pancreatitis, gallbladder disease). These conditions are listed in Table 1 and will not be discussed in detail in this article.

Functional abdominal pain is not a specific diagnosis but rather a description for a variety of symptoms. By definition, children who have abdominal pain lack serologic, mucosal, radiographic, and structural evidence of disease. The Rome Foundation is an independent organization that provides support for activities designed to create scientific data and educational information to assist in the diagnosis and treatment of functional gastrointestinal disorders (FGIDs) (http://www.romecriteria.org). Based on the Rome III criteria, there are currently four categories of abdominal pain–associated FGIDs in children: functional dyspepsia, irritable bowel syndrome (IBS), abdominal migraine, and childhood functional abdominal pain (Table 2). This article will focus on the diagnostic evaluation, pathogenesis, and treatment of

Abbreviations

CBT: cognitive behavioral therapy
FGID: functional gastrointestinal disorder
GI: gastrointestinal
IBS: irritable bowel syndrome

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Table 1. Differential Diagnosis of Chronic Abdominal Pain in Children

Organic gastrointestinal (GI) disorders
- Acid peptic disease (ie, esophagitis, gastritis, peptic ulcer disease)
- Infectious causes (ie, parasitic)
- Eosinophilic disease (eg, esophagitis, gastritis, enteropathy)
- Gallbladder disease (eg, cholelithiasis, cholecystitis, choledochal cyst)
- Pancreatic disorders (acute/chronic pancreatitis, pseudocyst)
- Chronic hepatitis
- Inflammatory bowel disease
- Polyps
- Foreign body
- Surgical disorders (eg, hernia, intussusception, appendicitis)
- Carbohydrate malabsorption
- Constipation
- Tumor

Organic non-GI disorders
- Respiratory inflammation/infection
- Recurrent urinary tract infection (pyelonephritis, cystitis)
- Ureteropelvic junction obstruction
- Nephrolithiasis
- Gynecologic disorders
- Porphyria
- Diabetes mellitus
- Lead poisoning
- Collagen vascular disease
- Sickle cell disease
- Trauma

Functional GI disorders
- Irritable bowel syndrome
- Abdominal migraine
- Functional dyspepsia
- Childhood functional abdominal pain

GI=gastrointestinal.

the abdominal pain–associated FGIDs. In addition, the role of acid peptic disorders and lactase deficiency in chronic abdominal pain will be discussed.

Causes of Chronic Abdominal Pain

The differential diagnosis of chronic abdominal pain is broad and includes both organic GI, organic non-GI, and FGIDs (Table 1). Perhaps most vital when evaluating a child afflicted with chronic abdominal pain is recognition of warning signs and symptoms elicited from a comprehensive history and physical examination (Table 3). Children who present with these symptoms and physical findings require prompt evaluation and possible referral. FGIDs are not uncommon; however, a diligent evaluation is paramount, even if suspicion is high, to exclude organic conditions.

Functional Gastrointestinal Disorders

Pathogenesis

The cause of abdominal pain–associated FGIDs in children is not completely understood. It is thought, however, that the origin is multifactorial and involves the enteric nervous system, central nervous system, visceral hypersensitivity to pain, psychological factors, and abnormal responses to both normal and abnormal physiologic stimuli. (2) A genetic origin for these conditions has been proposed; however, research in this area has just begun.

Visceral Hyperalgesia

Hypersensitivity to pain is believed to be an underlying feature of this category of FGIDs. It seems that there is a heightened nociceptive response to both physiologic and noxious stimuli in these patients. The origin of visceral hyperalgesia has been postulated by Miranda et al (2), who reported that "animal and human data suggest that there are at least 4 putative mechanisms that may help explain the development of visceral hypersensitivity following early life pain or stress: sensitization of central (spinal) neurons, sensitization of primary sensory neurons, impaired stress response (hypothalamic-pituitary-adrenal axis), and/or altered descending inhibitory control." Mechanisms proposed include increased nerve signaling, increased expression of receptors and related molecules, decreased nerve-firing threshold, and altered central nervous system modulation. Moreover, 5-hydroxytryptophan plays a critical role in the regulation of GI motility, secretion, and sensation. These changes are hypothesized to modify the relation between the enteric and central nervous systems or the "brain–gut" axis. In addition, FGIDs are associated with patients who experience early life events, such as infants operated on for pyloric stenosis, children with Henoch-Schönlein purpura, and children with cow milk protein allergy. (4)

Although these mechanisms and early life events can predispose patients to the development of visceral hyperalgesia, not all individuals will develop symptoms.

The Role of Motility

The role of GI motility in this subset of disorders cannot be understated. In the context of functional disorders,

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Table 2. Rome III Criteria for Abdominal Pain–Related Functional GI Disorders in Children

Functional dyspepsia
- Diagnostic criteria[a] must include all of the following.
  - Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus)
  - Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (ie, not irritable bowel syndrome)
  - No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the patient's symptoms

Irritable bowel syndrome
- Diagnostic criteria[a] must include both of the following:
  - Abdominal discomfort[b] or pain associated with two or more of the following at least 25% of the time:
    - Improvement with defecation
    - Onset associated with a change in frequency of stool
    - Onset associated with a change in form (appearance) of stool
  - No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the patient's symptoms

Abdominal migraine
- Diagnostic criteria[c] must include all of the following:
  - Paroxysmal episodes of intense, acute periumbilical pain that lasts for ≥1 hour
  - Intervening periods of usual health lasting weeks to months
  - The pain interferes with normal activities
  - The pain is associated with two of the following:
    - Anorexia
    - Nausea
    - Vomiting
    - Headache
    - Photophobia
    - Pallor
  - No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the patient's symptoms

Childhood functional abdominal pain
- Diagnostic criteria[a] must include all of the following:
  - Episodic or continuous abdominal pain
  - Insufficient criteria for other functional GI disorders
  - No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the patient's symptoms

Childhood functional abdominal pain syndrome
- Diagnostic criteria[a] must satisfy criteria for childhood functional abdominal pain and have, at least 25% of the time, one or more of the following:
  - Some loss of daily functioning
  - Additional somatic symptoms such as headache, limb pain, or difficulty sleeping

Reprinted with the permission of the Rome Foundation (http://www.romecriteria.org). GI=gastrointestinal.
[a] Criteria fulfilled at least once per week for at least 2 months before diagnosis.
[b] "Discomfort" means an uncomfortable sensation not described as pain.
[c] Criteria fulfilled two or more times in the preceding 12 months.

the cause of abdominal pain is postulated to be due to strong contractions and/or the resultant sensation of pain from distension of the GI tract. Visceral hyperalgesia in the setting of distension has been well documented in patients who have IBS as well as in patients who have functional dyspepsia. In two studies, inflation of a balloon in the stomach of those who had functional dyspepsia and the rectosigmoid region in patients who had IBS caused greater discomfort at lower balloon volumes than in healthy controls. (5)(6) Furthermore, mild dysmotility (ie, mild delayed gastric emptying) may be seen in patients with FGIDs (ie, functional dyspepsia).

Psychological/Sociologic Factors

Underlying psychological factors as well as heightened psychological responses to stimuli seem to play a role in the pathogenesis of the abdominal pain–associated FGIDs. The stress response as a result of underlying anxiety, depression, and other positive and negative stimuli is thought to modify GI motility. Caregiver anxiety is also

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Table 3. Alarming Signs and Symptoms

• Weight loss	• Family history of GI disease
• Recurrent oral ulcers	• Dysphagia
• Bilious emesis/hematemesis	• Anemia
• Unexplained fevers	• Leukocytosis
• Nocturnal symptoms	• Hypoalbuminemia
• Melena	• Unexplained rashes
• Hematochezia	• Chronic unexplained diarrhea
• Occult GI blood loss	• Acute abdomen (rebound, guarding)
• Joint symptoms	• Elevated inflammatory markers (ESR,CRP, platelets)
• Dysuria/hematuria/flank pain	• Jaundice/scleral icterus
• Delayed puberty	• Anal skin tags, fissures
• Linear growth failure	• Referred pain to back, shoulders

CRP=C-reactive protein; ESR= erythrocyte sedimentation rate; GI=gastrointestinal.
Adapted from Collins BS, Thomas DW. Chronic abdominal pain. *Pediatr Rev.* 2007;28(9):325.

a contributing factor. Children who have recurrent abdominal pain and have parents with IBS report more GI symptoms, more physician visits for GI symptoms, and have more school absences compared with children who have recurrent abdominal pain but whose parents do not have IBS. It is a common misconception that further testing aids in alleviating anxiety. Negative test results do not reassure the child's parents; rather, tests reinforce the parents' fear of an unknown organic disease, which makes it harder to introduce the concept of a functional disorder afterward. (7) The judicious ordering of laboratory studies, radiographic evaluations, and procedures should be limited to those children who have alarming symptoms (Table 3). Moreover, as with many disorders both organic and nonorganic, a biopsychosocial approach to diagnosis and treatment is most beneficial for the patient.

Other Proposed Mechanisms

Research of FGIDs in both adults and children is expanding rapidly. Adult IBS in particular has received a great deal of attention. Recent studies have examined small bowel bacterial overgrowth, acute infectious disorders that result in chronic changes, and enteric serotonin pathways as potential causes.

Diagnosis

Recognition of abdominal pain–associated FGIDs is difficult. A unique diagnostic tool to aid in confirmation does not exist. Comprehensive history and physical examination are of the utmost importance. Again, specific laboratory, radiographic, endoscopic, and surgical procedures should be reserved for those children who require further evaluation as deemed necessary by either the primary care physician or the specialist. Education of the patient and family about FGIDs cannot be overemphasized and should begin as the evaluation is initiated, especially if suspicion is high. In most cases, explanation of the pathophysiology of FGIDs helps alleviate the concerns related to symptoms and also lays the groundwork for reasonable expectations of the patient and family.

Treatment

In children who meet the criteria for diagnosis of FGIDs, treatment is multifactorial, with the aim of diminishing abdominal pain and associated symptoms. Treatment should begin with education, as mentioned earlier. Identifying potential triggers and eliminating them is crucial. The approach to the patient should be multidisciplinary, including medical treatment for pain, psychological treatment with cognitive behavioral therapy (CBT), and dietary modifications. Treatment of pain associated with FGIDs can include antispasmodic agents such as dicyclomine, tricyclic antidepressants, and selective serotonin reuptake inhibitors. Tricyclic antidepressants and selective serotonin reuptake inhibitors can be particularly beneficial for those patients who have comorbid anxiety or depression.

A time-limited trial of acid suppression (ie, proton pump inhibitor therapy) can be considered; however, the medication should be discontinued if there is no improvement in symptoms. Peppermint oil has been reported to be beneficial in children who have IBS. In one study, GI symptoms, including abdominal pain, improved after a 2-week course of peppermint oil capsules dosed on the basis of weight. Although data are conflicting, a time-limited empiric trial of peppermint oil may be beneficial. (8)

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CBT includes relaxation training, cognitive restructuring, guided imagery, self-monitoring, educational support, and modifying family response to illness. CBT has been shown to be very effective in the treatment of the abdominal pain–associated FGIDs. Although anecdotal, dietary modifications can include avoidance of irritating foods such as tomato-based foods, citrus-containing foods, caffeinated and carbonated drinks, and greasy and spicy foods. Probiotics also have been shown to be helpful in the treatment of FGIDs, but their mechanism of action is not clear. Based on a single randomized controlled trial of IBS in children, the 2010 American Academy of Pediatrics Clinical Report concluded that probiotics, specifically *Lactobacillus GG*, may be of benefit in children. However, a firm recommendation could not be made without further confirmatory studies. (9)

Functional Dyspepsia

Functional dyspepsia is defined according to the Rome III criteria as persistent or recurrent pain or discomfort (>2 months) centered in the upper abdomen (above the umbilicus). This pain is not relieved by defecation or associated with the onset of a change in stool frequency or stool form, as seen in IBS (Table 2). Children report a variety of symptoms, including epigastric pain relieved by meals, bloating, postprandial fullness, early satiety, and nausea. A recent history of a preceding viral illness with symptoms as described here could be consistent with postviral gastroparesis. Small, frequent meals, as well as time-limited empiric trials of acid-suppressing or prokinetic medication, may be helpful in these patients. Persistence of symptoms beyond 2 months would necessitate referral to a pediatric gastroenterologist for further evaluation.

