Enterovirus Infections
Noor, Krilov

Refeeding Syndrome
Pulcini, Zettle, Srinath

Parathyroid Disorders
Markowitz, Underland, Gensure

ONLINE
Visual Diagnosis: A 17-month-old Girl With Persistent Cough
Potisek, Shashy
Stay up-to-date in your practice with these leading-edge pediatric resources!

Visit shop.aap.org to order today!

AAP members save even more with already-reduced member pricing!

When you purchase AAP resources, you’re not only preparing your practice for quality patient care, you’re contributing to our mission of improving the health and well-being of children everywhere.

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®
| Vol. 37 No. 12 December 2016 |

**Editor-in-Chief:** Joseph A. Zimet, Sioux Falls, SD  
**Deputy Editor:** Hugh D. Allen, Houston, TX  
**Associate Editor, Index of Suspicion:** Philip R. Fischer, Rochester, MN  
**Associate Editor, Index of Suspicion:** Deepak M. Kamat, Detroit, MI  
**Associate Editor, Visual Diagnosis:** Mark F. Weems, Memphis, TN  
**Associate Editor, In Brief:** Henry M. Adam, Bronx, NY  
**Associate Editor, In Brief:** Janet Servent, Baltimore, MD  
**Associate Editor, CME:** Rani George, Miami, FL  
**Editorial Fellow:** Aarjun Jeeva, Toronto, ON  
**Early Career Physician:** Heather Campbell, Washington, DC  
**Editor Emeritus:** Lawrence F. Nazarian, Rochester, NY  
**Founding Editor:** Robert J. Haggerty, Canandaigua, NY  
**Managing Editor:** Luann Zanola  
**Publications Editor:** Sara Strand  
**Medical Copyediting:** Deborah K. Kuhlman  

**EDITORIAL BOARD**  
Robert D. Baker, Buffalo, NY  
Peter F. Belamarich, Bronx, NY  
Eyal Ben-Issac, Los Angeles, CA  
Theresa Auld Birgemann, Rochester, NY  
Stephen E. Dolgin, New Hyde Park, NY  
Lynn Garfunkel, Rochester, NY  
Rani George, Miami, FL  
Nupur Gupta, Boston, MA  
Gregory A. Hale, St. Petersburg, FL  
Thomas C. Havranek, Bronx, NY  
Jacob Hien, Bridgeport, CT  
Jeffrey D. Hord, Akron, OH  
Neal S. Lelito, Providence, RI  
Michael Macknin, Cleveland, OH  
Susan Massengill, Charlotte, NC  
Carrie A. Phillips, Portland, OR  
Peter Pizzutillo, Philadelphia, PA  
Mireem Rathore, Jacksonville, FL  
Jennifer S. Read, Rockville, MD  
E. Steve Roach, Columbus, OH  
Sarah E. Shea, Halifax, Nova Scotia  
Andrew Sirotnak, Denver, CO  
Mimini Weinstein, Toronto, ON  

**PUBLISHER:** American Academy of Pediatrics  
**Mark Gumin, Director, Department of Publishing**  
**Joseph Puskas, Director, Division of Journal Publishing**  

**Pediatrics in Review offers 16 CME articles per year. A maximum of six AMA PRA Category 1 Credits™ is earned after achieving a 60% score on each designated quiz.**  

**CME STATEMENTS:**  
The American Academy of Pediatrics (AAP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.  
The AAP designates this journal-based CME activity for a maximum of 1.00 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.  
This activity is acceptable for a maximum of 1.00 AAFP credit. These credits can be applied toward the AAP CMS/CPT® Award available to Fellows and Candidate Members of the AAP.  
The American Academy of Physician Assistants accepts certificates of participation for educational activities certified for AMA PRA Category 1 Credits™ from organizations accredited by ACCME. Physician assistants may receive a maximum of 1.00 hour of Category 1 credit for completing this program.  
This program is accredited for 1.00 NAPNAP CE contact hour: pharmacology (Rx) and psychopharmacology contact hours to be determined per the National Association of Pediatric Nurse Practitioners (NAPNAP) Continuing Education Guidelines.  
It has been established that each CME activity will take the learner approximately 1 hour to complete.  
*Continuing Professional Development*  

How to complete this activity:  
Pediatrics in Review can be accessed and reviewed in print or online at http://pedsinreview.aappublications.org. Learners can claim credit monthly online upon completion of each CME article. The deadline for completing this activity is December 31, 2018. Credit will be recorded in the year in which it is submitted. It is estimated that it will take approximately 1 hour to complete each CME article. This activity is not considered to be completed until the learner documents participation in that activity to the provider via online submission of answers. Course evaluations are online.

**Answer Key appears on page 549.**
Red Book® Atlas of Pediatric Infectious Diseases, 3rd Edition

Editor
Carol J. Baker, MD, FAAP

This best-selling resource aids in the diagnosis and treatment of more than 100 of the most commonly seen pediatric infectious diseases. Includes more than 1,200 full-color images to help you with disease recognition.

Effectively problem-solve emerging infectious diseases with these popular resources:

New! 4th Edition!

PREP®: ID
An Update of Pediatric Infectious Diseases and Antimicrobial Therapy

July 27-30, 2017 • Dallas, Texas • Westin Galleria Hotel

For a full listing of CME live activities, visit shop.aap.org/live-activities

Order today! Online at shop.aap.org • Phone at 888/227-1770 toll-free from 7:30 am to 5:00 pm CT
Enterovirus Infections

Asif Noor, MD,* Leonard R. Krilov, MD†

*Department of Pediatrics, Children’s Medical Center, Winthrop University Hospital, Mineola, NY.
†Department of Pediatrics, State University of New York, Stony Brook School of Medicine, Stony Brook, NY.

Education Gap

Clinicians must learn to recognize the spectrum of clinical syndromes associated with enteroviruses. Examples include the association of asthma exacerbation with enterovirus D68 and the association of acute eczema flare-up with coxsackievirus A16.

Objectives

After completing this article, readers should be able to:

1. Understand the epidemiology of enterovirus infections.
2. Recognize the wide spectrum of clinical presentations with enterovirus infection.
3. Plan appropriate laboratory evaluation for enterovirus infection.

CASE SCENARIO

During Monday morning clinic in mid-July, you refer 2 cases to the emergency department (ED). The first is a 2-week-old neonate who has had 1 day of decreased oral intake and a temperature of 102°F (38.9°C) at your clinic. The baby appears alert with normal findings on physical examination. Later in the morning you receive an update call from the ED attending physician. Examination of the cerebrospinal fluid (CSF) shows pleocytosis with 55 white blood cells/μL but normal glucose (68 mg/dL) and protein (90 mg/dL) measurements. The Gram stain is negative. The CSF is positive for enterovirus (EV) by polymerase chain reaction (PCR) assay.

The second case is a 5-year-old boy with a history of asthma who has had a cough for 3 days and difficulty breathing for 1 day. He does not respond to 2 back-to-back treatments with inhaled albuterol, so you refer him to the ED. He is subsequently admitted to the pediatric intensive care unit for management of status asthmaticus. A nasopharyngeal multiplex film array assay is positive for EV/rhinovirus.

INTRODUCTION

EV infections peak in the summer months; the pathogen remains one of the most common causes of community outbreaks encountered by pediatricians. The prevalence is determined by weather, with most EV infections seen in summer and fall in the temperate northern hemisphere and the virus circulating...
Evolution of enteroviruses (EVs) throughout the year in the tropics. EVs are highly contagious, spreading through fecal-oral and respiratory secretions. The organs affected and the severity of the illnesses are largely determined by virulence of the virus and immunity of the host. Molecular technology has helped in isolation of many newer serotypes. For example, EV D68 was responsible for a large outbreak of severe respiratory illness in children with asthma across the United States (initial reports from Missouri and Illinois) in 2014. (1) The testing strategy for EVs has evolved over the years, and widespread availability of PCR assays has provided clinicians with the ability to diagnose such infections rapidly.

**HISTORY**

Poliovirus is the most famous EV of the 20th century. President Franklin Roosevelt, who himself was affected by the virus, founded the National Foundation for Infantile Paralysis in 1938 to combat polio. As a result of the successful worldwide campaign for polio vaccination, the last case of infection was reported in 1980. Poliovirus has a long history. (2) The earliest descriptions of infection are found on an Egyptian stone (1580 BC) showing a man with a shrunken short leg, depicting characteristic effects of the infection. In 1908, Landsteiner and Popper isolated poliovirus in monkeys. It was not until 1949 that Enders and colleagues described virus growth in tissue culture. Ultimately their techniques led to recovery of many other EVs and enabled the development of polio vaccines over subsequent decades.

**VIRUS CHARACTERISTICS**

EVs belong to the family Picornaviridae (pico = small). Parechoviruses (PVs) and Saffold viruses (SVs) are now grouped with EVs because they share certain morphologic and functional properties.

The virion is nonenveloped, spherical, and about 30 nm in diameter. The genome is a positive sense RNA, with an approximate length of 7.4 kb. Infections occur with adsorption of the virus to cellular receptors, primarily integrins and immunoglobulin-like proteins. (3) After penetration, there is rapid replication (5-10 hours) inside the cytoplasm of the cell.

EVs are relatively stable viruses that can retain activity for several days at room temperature and can be stored indefinitely at freezer temperatures (−4°F [−20°C]). They are also stable at the low pH of stomach acid. EVs grow rapidly when adapted to susceptible host systems and can cause cytopathologic features within 2 to 7 days.

**CLASSIFICATION**

**Original Classification**

The original classification of EVs was based on differences in their effects in tissue culture and pattern of disease in experimentally infected animals. Human EVs were grouped as polioviruses and nonpolio EVs (echo-, coxsackie-, and other numbered EVs). At first, researchers believed that the human alimentary tract was a natural habitat for these viruses, hence, the name enterovirus. As more viruses were identified, the association of some of these viruses with human diseases was not known and they were grouped as enteric cytopathogenic human orphan or ECHO viruses.

The coxsackie groups of viruses were named after a small town, Coxsackie, near the Hudson River in New York, where Dalldorf and Sickles isolated the virus in mice in 1948 from fecal specimens.

**Reclassification**

Many EV strains have been isolated that do not fit into these categories, leading to the presently used revised classification. (4) This newer classification is based on molecular serotyping, which includes determination of the nucleotide (RNA) sequence encoding the viral polypeptide capsid (Table 1).

Recently, 2 echoviruses (E22 and E23) were reclassified as the initial members of the new genus Parechovirus as PV types 1 and 2 because they differ in terms of their genomics and proteomics from other EVs. Similarly, hepatitis A virus initially was assigned the designation EV72, but it was reclassified as the sole member of the Hepatovirus genus within the Picornaviridae family (Table 2).

Recently, the Cardiovirus genus of the Picornaviridae family has been expanded by identification of the Saffold viruses (SVs). Beginning with a strain isolated in 2007, 8 genetically distinct SVs have been identified. SVs have been recognized as a cause of mild human disease in children.

Recombination between circulating picornaviruses is a frequent event and is likely to increase genetic diversity and pose future challenges in classification.

**EPIDEMIOLOGY**

**Transmission**

EVs are spread from person to person via fecal-oral and respiratory routes. Most of the EVs are shed in the respiratory secretions for 1 to 3 weeks and in the feces for 2 to 8 weeks after primary infection. EV 71, the cause of hemorrhagic conjunctivitis, is spread via fingers, fomites, and tears. Infants, particularly those in diapers, are effective...
vehicles of transmission. Virus shedding by symptomatic and asymptomatic persons may contribute to transmission of these agents.

The incubation period for brief febrile illness due to EVs is 1 to 3 days and for poliovirus is 9 to 12 days.

Distribution and Season
EVs have worldwide distribution. Neutralizing antibodies for specific viral types have been noted in serologic surveys throughout the world (71 serotypes to date). In any given area, frequent fluctuations occur in the predominant types. Epidemics may be localized and sporadic, and they may vary in origin from place to place in the same year. (5) The prevalence of unrecognized infection far exceeds that of clinical disease.

Surveillance of Outbreaks
Data collected by the National Enterovirus Surveillance System (NESS) of the Centers for Disease Control and Prevention (CDC) has increased understanding of the epidemiology and nature of outbreaks. Between 1970 and 2005, 15 serotypes represented 83.5% of all EV isolates submitted from state and local public health laboratories. (6) EV detections were found to have remarkable seasonality, with the number of cases increasing sharply during summer and fall months and peaking in August. This summer-fall seasonality was more prominent for EV detections from CSF specimens (81.3%) in contrast to fecal (77.6%) or respiratory specimens (69.8%).

PATHOGENESIS
Human EVs are acquired directly or indirectly by ingestion of a virus shed in the feces or upper respiratory tract of infected contacts. Initial viral replication occurs in the upper respiratory tract and distal small bowel. Infectious virus is detectable in the ileal lymphoid tissue 1 to 3 days after ingestion of the virus, and fecal shedding can be detectable for 6 or more weeks (Fig 1).

Viral replication in the submucosal lymphoid tissue results in brief primary viremia that distributes virus to reticuloendothelial tissue in distant lymph nodes, liver, spleen, and bone marrow. Further replication in these organs leads to continued secondary viremia and dissemination of virus to target organs such as the central nervous system (CNS), heart, and skin. Organ-specific disease (ie, poliomyelitis, myocarditis) results from virus-induced cell necrosis and the accompanying inflammatory response. Many infected persons clear the infection before the secondary viremia and experience only transient symptoms or have an asymptomatic infection.

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterovirus</td>
<td>Human enterovirus A-D, Human rhinovirus A-C</td>
</tr>
<tr>
<td>Parechovirus</td>
<td>Parechovirus</td>
</tr>
<tr>
<td>Hepatovirus</td>
<td>Hepatitis A virus</td>
</tr>
<tr>
<td>Cardiovirus</td>
<td>Saffold virus</td>
</tr>
</tbody>
</table>


Vol. 37 No. 12 DECEMBER 2016 507
CLINICAL PRESENTATION

EVs other than poliovirus are not reportable; therefore, the actual burden of symptomatic infection is not available. EVs are believed to account for an estimated 10 to 15 million symptomatic infections in the United States every year.

Symptomatic infections range from a minor illness such as a common cold to fulminant sepsis and meningitis. The variation in presentation represents the wide variety of serotypes and the host’s immunity. NESS has provided valuable data since 1961 on the clinical association with specific serotypes and nature of community outbreaks (Table 3).

Asymptomatic Infection
An estimated 50% of EV infections are asymptomatic. Young age is associated with higher frequency of symptomatic infection. Asymptomatic infection from CV A16 occurs in only approximately 10% of children younger than age 5 years, whereas rates are reported to be higher in older children and adults. (7)

Nonspecific Febrile Illness
Most of the EVs cause a brief febrile illness with no other symptom or sign. Usually, there is a sudden-onset fever that can last up to 3 days. However, biphasic illness, characterized by an initial day of fever and a recurrence 2 to 3 days later for 2 to 4 days, can also be seen. Younger children can have malaise and older children can experience headache or a sore throat without pharyngeal injection. The physical examination and the white blood cell count usually yield unremarkable findings.

CNS Infections
Aseptic Meningitis. EVs are the most common cause of aseptic meningitis. Epidemic disease has occurred most commonly with CV B5 as well as echoviruses 4, 6, 9, 13, and 30 through 33. In general, aseptic meningitis is seen in young children, but adolescents and adults can also be affected during outbreaks.

The clinical course typically involves an initial episode of nonspecific fevers and follows a biphasic pattern, with fever recurrence in conjunction with CNS symptoms. Initial symptoms may also include headache, malaise, nausea, and vomiting. The headache usually is frontal or generalized and can be accompanied by photophobia. Physical examination typically demonstrates generalized muscle stiffness or spasm. The Kernig and Brudzinski signs are positive in fewer than 50% of cases. Pharyngitis occurs frequently, as does a maculopapular skin rash. The rash can have a petechial component, as seen in infections due to echovirus 9. Aseptic meningitis caused by EV 71 can have associated hand-foot-and-mouth (HFM) disease.

Examination of CSF reveals considerable variation among patients and even in the same patient on repeated examination. CSF leukocyte counts vary from a few cells to a few thousand per cubic millimeter; the median is in the range of 100 to 500 cells/mm³. The percentage of neutrophils also varies greatly. Initial examinations frequently reveal a predominance of neutrophils. Repeated evaluations of CSF demonstrate an increasing percentage of mononuclear cells. (8) CSF protein values are mildly elevated, and glucose concentrations usually are within normal ranges. Most patients have normal neurologic and cognitive outcomes.

Encephalitis. EVs are an uncommon (2%) cause of encephalitis in the United States. Echovirus 9 is most often the cause. Since the mid-1970s, epidemics of HFM disease associated with encephalitis have been reported in Asian-Pacific countries.

Nonpolio Paralysis. In contrast to polioviruses, which led to epidemic paralytic disease, the nonpolio EVs cause

![Figure 1. Timeline of events in enterovirus infection: pathogenesis. CNS=central nervous system, GI=gastrointestinal, PCR=polymerase chain reaction.](image)
sporadic paralytic disease. Paralytic disease has been reported in outbreaks due to CV A7 and EV 71. In 2014, a cluster of pediatric cases of acute flaccid myelitis was identified in the midst of an outbreak of EV D68 causing severe respiratory distress, although no direct link between EV D68 and paralytic disease was confirmed. (9)

Guillain-Barré syndrome, transverse myelitis, and cerebral ataxia have also been associated with EVs and echoviruses.

### Ocular Infections

Outbreaks of acute hemorrhagic conjunctivitis are typically due to EV 70 or CV A24. Presentation is characterized by a sudden onset of severe eye pain and associated photophobia. Subconjunctival hemorrhages are frequently present. Systemic symptoms, including fever, are rare.

### Skin and Mucous Membrane Infections

#### Herpangina

This is an enanthematous (mucous membrane) disease that presents with painful vesicles of the oral mucosa along with fever and sore throat. All age groups are affected, but it is most common in children ages 3 to 10 years. CVs A and B, PVs 1 and 6, EV 71, and SVs 2 and 3 are known causes of herpangina. The onset is sudden, with high temperatures (103°-104°F [39.4-40°C]). Higher temperatures (106°F [41.1°C]) and seizures may occur at disease onset. Young children may be irritable, occasionally listless, and anorexic for a few hours before the fevers appear. Older children frequently complain of headache and backache.

The oropharyngeal lesions usually erupt around the time of first fever. The characteristic lesions are small (1 to 2 mm) vesicles and ulcers (Fig 2). These lesions start as papules, become vesicular, and ulcerate in a short period of time. The lesions are discrete and surrounded by an erythematous ring, with an average of 5 to 6 lesions (range, 1-14). The most common site of the lesions is the anterior tonsillar pillars. The duration of illness is 3 to 6 days.

#### Newly Described Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Viral Type</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eczema coxsackium</td>
<td>CV A6</td>
<td>Acute onset of vesicles or erosions in children with atopic dermatitis. Milder and shorter course of illness.</td>
</tr>
<tr>
<td>Acute flaccid paralysis</td>
<td>EV 71; CV A7</td>
<td>Paralysis, but less severe illness and less bulbar involvement than poliovirus.</td>
</tr>
<tr>
<td>Acute respiratory illness</td>
<td>EV D68</td>
<td>Acute onset of cough, dyspnea, wheezing, and hypoxemia in children with history of asthma or wheezing.</td>
</tr>
</tbody>
</table>

### Table 3. Clinical Syndromes Associated With Enteroviruses

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Viral Type</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonspecific febrile illness</td>
<td>All viral types</td>
<td>Fevers for 3-4 days; can be biphasic. Minimal respiratory or GI symptoms.</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>CV B5; echoviruses 4, 6, 9, 13, and 30-33</td>
<td>Fever with meningeal signs. Mild CSF pleocytosis; normal protein and glucose.</td>
</tr>
<tr>
<td>Acute hemorrhagic conjunctivitis</td>
<td>EV 70; CV A24 (rare)</td>
<td>Sudden onset of eye pain with subconjunctival hemorrhage.</td>
</tr>
<tr>
<td>Herpangina</td>
<td>CV A &amp; B; PV 1 &amp; 6; EV 71; SV 2 &amp; 3</td>
<td>Fevers with painful vesicles or ulcers over posterior palate and/or tonsils.</td>
</tr>
<tr>
<td>Hand-foot-mouth</td>
<td>CV A (6, 16) &amp; B; EV 71; echovirus</td>
<td>Fever with enanthem (vesicles in the mouth) and exanthem (vesicles on hands and feet).</td>
</tr>
<tr>
<td>Carditis</td>
<td>CV B1-S</td>
<td>Myopericarditis presenting with heart failure or arrhythmias.</td>
</tr>
<tr>
<td>Nonspecific exanthem</td>
<td>CV A16 (most common), A6, A9; echovirus 9</td>
<td>Variable rash (vesicular, maculopapular, urticarial, petechial, purpuric) after fevers (+/-) for 1-2 days.</td>
</tr>
</tbody>
</table>

CSF = cerebrospinal fluid, CV = Coxsackievirus, EV = enterovirus, GI = gastrointestinal, PV = Parechovirus, SV = Saffold virus.
range from 100.4° to 102.2°F (38°-39°C) and last for 1 to 2 days. The oral vesicles usually are located on the buccal mucosa and tongue and are only mildly painful. The exanthem involves vesicles on the palms, soles, and the interdigital surfaces of the hands and feet. Onychomadesis (separation of the fingernail from the nail bed) has been reported 2 to 3 weeks after HFM disease (Fig 3).

The differential diagnosis for HFM disease includes varicella-zoster virus infection, herpes simplex virus infection, or aphthous ulcers. Unlike HFM, varicella lesions are more extensive, located more centrally, and in different stages simultaneously, and they usually spare the palms and soles. In herpetic gingivostomatitis, the lesions are primarily anterior in the mouth, and the child has a higher temperature, prominent cervical lymphadenopathy, and no rash. Aphthous ulcers are large, ulcerative lesions of the lips, tongue, and buccal mucosa that are extremely painful. In comparison to HFM disease, such ulcers are seen most commonly in older children and adults, involve multiple recurrences, have no rash, and typically are not associated with constitutional symptoms.

**Skeletal Muscle Infection**

Pleurodynia (Bornholm disease) is characterized by an acute onset of severe muscular pain in the chest and abdomen accompanied by fever. It is more common in older children and adolescents. CV B3 and B5 are the major causes of epidemic presentations. The muscular pain is sharp and spasmodic, with episodes typically lasting 15 to 30 minutes. During spasms, patients can have signs of respiratory distress or appear in shock, with diaphoresis and pallor. The illness usually lasts 1 to 2 days, but frequently a biphasic pattern is seen, with recurrences possible several weeks after the initial episode.

**Heart Infections**

Pathologic studies have shown that both the myocardium and the pericardium are involved in myopericarditis, which is why that term is preferred. CV B5 has been implicated as the most common causative agent, but types 2, 3, and 4 as well as echovirus type 6 can also cause myopericarditis.

Myopericarditis affects all ages, but physically active adolescents and adults are at higher risk. The usual presentation is fever, fatigue, and dyspnea on exertion, but more fulminant symptoms, including heart failure or dysrhythmia, can occur. Echocardiography may confirm diminished cardiac ejection fraction or show acute ventricular dilation. Serum concentrations of troponins are frequently elevated. The mortality rate for acute CV and echoviral heart disease is less than 5%. Children who survive acute CV myocarditis usually recover completely without any residual disability. An association between idiopathic dilated cardiomyopathy and group B CV has been suggested.

**NEWLY RECOGNIZED CLINICAL SYNDROMES**

**Asthma Exacerbation and EV D68**

EV D68 was first identified in 1962 during sporadic outbreaks of respiratory infections, but it emerged as a significant pathogen in 2014 when the United States experienced a nationwide outbreak. It was associated with severe respiratory illness in children with asthma or a history of wheezing. From mid-August 2014 to January 15, 2015, the CDC confirmed a total of 1,153 people in 49 states and the District of Columbia with respiratory illness caused by EV D68. (1)

**Eczema Coxsackium**

An atypical skin rash was reported in children with atopic dermatitis during the 2011 to 2012 outbreak of HFM disease associated with CV A6. This rash was characterized by accentuation of vesicles and erosions within areas of eczema and was termed “eczema coxsackium.” (10) This morphology was strikingly similar to eczema herpeticum caused by herpes simplex virus 1. However, eczema coxsackium is generally less painful and the child remains reasonably well.

EV infections, particularly CV A6, should be considered in the differential diagnosis of patients presenting with new-onset vesicles and extensive erosions in preexisting areas of eczema (Fig 4). EV PCR on the vesicle fluid allows for early diagnosis, thus potentially avoiding antibiotics or acyclovir.
SPECIAL HOST INFECTIONS

Neonatal Infection

Neonates are at high risk of disseminated disease resulting from EV infections acquired during the perinatal period. Most of the infections are due to echoviruses (serotypes 6, 9, and 11), group B CVs (serotypes 1 to 5), and PVs (serotype 3).

EV infections acquired perinatally present within the first postnatal week. Onset of serious EV infection beyond 10 days of age is uncommon. A wide range of clinical disease has been reported in neonates, including non-specific febrile illnesses, exanthems, and aseptic meningitis. The most severe manifestations are myocarditis with or without encephalitis, hepatitis, and pneumonia. The outcome of neonatal infection is strongly influenced by the presence or absence of passively acquired maternal antibody specific for the infecting EV serotype. EV infection should be considered in cases of neonatal sepsis when neither bacteria nor herpes simplex virus is isolated.

Infection in Immunocompromised Hosts

EVs are known to cause serious as well as persistent infections in patients with congenital or acquired defects in B-lymphocyte function. Persistent infections are seen in children with X-linked agammaglobulinemia or severe combined immunodeficiency syndrome or in adolescents with common variable immunodeficiency. Chronic infections also occur in bone marrow transplant recipients.
Echoviruses (particularly serotype 11) are responsible for most of these infections, but individual cases caused by group A and group B CVs have been reported.

Chronic meningoencephalitis, the most common clinical syndrome in these immunodeficient patients, typically presents with insidious headache, fatigue, mild meningeal symptoms, or seizures. The symptoms fluctuate in severity, disappear, or slowly progress. Persistent CSF pleocytosis and a high CSF protein concentration are characteristic of chronic EV meningoencephalitis. The prognosis for immunodeficient children who are persistently infected is poor.

INFECTION WITH POLIOVIRUS

Poliovirus infection occurs only in humans. Transmission is primarily through the fecal-oral and respiratory routes. The virus is present in the throat for 1 to 2 days before the onset of illness and is shed in feces for 3 to 6 weeks, rendering it contagious for this duration. Most poliovirus infections are asymptomatic (74%) or mild (4%). Acute paralytic disease may be caused by naturally occurring wild polioviruses or by mutated vaccine-derived polioviruses. In addition, rare cases of vaccine-associated paralytic poliomyelitis occur in recipients of oral poliovirus vaccine (OPV) or their close contacts.

In classic paralytic polio, the rapid onset of paralysis occurs 1 to 3 days after a minor febrile illness with sore throat, headache, and myalgias. The paralysis is asymmetric and affects the proximal muscles more than the distal muscles. Lower limbs are more frequently affected and sensation is usually intact except in severe cases. CSF analysis suggests aseptic meningitis, and the virus can be readily isolated from the throat or stool of an affected child. Postpolio syndrome is characterized by new onset of muscle weakness and atrophy occurring about 14 to 25 years after the initial infection. The affected muscle groups are usually the same as in the original illness.

In the United States, 4 doses of inactivated polio vaccine are recommended for routine immunization of all infants and children. In most countries, OPV remains the vaccine of choice. The original trivalent OPV induces humoral immunity to all types of poliovirus (1–3) in addition to local gastrointestinal mucosal immunity, which prevents spread of infection. In April and May 2016, a global switch from trivalent to bivalent OPV (1,3) was made because the only cases of type 2 paralytic polio were due to vaccine-related strains. To maintain immunity levels to type 2 polio, high-risk countries introduced inactivated polio vaccine (1–3) into routine immunization programs before the switch.

Polio was virtually eradicated from the western hemisphere by 1991. Four of the 6 regions of the World Health Organization have been certified polio-free: the Americas (1994), Western Pacific (2000), Europe (2002), and South East Asia (2014). Pakistan and Afghanistan continue to have ongoing polio transmission. In 2015, 74 cases of wild poliovirus were reported: 54 from Pakistan and 20 from Afghanistan.

LABORATORY DIAGNOSIS

The 3 common methods used to aid in the diagnosis of an EV infection are PCR, viral culture, and serology (Table 4).

**Polymerase Chain Reaction**

PCR is more sensitive (86%) than culture (30%) for identification of EVs in CSF and respiratory tract secretions. PCR has been most useful in detecting EV in CSF. (11) Four commercially available multiplex PCR panels are available in the United States that detect EVs in a swab from a nasopharyngeal specimen. Some of these assays report enterovirus together with rhinovirus (both are picornaviruses). PCR testing of fecal specimens has been less successful because of the presence of substances that inhibit the polymerization step.

**TABLE 4. Laboratory Diagnosis of Enteroviruses**

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>SENSITIVITY</th>
<th>SPECIFICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral culture (3-8 days)</td>
<td>Cell culture</td>
<td>0% to 80%</td>
<td>100%</td>
</tr>
<tr>
<td>PCR assay (1-2 hours)</td>
<td>CSF PCR</td>
<td>100% Variable</td>
<td>97% Variable</td>
</tr>
<tr>
<td></td>
<td>Respiratory multiplex PCR (picornavirus: EVs/rhinovirus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology (weeks)</td>
<td>Microneutralization</td>
<td>Limited use</td>
<td></td>
</tr>
</tbody>
</table>

CSF=cerebrospinal fluid, EV=enterovirus, PCR=polymerase chain reaction.
Virus Isolation
EVs can be isolated in cell culture from CSF, pericardial fluid, tissue, blood, or stool, with cytopathic effects usually seen between 2 and 5 days after inoculation in cell culture. Once isolated, the virus serotype can be identified for most of the common EVs with use of RNA sequencing. The chances of recovering a virus in cell culture are optimized by sampling multiple sites. Isolation of virus from stool is less definitive because unrelated intercurrent asymptomatic infections can occur.

Serology
Serology is of limited use in acute infections due to the need for acute and convalescent titers, cross-reactivity among different serotypes, and lack of sensitivity of immunoglobulin M assays.

The microneutralization test is the method used most widely for determining EV antibodies. This serotype-specific assay has limited usefulness in the routine diagnosis of EV infections because it is not feasible to incorporate all relevant live viral antigens into the assay. The methods based on neutralization are relatively insensitive, poorly standardized, and labor-intensive.

TREATMENT
No specific treatment for EV infections exists to date. The mainstay of management is supportive care whether the presentation is a mild cold or a life-threatening viremia.

Intravenous Immunoglobulin (IVIG)
Some evidence suggests that administering IVIG in neonatal EV infections can result in faster cessation of viremia. (12) IVIG treatment has been used in cases of chronic EV meningoencephalitis in immunodeficient patients. In addition, in cases of life-threatening EV infection, IVIG can be considered for older immunocompetent children, specifically for myocarditis and EV 71 neurologic disease, although supportive data comprise only anecdotal reports. A specific recommended dose is not known, but 400 mg/kg per day for 4 days or 2 g/kg in 1 dose has been used.

Pleconaril
Pleconaril is an antiviral agent with demonstrated activity against EVs. In a study comparing enteroviral meningitis treatment with pleconaril and control, the duration of disease was shortened from 9.5 days in controls to 4.0 days in drug recipients. (12) However, the drug is not licensed or available in United States at this time.