Irritable Bowel Syndrome

IBS is defined according to the Rome III criteria as abdominal discomfort or pain associated with two or more of the following at least 25% of the time: improvement with defecation, alteration in stool frequency, and variation in form of stool (Table 2). This disorder is categorized further as constipation-predominant IBS, diarrhea-predominant IBS, and combined IBS (alternating constipation- and diarrhea-related IBS). A biopsychosocial approach should be followed and must include an assessment of potential contributing psychological or sociologic stressors. Most clinicians agree that there is a large population of children who do not fulfill the criteria for IBS despite reporting similar symptoms. Some of these children most likely suffer from stool withholding because they report intermittent abdominal pain and constipation. Standard therapy for this subset of patients includes increasing dietary fiber and water intake, which improves transit through the gut. In addition, osmotic laxatives can be considered if dietary modification fails to provide adequate relief of symptoms in those patients who have constipation-predominant IBS. In most cases, treatment of constipation will relieve symptoms.

For the subset of children with diarrhea-predominant IBS, limiting carbohydrates (ie, fructose) as well as nonabsorbed carbohydrates (ie, sorbitol) will be beneficial. Recently, a diet low in fermentable oligo-, di-, and mono-saccharides and polyols has been shown to reduce symptoms of IBS. (10)(11) This diet includes restriction of fructo-oligosaccharides (eg, wheat, onion, garlic), galacto-oligosaccharides (eg, legumes), and polyols (eg, sugar-free gums, some fruits and vegetables).

In cases refractory to dietary therapy, slowing down motility with drugs such as diphenoxylate/atropine may be needed to improve quality of life. Again, identification and avoidance of food irritants and other triggers (ie, stressful situations, anxiety) will help provide relief to the majority of patients who have IBS. Even simple modifications, such as a school note from the physician for bathroom breaks whenever needed, help alleviate symptoms in some cases.

Abdominal Migraine

Abdominal migraine is defined according to the Rome III criteria as paroxysmal episodes of intense, acute periumbilical abdominal pain lasting 1 hour or more (Table 2). Distinguishing abdominal migraine from other disorders is the period of usual health between episodes. To meet criteria for diagnosis, two or more of the following must accompany the abdominal pain: anorexia, nausea, vomiting, headache, photophobia, and pallor. Commonly, a history of classic migraine will be derived from the patient's family history. The diagnosis of abdominal migraine should be reserved for those patients in whom other potential serious causes of paroxysmal abdominal pain have been ruled out.

Treatment is both supportive and preventative. Again, avoiding food and beverages (ie, caffeinated drinks) that are known triggers is helpful in many patients. Other stimuli include change in sleep patterns, stress, bright or flickering lights, and prolonged fasting. For those patients in whom episodes remain frequent, prophylactic medication can be used, such as propranolol and cyproheptadine. Sumatriptan can be used as abortive therapy for pain and nausea symptoms.

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Functional Abdominal Pain

A subset of children exists that does not meet criteria for the other abdominal pain–associated FGIDs (Table 2). These children experience episodic or continuous abdominal pain for 2 months or longer. Children who have functional abdominal pain and 25% of the time have some loss of functioning or further somatic complaints are classified as having childhood functional abdominal pain *syndrome*. Treatment involves reducing or eliminating symptoms as well as restoring the normal routine, including a return to the usual activities and school. In these patients, identifying risk factors and starting CBT early on have proven to be effective in pain relief for the majority of patients. (12) An empiric trial of a tricyclic antidepressant or selective serotonin reuptake inhibitor may aid in alleviation of symptoms.

Role of Acid Peptic Disorders in Chronic Abdominal Pain

The cause of acid peptic disorders is due to the loss of the normal balance between protective (bicarbonate secretion, mucus layer) and aggressive factors (acid, bile acids, caustic substances) within the upper GI tract. This imbalance can lead to esophagitis, gastritis, gastric ulcer, duodenitis, and duodenal ulcer formation. Removal of the offending substance (if present) and a time-limited empiric trial of acid suppression are useful in these patients. After discontinuation of acid suppression, if symptoms return, referral to a pediatric gastroenterologist is indicated.

The incidence of these disorders in children afflicted with chronic abdominal pain is not known. Many children will still meet criteria for one of the abdominal pain–associated FGIDs. Dyspepsia can be perceived by the patient as symptoms resulting from disordered digestion of food. Bloating, early satiety, nausea, and vomiting are other symptoms that may be reported. Sixty percent of patients with dyspeptic symptoms have functional or nonulcer dyspepsia, but the other 40% have structural or biochemical disease. Differentiation of acid peptic disorders from functional dyspepsia may be difficult. For this reason, other alarming symptoms (Table 3) should be reviewed carefully.

Certain clinical patterns can be helpful in determining the diagnosis of dyspepsia. Peptic ulcer disease–related symptoms usually occur 2 to 5 hours after meals or on an empty stomach. Symptoms also may occur at night (11 PM to 2 AM) when the circadian stimulation of acid secretion is maximal. The ability of alkali, food, and antisecretory agents to produce relief suggests the role of acid in this process. Gastroesophageal reflux disease can be suspected when symptoms of dyspepsia are accompanied by predominant complaints of heartburn and regurgitation. Functional biliary pain, characterized by a low gallbladder ejection fraction, also can present with dyspeptic symptoms, predominantly epigastric abdominal pain. Carney et al (13) reported that children who have abdominal pain, nausea, and a gallbladder ejection fraction of less than 15% are more likely to report resolution of symptoms after a cholecystectomy.

Another pain pattern is chronic pain emanating from the abdominal wall. This disorder frequently goes unrecognized or is confused with visceral pain, often leading to extensive diagnostic testing before an accurate diagnosis is achieved. The diagnosis usually can be established on the basis of the history and physical examination. A response to treatment with a topical or local anesthetic agent can provide confirmation. Nonsteroidal anti-inflammatory drug–induced dyspepsia is not uncommon. Careful history can reveal the cause, and use of the drug should be discontinued whenever possible. If needed, concomitant use of a proton pump inhibitor with nonsteroidal anti-inflammatory drugs has been proven beneficial in reducing symptoms.

Helicobacter pylori infection can lead to significant damage to the upper GI tract, specifically the stomach and duodenum. However, discovery of *H pylori* in the setting of abdominal pain does not indicate a causal relationship between the two factors. (14) Routine screening for *H pylori* in children who have functional abdominal pain is not recommended.

Role of Lactose Intolerance in Chronic Abdominal Pain

Lactose intolerance is defined in the American Academy of Pediatrics' clinical report as "a clinical syndrome of 1 or more of the following: abdominal pain, diarrhea, nausea, flatulence, and/or bloating following ingestion of lactose containing food substances" (15). Intolerance to lactose-containing foods (primarily dairy products) is common. In Europe and the United States, the prevalence is 7% to 20% in white adults and is as high as 80% to 95% among Native Americans, 65% to 75% among Africans and African Americans, and 50% in Hispanic individuals.

Congenital lactase deficiency is rare. Primary lactase deficiency, which is due to reduced genetic expression, can develop in children. The age of onset and prevalence varies among ethnic groups. Secondary lactase deficiency can occur after an insult (ie, gastroenteritis, celiac disease,

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inflammatory bowel disease) that causes mucosal injury. Symptoms in all cases are due to low intestinal lactase levels and the resulting malabsorption.

Patients who have FGIDs such as IBS have been found to have increased symptoms with lactose ingestion. A 5-year prospective study evaluated a lactose-restricted diet in patients who had lactose malabsorption and IBS. (16) The study demonstrated improvement in both short- and long-term symptoms as well as a reduction in outpatient visits by 75%. Due to the similarities in symptoms of both IBS and lactose intolerance, an empiric trial of a lactose-free diet can be tried as part of the evaluation. The diagnosis can be confirmed with a lactose breath hydrogen test or disaccharidase analysis from small intestine biopsy samples taken during an upper endoscopy.

Treatment with dietary changes include reduced dietary lactose intake, substitution of alternative nutrient sources to maintain energy and protein intake, administration of a commercially available enzyme substitute, and maintenance of calcium and vitamin D intake. Although lactose intolerance can cause abdominal pain, the exact prevalence of lactase deficiency in children who have chronic abdominal pain is not known. In a single-center, retrospective study, Croffie et al (17) reported that less than 1% of children who had recurrent abdominal pain were found to have lactase deficiency. The discovery of lactase deficiency during evaluation for chronic abdominal pain should be presented to the patient and family as a potential cause for the symptoms. However, it should also be conveyed that despite treatment for lactose intolerance, the symptoms could remain, and a direct causal relationship between the two cannot always be made.

Conclusions

Chronic recurrent abdominal pain in children is a common presenting complaint to primary care physicians and subspecialists alike. Initial evaluation should begin with a comprehensive history and physical examination. Providers should be aware of the common causes of chronic abdominal pain in children. Furthermore, knowledge of concerning signs and symptoms will help guide potential evaluation, management, and referral. A large percentage of children who have chronic abdominal pain will meet criteria for one of the abdominal pain–associated FGIDs. The Rome III criteria can serve as a diagnostic tool with this subset of children. Treatment of this class of FGIDs is multifactorial. The biopsychosocial model is helpful for the provider, patient, and family alike.

Summary

- Research suggests that 13% to 17% of the pediatric population report chronic abdominal pain. Careful attention to potential warning signs is paramount. Prompt referral is indicated if warning signs are present.
- For those patients with suspected functional gastrointestinal disorders, research and clinical consensus emphasize that education of the patient and family is important. Discussion of the etiology of functional gastrointestinal disorders should start at the beginning of the evaluation if suspicion is high.
- Limiting radiographic and serologic evaluation to those patients with concerning signs and symptoms has been shown to decrease caregiver anxiety. Moreover, ordering further evaluation can perpetuate the belief that an organic cause is present.
- Based on strong research evidence, cognitive behavioral therapy has been shown to be beneficial in the treatment of functional gastrointestinal disorders.
- Based on research evidence, although *Helicobacter pylori* infection and lactase deficiency can lead to abdominal pain, the frequency of these findings in children who have chronic abdominal pain is low. Routine screening for both entities is not recommended in children who have chronic abdominal pain.

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PIR Quiz

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Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for *AMA PRA Category 1 Credit™*. In order to successfully complete 2012 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

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1. A 7-year-old boy has had upper abdominal pain 2 to 3 times per week for the past 2 months, causing him to miss 8 days of school during the fall. His pain is not relieved after having a bowel movement. His stools are well formed and have not changed in character since the onset of the pain. Upper endoscopy reveals normal findings. Which of the following diagnoses matches this clinical presentation?