INFECTION CONTROL AND PREVENTION
Transmission can be reduced with simple measures such as handwashing and careful disposal of soiled diapers. When a child becomes ill with an EV infection, he or she should be kept out of school, swimming pools, and child care settings for the first few days until the fevers defervesce. In the health care setting, contact precautions are indicated for the duration of EV illness, particularly conjunctivitis. Immunocompromised children and pregnant women should be advised to avoid contact with a patient who has suspected EV infection.

Summary
• On the basis of strong research evidence, (6) enteroviruses (EVs) cause a wide range of clinical diseases with peak prevalence in the summer months. They are the most common cause of aseptic meningitis in children and are responsible for community outbreaks of hand-foot-and-mouth disease.
• On the basis of strong research, (4) the nomenclature of these EVs has changed with the discovery of new serotypes and is based on RNA sequencing.
• On the basis of some evidence, (11) polymerase chain reaction has a higher sensitivity for detecting EVs with a much shorter turnaround time than culture.
• On the basis of some evidence, (12) treatment is symptomatic, with no presently available antiviral therapy. Intravenous immunoglobulin can be considered in neonatal infections, cases of meningoencephalitis in immunocompromised patients, or life-threatening infections in immunocompetent children.
1. A previously healthy 15-year-old boy is admitted to the pediatric intensive care unit in July with a 4-day history of fever, nasal congestion, and increasing fatigue. Over the 2 days, he has had increasing shortness of breath. There are bilateral crackles on lung examination. His heart rate is 108 beats per minute, respiratory rate is 28 breaths per minute, and oxygen saturation on room air is 95%. Electrocardiography shows decreased QRS voltages. Viral respiratory polymerase chain reaction (PCR) panel is negative for adenovirus and positive for human rhinovirus/enterovirus. A serum level of which of the following is most likely to be elevated?
   A. Albumin.
   B. Bicarbonate.
   C. Calcium.
   D. Prealbumin.
   E. Troponin.

2. For the same 15-year-old boy in the previous question, which is the most likely outcome of his illness?
   A. Chronic congestive heart failure.
   B. Complete heart block.
   C. Complete recovery.
   D. Death.
   E. Persistent mitral regurgitation.

3. A previously healthy 11-year-old boy is admitted to the hospital in August with a 3-day history of headache, neck stiffness, and fever. Kernig and Brudzinski signs are negative, although he has mild pain with neck flexion. After lumbar puncture, cerebrospinal fluid (CSF) reveals 428 white blood cells per cubic millimeter with 21% neutrophils, 62% lymphocytes, and 17% monocytes. CSF glucose is 72 mg/dL and protein is 58 mg/dL. CSF Gram stain shows no organisms, and results of CSF culture, blood culture, and herpes simplex virus PCR are pending. Which of the following is the most appropriate next step in diagnosis?
   A. Blood Coxsackievirus immunoglobulin M.
   B. CSF enterovirus PCR.
   C. CSF viral culture.
   D. Stool enterovirus PCR.
   E. Stool viral culture.

4. A 16-year-old girl is admitted to the hospital with an 11-day history of headache and fatigue. Her maximum temperature at home was 101.1°F (38.4°C). Her past medical history includes recurrent acute bacterial sinusitis and acute otitis media. She has had 2 episodes of pneumonia. After lumbar puncture, the CSF PCR for enterovirus is positive. Her immunoglobulin (Ig)G measures 228 mg/dL (2.28 g/L), IgA is 25 mg/dL (250 mg/L), and IgM is 40 mg/dL (400 mg/L). Her tetanus and diphtheria antibody levels are low. T- and B-cell lymphocyte numbers are normal by flow cytometry. Management with which of the following should be considered if she continues to be symptomatic?
   A. Acyclovir.
   B. Bone marrow transplant.
   C. Ganciclovir.
   D. Interferon-γ.
   E. Intravenous immunoglobulin.

REQUIREMENTS: Learners can take Pediatrics in Review quizzes and claim credit online only at: http://pedsinreview.org.

To successfully complete 2016 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. 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.

This journal-based CME activity is available through Dec. 31, 2018, however, credit will be recorded in the year in which the learner completes the quiz.
5. A 2-month-old girl is admitted to the hospital for decreased feeding and temperature to 104°F (40°C) for 2 days. She is fussy but consolable and not lethargic. There are no focal findings on physical examination. A complete blood cell count and urinalysis yield unremarkable results. Urine and blood cultures are pending. A nasopharyngeal swab submitted for multiplex PCR panel is positive for enterovirus. Which of the following is indicated for infection control?

A. Airborne precautions.
B. Airborne and droplet precautions.
C. Contact precautions.
D. Droplet precautions.
E. Only standard precautions.
Refeeding Syndrome

Christian D. Pulcini, MD, ME, MPH, Stacey Zettle, MS, RD, LDN, Arvind Srinath, MD

*Department of Pediatrics, †Department of Clinical Nutrition, and ‡Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Children’s Hospital of Pittsburgh of University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA.

Practice Gap

Refeeding syndrome can have potentially devastating metabolic consequences. It is important for the clinician to identify at-risk populations and to evaluate, recognize, and effectively manage this condition.

Objectives

After completing this article, readers should be able to:

1. Define refeeding syndrome.
2. Analyze patient scenarios for refeeding syndrome risk factors.
3. Evaluate the patient at risk for refeeding syndrome.
4. Interpret refeeding syndrome sequelae.
5. Manage the patient with refeeding syndrome.

CASE EXAMPLES

• Case #1: A 3-month-old infant is directly admitted to the hospital by his pediatrician for failure to thrive.

• Case #2: A 16-year-old girl with anorexia nervosa fails outpatient treatment and is referred for emergency department evaluation. Five months ago, the patient’s body mass index (BMI) was 18 and Z-score was -1.05, indicating mild malnutrition. Her current BMI is 14 and Z-score is -3.95, indicating severe malnutrition. (1)

• Case #3: A 9-year-old boy with multiple medical problems who is tracheostomy- and gastrostomy tube-dependent is referred to the hospital because of a 9-lb weight loss in the last 2 months.

INTRODUCTION

Refeeding syndrome was first described in the 1940s. (2) However, there is little consensus on the evaluation and management of this condition, particularly in children. One of the primary reasons for this lack of agreement is the inherent difficulty in studying patients with refeeding syndrome. In the 1940s, the Minnesota Starvation Experiment prospectively examined the effects of prolonged starvation in adults via a randomized, controlled trial, but this remains one of the few experiments of its kind examining this condition. (3) The reason for the dearth of research is likely due to the highly morbid complications of refeeding syndrome and starvation. Scant

AUTHOR DISCLOSURE Drs Pulcini and Srinath and Ms Zettle 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.
evidence underlies the treatment recommendations for refeeding syndrome in pediatrics. Thus, current knowledge of this condition relies on cross-sectional and retrospective studies, and pediatric clinicians have limited tools to effectively evaluate and manage potential or recognized refeeding syndrome.

**DEFINITION**

Refeeding syndrome has been consistently described as the “electrolyte depletion, fluid retention, and altered glucose homeostasis that occurs in malnourished patients on commencing oral, enteral, or parenteral nutrition.”(4) The difficulty in clearly defining and diagnosing refeeding syndrome lies in the discrepancy between shifts in homeostatic mechanisms and clinical symptoms. Some suggest making the diagnosis based on the onset of clinical symptoms, (5) but many fluid and electrolyte changes occur in the absence of symptoms, and early awareness and appropriate therapy can decrease the chance of clinical deterioration. Thus, refeeding syndrome is defined as the metabolic and clinical changes that occur when a malnourished patient is aggressively nutritionally rehabilitated. (6)

**EPIDEMIOLOGY**

Partly due to the lack of a precise definition of refeeding syndrome and its numerous potential clinical manifestations, it is difficult to estimate a true incidence of the condition. (7) Hypophosphatemia is the most commonly reported and easily measured complication of refeeding syndrome. It is also the most widely reported surrogate marker for refeeding syndrome. An increased incidence of hypophosphatemia has been noted among those with eating disorders, most prominently among those with less than 68% of ideal body weight or BMIs less than 15.1. (8)(9) Other studies of the same patient population have identified hypophosphatemia in 27.5% of patients in the first week of nutritional rehabilitation. (10) Adult studies have shown a 61 times greater chance of hypophosphatemia in malnourished patients. In addition, patients who had severe hypophosphatemia had an all-cause mortality of 18.2% compared with 4.6% among those with no hypophosphatemia (P < .001). (11) In adults who require ICU level care, incidences of hypophosphatemia as high as 34% have been reported as well as increased rates of mechanical ventilation and length of stay. (12)(13)

Refeeding syndrome has been identified in cancer patients receiving nutrition support, with an incidence as high as 25%. (14)(15) The incidence of refeeding syndrome among patients admitted to the ICU for eating disorders is as high as 10%, with electrolyte disturbances cited as the most common manifestation. (16) Byrnes and Stangenes (17) identified multiple case reports illustrating the wide array of sequelae of refeeding syndrome, ranging from Wernicke-Korsakoff syndrome (acute/subacute) and acute edema/cutaneous distension syndrome to acute respiratory failure.

Perhaps the most important finding comes from the National Confidential Enquiry into Patient Outcome and Death of the United Kingdom, which reviewed records of 877 adult patients. (18) Researchers found that only 50% of those later identified as at risk for refeeding syndrome were correctly identified. Other studies have also highlighted the underreporting and underrecognition of refeeding syndrome. (19)

**RISK FACTORS**

Recognizing patients at risk for refeeding syndrome is perhaps the most important step for a clinician because it may prevent clinical sequelae. The general principles of reduced energy intake, poor absorption, and/or increased metabolic demands give rise to a variety of presentations and illnesses. (20) Some specific patient risk factors involving these principles are listed in Table 1.

**PATHOGENESIS**

An understanding of the mechanism of starvation (Fig 1) and refeeding state (Fig 2) is helpful to recognize the biochemical

---


<table>
<thead>
<tr>
<th>CATEGORIES</th>
<th>RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric</td>
<td>Anorexia nervosa, depression, chronic alcohol and drug use</td>
</tr>
<tr>
<td>Chronic Malnutrition</td>
<td>Prolonged fasting (≥5 days), failure to thrive, children with complex health needs, oncologic patients, kwashiorkor/marasmus</td>
</tr>
<tr>
<td>Renal/Endocrine</td>
<td>Diabetic hyperosmolar states, chronic diuretic use</td>
</tr>
<tr>
<td>Gastrointestinal Losses</td>
<td>Inflammatory bowel disease, chronic pancreatitis, short bowel syndrome, significant vomiting/diarrhea</td>
</tr>
<tr>
<td>Other</td>
<td>Child abuse and neglect/food insecurity/homelessness, acute weight loss of greater than 10% in 1-2 months, chronic infectious disease (AIDS, tuberculosis), cystic fibrosis, congenital heart disease, prolonged nil per os status</td>
</tr>
</tbody>
</table>
and clinical manifestations of refeeding syndrome. The most well-described manifestation of refeeding syndrome is hypophosphatemia, but hypokalemia, hypomagnesemia, and shifts in thiamine and trace elements can also occur (see the nutritional replacement portion of Fig 2). Fluid and glucose shifts are also important to monitor if refeeding syndrome is suspected.

Malnutrition/Starvation (Figs 1 and 2)
During periods of starvation, the liver transitions to gluconeogenesis, when fat and subsequently proteins are broken down. Salt and other electrolyte (notably phosphate, magnesium, potassium) shifts occur to accommodate fluid shifts and maintain homeostasis, although there is still total body depletion of these essential metabolites (which can explain why laboratory test results may be within normal ranges in the initial starvation phase).

Nutritional Replacement (Fig 2)
Refeeding results in hyperglycemia (due to lack of adequate insulin supply), leading to osmolar shifts, dehydration, and other common symptoms of elevated blood glucose. (5) Carbohydrates become the primary source of energy. The liver transitions to anabolism, halts gluconeogenesis, and begins to produce glycogen and protein.

Refeeding Syndrome (Fig 2)
The process of refeeding potentiates an intracellular shift of electrolytes to accommodate cellular processes. This poses a serious problem because the starved individual already has experienced whole body depletion of these electrolytes. The serum electrolytes are further decreased as those electrolytes cross into the cells. Hypokalemia and hypomagnesemia are caused by potassium and magnesium shifting rapidly into cells as glucose and amino acids are taken up. The switch in energy source to carbohydrates and a large increase in adenosine triphosphate production cause hypophosphatemia from glucose phosphorylation. Thiamine deficiency occurs for several reasons: 1) low reservoir due to nutritional depletion before refeeding syndrome; 2) shift from fats to carbohydrate use for energy production via glycolysis, which increases thiamine requirements; and 3) an increased role as cofactor for the new anabolic state created during refeeding (to synthesize glycogen, fat, and protein). (20) Hypernatremia can also occur to maintain positive ion homeostasis, which can lead to a hypervolemic state and possible edema.
RECOGNIZING THE CLINICAL MANIFESTATIONS OF REFEEDING SYNDROME

The clinical manifestations of refeeding syndrome vary widely and are outlined in Table 2, listed by the corresponding underlying biochemical abnormality.

MONITORING AND MANAGEMENT OF REFEEDING SYNDROME

The level of evidence for the following refeeding syndrome monitoring and management recommendations is limited to cohort studies and expert opinion, and clinical scenarios and settings vary widely in each of the studies. Therefore, clinicians should adjust the recommendations according to individual patients and practice settings. To frame the following recommendations, most electrolyte disturbances occur in the first 2 to 3 days of initiating refeeding but can occur up to 7 to 10 days later. (9)

Refeeding

The general agreement among experts is that initial refeeding must be slow. Recommendations vary widely, but starting at 50% of estimated caloric needs is prudent according to existing evidence (recommendations vary from 20%-75%). (11) For the highest-risk patients, the general recommendation is to start at 25%. Dietary advancement should occur over 3 to 7 days, with caloric increases of 10% to 25% per day until the recommended caloric goals are achieved. (25)

Monitoring

The first step in proper monitoring and management of patients with refeeding syndrome is recognition of those at risk and prevention of clinical deterioration. Monitoring can occur in an inpatient, outpatient, or a combination of the 2 settings, according to the patient’s clinical and social needs. If a patient is identified as at risk through careful history and physical examination (including detailed nutritional history), monitoring should commence upon presentation and can include:

- Continuous cardiorespiratory monitor (if available) for concerning cases, full vital sign collection every 4 hours (adjust as needed).
- Daily detailed physical examinations, with focus on the neurologic and cardiac evaluation (perform more often if concerned).
- Strict intake and output monitoring with calorie counts.
- Daily weights (goal weight gain is undetermined in children but is 1 kg/wk for adults).
- Baseline and at least daily metabolic profile, with phosphorus, magnesium, potassium, sodium, glucose, and renal function measured. Monitor more frequently

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>CARDIAC</th>
<th>PULMONARY</th>
<th>MUSCULOSKELETAL</th>
<th>HEMATOLOGIC</th>
<th>GASTROINTESTINAL</th>
<th>NEUROLOGIC</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophosphatemia*</td>
<td>Sudden death, arrhythmia, heart failure, hypotension, shock</td>
<td>Dyspnea, respiratory failure, impaired diaphragm function</td>
<td>Weakness, myalgia, rhabdomyolysis</td>
<td>Hemolysis, thromboeytopenia, leukocyte dysfunction</td>
<td>Confusion, delirium, paresthesias, paralyis, seizures, hallucinations, tetany, seizures, coma</td>
<td>Metabolic acidosis, insulin resistance, acute tubular necrosis</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Anirhythmia</td>
<td>Respiratory failure</td>
<td>Weakness, rhabdomyolysis, muscle necrosis</td>
<td>Nausea, vomiting, constipation</td>
<td>Paralysis</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>Anirhythmia</td>
<td></td>
<td>Weakness</td>
<td>Nausea, vomiting, diarrhea</td>
<td>Tremor, tetany, seizures, altered mental status, coma</td>
<td>Refractory hypokalemia and hypocalcemia, death</td>
<td></td>
</tr>
<tr>
<td>Vitamin/Thiamine Deficiency</td>
<td>Encephalopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lactic acidosis, death</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Hypotension</td>
<td>Respiratory failure</td>
<td>Weakness, rhabdomyolysis, muscle necrosis</td>
<td>Nausea, vomiting, constipation</td>
<td>Paralysis</td>
<td>Infection, death</td>
<td></td>
</tr>
<tr>
<td>Fluid Overload</td>
<td>Heart failure</td>
<td></td>
<td>Edema</td>
<td></td>
<td></td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Trace Element Deficiency</td>
<td>Anirhythmia, heart failure</td>
<td></td>
<td></td>
<td></td>
<td>Encephalopathy</td>
<td>Metabolic acidosis</td>
<td></td>
</tr>
</tbody>
</table>

*Most commonly reported mechanism of refeeding syndrome.
if electrolyte replacement is needed and/or if there are concerning trends. If parenteral nutrition is being used, obtain initial and weekly hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, total and direct bilirubin, alkaline phosphatase, albumin, total protein), cholesterol, coagulation profile, and triglycerides.