   A. Abdominal migraine
   B. Acid peptic disease
   C. Functional dyspepsia
   D. Inflammatory bowel disease
   E. Irritable bowel syndrome

2. A 11-year-old girl has a history of periods of intense periumbilical pain with nausea and vomiting that last 4 to 6 hours and occur daily for almost a week. These episodes have occurred each fall since she was in the first grade. Typically, she tries to sleep between bouts because the pain is so exhausting. During the remainder of the year, she is well. Her mother reports that she has had nausea and vomiting only once outside of these bouts and that was when everyone in the family had gastroenteritis. Which of the following diagnoses matches this clinical presentation?

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A. Abdominal migraine
B. Acid peptic disease
C. Functional dyspepsia
D. Inflammatory bowel disease
E. Irritable bowel syndrome

3. A 13-year-old-girl has had daily abdominal pain that is at least 3/10 in intensity for the past 4 months. Sometimes, the pain is located in either the right or left lower quadrant, but primarily the pain is periumbilical or diffuse. The pain is not associated with her menses, which started when she was 11 years old. Since the onset of her pain, she has developed diarrhea, which she describes as a loose stool after every meal, after which the pain usually lessens. She has had a normal urinalysis and negative pelvic ultrasonography. Which of the following diagnoses matches this clinical presentation?

A. Abdominal migraine
B. Acid peptic disease
C. Functional dyspepsia
D. Inflammatory bowel disease
E. Irritable bowel syndrome

4. A 14-year-old boy had a 3-day bout of gastroenteritis approximately 6 weeks ago. Ever since, he has complained of almost daily epigastric pain that is relieved by eating; however, he feels bloated and even nauseated if he has more than a snack or small meal. He denies constipation or diarrhea. Which of the following diagnoses matches this clinical presentation?

A. Abdominal migraine
B. Acid peptic disease
C. Functional dyspepsia
D. Inflammatory bowel disease
E. Irritable bowel syndrome

5. A 14-year-old mildly overweight girl had recurrent abdominal pain for more than 1 year during toddlerhood. A motility study revealed mildly delayed gastric emptying. For the past 6 months, she has been trying to lose weight by restricting her diet. She has noted that her stools have become harder and less frequent, and she often has diffuse abdominal pain and cramping that is relieved by having a bowel movement. Which of the following diagnoses matches this clinical presentation?

A. Abdominal migraine
B. Acid peptic disease
C. Functional dyspepsia
D. Inflammatory bowel disease
E. Irritable bowel syndrome

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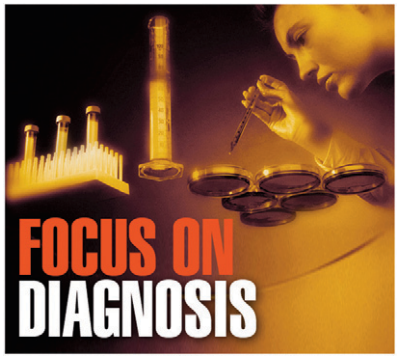

Author Disclosure
Dr Mezoff has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Dysphagia

Ethan A. Mezoff, MD

Introduction

Dysphagia, or difficulty with swallowing, may present alone or with accompanying signs and symptoms. The evaluation of dysphagia is guided by an accurate and thorough history, taken in consideration of the vast differential diagnosis. A brief review of the physiology of swallowing is followed by a differential diagnosis and historical points that should direct the diagnostic evaluation. Finally, a review of diagnostic and treatment options is presented.

Physiology of Swallowing

Swallowing prepares and transfers a bolus of consumed or secreted substance from the mouth to the stomach. Initially, the pooling of oral secretions forms a bolus, with or without masticated food. This bolus is then transferred to the upper esophagus during the oropharyngeal phase of swallowing. During this phase, the epiglottis covers the larynx to prevent aspiration of the bolus. Additionally, the soft palate is elevated against the nasopharynx to prevent nasal regurgitation of the bolus. Transfer of the bolus to the stomach then occurs through peristaltic muscle contractions of the circular and longitudinal smooth muscles of the esophagus and relaxation of the lower esophageal sphincter. The developmental milestone of swallowing typically is reached at 34 weeks gestational age in premature infants.

Differential Diagnosis

It is best to separate oropharyngeal from esophageal causes when considering the differential diagnosis of dysphagia. Oropharyngeal causes, in general, are grouped as neuromuscular, infectious/inflammatory, or structural (Table 1). Esophageal causes are divided into structural causes, dysfunctions of motility, and mucosal disorders (Table 2).

History and Physical Examination

The importance of a thorough and accurate history cannot be overstated. In adults presenting with dysphagia, the likely diagnosis may be uncovered while obtaining a history in approximately 75% of patients. (1) Adolescents may provide an accurate history; however, infants may present with nonspecific feeding symptoms such as poor interest, neck muscle strain, or stridor. Drooling between meals also may be present. Initially, an assessment of airway patency and respiratory effort is necessary. At this time, considerations should be made for conditions requiring urgent treatment, including foreign body aspiration, caustic ingestion, epiglottitis, myasthenia gravis, tetanus, and diphtheria. Next, the focus should be on distinguishing between oropharyngeal and esophageal causes.

Oropharyngeal Causes

In general, oropharyngeal causes of dysphagia are indicated by delayed swallow initiation, postnasal regurgitation during swallow, cough with swallow, drooling, or persistent throat clearance. Owing to referred viscerosomatic sensation, neck symptoms do not indicate oropharyngeal rather than esophageal origins. When structural lesions are not readily apparent,

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Table 1. Oropharyngeal Causes of Dysphagia

Neuromuscular Causes	Infectious/Inflammatory Causes	Structural Causes
Amyloidosis	Botulism	Cleft lip
Brain tumor	Coxsackievirus	Cleft palate
Cerebral palsy	Cytomegalovirus	Congenital esophageal web
Cerebrovascular accident	Diphtheria	Goiter
Dystonic reaction	Epiglottitis	Lymphadenopathy erythematosus
Guillain-Barré syndrome	Encephalitis	Tetanus
Multiple sclerosis	Herpes simplex virus	
Myasthenia gravis	Juvenile dermatomyositis	
Sarcoidosis	Neurosyphilis	
Systemic lupus	Peritonsillar abscess	
	Polio	
	Retropharyngeal abscess	

one may proceed to evaluation for neuromuscular or infectious/inflammatory disorders.

The nature of the onset of symptoms may help to refine further the differential diagnosis. Sudden onset generally indicates neurologic dysfunction, possibly due to a cerebrovascular accident in populations at risk. Subacute onset can be seen with infectious or autoimmune causes. Although rare, progressive onset may indicate external mass effect. Persistent, nonprogressive symptoms can suggest static neurologic dysfunction due to cerebral palsy or subtle structural abnormalities such as cleft palate or choanal atresia.

Systemic signs and symptoms may provide the astute clinician with further clues. Feeding refusal with oral mucosal lesions and an otherwise reassuring examination may indicate coxsackievirus, herpes simplex virus, or cytomegalovirus. Fevers in the context of oropharyngeal dysphagia may indicate retropharyngeal or peritonsillar abscess. Encephalitis and neurosyphilis also are considerations when the patient demonstrates focal neurologic findings, seizures, or altered mental status. Any neurologic process affecting bulbar function may cause swallowing dysfunction. Botulism or myasthenia gravis will present with diffuse weakness. Drug-induced dyskinesia will be indicated by other extrapyramidal effects. Finally, rash may be expected with a rare cause of dysphagia, juvenile dermatomyositis.

Esophageal Causes

Esophageal causes of dysphagia present with retrosternal chest pain or "sticking" sensations with swallowing. The presence of symptoms when swallowing both solids and liquids indicates motility dysfunction. Examples of motility dysfunction include achalasia (failure of the lower esophageal sphincter to relax) or diffuse esophageal spasm, both rare. Difficulty swallowing solid materials only indicates an obstructive process. Obstructive processes can be intrinsic to the esophagus, such as stricture caused by chronic inflammation associated

Table 2. Esophageal Causes of Dysphagia

Motility Disorders	Structural	Esophagitis
Achalasia	Intrinsic	*Candida* infection
Diffuse esophageal spasm	Esophageal web	Caustic ingestion
Scleroderma	Zenker diverticulum	Chlamydia infection
	Stricture	Crohn disease
	Extrinsic	Eosinophilic esophagitis
	Foreign body	Gastroesophageal reflux disease
	Mediastinal mass	Herpes simplex virus
	Pulmonary sling	Pill esophagitis
	Vascular ring	

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with gastroesophageal reflux disease, Crohn disease, or eosinophilic esophagitis. Mediastinal masses, vascular rings, and pulmonary slings cause obstruction from outside the esophagus.

Finally, pain generally indicates esophagitis. Infectious esophagitis is usually caused by *Candida*, or, less frequently, herpes simplex virus or cytomegalovirus, and should prompt immunodeficiency evaluation and human immunodeficiency virus infection screening. Intermittent pain following meals may indicate gastroesophageal reflux disease, and pain in male teens also should prompt consideration of eosinophilic esophagitis. Finally, it is important to remember that 20% to 40% of those with Crohn disease experience esophageal involvement.

Diagnostic Evaluation

Laboratory evaluation of the child presenting with dysphagia should proceed according to findings on the history and physical examination. Several radiologic and procedural techniques for evaluation are available although extensive workup may not be necessary to arrive at the correct diagnosis.

Videofluoroscopic barium studies involve the administration of contrast for the radiographic observation of swallowing. A barium swallow study observes the oropharyngeal phase of swallowing. This test is done with the collaboration of a speech and language therapist who may tailor treatments with the use of results from this study. Liquids, semisolids, and solid foods are tested. In addition to observing bolus handling through the oropharyngeal swallow, the study may reveal aspiration. A drawback to this test is the use of radiation directed at the head. In addition to permitting observation of the esophageal phase of swallowing, barium esophagography evaluates for extraesophageal causes of dysphagia, which may be missed by endoscopy.

Fiberoptic endoscopic evaluation of swallow with or without sensory testing involves the passage of a flexible endoscope through a nostril to observe pharyngeal soft tissue structures directly, immediately before and after swallowing. The procedure may detect laryngeal penetration of the food bolus as well as incomplete clearance. Sensory testing involves the use of a puff of air to stimulate the laryngeal adductor reflex, which is responsible for the airway protection response. Limitations include the need for technical expertise and the possibility of patient intolerance.

Upper endoscopy is used to observe the esophageal mucosal appearance directly and obtain tissue biopsies when indicated. This test may detect and differentiate among causes of esophagitis. Also, endoscopy may reveal remnant food particles, indicating the possibility of dysmotility. Sedation is necessary for this procedure.

Esophageal manometry measures esophageal pressures and pressure changes during swallowing. Manometry involves passage of a catheter with pressure sensors along its length. This study is used to evaluate for motility disorders.

Treatment

The treatment of dysphagia depends on its cause and severity. With severe cases or in those patients with excessive salivary excretion, medical or surgical management of secretions may be necessary. A treatment plan is determined best by a multidisciplinary team, including a dietician, behavioral psychologist, speech and language pathologist, occupational therapist, and physician. Nutritional goals should be set immediately for all patients. In some cases, maintaining nutrition will require temporary or permanent feeding tube placement. If possible, swallowing rehabilitation is attempted by using texture modification, strengthening exercises, and rate control. The risk of aspiration must be taken into consideration for all patients.

Summary

- **The evaluation of the child with dysphagia requires a basic understanding of the swallowing mechanism, a detailed history, and thoughtful consideration of the differential diagnosis. Further testing will be well guided by this approach.**
- **Treatment is diagnosis-specific but should take into consideration the management of oral secretions, potential for aspiration, and nutritional needs.**

ACKNOWLEDGMENT. I thank Dr Adam Mezoff for his guidance and critical review of this manuscript.

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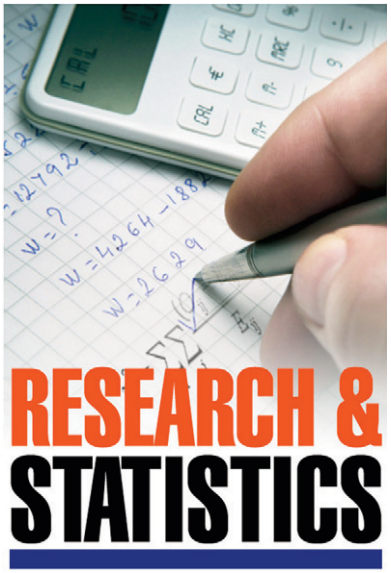

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Qualitative Research Methods

Kamila B. Mistry, PhD, MPH*

Case Study

You are evaluating a 4-month-old girl. On reviewing her history, you determine that the infant is not up to date on her vaccinations. You review the recommended immunization schedule with the parents and identify which vaccines were missed at 2 months. Both parents show reluctance to have their daughter vaccinated. You inquire about their reasons for not wanting to immunize; however, they do not provide any explanations. You wonder what the possible reasons could be for their perceptions regarding vaccinations. Your literature review reveals a qualitative study by Benin et al ("Qualitative analysis of mothers' decision-making about vaccines for infants: the importance of trust") that might offer some insight. (1)

What Is Qualitative Research?

Qualitative research is a systematic form of inquiry aimed at gaining a deeper understanding of the context of experiences, processes, and behaviors. This methodology provides a framework for investigating research questions that focus on understanding the "why" and "how" regarding human behaviors and beliefs, and often are used to generate hypotheses or build theory. (2) Qualitative methods traditionally have been used in the social sciences but also are used in clinical research, particularly when experiences and their underlying meaning cannot be measured by using standardized quantitative approaches. (2)(3)

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Qualitative and quantitative approaches share many similarities. Both involve defining research aims, selecting samples, and collecting and analyzing data. However, when and how these steps are accomplished is distinct for each method. Table 1 provides an overview of qualitative and quantitative approaches and compares key differences. Although there is no one best methodology, one approach may be a better "fit" for a particular research question. Qualitative and quantitative approaches often complement each other and can be combined (ie, mixed methods) to best address questions of interest.

There are many varieties of qualitative research; however, a few common features include the following: (1) the researcher attempts to capture data from the point of view of participants; (2) the data collection methods and analysis are concerned with gaining a "holistic" overview of the context under study; and (3) the researcher is interested in meaning gained through words or pictures in a descriptive way, rather than specified outcomes or products. (4)(5)

Sampling and Data Collection Methods

Samples in qualitative studies tend to be small and purposeful (ie, targeting subgroups with particular characteristics) rather than larger and random, as in many quantitative study designs. For instance, in the study by Benin et al (1), a two-sample approach was used to narrow focus and gain enough information on the main group of interest, the "nonvaccinators." In qualitative research, sampling involves balancing resources (time and funding) with the goal of

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Table 1. **Comparing Qualitative and Quantitative Approaches to Research**

Variable	Qualitative	Quantitative
Purpose of study/research question	• Contextualization • Building theory • Deepening understanding of phenomenon	• Testing hypotheses • Quantifying variation • Describing (causal) relationships • Generalizability
Sample	• Small • Purposeful	• Large • Representative
Data collection methods	• In-depth interviews • Focus groups • Direct observation	• Descriptive surveys • Case-control studies • Randomized controlled trials
Data analysis	• Nonstatistical, iterative process • Focus on text and describing patterns and characteristics	• Statistical • Focus on numeric comparisons, measurements, and predictions

ensuring that you have a sufficient number of "information-rich cases" who can elucidate the processes under investigation, and does not involve making "sample-to-population" generalizations. (1)(2)(4)

Data collection methods also vary considerably, depending on the nature of the research question. There are a number of specialized techniques; however, the primary methods include *direct observation, in-depth interviews,* and *focus groups. Direct observation* involves the systematic noting of events, behaviors, or objects within a specified setting. Initially, the researcher makes observations on the broad area of interest and records information using field notes (ie, nonjudgmental, detailed descriptions) that can be used later to determine patterns and create observational checklists. (4)

In-depth interviews have been described as "a conversation with a purpose."(4) Standardized interview guides with specific open-ended questions often are used in studies that involve multiple sites or larger numbers of participants to ensure a level of systematization and comparability across participants. (1) The study by Benin et al used in-depth interviews with a set of predetermined open-ended questions and probes (for elaboration) to assess mothers' knowledge and attitudes about vaccinations.

Focus groups are a specialized type of in-depth interview that have a long tradition in marketing research but also are used by social science and clinical researchers. This methodology uses a set of open-ended questions to allow for interaction among participants and therefore can provide insight into why and how attitudes are formed. Focus groups are not used to create consensus but rather to gather data on perceptions and to better understand how individuals listen to others in forming their opinions. Groups generally are composed of seven to 10 participants who have common characteristics relevant to the study questions. The interviews are conducted in a series of 3 or more to facilitate detection of patterns or trends across groups. (2)(4) The researcher (or a trained moderator) plays a key role in creating a supportive environment in which participants can express differing points of view. (3)(4)

Analysis

The nature of qualitative data analysis is iterative and involves three concurrent activities: *data reduction, data display,* and *conclusion drawing/verification.* (3) It is important to note that, unlike many quantitative methodologies, analysis begins as data are being collected and can be used to refine the focus of the study as it progresses.

Data reduction is the process of abstracting and distilling to produce summaries and themes. *Data display* includes methods designed to examine relationships and organize information into a more accessible and compact form, to aid in characterizing (coding) data and drawing conclusions. Displays can include matrices, graphs, and network diagrams.

Conclusion drawing/verification is not meant to generate a "final" conclusion but rather refers to the process of noting patterns and regularities in transcripts or field notes while remaining open as additional data are collected. Data verification is akin to the concept of validity in quantitative research. In the study by Benin et al (1), these three interconnected activities make up the "analysis."

The process is fluid, and the researchers shift between the activities before, during, and after data collection to generate results and draw conclusions. This approach to managing data is appropriate for qualitative research studies, although it differs from quantitative studies, which generally

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involve conducting statistical analyses to test predetermined hypotheses.

Limitations and Strengths of Qualitative Methods

The main disadvantage of a qualitative approach is that findings cannot be generalized to a particular population. The goal of qualitative research is to develop a deeper understanding of a particular phenomenon, rather than to determine a causal link between a specific set of factors. As such, the findings of qualitative research are not tested for statistical significance; however, drawing conclusions from data is possible through noting patterns and themes, and even comparing and contrasting data to sharpen an understanding of the results. As with quantitative research, the strength of the results rests on the quality of data collection and the appropriateness of the analytic methods used by the researchers. (3)

Conclusions

In this case, you were interested in gaining a deeper level of understanding regarding possible reasons underlying the parents' refusal to vaccinate. The qualitative approach used by Benin et al (1) allowed for the full range of possible promoters and inhibitors of mothers' acceptance of vaccinations to be explored adequately by using in-depth interviews. They found that a trusting relationship with the pediatrician or other health-care providers emerged as a key factor in the decision-making process regarding vaccines among new mothers. A quantitative study may not have uncovered or addressed this issue. These results may be relevant for future research and for practice in emphasizing trust building to promote vaccination of children.

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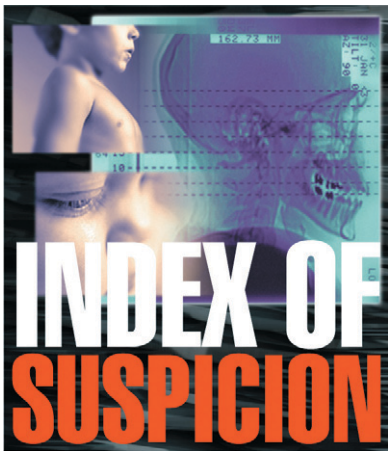

The reader is encouraged to write possible diagnoses for each case before turning to the discussion.

The editors and staff of *Pediatrics in Review* find themselves in the fortunate position of having too many submissions for the Index of Suspicion column. Our publication slots for Index of Suspicion are filled through 2013. Because we do not think it is fair to delay publication longer than that, we have decided not to accept new cases for the present. We will make an announcement in *Pediatrics in Review* when we resume accepting new cases. We apologize for having to take this step, but we wish to be fair to all authors. We are grateful for your interest in the journal.

Author Disclosure

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Case 1: Perinasal and Perioral Rash in a 2-year-old Girl
Case 2: Intractable Myoclonic Seizures in a 2-year-old Boy
Case 3: A 2-month-old Girl Who Has Failure to Thrive, Neutropenia, and Anemia

Case 1 Presentation

A 2-year-old white girl presents with a 2-month history of a rash around her mouth and nose. On examination, she has perioral and perinasal pink papules and papulopustules, which coalesce to form thin plaques, as well as occasional periorbital papules and a small area of crusting in the perinasal region (Fig 1). The rash is nonpruritic but accompanied by a burning sensation. Notably, the patient's vermilion border is spared.

Her past medical history is significant for a congenital cystic adenomatoid malformation (surgically resected at 6 weeks of age), atopic dermatitis, seasonal rhinitis, and asthma, requiring fluticasone propionate (44 mcg/puff twice daily) via a metered dose inhaler with spacer and face mask for the past 6 months (Fig 2). The dermatitis has been treated with over-the-counter cream and ointment without relief, but no topical products containing hydrocortisone have been used. The patient is seen by a dermatologist for the cause of the persistent facial rash, and her history and findings on physical examination lead to a presumptive diagnosis.

Frequently Used Abbreviations

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

Case 2 Presentation

A 2-year-old boy presents with a history of seizures since the age of 9 months. The first episode started as a febrile seizure and led to status epilepticus. He was diagnosed as having generalized epilepsy of unknown origin after evaluation by a neurologist and EEG. The seizure activity initially was generalized and tonic-clonic in nature. He would drop and exhibit jerking movements of the arms and legs, followed by generalized tonic posturing, accompanied also by rolling back of the eyes, drooling, and oral cyanosis. Recently, however, his seizures have consisted of myoclonic jerks, mainly of the upper extremities and torso, accompanied by twitching of the eyelids.

The child has been placed on multiple anti-epileptic medications including topiramate, levetiracetam, clonazepam, and lamotrigine, all of which have been ineffective. His seizures finally are partially controlled on divalproex sodium. However, he continues to have numerous seizures, which his parents feel are exacerbated by exposure to light. They have been keeping the child in a dark room with sunglasses

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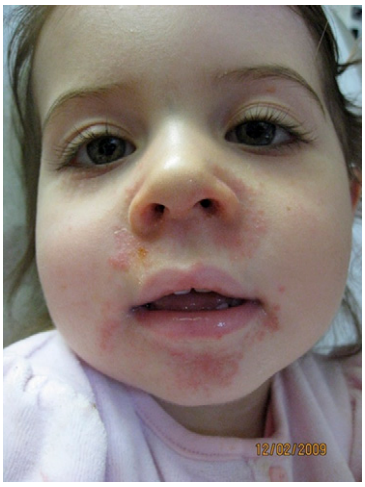

Figure 1. Perioral and perinasal pink papules and papulopustules that have coalesced to form thin plaques, occasional periorbital papules, and a small area of crusting in the perinasal region.

on for most of the time he is awake, which has decreased the frequency of seizures. The mother notes also that she can decrease the seizure activity by covering his eyes.