- Prealbumin, albumin, and zinc measurements can be considered, especially in those who have the highest risk profile for refeeding syndrome.
- Urinary electrolyte monitoring can be considered.

A multidisciplinary team of physicians, nurses, pharmacists, and dietitians is often needed to provide adequate care of children with potential and diagnosed refeeding syndrome. (20)(26))

**Vitamin and Mineral Replacement**

There is wide debate over whether thiamine should be administered before feeding. In general, available evidence suggests that clinicians can consider administering 100 to 300 mg/day oral thiamine (50-100 mg intravenously) before feeding because it is tolerated well with no daily upper limit. (20) Thiamine at this dose should be administered for a total of 3 days. Thiamine replacement should be increased for Wernicke encephalopathy and for confirmed thiamine deficiency, although these scenarios are rare. (20) The dose should be adjusted according to weight, and we suggest following the general recommendations of a practitioner’s available pharmacist/dietitian.

A multivitamin with or without iron (because the utility of initial iron therapy is yet unclear) should also be administered either orally or intravenously. The multivitamin should be administered as soon as a patient is recognized as being at risk for refeeding syndrome.

**Fluid**

Fluid overload is a common complication of refeeding syndrome and, therefore, fluids should be closely monitored with daily examinations and laboratory studies as outlined previously. However, data on how much fluid to provide in pediatric patients who are at risk for refeeding syndrome are lacking. To avoid fluid overload during necessary rehydration, we suggest administration of maintenance rates to achieve basic needs without causing fluid overload. Clinicians should pay attention to sodium intake, which should be restricted further if edema develops. (9)

**Correcting Electrolyte Disturbances**

Debate surrounds whether electrolyte disturbances detected at presentation should be addressed before refeeding, and there is no good evidence to suggest correction is better before or during feeding. Evidence from the National Institute for Health and Care Excellence group suggests that correcting electrolyte imbalances while starting feeding is the best method to achieve expedited homeostasis with little risk. (26) Table 3 outlines electrolyte replacement.

---

### Table 3. Major Electrolyte Disturbances in Refeeding Syndrome and Recommended Treatment (14)(17)(24)

<table>
<thead>
<tr>
<th>ELECTROLYTE DISTURBANCE</th>
<th>SEVERITY</th>
<th>MAINTENANCE (PO)</th>
<th>TREATMENT</th>
<th>MAXIMUM DOSE</th>
<th>ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophosphatemia</td>
<td>Mild: 2.3-2.7 mg/dL (0.74-0.87 mmol/L) Moderate: 1.5-2.2 mg/dL (0.48-0.71 mmol/L) Severe: &lt;1.5 mg/dL (0.48 mmol/L)</td>
<td>0.3-0.6 mmol/kg per day</td>
<td>0.3-0.6 mmol/kg per day PO* 0.08-0.24 mmol/kg IV over 6-12 hours*</td>
<td>Single dose: 15 mmol/kg (IV) Daily: 1.5 mmol/kg (IV)</td>
<td>Over 6-12 hours, measure phosphate 2-4 hours after infusion completion</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>Mild/Moderate: 1.0-1.8 mEq/L (0.50-0.90 mmol/L) Severe: &lt;1.0 mEq/L (0.50 mmol/L)</td>
<td>0.2 mmol/kg per day</td>
<td>25-50 mg/kg per PO dose (0.2-0.4 mEq/kg per dose)*</td>
<td>Single dose: 2,000 mg (16 mEq) (oral)</td>
<td>Over 4 hours</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Mild/Moderate: 2.5-3.4 mEq/L (2.5-3.4 mmol/L) Severe: &lt;2.5 mEq/L (2.5 mmol/L)</td>
<td>1-2 mmol/kg per day</td>
<td>0.3-0.5 mEq/kg per dose** (IV)</td>
<td>Single dose: 30 mEq/dose (IV)</td>
<td>Over at least 1 hour, measure potassium 2 hours after infusion completion</td>
</tr>
</tbody>
</table>

*50% less for impaired renal function.
**Urine output must be 0.5 mL/kg per hour or greater, continuous monitoring recommended while replacing potassium.

IV = intravenous; PO = oral.
Hypoglycemia and hyperglycemia have not been shown to cause substantial morbidity or mortality in this population. Accordingly, these conditions should be addressed as dictated by local practice patterns.

ENTERAL VERSUS PARENTERAL FEEDING

The advantages of enteral feeding are well documented, and this also holds true for malnourished patients. (26) If enteral feeding can be initiated within the caloric and nutritional recommendations stated previously (whether by mouth, nasogastric tube, or other postpyloric feeding method), it is recommended over parenteral feeding. The choice of administration route depends on the patient. A variety of enteral formulas is available to achieve the necessary caloric and nutritional needs, and this choice should be tailored according to the patient's needs and formula availability.

Overall, enteral feedings should begin as soon as possible. Due to the higher infection risk and other complications associated with parenteral nutrition, (27) it should only be initiated if a patient is unable to tolerate the number of calories recommended by an enteral route. This may especially apply to patients with obstructive physiology or malabsorption and/or illness, which would preclude enteral feeding. Parenteral nutrition should be discontinued as soon as possible. The only definitive recommendations are based on a low-level quality of evidence from the adult literature and suggest that when patients can tolerate 60% of needed calories by an enteral route, parenteral nutrition may be discontinued, with no tapering necessary. (25)(29) Some pediatric practitioners may prefer to achieve 100% of needed calories before discontinuing parenteral nutrition in children, based on the poor quality of adult evidence suggesting otherwise. Evidence on the composition of parenteral nutrition also is conflicting, but general recommendations for malnourished patients that have previously been identified as safe include the following composition in relation to total calories: (24)(28)

- 20% protein
- 65% carbohydrates (dextrose)
- 15% fat

The clinician and care team must be diligent in calculating caloric, fluid, and nutritional needs as well as confirming that the composition of parenteral nutrition is appropriate.

CASES REVISITED

Case #1: A 3-month-old infant (birthweight 3.3 kg) is directly admitted to the hospital by his pediatrician because of failure to thrive. The family missed their 2-month appointment and has only had a single encounter with a pediatrician at postnatal day 5, when the infant had regained his birthweight. At that time, the patient's weight was in the 38th percentile. He is now in the 3rd percentile for weight. By eliciting a further history (including detailed nutritional history) and performing a complete physical examination, clinicians discover that the infant received inadequate calories and that there are no suspected underlying medical conditions causing failure to thrive. Clinicians note decreased subcutaneous tissue on the buttocks and face. Initial metabolic profile that includes phosphorus of 4.8 mg/dl (1.55 mmol/L) (normal 4-6.5 mg/dl [1.20-2.10 mmol/L]) and magnesium of 2.1 mEq/L (1.05 mmol/L) (normal 1.6-2.4 mEq/L [0.80-1.20 mmol/L]) do not identify any concerning electrolyte abnormalities. (29)

- Initial Management: Order metabolic profile with magnesium and phosphorus
- Inpatient Monitoring: Initiate cardiorespiratory monitoring, obtain vital signs every 4 hours, conduct daily physical examinations, maintain strict intake and output with calorie counts, obtain daily weights (goal of weight gain is 20-30 g/day for infants), and obtain at least daily metabolic profile with phosphorus and magnesium while hospitalized.
- Inpatient Feeding: Administer 100 mg thiamine by mouth, and then initiate formula feeding at 50% estimated needs (in this case, approximately 50-60 kcal/kg per day for infants), slowly increasing by 25% each day. Administer multivitamin daily. The infant gained an average of 35 g/day over the course of the first 4 days of hospitalization. There were no concerning vital sign changes or electrolyte abnormalities. The infant was discharged to a safe, reliable environment. Follow-up weights obtained daily by the primary care physician for 3 days after discharge indicated appropriate weight gain. At his 6-month health supervision visit, the infant’s weight was at the 16th percentile.

Case #2: A 16-year-old girl with anorexia nervosa fails outpatient treatment and is referred for emergency department evaluation. Five months ago, the patient’s BMI was 18 and Z-score was -1.05, indicating mild malnutrition. Her current BMI is 14 and Z-score is -3.95, indicating severe malnutrition. Her weight-for-height Z-score has declined by 3, also indicating severe malnutrition. (1) On physical examination, she has pallor, temporal wasting, thinning hair, and a global decrease in subcutaneous fat tissue. She tearfully admits that she relapsed and had been “cheeking” her food to prevent ingestion.

Initial metabolic profile documents her potassium at 2.5 mEq/L (2.5 mmol/L). There are no symptoms or signs of hypokalemia.

- Initial Management: Same as detailed in Case #1.
- Inpatient Monitoring: Same as detailed in Case #1.
- Inpatient Feeding: Administer 200 mg thiamine, then 0.3 mEq/kg potassium over 1 hour, with measurement 2 hours after administration. Insert nasogastric tube if necessary, initiate feeding at 50% estimated caloric
needs, and slowly increase by 25% each day. Administer multivitamin daily.

The adolescent was engaged in inpatient treatment for 2 weeks. She had borderline hypophosphatemia and hypomagnesemia, which was treated via slowing the increase in feedings. She did not require any additional electrolyte supplementation. After 2 weeks, she had gained 6 lb. With the assistance of mental health clinicians, she was discharged to a half-day inpatient treatment facility and her weight continued to improve.

**Case #3**: A 9-year-old boy with multiple medical problems who is tracheostomy- and gastrostomy tube-dependent is referred to the hospital because of a 9-lb weight loss in the last 2 months. His body weight before the loss was 71 lb. His parents are unsure how much nutrition he has been receiving. Further questioning reveals that the boy had relocated to new housing and had not been receiving consistent home health nursing for the last 2 months. The parents are unclear as to how much they are supposed to feed him via gastrostomy tube and he is now nil per os. The parents also report nonspecific intolerance of feedings for at least 1 month, leading them to administer water or rehydration fluids instead of formula. On physical examination, the patient’s respirations are somewhat labored, and the parents admit that he seems “out of it” when the examiner notes worsening mental status from the previous examination. Findings on history and physical examination raise no concerns for physical abuse. Initial metabolic profile is notable only for hypoglycemia (34 mg/dL [1.89 mmol/L]) and mild hyponatremia (136 mEq/L [136 mmol/L]). Dextrose is administered through peripheral intravenous access in the emergency department according to institutional recommendations and his glucose increases to 126 mg/dL (6.99 mmol/L). His neurologic findings improve in the emergency department, with his parents noting that “he seems more himself.”

**Initial Management**: Order metabolic profile with magnesium and phosphorus. Also order hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, total and direct bilirubin, alkaline phosphatase, albumin, total protein), prealbumin, cholesterol, triglycerides, coagulation studies, electrocardiography, and complete blood cell count with differential count because of the high risk for refeeding syndrome and potential need for parenteral nutrition.

**Inpatient Monitoring**: Initiate cardiorespiratory monitoring; obtain vital signs with neurologic examination every 2 hours until stable; complete daily full physical examinations; measure strict intake and output with calorie counts; obtain daily weights; and obtain daily metabolic profile with phosphorus and magnesium for 7 days (then 3 times in following week) and weekly hepatic enzymes, albumin, prealbumin, cholesterol, triglycerides, and coagulation studies.

**Inpatient Feeding**: Administer 100 mg thiamine, place peripherally inserted central catheter line, start parenteral nutrition at 25% of estimated needs, and advance by 10% each day (very high risk so starting and moving slower). Start enteral feedings at 25% of estimated needs, increasing by 10% each day. Continue parenteral feedings until 60% of calories can be obtained by enteral route, then discontinue. Administer multivitamin daily.

On day 3 of hospitalization, the patient develops severe hypophosphatemia (1.3 mg/dL [0.42 mmol/L]), which is replaced with intravenous phosphate 0.2 mmol/kg. His physical examination findings do not change during this period. He is discharged on hospital day 8 with scheduled laboratory follow-up on full enteral feeding through the now functional gastrostomy tube. His formula is changed and is well tolerated. His primary care physician has performed monthly weight checks, home nursing was confirmed in the hospital, and he continues to maintain good nutritional status.

**Summary**

- Refeeding syndrome, or the potential for refeeding syndrome, is often underrecognized in children.
- A host of underlying conditions and pathologies put children at risk for refeeding syndrome.
- It is of the utmost importance for clinicians to recognize at-risk patients to allow institution of proper monitoring and management.
- Despite the lack of quality evidence for treating patients with refeeding syndrome, the condition is difficult to study. Nonetheless, retrospective primary data along with an interdisciplinary team can aid clinicians in achieving optimal outcomes.
PIR Quiz

There are two ways to access the journal CME quizzes:
1. Individual CME quizzes are available via a handy blue CME link under the article title in the Table of Contents of any issue.
2. To access all CME articles, click “Journal CME” from Gateway’s orange main menu or go directly to: http://www.aappublications.org/content/journal-cme.

**REQUIREMENTS:**
Learners can take Pediatrics in Review quizzes and claim credit online only at: http://pedsinreview.org.

To successfully complete 2016 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. 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.

This journal-based CME activity is available through Dec. 31, 2018, however, credit will be recorded in the year in which the learner completes the quiz.

1. A 6-month-old boy is brought to you for poor feeding. He is at the 75th percentile for height and at less than the 3rd percentile for weight. He has been living with his 18-year-old mother, who is his sole caregiver. She relates that he does not seem very interested in eating. On physical examination, the infant is thin and lethargic. You admit the infant to the hospital for intensive nutritional management. Which of the following laboratory findings is most likely to be seen in this infant as a complication of refeeding?
   A. Hyperkalemia.
   B. Hypermagnesemia.
   C. Hypernatremia.
   D. Hypocalcemia.
   E. Hypophosphatemia.

2. You are admitting a 13-year-old girl to the hospital with an 18-lb weight loss in the past month. You discuss a plan for hydration and fluid management with your ward team. You request daily laboratory monitoring. Over the first few days of hospitalization, you observe increasing glucose values. Which of the following is the most likely cause of this finding?
   A. Carbohydrate-based diet.
   B. Decreased insulin supply.
   C. Fluid restriction.
   D. Increased appetite.
   E. Overhydration.

3. A 2-year-old boy with severe malnutrition is admitted to the hospital for initial refeeding. You discuss vitamin supplementation with the pharmacist who works on the inpatient unit. While this patient will require multivitamin supplementation, deficiency of which of the following vitamins is most important to correct?
   A. Beta-carotene.
   B. Cobalamin.
   C. Folic acid.
   D. Phylloquinone.
   E. Thiamine.

4. You admit a 15-year-old girl to the hospital with a history of a 25-lb weight loss over the past 2 months for intense nutritional management. She has hair loss, fatigue, and constipation. Today in rounds with the ward team, she appears very swollen. You discuss with the team her care plan. Which of the following is the next best step in management of this patient?
   A. Aggressive diuresis.
   B. Compression stockings.
   C. Evaluation for syndrome of inappropriate secretion of antidiuretic hormone.
   D. Fluid management due to her high risk of volume overload.
   E. Limitation of dietary salt intake.