Given the intractable myoclonic seizures and photosensitivity, genetic testing is performed and reveals the diagnosis.

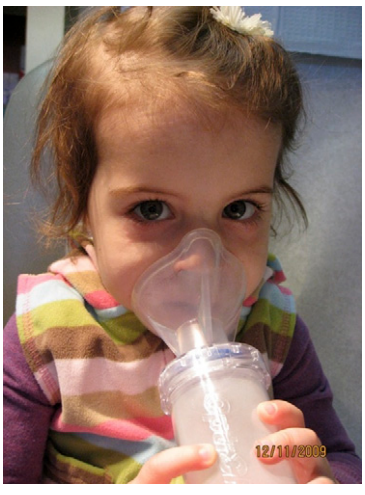

Figure 2. Patient using metered dose inhaler with spacer and face mask.

Case 3 Presentation

A 2-month old girl is referred for failure to thrive. She was born full term with a weight at the 10th to 25th percentile and now weighs less than the third percentile. She is breastfed exclusively and reportedly feeds well. Supplementation with formula has been tried without improvement in her weight gain.

On admission, the infant is notably small for her age. Her length and head circumference are at 10th to 25th percentile. Physical examination reveals her to be irritable but consolable, with mild hypotonia and dry skin. Findings on the rest of the examination are normal.

The initial laboratory evaluation reveals a normal urinalysis, serum ammonia level, and thyroid studies. A complete metabolic panel reveals serum protein of 3.6 g/dL and serum albumin of 2.4 g/dL. She has mildly elevated aspartate aminotransferase and alanine aminotransferase levels at 75 U/L and 54 U/L, respectively. Her complete blood count reveals an Hgb concentration of 9.4 g/dL with a mean corpuscular volume of 105 fL, a platelet count of 230 $\times$ 10^3/mcL, and a WBC count of 12.1 $\times$ 10^3/mcL with 56% neutrophils, 32% lymphocytes, and 12% monocytes.

Over the next several days, she is given formulas with increasing calories and fails to gain appropriate weight. She also continues to have approximately six loose stools per day. Fecal fat testing reveals large fat globules. Sweat chloride testing is normal.

A repeat blood count reveals a WBC count of 10.5 $\times$ 10^3/mcL with only 5% segmented neutrophils (absolute neutrophil count 525/mcL). Her Hgb level is now 8.1 g/dL, and the platelets are decreased to 173 $\times$ 10^3/mcL. Pancreatic enzymes are added to her formula, resulting in firmer stools. A genetic test is sent that confirms the diagnosis.

Case 1 Discussion

The presentation of papulopustular lesions in a periorificial (surrounding an opening) distribution along with a history of routine corticosteroid exposure to the area is characteristic of periorificial (perioral) dermatitis (POD).

The Condition

POD is a persistent papulopustular eruption that presents as discrete 1- to 2-mm papules irregularly grouped on an erythematous background, primarily around the mouth, with frequent involvement also of the perinasal and orbital (especially infraorbital) regions. Sparing of the vermilion border of the lips is characteristic. Histopathologically, the eruption is characterized by subtle eczematous changes in the perifollicular skin.

In adults, POD is most common in females aged 16 to 45, associated with the increased use of cosmetics and other topical facial products in this population. Although less well-described in the pediatric age group, recent reviews have revealed a higher incidence of POD in children under age 6 years as compared with older children. A gender predominance has not been determined in the pediatric population.

The exact cause of POD is unknown; however, an impaired skin barrier has been described as a critical causative factor in its development. Patients who have atopy or other intrinsic causes of skin barrier dysfunction may thus be predisposed to develop POD. Although no large association studies have been performed, a personal or family history of atopy is observed with high frequency in patients who have POD. A variety of extrinsic

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allergens and irritants, such as cosmetics, moisturizers, sunscreens, and fluoride-containing toothpastes, may trigger the initial epidermal dysfunction.

POD typically is aggravated markedly by topical corticosteroids, and exposure to steroids through topical products or inhaled medication, as in this patient, also may precipitate the dermatitis. A common scenario in children is the presence of an initial irritant contact dermatitis, treated with topical corticosteroids by family or physicians, leading to POD as a secondary eruption. Thus, the elimination of irritants and avoidance of all topical skin care products, particularly topical corticosteroids, is essential for healing and prevention of POD.

Differential Diagnosis

The differential diagnosis of POD in the pediatric population includes allergic or irritant contact dermatitis, acne vulgaris, atopic dermatitis, seborrheic dermatitis, and lip licker's dermatitis. Unlike contact dermatitis and lip licker's dermatitis (caused by habitual licking of the lips and surrounding skin), POD rarely involves the vermilion border. An absence of comedones can distinguish POD from acne vulgaris. In atopic dermatitis, pruritus is always present, and the extremities or trunk usually are involved in addition to the face, whereas in POD, pruritus may or may not be present, but a burning sensation or feeling of tightness is reported more commonly.

Seborrheic dermatitis, typically seen in either infants or adolescents, should be considered when the perinasal region is the sole location of involvement; presence of waxy scale near the scalp and eyebrows supports this diagnosis. In cases in which allergic contact dermatitis is suspected, patch testing can help to identify causative environmental allergens.

Treatment and Prognosis

To limit skin exposure to the corticosteroid, the patient's parents began washing her face with soap and water after every treatment, and she began the application of topical erythromycin 2% ointment twice daily to the affected areas. Although several medications have been used in the treatment of POD, topical 0.75% metronidazole gel has been associated with a good clinical outcome in at least one study, although this preparation is not licensed for use in children. These antibiotics are chosen for their anti-inflammatory properties and may prevent secondary infection of the dermatitis; if infection is suspected, appropriate diagnostic procedures should be performed.

Corticosteroids of any potency should be avoided, and patients who have experienced temporary alleviation with steroids should be advised of a rebound flare in erythema, papules, or pustules upon cessation that may continue for days to weeks if not treated otherwise. Families should be aware that the dermatitis commonly takes several weeks to resolve: averages of 7 weeks and 3 to 6 months have been reported. A several week course of topical metronidazole may be used solely or in combination with oral antibiotics (typically erythromycin, or doxycycline and tetracycline in children older than 8 years), particularly in more persistent or severe cases. POD may recur without obvious cause but improves spontaneously over time.

This patient's lesions began to show improvement within 10 days, and erythromycin was discontinued after 3 weeks. The dermatitis had completely resolved in 1 month. She continued to wash her face after she used the inhaler and has had no recurrence.

Lessons for the Clinician

- POD is a persistent, uncomfortable facial inflammatory condition, caused or exacerbated by glucocorticosteroids, which can be frustrating for patients and their families because it is misdiagnosed often as a steroid-responsive dermatosis.
- When POD in children is associated with inhaled corticosteroids, the eruption may be prevented simply with thorough cleansing of the facial skin after each exposure to the steroid.

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Case 2 Discussion

Genetic testing revealed that the boy has a severe-type mutation in the SCN1A gene. Both parents tested negative for this mutation indicating a *de novo* mutation in the patient. Thus, a diagnosis of Dravet syndrome, previously known as severe myoclonic epilepsy of infancy, is established.

The Condition

Dravet syndrome is a debilitating condition first described by Charlotte Dravet in 1978 in a group of children who had seizures beginning in infancy, normal early development, and a devastating course characterized by ongoing seizures and cognitive decline. (1) The disorder is relatively uncommon, with an incidence ranging from 1 in 40,000 to 1 in 20,000. Genetic

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mutations in the SCN1A gene encoding the α-1 subunit of a neuronal voltage-gated sodium channel are detected in up to 80% of patients who have Dravet syndrome. In 95% of these patients, the mutations arise *de novo*, which explains the lack of a family history of seizures in this condition.

The disease starts with prolonged febrile seizures during the first year after birth that progress frequently to status epilepticus. After 12 months of age, seizures develop without associated fever and the children develop other seizure types, including myoclonic, partial, and atypical absence seizures. Unlike the general population of individuals who have epilepsy, in which only 3% to 5% of patients have photosensitive seizures, 40% of children afflicted with Dravet syndrome demonstrate photosensitive seizures, in which light triggers seizure activity.

Dravet syndrome is associated with significant morbidity. Patients commonly have normal psychomotor development initially, but usually plateau by age 2 to 3 years. Subsequently, a gradual developmental delay is noted, and significant regression in skills may occur. This decline is thought to be caused by epileptic encephalopathy resulting from interictal epileptiform discharges. Most children become severely developmentally delayed and are unable to function independently. The mortality rate associated with the condition is 16% to 18%.

Differential Diagnosis

The differential diagnosis of Dravet syndrome includes generalized epilepsies of childhood. The myoclonic epilepsies of childhood constitute a specific group of seizure disorders that have diverse causes and outcomes but are typified by repetitive seizures with brief symmetrical forward jerking of the body that poses a risk of injury to the face.

- Benign myoclonus of infancy has a self-limiting course, with resolution of seizures by 2 years of age, normal development, and normal EEG findings.
- Infantile spasms present around 6 month of age with EEG revealing a chaotic pattern described as hypsarrhythmia. Approximately 20% of infants are classified as having the cryptogenic variety, which carries a good prognosis. The rest are classified as symptomatic and have a higher incidence of neurocutaneous syndromes; structural brain defects; prenatal, perinatal, or postnatal infections; and hypoxic ischemic encephalopathy. The risk of mental retardation is 80% to 90% and is related to the underlying neurologic disorder.
- Complex myoclonic epilepsies are a group of disorders that have a high incidence of mental retardation and a poor prognosis. These conditions present around age 12 months with focal or generalized tonic-clonic seizures, usually after a viral upper respiratory illness and often resulting in status epilepticus. Myoclonic seizures follow, which are refractory to anticonvulsants with slow spike waves on EEG.
- Typical myoclonic epilepsy of early childhood presents between 6 months and 4 years with approximately one half of patients also having tonic clonic seizures. Mental retardation is uncommon, but most patients develop learning, language, and behavior problems. EEG reveals fast spike waves and approximately one third of the patients have a positive family history.
- Juvenile myoclonic epilepsy presents during the teenage years, with frequent myoclonic jerks on waking up in the morning. Patients who have this disorder have a good prognosis, normal neurologic examination, 4 to 6/second irregular spike and wave pattern on EEG, and excellent response to valproate, which is needed for life.

Management

Seizures in patients who have Dravet syndrome often are refractory to anti-epileptic medications and may be exacerbated by carbamazepine and lamotrigine. Anti-epileptic medications such as valproic acid and benzodiazepines may reduce the frequency and duration of seizures, but they do not eliminate epileptic activity completely. Ketogenic diets (high fat, low carbohydrate, and moderate protein) also have shown to have some favorable effects in patients who have Dravet syndrome by reducing the number of seizures. The increase in ketone bodies that results from these diets has been thought to have an anti-epileptic effect.