5. You are evaluating a 5-year-old boy who was admitted with severe malnutrition due to abuse and neglect. He was started on parenteral nutrition and is slowly gaining weight. He is starting to eat and is now taking about 70% of his calories by mouth. You discuss discontinuing parenteral nutrition with the boy’s new foster parents. His foster parents are adamant that he needs to continue receiving parenteral nutrition until he is at his expected weight. Which of the following is the most appropriate way to address the concerns of the new foster parents?
   A. Continue parenteral nutrition until he is at his expected weight.
   B. Explain that parenteral nutrition carries a concern for potential infection.
   C. Instruct them to limit his oral diet to carbohydrates.
   D. Prescribe probiotics to improve his overall nutrition.
   E. Suggest they seek out dietary supplements that are not present in the parenteral nutrition.
practice gap
hypocalcemia is not uncommon in pediatric practice, but hypercalcemia is. clinicians should improve their ability to recognize the variants in the differential diagnosis related to parathyroid diseases.

objectives
after completing this article, readers should be able to:
1. describe the differential diagnosis of parathyroid diseases that result in hyper- and hypocalcemia.
2. delineate the approach to making the diagnosis of parathyroid diseases and necessary therapies.

introduction
parathyroid hormone (PTH) is a peptide hormone that is the primary regulator of calcium concentrations in the bloodstream. PTH is released in response to a variety of signals, most importantly in response to low serum calcium concentrations. As a true hormone, it travels through the bloodstream to target tissues, primarily in the bone and kidney, where it has a variety of effects that serve to increase serum calcium, thus providing a correction for the original stimulus for release. PTH serves as an important regulator of bone turnover and in different settings can have either anabolic or catabolic effects in bone. Although PTH can mobilize phosphorus and calcium in bone, it also increases phosphate excretion, resulting in a net lowering of phosphate concentrations in the bloodstream. Given its central role in this important homeostatic process, a number of disorders are caused by abnormalities of PTH function.

biochemistry
PTH is an 84-amino acid protein, with the first 34 amino acids being essential for full activity. (i) PTH signals through a G-protein-coupled receptor. (ii) PTH shares this receptor with another peptide, PTH-related peptide (PTHrP), which is a paracrine factor that has important functions throughout the body, including regulation of the growth plates. That 2 peptides share the same receptor becomes important when considering the phenotypes of pathologic conditions involving either overproduction of PTH or PTHrP or activating and inactivating mutations of the PTH/PTHrP receptor. The PTH/PTHrP receptor signals primarily through the G-protein Gsα, triggering intracellular signaling via activation of adenylate cyclase and increasing intracellular concentrations of

author disclosure
Drs Markowitz, Underland, and Gensure have disclosed no financial relationships relevant to this article. This commentary does not contain discussion of an unapproved/investigative use of a commercial product/device.
cyclic adenosine monophosphate (cAMP). The PTH/PTHrP receptor can also signal through an inositol triphosphate mechanism and through direct interactions with the intracellular scaffold protein NHERF-1 and NHERF-2. (2)

REGULATION

PTH is produced in the 4 parathyroid glands, which are found near the thyroid gland. PTH can also be produced within the thymus in some individuals. PTH release is primarily regulated by serum calcium. Decreased serum calcium leads to decreased binding of calcium to the calcium-sensing receptor (CaSR). (3) This, in turn, activates phospholipase C, which increases uptake of calcium into intracellular stores. The decreased intracellular calcium concentrations cause fusion of PTH-containing vesicles with the cell membrane, (4) releasing PTH into the circulation. Several other stimuli can increase PTH release, including increased serum phosphorus and decreased 1,25-dihydroxyvitamin D (1,25D) concentrations.

BIOLOGICAL EFFECTS

The key target tissues for PTH are bone, kidney, and skin. In the bone, PTH/PTHrP receptors can be found on osteoblasts, and PTH has the direct effect of stimulating osteoblasts to induce bone formation. (5) However, once stimulated, osteoblasts express receptor activator of nuclear factor κ-B ligand (RANKL) and macrophage colony-stimulating factor, which can induce differentiation of preosteoclasts into osteoclasts. Osteoblasts also produce osteoprotegerin, which is an inhibitor of RANKL. Depending on dose and duration of exposure to PTH, these can lead to either net anabolic or catabolic effects in bone (6)(7) but always result in increased bone turnover.

In the kidneys, PTH acts in the proximal convoluted tubule to increase concentrations of 1-α-hydroxylase, the enzyme that converts 25-hydroxyvitamin D into its active form, 1,25D. 1,25D exerts its primary effect in the intestine to increase absorption of calcium and, to a lesser extent, phosphorus (Fig 1). PTH also acts directly in the distal convoluted tubule and thick ascending limb of the nephrons to increase calcium reabsorption, but with sustained increases in PTH, the increased serum calcium from PTH’s other actions overrides this effect, resulting in net increased calcium excretion. The actions of PTH in the kidney are most critical to its ability to increase serum calcium, as is evident in the disorder pseudohypoparathyroidism (PHP), where a selective renal resistance to PTH results in severe hypocalcemia. (8)

Although PTH has a net effect in the body of increasing serum calcium, it has opposite effects on serum phosphorus. Activation of bone formation and ultimately bone removal release phosphorous stores from bones, but potent effects in the kidney to increase phosphorus excretion cause a net decrease in serum phosphorus. These effects are mediated through downregulation of the sodium phosphorus co-transporters NaPi-2A and NaPi-2C in the proximal convoluted tubule. (9) The net loss occurs despite direct effects of 1,25D to increase intestinal phosphorus absorption and decrease phosphorus excretion in the kidney.

HYPOPARATHYROIDISM

Normally, the parathyroid glands respond to a decrease in extracellular calcium concentration, detected by the membrane-bound CaSR, by releasing preformed PTH into blood and initiating the cellular production of more hormone. Failure of the glands to respond normally to this signal is termed hypoparathyroidism. It is characterized by inappropriately low PTH concentrations relative to the degree of hypocalcemia. When PTH is produced and released into the circulation appropriately but fails to have calcemic effects, it is termed pseudohypoparathyroidism (PHP). Regardless of cause, the common finding is low extracellular calcium concentrations. The hallmark symptoms are related to the associated hypocalcemia.

Hypoparathyroid Disease

Clinical Presentation. Hypocalcemia-related events lead to the suspicion of parathyroid diseases. The classic findings are neuromuscular, resulting in sustained or intermittent involuntary contractions termed tetany. These may occur in the hands and feet, presenting typically with the fingers extended and ulnar deviated, with thumb folded in underneath the fingers (Fig 2).

Although rigid, the fingers can be bent. Upon release, they spring back to the extended position and remain so until hypocalcemia is corrected. Intermittent contractions of large muscle groups are recognized as seizures. Typically they are short, lasting 1 minute or less, but repetitive. An initial lack of a postictal phase after the first events can lead to confusion as to whether a seizure has actually occurred. With recurrences, fatigue sets in and patients can appear lethargic. Contraction in the airway, especially in the larynx, causes stridor with partial occlusion and cyanosis with complete occlusion. Bronchospasm can present as wheezing. Other nonhypocalcemia-induced symptoms that may be present and are related to the cause are discussed in the review of the differential diagnoses.
**Clinical Signs.** The easy irritability of the neuromuscular system allows for bedside signs. The Chvostek sign is elicited by tapping on the facial nerve as it surfaces to the cheek right under the maxillary bone about 1 to 2 cm anterior to the tragus of the ear. A positive sign occurs when the tap results in a twitch at the corner of the mouth on the ipsilateral side. The Trousseau sign is performed by inflating an arm cuff above systolic blood pressure and keeping it inflated for 3 to 5 minutes. A positive sign consists of a complaint of tingling in the hand and the development of tetany. A QTc interval of greater than 0.425 on electrocardiography is consistent with hypocalcemia.

**Radiographic and Laboratory Findings.** Radiographic findings include: shortened fourth and fifth metacarpals and metatarsals (see the section on pseudohypoparathyroidism type 1a) and calcifications of the basal ganglia in long-standing cases (generally >8 years). (10) The latter may contribute to central nervous system (cognitive) dysfunction. (11) In addition to hypocalcemia, hyperphosphatemia with alkaline phosphatase in the normal range is found on laboratory analyses.

**Differential Diagnosis.** There are both congenital and acquired causes of hypoparathyroidism, which are summarized in Fig 3.

An explosion in gene identification has contributed to the understanding of hypoparathyroidism. Mutations that cause embryologic deficiencies can result in absent or underdeveloped (hypoplastic) parathyroid glands. Examples of single-gene causes include the embryologic development factors: Hoxa3, Pax2,9, Eya1, Six1,4, and GCM2. Deletion of the gene coding for the transcription factor GATA3 results in the triad of hypoparathyroidism, deafness, and renal dysplasia (Barakat syndrome). (12) Mutations in the gene encoding tubulin-specific chaperone E (TBCE) results in either the Sanjad-Sakati syndrome in which hypoparathyroidism is accompanied by failure to thrive, microcephaly, and marked intellectual disability, or Kenny-Caffey syndrome, in which intelligence can be normal but skeletal findings are marked by thickened long bones at birth. (13)

The responsiveness to extracellular calcium is dependent on the CaSR located on the surface of the parathyroid cell. Low calcium concentrations in blood result in intracellular signal transduction via this G-protein-coupled receptor, leading to the production and release of PTH. Gain-of-function mutations in the CaSR gene result in diminished parathyroid responsiveness to low calcium concentrations. (14) Finally, the parathyroid glands may be present, the CaSR responsive, and the intracellular machinery for PTH functional, but the gene coding for PTH is mutated, resulting in a nonfunctional or absent circulating product.

Chromosomal microdeletions (22q11.2, 10p15.3p14) also can result in hypoplastic or absent parathyroid glands in association with defined syndromes. The best known of these is DiGeorge syndrome (velocardiofacial syndrome), which includes maldevelopment of tissues between the
heart and palate. (15) Microdeletions may occur in non-nuclear DNA. For example, mitochondrial DNA deletions resulting in the Kearns-Sayer syndrome are also associated with hypoparathyroidism, although the specific mechanism is not identified. (16)

Acquired hypoparathyroidism may be due to iatrogenic and noniatrogenic causes: intentional surgical removal of all parathyroid tissue for the treatment of parathyroid hyperplasia or accidental destruction, as during thyroidectomy or tumor resection. The treatment of chronic anemia diseases such as thalassemia with repeated blood transfusions can result in iron overload of multiple organs, including the parathyroids, if concomitant iron chelation therapy is not provided.

Noniatrogenic causes can be subdivided into 3 categories: transient, infiltrative, and destructive. Maternal hypercalcemia during pregnancy suppresses parathyroid gland development, but neonates recover within months after delivery. (17) Another reversible cause of hypoparathyroidism is due to abnormal concentrations of magnesium (both hypo- and hypermagnesemia). Metals such as copper in patients with poorly treated Wilson disease accumulate in the parathyroid glands, causing loss of function. This may be reversible with treatment. (18)

Neck tumors and granulomatous diseases may invade the parathyroids. Progressive destruction of the glands occurs in the polyglandular autoimmune syndrome type 1 that also includes chronic mucocutaneous candidiasis (nails, mouth, intestine, vagina) and adrenal failure. The source of this disease is generally attributed to a dysfunctional product of the AIRE (autoimmune regulator) gene, although other genes may contribute. (19) Additional nongenetic factors leading to clinical presentation in this disease can be inferred by its delayed appearance but are unknown.

Treatment. Because circulating 1,25D (calcitriol) is produced in the kidneys under PTH stimulation of the 1-α-hydroxylase enzyme that converts 25-hydroxyvitamin D to calcitriol, concentrations are low in hypoparathyroidism. Without calcitriol, intestinal calcium absorption is diminished. Thus, the standard therapy historically has been to bypass this enzymatic block due to PTH deficiency and administer calcitriol in doses sufficient to maintain serum/blood calcium concentrations without inducing hypercalciuria/hypercalcemia. Synthetic PTH, which has been successfully used in the treatment of postmenopausal osteoporosis, could be considered as replacement for the endogenous deficit. However, concerns about bone tumor development in juvenile animals treated with PTH have raised questions about employing this product in children. In addition, as with insulin, it must be administered by injection several times a day whereas calcitriol is administered orally. Calcium must also be administered enterally either in food or as a supplement to provide the recommended daily intakes.

**Pseudohypoparathyroidism**

PHP is defined by a failure of PTH to correct hypocalcemia, that is, serum/blood calcium concentrations remain low despite elevated PTH concentrations.

---

**Figure 3.** Differential diagnosis flow diagram for hypocalcemia. AHO=Albright hereditary osteodystrophy, CaSR=calcium-sensing receptor, Cu=copper, Fe=iron, Mg=magnesium, PHP=pseudohypoparathyroidism, PTH=parathyroid hormone.
Clinical Presentation. As in hypoparathyroidism, presenting symptoms are often attributable to hypocalcemia. Additional symptoms are specific to the cause and may include short stature, abnormal bones, and fetal or early neonatal death.

Clinical Signs. The usual diagnostic signs related to hypocalcemia, such as the Chvostek, may be elicited. Short stature, obesity, round face, and shortened metacarpals and metatarsals (Fig 4) can be found in Albright hereditary osteodystrophy. The laboratory findings in PHP are generally similar to those seen in patients with hypoparathyroidism, with the exception of a subgroup that features elevated alkaline phosphatase.

Causes. Almost all causes of PHP are genetic disorders (Fig 3). They can be distinguished on the basis of physical appearance, the level of unresponsiveness to PTH, and the identity of the dysfunctional gene. The genetics of these autosomal dominant diseases are complex and include mutations and epigenetic changes, primarily lack of appropriate methylation. There is parental imprinting such that inheritance of the defective allele from only the mother results in the disease.

Ironically, loss-of-function mutations in the PTH receptor \((PTHR1)\) are not associated with PHP. They do present with skeletal changes of either advanced ossification in the recessively transmitted and lethal Blomstrand chondrodysplasia or skeletal maturation delay with normal calcium values in Eiken syndrome. (20)

The disorders can be categorized by their (lack of) renal responsiveness to exogenously administered PTH. In PHP type I, patients fail to increase urinary cAMP or phosphate excretion after a dose of PTH. There are several variants. Type Ia is also known as Albright hereditary osteodystrophy. The cause is lack of adequate expression of the \(\alpha\) subunit of the G-protein that is responsible for PTH signal transduction. (8) The gene is located on chromosome 20, and the mutated allele is inherited from the mother only. (21) In PHP Ib, the biochemical profile is the same but there is no phenotype correlation. No gene mutation has been identified, but methylation defects in \(GNAS\) exon 1A of the same gene have been described. (22) More rarely, PHP Ib is attributed to reduced expression of \(STX16\), a gene located in proximity to the \(\alpha\)-G subunit gene that may regulate \(GNAS\) \(\alpha\) methylation. (23) PHP Ib is also tissue-specific. The imprinting is restricted primarily to the kidney. Thus, PTH-induced osteoblast stimulation can result in a rise in serum alkaline phosphatase values.

PHP type II, like type Ib, is restricted to findings in the kidney and does not share the phenotype of PHP Ia. Unlike in PHP Ib, there is cAMP responsiveness to a dose of PTH.

Figure 4. Hand and radiograph in child with pseudohypoparathyroidism ia documents shortened metacarpals in the fourth and fifth digits.
but no increase in urinary phosphate. Thus, the defect occurs post-PTH receptor and its associated G-protein as a failure to respond to the cAMP messenger. Its cause remains unknown. Patients with vitamin D deficiency, with or without the bony manifestations of rickets, can appear to be resistant to PTH in that PTH concentrations may be elevated appropriately for the degree of hypocalcemia but serum phosphate concentrations are also elevated, as found in PHP. (24) In rickets due to vitamin D disorders, PTH typically induces phosphaturia, resulting in low serum phosphate concentrations. Correction of the vitamin D disorder also corrects the PHP.