Monocular or binocular occlusion using a cupped hand or patch has been advocated as a method of aborting myoclonic jerks whenever patients are exposed to a provocative visual stimulus. Interruption of binocular vision appears to control seizure activity because the visual input to the brain is reduced by half.

Clinical Course

The boy was continued on divalproex sodium, which decreased his seizure activity. In addition, he was started on a course of monocular patching (6 hours per eye alternating through the day), which resulted in a further reduction in his seizure frequency. He is now able to go outdoors in dim light and function better.

Lessons for the Clinician

- Dravet Syndrome should be suspected in children who:
  - Present in febrile status epilepticus before age 12 months

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  - Are unresponsive to commonly used anti-epileptic medication
  - Have light-induced seizures
  - Have significant regression in psychomotor skills after developing normally
- Genetic testing reveals SCN1A gene mutation and can confirm the diagnosis.
- Management is difficult and outcomes are poor due to epileptic encephalopathy.
- Carbamazepine and lamotrigine should be avoided in suspected cases because they may worsen the seizures.

(*Sanjeev Tuli, MD, Nausheen Khuddus, MD, Sonal Tuli, MD, University of Florida, Gainesville, FL*)

Case 3 Discussion

In view of neutropenia and apparent pancreatic insufficiency, genetic testing was sent for Shwachman-Diamond syndrome (SDS). The diagnosis was confirmed when the girl was found to have two common mutations in the SDS gene.

The Condition

SDS is an autosomal recessive condition caused by a mutation of alleles at 7q11. Heterozygotic individuals often are not identifiable at birth but will manifest the condition starting in infancy. All patients afflicted with SDS manifest gastrointestinal symptoms related to exocrine pancreatic dysfunction and also will have bone marrow dysfunction. As in this patient, failure to thrive is a common presentation.

Dysfunction of exocrine pancrease presents as malabsorption, steatorrhea, malnutrition, and failure to thrive. However, these symptoms may resolve over time, which can make the diagnosis more difficult in older children. Evaluation of this dysfunction may reveal an abnormal pancreatic stimulation test, elevated fecal fat excretion, decreased serum trypsinogen or isoamylase, and decreased serum levels of vitamins A, D, E, and K. Pancreatic enzyme supplementation is required.

Bone marrow dysfunction is another important component of the syndrome. Although the associated findings are variable, almost all children have neutropenia. Approximately two thirds will have cyclic neutropenia, and one third will have chronic neutropenia. This neutropenia, along with poor neutrophil chemotaxis, increases their risk for bacterial, viral, and fungal infections. For this reason, prompt attention to febrile illnesses is required. In fact, the neutropenia typically is recognized long before a diagnosis of SDS is made. Additionally, other cell lines may be low, with macrocytic anemia and thrombocytopenia being common findings. Leukemia and aplastic anemia may occur in some of these children. Bone marrow analysis classically reveals hypoplasia with fat infiltration, although the findings are variable.

Other symptoms are associated frequently with this syndrome. Various skeletal abnormalities are noted often, including metaphyseal dysostosis and rib cage abnormalities. This patient was noted to have an abnormal right clavicle but had no history of trauma. An orthopedic specialist should be involved when there are skeletal deformities. Many children who have SDS also have some liver dysfunction, with elevated liver enzymes, and may have hepatomegaly. Delayed dental development, eczema and ichthyosis, and urinary tract abnormalities also are common.

Differential Diagnosis

The clinician must consider alternate diagnoses for common manifestations of SDS. Cystic fibrosis should be ruled out with a sweat chloride test, because it is a much more common cause of pancreatic exocrine insufficiency. Other conditions that cause pancreatic dysfunction include Johanson-Blizzard syndrome and Pearson syndrome. Bone marrow dysfunction requires consideration of conditions such as Diamond-Blackfan anemia, Fanconi anemia, dyskeratosis congenita, aplastic anemia, and immunodeficiencies.

Management

Close follow-up over time is required because these children suffer from malnutrition and poor growth. Pancreatic enzyme supplementation helps with digestion and absorption. Supplementation of fat-soluble vitamins (A, D, E, and K) also may be indicated. Frequent monitoring of growth and development is vital.

Involvement of a hematologist and periodic blood counts and bone marrow evaluations are required due to the increased risk for malignancy. The only potential curative measure for the hematologic manifestations of SDS is a hematopoietic stem cell transplant. There is an increased susceptibility to serious infections, which may require more aggressive use of parenteral antibiotics.

Prognosis

Although children who have SDS typically are below the third percentile for size, with appropriate treatment and nutrition they can have normal growth velocities. Hepatic dysfunction typically resolves by age 5 years. Although they do remain at increased risk of infections, close follow-up and appropriate treatment can minimize this complication. An important lifelong association to be aware of is the increased risk for leukemia, specifically acute myelogenous leukemia. Although information is limited,

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the risk may be 25% or higher than the general population and the outcome of this condition generally is poor.

Lessons for the Clinician

- Although growth failure in children is related most often to social and environmental factors, a large differential diagnosis must be considered.
- A logical and progressive evaluation for growth failure often will lead to the underlying diagnosis.
- The common presenting features of SDS are related to bone marrow dysfunction and exocrine pancreatic dysfunction.

(Marc Yester, MD, Michael Kidder, MD, Wake Forest Baptist Medical Center, Winston-Salem, NC)

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In Brief

Aminoglycosides

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Author Disclosure

Drs Kothari and Krilov 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.

Clinical Response to Aminoglycoside Therapy: Importance of the Ratio of Peak Concentration to Minimal Inhibitory Concentration. Moore RD, Lietman PS, Smith CR. *J Infect Dis.* 1987;155(1):93–99

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Aminoglycosides were first introduced in the 1940s and are used widely for specific and empiric treatment of infections caused by aerobic gram-negative organisms. The suffix of each agent in the class denotes its origin: *–mycin* indicates aminoglycosides derived from *Streptomyces* species, whereas *-micin* identifies derivation from *Microsporum* species. Aminoglycosides currently approved for use in the United States are gentamicin, amikacin, tobramycin, streptomycin, neomycin, kanamycin, and paromomycin.

Aminoglycosides inhibit protein synthesis by binding irreversibly to the 30S subunit of the bacterial ribosome. Their passage through the cell wall is facilitated by concomitant therapy with β-lactam antibiotics or vancomycin. The attachment to the ribosomal subunit requires energy and oxygen and is inhibited by hyperosmolarity, low pH, and anaerobic conditions.

Aminoglycosides are administered intravenously over 15 to 30 minutes for traditional three times a day dosing, and, to minimize their toxicity, over 30 to 60 minutes for higher-volume once-daily dosing. After intramuscular injection, these drugs are absorbed completely, although conditions causing hypotension and impaired tissue perfusion may slow the absorption. Peak serum concentrations are achieved within 30 to 60 minutes.

Topical application over inflamed tissues and enteral formulations results in minimal systemic absorption. When an aminoglycoside is instilled into the pleural space or peritoneal cavity, its absorption is rapid and may lead to significant toxicity. Aerosol preparations lead to a higher concentration in bronchial secretions; nebulized tobramycin, for example, is useful in treating chronic bronchiectasis.

Penetration across an intact blood–brain barrier is poor. However, when there is inflammation of the meninges, approximately 20% to 25% of the serum concentration can be attained in the cerebrospinal fluid. Because that drug level is still below the minimum inhibitory concentration for gram-negative organisms, aminoglycosides are not recommended as monotherapy for meningitis but can be useful as part of combination therapy.

Once administered, aminoglycosides are distributed rapidly in extracellular body water, with slow accumulation in tissues. Aminoglycosides cross biologic membranes poorly because of their relatively large size, surface charges, and lipid solubility. Important exceptions are the proximal convoluted tubules in the kidneys and the inner ear cells, where a high concentration of the drug accumulates. Urine concentrations, for example, exceed concentrations in plasma by 25 to 100 times.

Aminoglycosides are rapidly bactericidal, and antimicrobial activity is achieved by virtue of their concentration-dependent killing, postantibiotic effect, and synergy with other drugs. Their activity is directly proportional to peak serum concentration, and maintaining a peak/minimum inhibitory concentration ratio of 8 to 10 leads to maximum bacterial killing. Aminoglycosides have persistent antimicrobial

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activity even after peak levels have fallen, a quality that is called the postantibiotic effect. An initial high concentration of aminoglycoside correlates with a longer duration of this effect, and the postantibiotic effect increases with higher concentrations of oxygen, lower bacterial inoculums, and higher pH.

The volume of distribution in neonates and infants age less than 6 months is greater because of increased total body water and immature renal function. The result is a prolonged half-life, which mandates reduced doses: a twice-daily regimen, rather than the thrice-daily schedule that is traditional in older infants and children, is the standard of care in this age group. With these regimens, the peak drug level should be obtained 30 minutes after the end of infusion and the trough level right before the next dose is due.

In general, peak levels correlate with efficacy and trough levels with the risk for toxicity. For example, trough levels of greater than 2 μg/dL for gentamicin or tobramycin correlate with an increased risk of toxicity. When the trough level is too high, either the dose can be decreased or the interval between doses can be increased. The trough level should then be rechecked after three to five doses. For susceptible organisms, peak levels of 8 to 10 μg/dL are the goal for gentamicin and tobramycin. Over the past decade, extended-interval aminoglycoside dosing, in which the total daily dose is given as a single dose (usually every 24 hours), has been evaluated as an effective method of administering aminoglycosides with improved efficacy and a similar safety profile. However, nomograms for monitoring serum drug levels with once-daily dosing have not been validated in children.

The major adverse effects of aminoglycosides are nephrotoxicity, ototoxicity, and neuromuscular blockade. Because of the potential for nephrotoxicity, dosing of aminoglycosides must be adjusted in patients who have decreased renal function. The risk for toxicity is worsened with concomitant use of nephrotoxic drugs or medications that promote neuromuscular blockade. Allergic reactions are uncommon, and aminoglycosides do not induce an inflammatory reaction, which decreases the likelihood of phlebitis at intravenous sites or pain at the site of intramuscular injection.

Aminoglycosides are used most often in combination with other antibiotics for septicemia, nosocomial respiratory infections, complicated intra-abdominal infections, and urinary tract infections caused by susceptible aerobic gram-negative rods (Tables 1 and 2). Gentamicin, tobramycin, and amikacin are effective in the empiric treatment of infections caused by gram-negative bacilli, including *Pseudomonas aeruginosa*, as well as gram-positive cocci, including *Staphylococcus aureus* and *Enterococcus*. When used against those organisms, aminoglycosides are always combined with a β-lactam antibiotic or vancomycin. Aminoglycosides have no activity against pneumococci or anaerobes.

Table 1. Empiric Indications for Aminoglycosides

Neonatal sepsis
Febrile neutropenia
Meningitis
Sepsis
Otitis externa
Infective endocarditis
Intra-abdominal infections
Nosocomial pneumonia

After the antimicrobial susceptibility results are available, aminoglycosides may be continued for specific indications. Tobramycin and amikacin demonstrate greater in vitro activity against *P aeruginosa*, whereas gentamicin is more effective against *Serratia*; for other gram-negative bacilli, amikacin, gentamicin, and tobramycin seem to have equal efficacy. Streptomycin and gentamicin are used in the treatment of plague and tularemia, as well as in combination with doxycycline for brucellosis. Streptomycin also is indicated for the treatment of resistant tuberculosis.