Treatment. As with hypoparathyroidism, the mainstay of therapy for PHP is calcitriol together with an oral source of calcium. The dose of calcitriol can begin at 20 ng/kg per day, followed by titration every 3 days to achieve the desired ionized calcium range. Careful follow-up assessment of blood and urine calcium concentrations is necessary to provide sufficient medication without causing hypercalcemia/hypercalciuria complications.

HYPERPARATHYROIDISM

Because PTH responds to serum calcium concentrations, assessment of calcium is critical for determining the cause. In conditions of high calcium values, the parathyroid glands should decrease production and release of PTH, resulting in low serum values. If serum calcium and PTH concentrations are concomitantly high, this is termed most commonly as primary hyperparathyroidism. Appropriately elevated PTH values in response to low calcium concentrations is termed secondary hyperparathyroidism and indicates normal parathyroid gland responsiveness. Tertiary hyperparathyroidism is a term reserved for end-stage renal disease after renal transplant when the mass of parathyroid tissue produced during renal failure fails to respond normally to the serum calcium signal. Table 1 lists laboratory values according to type of hyperparathyroidism.

This section focuses on primary hyperparathyroidism and includes brief discussions of secondary and tertiary hyperparathyroidism in addition to addressing common genetic syndromes producing primary hyperparathyroidism.

Primary Hyperparathyroidism

Symptoms and Signs. Primary hyperparathyroidism presents with hypercalcemia. Symptoms include abdominal pain, constipation, nausea and vomiting, flank pain, hematuria, polyuria, and changes in mentation progressing to stupor and coma. Manifestations may be subtle and can include fatigue, depression, and hypertension-related headache. Signs include weakness, loss of reflexes, bradycardia, and band keratopathy. Primary hyperparathyroidism may also present with bone disease characterized by generalized demineralization and subperiosteal resorption. With prolonged disease, cysts with a hemorrhagic component, known as brown tumors, may be found on radiography. These resolve upon reduction of PTH concentrations. (25)

Differential Diagnosis (Table 2). The differential diagnosis for primary hyperparathyroidism encompasses benign and potentially lethal causes, including sporadically occurring parathyroid adenomas or hyperplasia and diseases associated with specific known gene mutations (Fig 5).

Inherited loss-of-function mutations in both alleles of the CaSR gene result in a potentially lethal form of hyperparathyroidism known as neonatal severe primary hyperparathyroidism. This presents in the first 6 months after birth with polyuria, dehydration, failure to thrive, and hypertonia. Survivors may have poor developmental outcomes. (26) Serum PTH and calcium concentrations are extremely high. If only 1 allele of this gene is affected, the infant has the more common and benign familial hypocalciuric hypercalcemia. This autosomal dominant mutation leads to a different “set point” for PTH suppression, with calcium values that are higher than the reference range and inappropriately normal or mildly elevated PTH values. The CaSR also operates in the renal tubule to modulate filtered calcium reabsorption. A decrease in the receptor’s function results in a decrease in urinary calcium, thus offering protection against the development of calcium stones. A urine calcium/creatinine clearance ratio of less than 0.01 is consistent with this.

### Table 1. Hyperparathyroidism Laboratory Values

<table>
<thead>
<tr>
<th>TYPE OF HYPERPARATHYROIDISM</th>
<th>CALCIUM</th>
<th>PHOSPHORUS</th>
<th>CALCITRIOL</th>
<th>ALKALINE PHOSPHATASE</th>
<th>URINE CALCIUM/CREATININE RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>High</td>
<td>Low</td>
<td>High/Normal</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Secondary</td>
<td>Normal/Low</td>
<td>Low</td>
<td>High/Normal</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Tertiary</td>
<td>High</td>
<td>Low</td>
<td>High/Normal</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>
diagnosis. Measuring the serum calcium of the parents may be helpful in confirming the clinical suspicion. (27) Gene analysis is helpful but not essential in most cases. Parathyroidectomy is not indicated for this disorder.

Later-onset hyperplasia of the glands or single adenomas may also cause primary hyperparathyroidism. Adenomas occur due to somatic mutations in 1 cell, providing a survival advantage and leading to clonal proliferation. (25) In adults, these causes of hyperparathyroidism are relatively common. Most often, they are identified after hypercalcemia is detected on routine biochemical screening. However, the condition is much more likely to be suspected in a child when he or she presents with hypercalcemia-related symptoms. (28)

Parathyroid carcinoma can occur, but it is extremely rare, even in the adult population (less than 1% of those who have hyperparathyroidism), and is difficult to differentiate histologically from an adenoma. Affected patients present with very elevated PTH and calcium values, but this combination may also be seen with large bulky adenomas. (29) Other signs of carcinoma include a palpable neck mass and vocal hoarseness. The carcinoma has a 50% recurrence rate and may metastasize to the lungs. (25) A diagnosis of parathyroid carcinoma is based on the invasiveness of the lesion. Genetic syndromes associated with primary hyperparathyroidism include multiple endocrine neoplasia (MEN)1,

<table>
<thead>
<tr>
<th>TYPE OF HYPERPARATHYROIDISM</th>
<th>DIFFERENTIAL DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Parathyroid adenoma</td>
</tr>
<tr>
<td></td>
<td>Parathyroid hyperplasia</td>
</tr>
<tr>
<td>Secondary</td>
<td>Vitamin D deficiency</td>
</tr>
<tr>
<td></td>
<td>1-α-hydroxylase deficiency</td>
</tr>
<tr>
<td></td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td></td>
<td>Malabsorption</td>
</tr>
<tr>
<td></td>
<td>Hereditary vitamin D-resistant rickets</td>
</tr>
<tr>
<td></td>
<td>Malnutrition</td>
</tr>
<tr>
<td></td>
<td>Intestinal disease</td>
</tr>
<tr>
<td></td>
<td>Medications affecting vitamin D metabolism</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Renal failure</td>
</tr>
</tbody>
</table>

Later-onset hyperplasia of the glands or single adenomas may also cause primary hyperparathyroidism. Adenomas occur due to somatic mutations in 1 cell, providing a survival advantage and leading to clonal proliferation. (25) In adults, these causes of hyperparathyroidism are relatively common. Most often, they are identified after hypercalcemia is detected on routine biochemical screening. However, the condition is much more likely to be suspected in a child when he or she presents with hypercalcemia-related symptoms. (28)

Parathyroid carcinoma can occur, but it is extremely rare, even in the adult population (less than 1% of those who have hyperparathyroidism), and is difficult to differentiate histologically from an adenoma. Affected patients present with very elevated PTH and calcium values, but this combination may also be seen with large bulky adenomas. (29) Other signs of carcinoma include a palpable neck mass and vocal hoarseness. The carcinoma has a 50% recurrence rate and may metastasize to the lungs. (25) A diagnosis of parathyroid carcinoma is based on the invasiveness of the lesion. Genetic syndromes associated with primary hyperparathyroidism include multiple endocrine neoplasia (MEN)1,
hyperparathyroidism jaw-tumor syndrome, and MEN2A. Active investigations of cases of nonsyndromic parathyroid adenomas or hyperplasia are likely to discover other genetic causes of primary hyperparathyroidism. (30)

MEN1 is characterized by 4-gland hyperplasia and is associated with pituitary tumors, insulinomas, or gastrinomas (the classic PPP for parathyroid, pituitary, and pancreas disease). It is due to mutations in the MENIN gene, which codes for a tumor suppressor product. Generally, MEN1 presents in the second to third decade, although it has been described in the first decade. Surgical treatment involves a total parathyroidectomy (because parathyroid disease tends to recur if fewer than 3 glands are removed) with a concurrent bilateral cervical thymectomy because of the risk for ectopic parathyroid and associated thymic carcinoid syndromes noted in this syndrome. (25)(31)

MEN2A describes a syndrome composed of medullary thyroid carcinoma, pheochromocytoma, and parathyroid adenoma(s). Parathyroid disease is less common than in MEN1 (90% versus <50%) and generally occurs later, beginning in the third decade, but has been reported in children. It is due to a mutation in the RET proto oncogene. (25) MEN2A surgical treatment involves only the enlarged gland, but consideration of the risk of associated medullary thyroid carcinoma may lead to more extensive surgery. (32)

Jaw-tumor syndrome, which is caused by a mutation in the HRPT2 gene leading to increased cell proliferation, has a higher risk for both parathyroid carcinoma and adenoma. Treatment should involve removal of tumor as well as involved muscles. (32) It is also associated with Wilms tumor and polycystic renal disease. (25) Due to the differences in management of these diseases, it is important to elicit a family history in pediatric patients with primary hyperparathyroidism and, in some circumstances, obtain the appropriate genetic testing.

**Evaluation.** The hallmark laboratory findings of primary hyperparathyroidism are an elevated serum calcium concentration in the presence of an elevated or inappropriately normal range PTH value (Table 1). Normally, high calcium levels suppress PTH. This differentiates primary from secondary hyperparathyroidism, which is characterized by an elevated PTH and normal or low serum calcium value. The initial laboratory evaluation should include ionized calcium, phosphorous, renal and liver function tests, electrolytes, magnesium, urinalysis, and urine calcium and creatinine. Because intact or functional PTH has a short half-life of a few minutes, the PTH should be assessed at the same time as the serum or blood calcium. Of note, pediatric patients (especially neonates) have higher phosphorous and alkaline phosphatase values compared to adult patients, so the use of age-appropriate reference ranges is important. If PTH effects are fully manifest, the consequences of increased PTH-induced phosphaturia and bicarbonaturia will be reflected in lower-than-normal serum phosphate and bicarbonate values and a neutral or alkaline pH urine, ie, a renal tubular acidosis picture. PTH induction of bone turnover coupled with low phosphate results in increased serum bone-derived alkaline phosphatase. (28)(33) Also associated with hypercalcemia is a short QTc interval on electrocardiography that is generally considered less than 360 msec. (33) Perhaps because the disease is diagnosed after symptom onset, which is later in the disease course, the biochemical findings in primary hyperparathyroidism in children are more severe than in adults. (34)

Imaging to define the source of the hyperparathyroidism may include renal and neck ultrasonography and 99 mTc sestamibi scanning, which may be combined with single-photon emission computed tomography or 123I technology. These techniques can localize adenomas in 80% to 90% of older children, but they are not as helpful with multigland hyperplasia. (25) Computed tomography scan (including 4-dimensional imaging) may also be used. Venous sampling, which looks for PTH gradients to localize a site of high PTH secretion, may be used in combination with imaging modalities to localize an ectopic abnormal gland. However, imaging in primary hyperparathyroidism is more likely to be used for surgical planning than for diagnosis. (32) Radiographs to confirm hyperparathyroid bone disease are not obtained routinely because the diagnosis is based on the biochemical profile; bone disease should resolve gradually after the PTH concentration normalizes.

**Treatment.** Parathyroid removal versus medical management is a source of debate for adult patients with primary hyperparathyroidism, but for patients younger than age 50 years, surgical removal is the generally agreed upon treatment of choice. (25) Surgery generally has a good prognosis. (26) Intraoperative PTH blood sampling can be used to assess surgical success and should demonstrate a decrease of at least 50%. For patients waiting to undergo surgery or those who are not surgical candidates, bisphosphonates and calcimimetics may be used. (35) In pediatrics, surgical excision is the treatment of choice. Calcimimetic use is rare and primarily is employed as a bridge to definitive surgical treatment. Calcimimetics act on the CaSRs, reducing the amount of PTH produced. They do not treat the underlying cause of hyperparathyroidism. Complications of surgery can include vocal cord paralysis and permanent hypoparathyroidism, but such complications occur in fewer than 1% to 4% of cases. Causes of surgical failure can be misdiagnosis of single versus multigland disease or parathyroid adenomas located in ectopic locations. (25)
Treatment for neonatal severe primary hyperparathyroidism is a 4-gland parathyroidectomy although, rarely, conservative measures including fluids, calciuretic agents, and bisphosphonates have been used with varying degrees of success. (36)

After surgical removal, more severe cases of primary hyperparathyroidism can manifest with hungry bone syndrome in which extraskeletal calcium is deposited into mineral-depleted bone. Hypocalcemia may result. Patients with very high alkaline phosphatase concentrations are more likely to develop postoperative hypocalcemia, and monitoring serum calcium beginning postoperatively and subsequently every few days after surgery is paramount. (25) Such patients may require intravenous calcium initially after surgery and the initiation of high doses of enteral calcium together with calcitriol. (33) Calcitriol is needed because PTH is a primary inducer of its production, and low PTH results in low calcitriol levels with diminished calcium absorption (Table 3). The need for supplemental calcium plus calcitriol often persists for 1 year after surgery.

Secondary Hyperparathyroidism

Symptoms. Secondary hyperparathyroidism is a state of appropriate elevation of PTH in response to a low or falling calcium stimulus (Fig 5). Symptoms relate to the hypocalcemia when not adequately corrected and were described previously.

Differential Diagnosis (Table 2). The causes of secondary hyperparathyroidism include inadequate calcium intake (isolated or part of a more general malnutrition), vitamin-D related disorders, malabsorption, and chronic kidney disease. (33)

Any problem in the vitamin D pathway may result in secondary hyperparathyroidism. The activated form of vitamin D, calcitriol (1,25D), increases intestinal calcium absorption. In vitamin D deficiency, inadequate substrate is available for calcitriol production. Vitamin D deficiency occurs because of lack of ultraviolet B radiation of skin to induce its production, inadequate intake, malabsorption, increased catabolism, or renal losses. End-organ resistance may also occur due to a diminished or nonfunctioning calcitriol receptor (known as the vitamin D receptor) that results in decreased calcium absorption. Also, inborn errors of the 1-alpha-vitamin D hydroxylase gene that result in nonfunctioning enzyme preclude calcitriol production.

The intermediary metabolite, 25-hydroxyvitamin D, is produced from vitamin D in the liver. Liver diseases and medications that stimulate hepatic catabolic pathways result in inadequate 25-hydroxyvitamin D production. Because the source of circulating hormonal calcitriol is the proximal renal tubule cell, end-stage kidney disease is associated with reduced plasma calcitriol concentrations.

In all of these situations, the sequence is the same: decreased calcium absorption is followed by a decrease in blood calcium concentration, which is corrected by an increase in PTH and ensuing bone calcium release. (25)

Evaluation. Biochemical evaluation of secondary hyperparathyroidism includes measurement of both total and ionized calcium, electrolytes, renal and liver function tests, serum phosphate, 25-hydroxyvitamin D, 1,25D, magnesium, and urine calcium and creatinine. Eliciting both a dietary and family history is important, and examination for signs of rickets is necessary.

Treatment. Treatment of these diseases may include calcium and vitamin D supplementation or administration of calcitriol (1,25D), depending on the cause. (25)

Tertiary Hyperparathyroidism

Tertiary hyperparathyroidism is rare in the pediatric population and occurs in the setting of persistent secondary hyperparathyroidism leading to parathyroid hyperplasia and subsequent autonomous PTH secretion (Fig 5). The most common situation is chronic kidney disease with uncontrolled secondary hyperparathyroidism. Patients may later develop tertiary hyperparathyroidism after renal transplant. Much like primary hyperparathyroidism, tertiary hyperparathyroidism presents with elevated serum calcium and elevated to inappropriately normal PTH (the history in this case is what differentiates the two entities). The incidence has been described as 0.5% to 5.6% of patients after renal transplant. Treatment may involve parathyroidectomy or, in some cases, calcimimetics. (37)
Summary

- On the basis of strong evidence, parathyroid hormone (PTH) is a peptide hormone that signals through a G-protein-coupled receptor (1) and is regulated primarily by changes in serum calcium. (3)
- On the basis of strong evidence, PTH acts through bone and kidney to raise serum calcium concentrations (6)(7) and lower serum phosphorus concentrations. (9)
- In hypoparathyroidism, low PTH levels result in low serum calcium, causing tetany and seizures. Clinical signs include Chvostek and Trousseau signs.
- Among the variety of causes for inherited hypoparathyroidism are specific gene defects, Barakat syndrome, Sanjad-Sakati syndrome, Kenny-Caffey syndrome, gain-of-function calcium-sensing receptor mutations, PTH gene mutations, and DiGeorge syndrome.
- On the basis of strong evidence, acquired hypoparathyroidism can result from surgical removal of the parathyroid glands, iron overload, magnesium disorders, Wilson disease, or autoimmune polyglandular syndrome type 1.
- Treatment of hypoparathyroidism is with calcium and activated vitamin D (calcitriol).
- On the basis of strong evidence, pseudohypoparathyroidism is characterized by low calcium despite high PTH concentrations, indicating resistance. Type la is caused by mutations in the GNAS1 gene and is known as Albright hereditary osteodystrophy. Type lb is caused by defects in GNAS1 methylation and does not result in osteodystrophy. (8)
- In primary hyperparathyroidism, high serum calcium occurs with inappropriately high PTH levels.
- Clinical signs and symptoms of primary hyperparathyroidism include abdominal pain, constipation, nausea and vomiting, flank pain, hematuria, polyuria, stupor, coma, weakness, loss of reflexes, and bradycardia.
- Bone lesions called brown tumors can be seen on radiography.
- The broad differential diagnosis of primary hyperparathyroidism includes neonatal severe hyperparathyroidism and familial benign hypocalciuric hypercalcemia, both of which are caused by inactivating mutations of the calcium-sensing receptor.
- Parathyroid gland hyperplasia or parathyroid adenomas can cause PTH overproduction, which is common in adults but rarer in children.
- Parathyroid carcinoma is extremely rare and often fatal.
- Parathyroid adenomas can occur as part of a syndrome such as multiple endocrine neoplasia (MEN)1, hyperparathyroidism-jaw tumor syndrome, or MEN2A.
- Evaluation for hyperparathyroidism includes neck ultrasonography and sestamibi scan to detect and localize parathyroid adenomas.
- Treatment of hyperparathyroidism is surgical removal.
- If the PTH is elevated in response to hypocalcemia, this is termed secondary hyperparathyroidism.
- In tertiary hyperparathyroidism, hyperplastic parathyroid tissue loses responsiveness to calcium signaling.
- On the basis of strong evidence, secondary hyperparathyroidism is commonly seen with vitamin D deficiency. Chronic kidney disease can also cause secondary hyperparathyroidism, which can progress to tertiary hyperparathyroidism when it is long-standing. (25)

References for this article are at http://pedsinreview.aappublications.org/content/37/12/524.
PIR Quiz

There are two ways to access the journal CME quizzes:
1. Individual CME quizzes are available via a handy blue CME link under the article title in the Table of Contents of any issue.
2. To access all CME articles, click “Journal CME” from Gateway’s orange main menu or go directly to: http://www.aappublications.org/content/journal-cme.

REQUIREMENTS:
Learners can take Pediatrics in Review quizzes and claim credit online only at: http://pedsinreview.org.

To successfully complete 2016 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. 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.

This journal-based CME activity is available through Dec. 31, 2018, however, credit will be recorded in the year in which the learner completes the quiz.

1. A 9-year-old boy presents to the emergency department with diffuse abdominal pain, nausea, and vomiting 2 hours after sustaining blunt trauma to the abdomen when he fell off his bike and hit the handlebars. Laboratory studies show elevated amylase, lipase, and hypocalcemia. He is diagnosed with acute pancreatitis and admitted for intravenous fluid hydration and management. Which of the following findings is expected to be seen as a result of the hypocalcemia?
   A. Decreased QTc interval on electrocardiography.
   B. Normal or slightly decreased phosphorus.
   C. Positive Trousseau sign.
   D. Rigidity of fingers (cannot be bent).
   E. Hypophosphatemia.

2. You are called to the newborn nursery to evaluate a 3-day-old newborn who was noted by the nursing staff to have twitching of both hands. She was born at term via repeat cesarean delivery. On physical examination, she is mildly cyanotic and has a mild cleft palate. Heart examination documents a grade III/VI murmur. Laboratory studies reveal calcium of 6.9 mg/dL (1.73 mmol/L) and phosphorus of 9 mg/dL (2.91 mmol/L). The remainder of her electrolyte measurements are within normal limits, including normal serum glucose and sodium. Which of the following is the most likely cause of the clinical findings described in this patient?
   A. DiGeorge syndrome.
   B. Kenney-Caffey syndrome.
   C. Maternal hypocalcemia during pregnancy.
   D. Loss-of-function mutations in the parathyroid hormone (PTH) receptor.
   E. Sanjad-Sakati syndrome.

3. A 9-month-old boy is brought to the clinic by his consanguineous parents for the evaluation of multiple subcutaneous nodules that have been present since birth but are increasing in size. Physical examination reveals multiple 5- to 7-mm hard subcutaneous nodules over the extremities. In addition, the patient is at greater than the 95th percentile for weight and less than the 25th percentile for height. He has a round face with short metacarpals and metatarsals. He is diagnosed with Albright hereditary osteodystrophy. Which of the following best describes the pathophysiology of the pseudohypoparathyroidism seen in patients who carry this diagnosis?
   A. Absence of the parathyroid glands.
   B. Decreased synthesis of PTH.
   C. Normal PTH release but failure of tissues to respond.
   D. Normal PTH synthesis but failure to release it.
   E. Synthesis of defective PTH.

4. A 17-year-old girl presents with polyuria, nausea, vomiting, abdominal pain, and fatigue. Laboratory studies reveal calcium of 12 mg/dL (3 mmol/L), phosphorus of 2.1 mg/dL (0.68 mmol/L), and urine calcium/creatinine ratio of 2.2. Which of the following is the most appropriate next serum study to order in this patient?
   A. Calcium/creatinine ratio.
   B. Cortisol.
   C. Insulinlike growth factor 1.
   D. PTH.
   E. Thyrotropin.
5. A 16-year-old girl presents with tetany and hypocalcemic seizure. Physical examination shows positive Trousseau and Chvostek signs. Laboratory studies document elevated serum PTH. You diagnose secondary hyperparathyroidism. Which of the following diagnoses may lead to secondary hyperparathyroidism?

A. Chronic kidney disease.
B. Hypervitaminosis D.
C. Kearns-Sayer syndrome.
D. Multiple endocrine neoplasia (MEN)1.
E. Parathyroid adenoma.
A previously healthy, fully vaccinated 7-month-old boy presents to the emergency department with a history of 3 hours of temperature to 100.5°F (38.1°C), vomiting, mildly decreased activity, and a bulging anterior fontanelle (Fig) noted by his mother. The mother has a history of inactive herpes simplex virus (HSV) infection treated with acyclovir before and during delivery. Two weeks ago, the patient had an erythematous rash that had resolved with topical hydrocortisone.

On physical examination, all of the boy’s growth parameters are tracking, with weight in the 50th percentile, head circumference at 15th percentile, and length at the 60th percentile. His temperature is 100.8°F (38.2°C), pulse is 130 beats per minute, and respiratory rate is 28 breaths per minute. The anterior fontanelle is tense with normally spaced cranial sutures. Funduscopic examination shows no findings of note and cranial nerve examination reveals no abnormality. The neck is supple with full range of motion and the tympanic membranes are clear bilaterally. Skin examination shows 2 café-au-lait macules and no petechiae. The rest of the examination findings are within normal parameters.

Results of initial laboratory evaluation show normal complete blood cell count, chemistry panel, hepatic function panel, coagulation panel, C-reactive protein, and thyrotropin. Blood and urine are sent for cultures. Computed tomography (CT) scan of the head yields unremarkable results. Following lumbar puncture (LP), cerebrospinal fluid (CSF) cell count is 1 white blood cell (WBC)/μL (79% lymphocytes, 0% neutrophils, and 21% monocytes) and opening pressure is greater than 35 cm H2O. CSF protein and glucose are within the normal ranges. CSF samples are sent for HSV1 and 2 DNA polymerase chain reaction (PCR) testing and acyclovir is initiated empirically. The patient is admitted to the general pediatrics service. The diagnosis is made after thorough laboratory and radiographic investigation.

DISCUSSION

After the LP, the patient was hospitalized, his emesis resolved, and he was able to consume adequate oral intake overnight. Magnetic resonance imaging (MRI) and magnetic resonance venography showed no intracranial abnormality or evidence of venous sinus thrombosis. Additional study of CSF fluid was requested for human herpesvirus-6 (HHV-6) DNA PCR and cytopathologic review by pathologist.
The patient remained febrile despite receiving ibuprofen, and his fontanelle remained flat after the LP. Results of his neurologic examination remained normal throughout his hospital stay. His ophthalmic examination was negative for papilledema and retinal hemorrhages. He developed an erythematous macular lacy rash on the head, trunk, and lower extremities on hospital day 2. CSF, blood, and urine cultures showed no growth. HSV1 and 2 PCR testing and metabolic disorder evaluation that included organic acids, amino acids, acylcarnitine, and carnitine profiles were negative. On hospital day 3, plasma DNA PCR for HHV-6 was reported as positive, confirming the diagnosis of transient intracranial hypertension of infancy, which is a form of benign intracranial hypertension frequently associated with HHV-6 (a.k.a. roseola infantum). The patient made a full recovery with supportive care and was discharged from the hospital.

The Condition
Transient intracranial hypertension of infancy can occur when infections impair normal CSF dynamics and generate increased intracranial pressure (ICP) via an unknown mechanism. Intracranial hypertension can present with somnolence, apathy, irritability, or bulging of the anterior fontanelle. In the absence of intracranial lesions or central nervous system infections, the intracranial hypertension is usually benign and self-limited. (1) In some children, such as the patient in this case, the intracranial hypertension can resolve after a single LP via reduction in ICP. Previous cases of transient intracranial hypertension of infancy have been associated with roseola, enterovirus, acute otitis media, vaccination, or other febrile illnesses. In a study of 176 infants with roseola infantum, 26% had bulging of the anterior fontanelle.

Differential Diagnosis
The differential diagnosis for fever, vomiting, and increased ICP in an infant is broad. Transient intracranial hypertension of infancy, believed to be due most often to viral causes, was high on the differential diagnosis for this infant. Given that the CSF had just 1 WBC/μL with a lymphocytic predominance, viral meningitis was possible but less likely. Theoretically, transient intracranial hypertension of infancy may be an early presentation of HSV meningitis, especially given the maternal history of HSV infection in this case. However, for an infant who appears well with no evidence of serious bacterial infection, observation without LP may also be reasonable. (2)

Intracranial hemorrhage or trauma was unlikely for this infant given the negative head CT scan, normal ophthalmic examination findings, and lack of supporting history, although structural causes (mass lesions and anatomic variants) of increased intracranial pressure and venous thrombosis were considered.

Although the infant had café-au-lait macules, he did not have other findings suggestive of underlying genetic syndromes. He also did not have other findings that would suggest metabolic disorders. Moreover, these would present in a more chronic or subacute course.

Although MRI and thorough evaluation for metabolic disorder were performed for this patient, these may not always be necessary, especially if the history and laboratory indices are consistent with the clinical presentation of transient intracranial hypertension of infancy.

Treatment
Nonsurgical treatments have been used in older children and adults with goals of symptom relief and preservation of vision in those with ongoing symptoms and papilledema. Carbonic anhydrase inhibitors have been shown to resolve symptoms in greater than 50% of patients. Short-term corticosteroids with a gradual taper are occasionally used after failure of carbonic anhydrase inhibitor therapy and described primarily in retrospective studies. (1)

Lessons for the Clinician
• Transient intracranial hypertension of infancy should be considered in the differential diagnosis for infants presenting with a bulging fontanelle when there is no clinical, laboratory, or imaging support of intracranial pathology.
• Roseola and enterovirus infections, acute otitis media, and other febrile illnesses have been associated with transient intracranial hypertension of infancy and should be considered during the evaluation of an infant with a bulging fontanelle.
• The increased intracranial pressure seen in transient intracranial hypertension of infancy may resolve when lumbar puncture is performed.

• Transient intracranial hypertension of infancy remains a diagnosis of exclusion, and thorough evaluation and empiric treatment for life-threatening causes of bulging fontanelle should always be considered.

References and Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/37/12/536.
Facial Cellulitis in a 4½-year-old Girl

Nathalie Schindler, MD,* Victoria Price, MD†

*Division of Pediatric Emergency Medicine, Department of Pediatrics, McMaster Children’s Hospital, McMaster University, Hamilton, Ontario, Canada.
†Division of Paediatric Hematology/Oncology, Department of Paediatrics, IWK Health Centre, Dalhousie University, Halifax, Nova Scotia, Canada.

PRESENTATION

A 4½-year-old girl presents to the emergency department with a 2-day history of right cheek erythema, pain, and fever. Her past medical history includes trigonocephaly, bilateral optic nerve atrophy with vision loss, possible very mild hearing loss, pituitary hypoplasia with normal endocrine function, left nasolacrimal duct obstruction, spontaneously closed ventricular septal defect, chronic anemia, and symmetric growth restriction.

On physical examination, she appears well. Her oral temperature is 102.6°F (39.2°C), heart rate is 120 beats per minute, respiratory rate is 24 breaths per minute, blood pressure is 100/50 mm Hg, and oxygen saturation is 100% in room air. Her weight is 13 kg (<5th percentile). Oral examination reveals a dental abscess causing severe cellulitis of her right cheek. Her teeth are hypoplastic. Her oropharynx is normal. She has reactive cervical lymphadenopathy. Her neck range of motion is normal. Cardiac and respiratory examinations yield normal results. Her abdomen is soft and she does not have hepatosplenomegaly. The remainder of her examination findings are within her normal limits.

She is hospitalized and started on intravenous clindamycin. On the day of admission, a dental panoramic radiograph is taken, which reveals abnormal-appearing bone and teeth. She undergoes a dental extraction as well as incision and drainage of the abscess. Her mandibular bone appears necrotic and dense. A bone sample is sent to pathology. Additional evaluation leads to the diagnosis.

DISCUSSION

The pathology report confirmed the diagnosis of osteomyelitis of the mandible. She underwent a bone scan that revealed intense uptake in the mandible as well as generalized increased skeletal uptake. A skeletal survey revealed her underlying diagnosis of osteopetrosis (OP) (Figs 1 and 2). OP is also known as Albers-Schönberg disease and marble bone disease.

This patient was found to have biallelic homozygous CLCN7 gene mutation causing malignant OP (MIOP). This is the first known case with this specific mutation. MIOP, which is a progressive disease, usually begins to present...
clinically within the first few months after birth. Her described medical problems were consistent with MIOP. She was also found to have mild conductive hearing loss consistent with middle ear dysfunction and likely due to abnormalities of the ossicles. Her lacrimal duct obstruction was due to bony stenosis. Her intellectual development was normal.

The Condition
OP represents a group of rare, inheritable disorders of bone caused by absent or dysfunctional osteoclast activity that prevents normal bone remodeling and growth. This results in an imbalance between bone formation and resorption. Cases of OP with osteomyelitis of the jaw as a complication or an initial presentation of the disease are described. There are multiple forms of OP. MIOP is a severe form of OP. This autosomal recessive type occurs in infants and children.

Clinical Manifestations
Clinically, the bones are fragile despite increased bone mass. The dense bones encroach on bone marrow cavities, resulting in bone marrow suppression and extramedullary hematopoiesis with hepatosplenomegaly. Loss of bone marrow space leads to anemia and an increased risk of infections such as pneumonia and osteomyelitis due to neutropenia. Abnormal tooth formation and eruption occurs. Growth impairment is substantial. As bones become denser, nerve entrapment syndromes may occur, such as optic nerve atrophy from encroachment as well as pituitary dysfunction. Death can occur from obstructive hydrocephalus, infection, and respiratory disease.

Those with OP often have delayed dental eruption and poor tooth quality, which increases their risk of dental infections, caries, and abscesses. Routine dental care is important to prevent these infections, which can progress into osteomyelitis of the jaw (more commonly mandibular but also maxillary). The risk of osteomyelitis is believed to be due to compromised vascular supply to the bone as well as general immunosuppression.