Table 2. Aminoglycosides Antimicrobial Spectrum

Organisms	Drugs Used in Combination
Klebsiella spp	Yes
Enterobacter aerogens	Yes
Serratia marcescenes	Yes
P aeruginosa	Yes
Francisella tularensis	Monotherapy
Brucella abortus	Yes
Yersinia pestis	Monotherapy
Vibrio vulnificus	Yes
Viridans streptococci	Yes
Enterococcus faecalis	Yes
S aureus	Yes
Staphylococcus epidermidis	Yes
Mycobacterium avium intracellulare	Yes
Mycobacterium tuberculosis	Yes
Entamoeba histolytica	Monotherapy
Cryptosporidium parvum	Monotherapy

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Comments: For obvious reasons of convenience and cost, especially for agents that must be administered parenterally, less frequent dosing is desired. The strategy of extended-interval dosing for aminoglycosides is becoming more and more common for adults. The regimen uses a higher dose of drug, thus providing a higher initial peak concentration, which apparently enhances bacterial killing. Because of the postantibiotic effect of aminoglycosides, their efficacy does not seem to be compromised by the longer duration below the peak. In fact, the extended duration below the peak seems to reduce toxicity. With extended dosing, a single serum level of the aminoglycoside can be obtained 6 hours after administration, and the optimal dosing interval (24 vs 36 vs 48 hours) is then determined with a nomogram. And there is the rub: no nomogram is yet available for infants or children, who, as we well know, are not simply little adults.

Henry M. Adam, MD
Editor, In Brief

Clarification

In the July 2012 article "Juvenile Idiopathic Arthritis" (Espinosa M, Gottlieb B. *Pediatr Rev.* 2012;33(7):303–313), the author makes it clear in the text that methotrexate has not been approved by the U.S. Food and Drug Administration for treating juvenile idiopathic arthritis, despite its efficacy in treating the condition. Thus, the disclosure statement at the beginning of the article should read "does include" rather than "does not include."

Corrections

In the September 2012 article "Pertussis in Childhood" (Snyder J, Fisher D. *Pediatr Rev.* 2012;33(9):412–421), the first sentence of the second paragraph under "Management" should read, "Although the clinical course of pertussis is not readily affected by treatment, the use of an appropriate antibiotic is indicated, even in the *paroxysmal* phase…".

In the August 2012 article "Vitamins" (Lauer B, Spector N. *Pediatr Rev.* 2012;33(8):339–352), the statement appears that niacin is not present in cereals or corn. Niacin is present in cereals, but not in corn. Question 2 of the quiz at the end of the same article describes a child from a vegetarian family who develops yellow skin with clear sclerae and is at risk for hair loss. The question is designed to make the point that children who ingest large amounts of yellow vegetables can develop carotonemia as well as minor effects of hypervitaminosis A, such as hair loss. They are not at risk for severe consequences, such as increased intracranial pressure. The journal regrets these errors.

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In Brief

Hymenoptera Stings

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Author Disclosure

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Stinging Insect Hypersensitivity: A Practice Parameter Update 2011. Golden DB, Moffitt J, Nicklas RA. *J Allergy Clin Immunol*. 2011;127(4):852–854.e1–e23

Allergic Reactions to Stinging and Biting Insects and Arachnids. Järvinen KM. *Pediatr Ann*. 2009;38(4):199–209

Anaphylaxis and Insect Allergy. Demain JG, Minaei AA, Tracy JM. *Curr Opin Allergy Clin Immunol*. 2010;10(4):318–322

The order Hymenoptera includes three distinct families: bees (*Apidae*), wasps (*Vespidae*), and ants (*Formicidae*). All members of this order are capable of stinging and have the potential to cause anaphylactic and nonanaphylactic reactions in humans. The insects differ in their normal behavior and method of envenomation.

Honey bees and bumblebees have barbed stingers and die after a single sting. They live in commercial hives and tree hollows and tend to sting only when provoked. Wasps, hornets, and most yellow jackets, all members of the *Vespidae* family, do not have barbed stingers and can sting multiple times. They tend to be more aggressive than bees, stinging without provocation. Wasps build honeycombs in shrubs and under eaves, hornets build nests in trees or shrubs, and yellow jackets build nests in the ground.

Finally, harvester and fire ants envenomate by anchoring their mandibles into the skin and pivoting; both are capable of multiple stings. These ants build large nests in mounds 1 to 2 feet in diameter and at least several inches in height. They bite aggressively if their nests are disturbed. Knowing the nesting locations and typical behavior of the insects helps in counseling patients on avoidance.

Hymenoptera stings can result in a wide spectrum of responses, from local swelling to anaphylaxis. The typical reaction involves localized pain, pruritus, erythema, and mild swelling at the sting site. For bee stings, treatment involves removal of the stinger by gentle scraping to avoid releasing more venom, applying ice packs, and using mild analgesics such as acetaminophen and antihistamines. These mild reactions resolve within hours to days.

More involved local reactions can lead to significant swelling and erythema contiguous to the site of the sting. This swelling can be life-threatening if in proximity to the airway. In evaluating these more extensive reactions, cellulitis may be considered, but tissue infection would be unlikely in the 24 to 48 hours after a sting, and antibiotics rarely are needed. Treatment continues to be supportive, although oral corticosteroids may be warranted. Large local reactions can take 5 to 10 days to resolve. These patients often have similar reactions with repeat stings. The risk of future anaphylaxis in patients after a large local reaction is not more than 5% to 10%.

The most severe reaction to a Hymenoptera sting is an acute systemic reaction (anaphylaxis), which accounts for ~40 to 50 fatalities per year in the United States. Potentially life-threatening reactions occur in 0.4% to 0.8% of all children. Symptoms can be cutaneous (hives, angioedema, including laryngeal), respiratory (throat tightening, cough, wheezing), circulatory (dizziness, hypotension, shock), and gastrointestinal (abdominal pain, nausea, vomiting). These reactions are almost all immunoglobulin E mediated. Immediate treatment involves prompt recognition, epinephrine injection, supportive therapy, and transport to an emergency department.

After the acute treatment, education on insect avoidance, prescription of injectable epinephrine, and referral to an allergist for skin testing and venom immunotherapy is advisable. Immunotherapy reduces the risk of systemic reactions in patients who have a history of systemic reactions, with an efficacy up to 98%. An exception to this course of management is made for patients younger than 16 years who experience an isolated cutaneous systemic reaction (generalized hives). These patients have a less than 1% risk of anaphylaxis if re-stung. For this reason, children younger than 16 years who experience a large local reaction or only generalized hives usually are not candidates for immunotherapy desensitization and do not require skin testing. Consultation with an allergist about proper management of an individual patient is prudent.

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Sometimes indistinguishable from an anaphylactic reaction is a toxic reaction from a large number of stings. This response is due to massive envenomation, leading to extensive edema and hypotension. The number of stings needed is estimated to be greater than 100. Treatment in these situations continues to be supportive.

For all types of reactions, counseling on prevention is necessary. Any known nests in the vicinity of the patient's home should be removed. Patients should be advised against walking barefoot and should wear long pants and sleeves when outdoors. Perfumes and bright or flowery patterned clothing may attract some stinging insects, so these should be avoided also. Patients should avoid eating or drinking outside and must be aware that nonspecific insect repellants do not repel Hymenoptera.

Comments: Insect stings cause more systemic reactions than insect bites and are a common cause of concern among parents. It is important to note that more severe reactions to insect stings occur much less commonly in children than in adults (mostly those older than 45 years).

More severe systemic responses are defined as involvement of two organ systems distant from the site of the sting and can result in angioedema, flushing, hoarseness, and wheezing, as well as hypotension, abdominal pain, vomiting, or uterine cramping. Although it is important to diagnose and counsel on systemic responses, the good news is that children experience different allergic responses than adults. Of those who experience systemic reactions, children have limited to mild involvement in 60% of cases, compared with 15% in adults.

As mentioned by Drs Zirngibl and Burrows, prospective studies in children have noted that fewer than 1% of patients have more severe reactions than the prior reaction; insect allergy skin testing and immunotherapy are therefore not warranted in children younger than 16 years. The immunoglobulin E–mediated biphasic reaction of anaphylaxis may include an immediate response within minutes to hours and a delayed response that occurs hours later. Because there is no way to predict which child might develop the delayed response, children who present to the emergency department should be observed for 4 to 6 hours after resolution of symptoms.

Parents must be educated about interventions for systemic reactions. These procedures include immediate epinephrine administration, which can be injected through clothing, followed by transport to an emergency department for additional treatment. Prescribing epinephrine for children who experience generalized acute urticaria is warranted because of the few patients having a risk of more severe reactions in the future.

Having epinephrine available and education about administration are warranted because studies have shown that epinephrine is underutilized. The most common reasons include use of an antihistamine in place of epinephrine or lack of a prescription. Epinephrine should be stored away from sunlight or extreme temperatures to protect the drug from degradation. For patients at risk for severe anaphylaxis, the recommendation is to carry two doses of epinephrine because both may be needed at the time of sting. A medical identification bracelet or necklace is recommended. Practice parameters suggest referral to an allergist when the patient has experienced a systemic reaction, he or she would benefit from additional education regarding avoidance or emergency treatment, or is a candidate for venom immunotherapy (the latter not usually a pediatric recommendation).

Janet Serwint, MD
Consulting Editor

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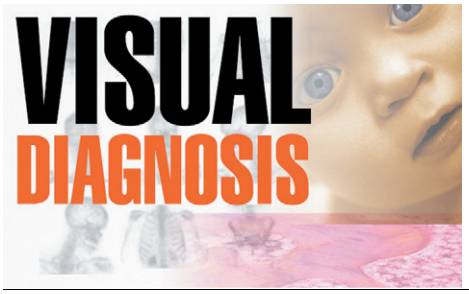

Abnormal Nails in an Infant

Natalie P. Cunningham,* Peter J. Green, FRCP†

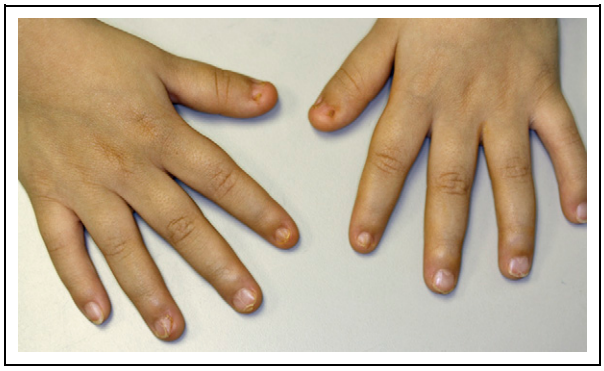

Figure 1. Nail dystrophy, most pronounced on thumbnails and less so on the nails of the fifth digits.

Author Disclosure

Ms Cunningham and Dr Green 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.

The editors and staff have been gratified by the large number of submissions by readers from all over the world to the Visual Diagnosis column. At the present time, the journal has so many cases in production that we cannot accept new manuscripts for a while. We will indicate in the journal when readers can resume sending offers to write cases and discussions.

Presentation

A dermatologist has been following a 3-year-old girl for unusually shaped fingernails noted at birth. Her history is as follows.

At age 6 months, the patient's primary care physician referred her to the dermatology service after the child's adoptive mother expressed concern about her daughter's small, misshapen fingernails. The infant was born after a pregnancy complicated by maternal smoking. She was induced at term due to failure to progress and eventually required vacuum extraction, weighing 2.405 kg at birth with Apgar scores of 9 and 9 at 1 and 5 minutes, respectively. There had been no concerns with her growth or development, and she was an active and happy child. She took no medications and had no known allergies. Her family history included a biological mother with attention-deficit/hyperactivity disorder and substance abuse and a healthy maternal half-brother. Little was known about the biological father, but the biological mother indicated that the father had abnormal nails.

Physical examination at 6 months revealed an alert, well-appearing infant in no acute distress. Vital signs were within normal limits for her age, and she was growing between the

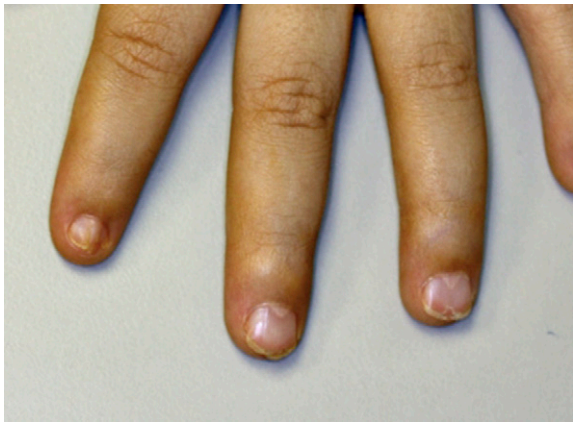

Figure 2. Fingernails display triangular shaped lunulae.

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50th and 75th percentiles for height, weight, and head circumference. She was normal in appearance. There were no dysmorphic features on her head, face, or torso. Her fingers were slightly tapered with normal creases. The nails of her fingers on both hands were small and unusually shaped with longitudinal grooving, most pronounced on her thumbnails and less so on the nails of the fifth digits. Her toenails were unaffected. Given the nonspecific nail features, the dermatologist recommended seeing the infant 1 year later.

At age 17 months, the child was re-evaluated. The fingernails remained misshapen (Fig 1) but now had triangular shaped lunulae (Fig 2). Because a clinical diagnosis was suspected, plain radiographs of the pelvis and knees were performed. However, the radiographs were inconclusive, and the patient was asked to return 1 year later.

The patient is seen now at age 31 months. This time, repeat radiographs of the knees and pelvis display decreased ossification of the patellae (Fig 3) and a subtle horn on the right iliac wing of the pelvis (Fig 4). Further laboratory examination reveals persistent hematuria and proteinuria on urinalysis.

A clinical diagnosis is made.

Diagnosis: Nail Patella Syndrome

The clinical presentation and radiographic findings are consistent with nail patella syndrome (NPS). Genetic testing confirmed the diagnosis, demonstrating a mutation in the LMX1B gene.

Discussion

NPS is a rare autosomal dominant disorder due to mutations in the gene LMX1B and heralded by a tetrad of dermatologic and musculoskeletal features that include dystrophic nails, hypoplastic or abnormal patellae, elbow dysplasia, and iliac horns. NPS is referred to also as hereditary osteo-onychodysplasia (HOOD syndrome), Turner-Kieser syndrome, Österreicher syndrome, or Fong disease. The incidence of NPS has been estimated historically at 1:50,000 (1); however, the incidence may be much lower. One half of patients born with NPS have renal involvement demonstrated by hematuria, loss of filtration with proteinuria, and nephrotic range proteinuria.

Abbreviations

ACE: angiotensin-converting enzyme
NPS: nail patella syndrome

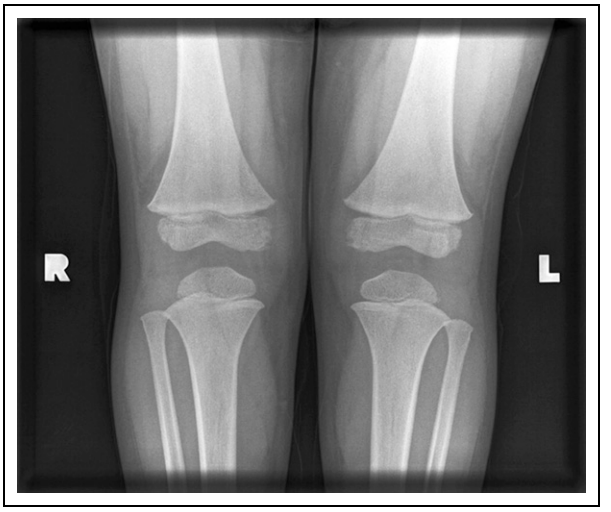

Figure 3. Decreased ossification of the patellae.

The mutation connected with NPS involves LMX1B, an LIM homeodomain transcription factor gene mapped to chromosome 9q34.1 and specifically linked to the ABO blood group locus. (1) Studies by Chen et al using homozygous knockout mice suggested LMX1B's roles in dorsoventral patterning of limb development and renal cellular differentiation. (2) LMX1B has since been associated with the development of the anterior chamber of the eye and the central nervous system. Over 150 different mutations causing loss of function of LMX1B have been described to date, according to the Human Gene Mutation Database 2003 update. This genotype is highly penetrant; most patients with the NPS genotype present with symptoms or signs of the disease. Disease severity

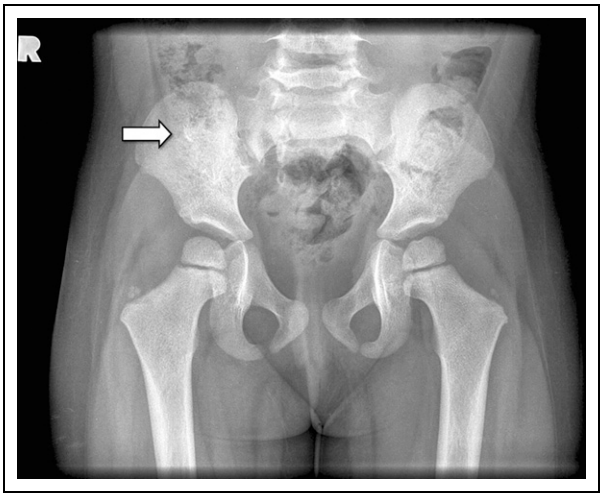

Figure 4. Subtle horn (arrow) on iliac wing of the right pelvis.

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has unpredictable individual, inter- and intrafamilial variability. The mechanism underlying phenotypic variation remains unknown.

Nail abnormalities, present at birth in 80% to 90% of affected individuals, include absence but more commonly hypoplasia or dysplasia in the form of nail ridging, splitting, spooning, fragility, and discoloration. Although a single triangular lunula can be due to trauma, involvement of multiple nails is more specific for NPS. (3) Nail lesions are symmetric and often most severe at the thumb, with decreasing severity as the nails become more ulnar; toenail involvement is less common.

Hypoplastic or absent patellae are noted in 74% to 93% of cases. Knee dysplasia and hypoplasia of the lateral femoral condyle can lead to dislocation, pain, and arthritis at the knee. Elbow dysplasia is present in 93% with hypoplasia of the radial heads and capitellum, potentially causing posterolateral subluxation and dislocation. (4) Iliac horns, which are asymptomatic bony pyramidal protuberances arising from the dorsolateral aspect of the iliac crests, are considered pathognomonic for NPS but are present in only 30% to 70% of individuals with NPS.

Approximately 50% of patients with NPS have renal disease, including proteinuria, hematuria, and frank renal failure. Lemley (3) proposed two patterns of renal involvement: 1) asymptomatic, accelerated, age-related loss of filtration function and 2) nephrotic range proteinuria, occurring in 5% to 10% of patients, with onset in childhood or early adulthood, a predictor of progression to end-stage renal disease. Urinalysis often is done when a diagnosis of NPS is suspected to screen for kidney involvement. Renal biopsy is unnecessary for patients with NPS unless urinary signs and symptoms suggest another form of kidney disease. (3)

Other findings associated with NPS have been described. Ocular hypertension is present in 7% of individuals who have NPS, and primary open angle glaucoma occurs in 10%. Lester sign, or darker pigmentation of the iris at the pupillary margin, appears in the general population but is more common in individuals with NPS (~50%). Patients with NPS also can have 8% to 20% lower bone mineral density compared with normal controls, thereby increasing their risk for fractures and scoliosis. Disrupted development of the mesencephalic dopaminergic and hindbrain serotonergic neurons may account for the association of NPS with major depressive disorder and attention deficit disorder. Up to 25% of patients with NPS experience numbness, paresthesia, decreased pain, and reduced temperature sensation, which may be related to disrupted development of dorsal horn neurons.

Diagnosis

Diagnosis often can be made clinically at birth or thereafter by history and physical examination, assisted by ancillary investigations that include urinalysis, diagnostic imaging, and ophthalmologic examination. NPS may not be considered, given the subtle phenotype and the relative unfamiliarity of physicians with the disease. With clinical suspicion, patients often undergo radiographic imaging first. The most common radiographic findings in NPS include iliac horns, hypoplasia or absence of the patella, elongated radius, and hypoplasia of the radius and capitellum. Genetic consultation may be appropriate to confirm the diagnosis, but genetic sequencing (85% sensitive) is not always necessary.

Management

The care of patients with NPS involves a multidisciplinary approach by clinicians in primary care, dermatology, nephrology, orthopedics, and ophthalmology. Care generally is symptomatic. Annual urinalysis is recommended to screen for proteinuria and hematuria. However, there is little evidence to indicate that intervention will affect progression of kidney disease. (3) Despite decreased bone density and increased risk for fracture, it is unclear whether patients with NPS should undergo early bone mineral density screening. Patients should have annual ophthalmologic screening for early detection of ocular hypertension and glaucoma. Genetic counseling is appropriate, and parents of an affected individual with NPS should be examined closely for subtle features of NPS. Surgical intervention for chronic orthopedic problems of elbows, knees, and feet is reserved for significant functional impairment.

The ultimate prognostic feature for NPS is the extent of renal disease. Because angiotensin-converting enzyme (ACE) inhibitors slow progression of other nondiabetic proteinuric glomerular diseases, they may have a similar impact in NPS nephropathy. Although ACE inhibitors have been effective anecdotally, this therapy has yet to be studied rigorously in NPS. In one case report, combination therapy with ACE inhibitors and angiotensin receptor blockers has resulted in complete remission of proteinuria in a patient with NPS nephropathy. (5) Corticosteroid-responsive, frequently relapsing nephrotic syndrome in a patient with NPS suggests that corticosteroid therapy might be worthwhile. Cyclosporin, used with some success in the treatment of Alport syndrome, another genetic kidney disease, may be an alternative treatment when ACE inhibitors are contraindicated. Renal transplant has been anecdotally

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successful without recurrence of disease or development of anti-glomerular basement membrane antibodies in individuals with end-stage renal disease.

Patient Course

The patient underwent renal biopsy, which revealed a histologic pattern similar to minimal change disease. She is followed by ophthalmology and to date has normal intraocular pressure and no signs of glaucoma. She has reduced extension at the elbows by 10 to 15 degrees and has difficulty with supination. She was referred to medical genetics for counseling.

Summary

- Nail patella syndrome (NPS) is an autosomal dominant disorder due to mutations in the gene LMX1B.
- The clinical tetrad of NPS includes dystrophic nails with triangular lunulae, hypoplastic or abnormal patellae, elbow dysplasia, and iliac horns.
- When NPS is suspected, plain radiographs of the pelvis and knees are appropriate initial diagnostic examinations.
- The ultimate prognostic feature for NPS is presence of renal disease. One half of NPS patients have renal disease, including proteinuria, hematuria, and frank renal failure.

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Suggested Reading

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