Diagnosis
OP is a clinical diagnosis that is confirmed by the radiographic appearance of the bones. OP must be considered in a child with abnormal bone formation, growth restriction, conductive hearing loss, recurrent infections, chronic anemia, and vision problems. Radiographs reveal dense-appearing bone as well as pathologic fractures. The classic radiograph finding is the “bone-in-bone” appearance (Fig 1). Other findings include lucent bands; a funnel shape at the metaphyses of long bones (“Erlenmeyer flask”) (Fig 2); and sclerosis of the skull, pelvis, and vertebral end plates.

Figure 1. Radiograph of hand showing “bone-in-bone” appearance characteristic of osteopetrosis.

Figure 2. Radiograph of lower extremity showing lucent bands and a funnel shape at the metaphyses of long bones (“Erlenmeyer flask”).
Management

Hematopoietic stem cell transplant is the only curative treatment for MOIP. Without treatment, the condition is usually fatal by age 10 years. Causes of death are often related to septicemia due to osteomyelitis complicated by pancytopenia.

This patient underwent a bone marrow transplant from a matched donor. Her growth has improved slightly, although she has had pathologic fractures and persistent chronic pain.

Lessons for the Clinician

- Osteopetrosis must be considered in children with pathologic fractures, recurrent infections (especially osteomyelitis), and growth restriction.
- The diagnosis is both clinical and radiological.
- Expedited referral to hematology/oncology is warranted for bone marrow transplant because malignant osteopetrosis is a lethal disease.

*Suggested Readings for this article are at [http://pedsinreview.aappublications.org/content/37/12/539](http://pedsinreview.aappublications.org/content/37/12/539).*
Lauren Pommert, MD,* Hayley Friedman, MD, MS,* David Wathen, DO,* Shermini Saini, MD*

*Saint Louis University at SSM Cardinal Glennon Children’s Medical Center, Saint Louis, MO.

PRESENTATION

A previously healthy 16-year-old Asian-American boy presents to the emergency department with the acute onset of jaundice and an approximately 1 week history of dark, tea-colored urine, described by the patient as “almost black,” with dysuria. In the previous 3 weeks, he has had progressive fatigue, decreased appetite, dizziness, blurred vision, headaches, and sore throat. His immunizations are up to date. Family history is not contributory. He has no known sick contacts and no recent medications. He endorses unprotected sexual activity but denies illicit drug use, travel, or animal contacts.

Physical examination reveals a diffusely jaundiced boy with scleral icterus and a heart rate of 92 beats per minute, respiratory rate of 20 breaths per minute, and blood pressure of 120/70 mm Hg. His lungs are clear, and he has no murmur, pharyngeal erythema or exudate, abdominal tenderness, hepatosplenomegaly, or lymphadenopathy.

Laboratory results reveal the following:

- Hemoglobin, 11.6 g/dL (116 g/L)
- Hematocrit, 32.7% (0.33)
- Mean corpuscular volume, 86.3 fl (86.3/µm³)
- Mean corpuscular hemoglobin, 30.6 pg/cell
- Mean corpuscular hemoglobin concentration, 35.5 g/dL (355 g/L)
- Reticulocyte count, 1.66% (0.02)
- White blood cell (WBC) count, 6,100/µL (6.1 x 10⁹/L)
- Platelet count, 124 x 10⁹/µL (124 x 10⁹/L)
- Total bilirubin, 8.0 mg/dL (136.83 µmol/L)
- Direct bilirubin, 0.83 mg/dL (14.2 µmol/L)
- Direct Coombs test, positive
- Direct antiglobulin test (DAT), immunoglobulin (Ig)G positive
- Antibody screen, negative

Urinalysis shows 2+ protein, 3+ blood, 2+ ketones, 1+ bilirubin, urobilinogen 4.0 EU/dL, and 2 to 3 red blood cells (RBCs) on urine microscopy. Aspartate aminotransferase is mildly elevated at 46 U/L (0.77 µkat/L), but alanine aminotransferase, total protein, albumin, and γ-glutamyl transferase values are within normal limits. Review of the peripheral smear shows normal morphology of WBCs, platelets, and RBCs with few spherocytes (Fig).
DISCUSSION

The differential diagnosis on initial presentation was broad and included autoimmune hemolytic anemia (AIHA), poststreptococcal glomerulonephritis, immunodeficiency, and infection. Before knowledge of the patient’s DAT test results, membranopathies such as hereditary spherocytosis and enzymopathies such as glucose-6 phosphate dehydrogenase (G6PD) deficiency were also in the differential diagnosis. Additional studies following admission further supported a hemolytic process, including: elevated lactate dehydrogenase (LDH) at 500 U/L (8.35 μkat/L), low haptoglobin of less than 8 mg/dL (80 mg/L), and DAT 2+ IgG and 2+ polyspecific (IgG + complement). Creatinine kinase, antibody screen, G6PD, antinuclear antibody, antistreptolysin O titer, and osmotic fragility tests all yielded normal results. Mononuclear spot test was positive and Epstein-Barr virus (EBV) titers showed elevated IgM and IgG, suggesting a recent infection. Overall, the adolescent’s laboratory results and clinical presentation were consistent with AIHA, believed to be cold antibody-mediated or a combination of warm and cold reactive antibodies, likely triggered by his recent EBV infection.

Through the course of his admission, the patient’s hemoglobin steadily declined and on hospital day 5 was

<table>
<thead>
<tr>
<th>TABLE. Warm and Cold Antibody-mediated Hemolytic Anemias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COLD ANTIBODIES</strong></td>
</tr>
<tr>
<td>Temperature reactivity</td>
</tr>
<tr>
<td>Autoantibody</td>
</tr>
<tr>
<td>Population</td>
</tr>
<tr>
<td>Site of hemolysis</td>
</tr>
<tr>
<td>Complement activation</td>
</tr>
<tr>
<td>Causes</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
</tbody>
</table>
down to 6.3 g/dL (63 g/L). Because cold antibody-mediated hemolytic anemias are generally not responsive to corticosteroids, systemic corticosteroids were not initiated early in his hospital course. However, due to his progressive symptomatic anemia, including nausea, dizziness, and fatigue, and the possibility of a combination of warm and cold reactive autoantibodies, methylprednisolone (2 mg/kg intravenous every 6 hours) was empirically started on day 5. Twenty-four hours later, his hemoglobin continued to decline to 5.9 g/dL (59 g/L), with a relatively low reticulocyte count of 3.9% (0.04) and worsening symptoms of anemia, which increased the suspicion of corticosteroid-nonresponsive AIHA. At that time, the blood bank performed preliminary screening for a cold reactive antibody, which revealed increased hemolysis with + DAT reactivity when the patient’s blood sample was cooled to 4°C.

The patient was transferred to the ICU where he was transfused with 2 units of packed RBCs using a blood warmer and was closely monitored for brisk hemolysis that could result in possible kidney and cardiac damage. Confirmatory testing for the identification of cold reactive antibodies had not been ordered previously because of the significant volume of blood required for this testing and attempts to minimize iatrogenic blood loss in the setting of his progressive symptomatic anemia. Samples obtained prior to the transfusion later revealed + anti-IgG, 2+ anti-C3, and negative eluate, a pattern strongly suggestive of a cold autoantibody. Testing was negative for any detectable warm antibodies.

On the morning after transfusion, his hemoglobin improved to 7.8 g/dL (78 g/L) and remained at the same level for the next 24 hours, at which time he was stable for discharge on hospital day 8. Throughout the duration of his admission, hepatic and renal function were closely monitored and remained stable. At outpatient follow-up evaluation 3 days later, his hemoglobin was 8.9 g/dL (89 g/L) and reticulocyte count was elevated at 8.9% (0.09). Twelve days after discharge, hemoglobin was again stable at 9.1 g/dL (91 g/L), with a reticulocyte count of 10% (0.10).

The Condition

AIHA is a rare disease characterized by antibody-mediated RBC destruction. Diagnosis is based on clinical symptoms of anemia and laboratory tests confirming hemolysis (normocytic or macrocytic anemia, reticulocytosis, elevated indirect bilirubin, low serum haptoglobin, elevated LDH, and positive DAT). The severity of AIHA may range from isolated mild anemia to serious sequelae, including ischemic cardiac disease due to profound anemia, renal failure due to hemolysis, and rarely, disease progression to chronic lymphoproliferative disorders.

AIHA can be broadly classified as either primary or secondary:

- **Primary or idiopathic:**
  - Warm antibody
  - Cold antibody
  - Paroxysmal cold hemoglobinuria (PCH)

- **Secondary:**
  - Infection
  - Drugs, toxicity
  - Malignancy
  - Systemic autoimmune diseases
  - Immunodeficiencies

The antibodies that cause AIHA are classified based on whether they bind to the erythrocyte membrane antigens more optimally at 37°C (warm antibody, typically IgG, binds to RBCs in the central circulation) or at 4°C (cold antibody, typically IgM, which subsequently mediates RBC destruction by fixing complement and binding to RBCs in the peripheral circulation). PCH is a form of AIHA in which IgG can behave as a cold antibody (a.k.a. the Donath-Landsteiner autoantibody) and mediate RBC destruction through complement activation. Some patients can have a mixed profile of warm and cold autoreactive antibodies.

The most common form of primary AIHA in children is due to warm IgG-mediated antibodies. Cold reactive IgM antibodies are more common in adults with AIHA. When children are found to have cold autoantibodies, the condition is usually due to IgG that develops in response to infections, classically *Mycoplasma*, but also cytomegalovirus, EBV, and other viral infections (Table).

Treatment

The management of cold antibody-mediated hemolytic anemia differs significantly from that for warm antibody disease. Although warm antibody hemolysis can be treated with corticosteroids, cold antibody disease tends to be resistant to this treatment due to the high density of C3 complement on RBC surfaces. The course of cold antibody AIHA is often self-limited, and treatment is generally supportive, including cold avoidance to minimize hemolysis. If patients develop symptomatic anemia, they may require RBC transfusions, which should be administered using a warmer, and patients should be closely monitored for rapid hemolysis, which can cause serious morbidity, including ischemic cardiac disease and kidney failure. Patients who have refractory or chronic anemia may require repeat transfusions, immune-modulating medications, intravenous immunoglobulin, plasmapheresis, or splenectomy.
Lessons for the Clinician

- Infections are the leading cause of autoimmune hemolytic anemia (AIHA) in children.
- Cold antibody-mediated AIHA may be related to autoimmune disease, lymphoproliferative disorders, or infections such as *Mycoplasma pneumoniae* and infectious mononucleosis. Cold antibody-mediated AIHA is usually not responsive to corticosteroids, and first-line therapy is generally supportive care.
- In the event of symptomatic anemia, warmed packed red blood cell transfusions may be considered first-line therapy in addition to cold avoidance. Patients receiving transfusions may need to be closely monitored in an ICU setting for adverse reactions, including brisk hemolysis.
- When in doubt about whether a patient with AIHA has a warm or cold reactive antibody, use a blood warmer for any necessary transfusions.

ACKNOWLEDGMENTS

The authors wish to thank Karen Moser, MD, for providing the image.

*Suggested Readings for this article are at* http://pedsinreview.aappublications.org/content/37/12/542.
Every 4 minutes in the United States, a child is placed into foster care. In 70% of cases, placement follows investigation by child protective services into reports of suspected neglect, physical abuse, sexual abuse, or psychological maltreatment. Nearly all other cases represent adolescents ordered into care by the courts, mostly as a result of a juvenile justice issue. Fewer than 1% of children in foster care are placed voluntarily by their parents or other family caregivers. Most children entering foster care are able to live in the households of relatives or unrelated foster parents, but 1 in 7 is placed in a group home or residential treatment facility.

Fewer children are in foster care than in the past. There were 400,000 in 2014, a reduction of 20% compared to 10 years previously. Although racial disparities within the system have also diminished, children classified as African-American or multiracial still comprised 25% of those in foster care in 2014, a significant overrepresentation relative to the population distribution of the United States.

More than two-thirds of children enter foster care from an environment characterized by extreme poverty; mental illness or substance abuse in a caregiver; or exposure to violence, criminal activity, or homelessness. Once in foster care, the lives of many children continue to be characterized by extreme poverty; mental illness or substance abuse in a caregiver; or exposure to violence, criminal activity, or homelessness. Once in foster care, the accumulation of adverse experiences during childhood creates toxic stress of immense magnitude and long-term consequence.

Federal law mandating that children remain in the schools they attended before foster placement provides a thread of continuity. Across a large body of observational research, kinship placement has been associated with resiliency in the form of enhanced child well-being and half the rates of behavioral problems, mental health disorders, and placement disruption.

Permanency is ultimately achieved for 20% of children in foster care through adoption. Another 20% remain in foster care until they age out at age 18 or 21 years, depending on the state. The remaining 60% are able to be reunified with a parent or other family caregiver, although 30% of those returning home re-enter foster care within 1 year.

The pediatrician should pay special attention to several groups overrepresented among those in foster care. These include children with medical complexity, physical or intellectual disabilities, or serious emotional or psychiatric disturbance and those who are identified as unaccompanied refugee minors, LGBTQ, pregnant, or already parents.

Mental health evaluation of children in foster care is extremely challenging. Psychotropic medications are commonly prescribed for extended periods, often in combination, compounding exposure to risk. The manifestations of immense toxic stress on a child or adolescent may mimic signs and symptoms of a range of physical and psychiatric disorders. A “trauma-informed” approach to care should be standard, in which the impact of trauma on the child is recognized and
incorporated into diagnostic and therapeutic decision-making and into counseling provided to the child and caregivers. Highly collaborative or co-located pediatric medical and mental health services are ideal settings for the provision of longitudinal care to children in foster placement.

Rates of sexual activity, sexually transmitted infections, pregnancy, and sexual exploitation are significantly increased among adolescents in foster care. The transition out of foster care into adulthood may be accompanied by an array of heightened risks and experiences of abandonment. With the enactment in 2010 of the Affordable Care Act (PL 111-148), Medicaid coverage was extended until age 26 years for this group. An orderly transfer of care to an adult “medical home” can be even more challenging to oversee for youth aging out of foster care than for other young adults with special health care needs.

In keeping with American Academy of Pediatrics policy, a child should be seen by the pediatrician 3 times during the first 3 months in foster care for the following purposes:

- Within the first 72 hours: A complete physical examination that includes detailed inspection of the skin throughout and attention to oral health as well as treatment of active, ongoing conditions.
- Within 1 month of placement: A comprehensive assessment that features a more in-depth history, ideally from the birth family, if feasible; review of outside records; administration of standardized screens targeting developmental, behavioral, and emotional disorders; referral and treatment, as indicated; and, for adolescents, additional assessment, screening, and intervention in the domains of sexual and reproductive health and alcohol, nicotine, and substance abuse.
- One to 2 months later: An opportunity to continue investigating and intervening in areas addressed at the previous visit, check on the progress of any referrals, and look for signs that the child is not thriving in the foster placement. Subsequent outpatient care should be scheduled approximately twice as often as for children who are not in foster care.

Despite special preparation and training, foster parents may feel unprepared or inadequately supported to meet the complex needs of children placed in their care. Substantial time must be devoted by the pediatrician to care coordination, both during and outside of office visits. This involves soliciting and reviewing historical information from multiple sources because care may have been fragmented and poorly coordinated before placement; engaging in contact with subspecialists, mental health personnel, caseworkers, and legal professionals; ordering needed medications, supplies, and durable medical equipment; incorporating birth parents into ongoing medical care; ensuring adherence to regulations around permission (consent) for routine and emergency care and elective procedures; and conducting foster parent education and training.

Most, if not all, of this work remains unreimbursed, an important focus of advocacy. A different type of compensation derives from the professional gratification of taking part in improving the quality of life of children in foster care, collaborating with other skilled, caring professionals and foster parents, and following the children through to the enactment of permanency plans that provide a foundation for continued recovery and resiliency.

COMMENT: The finding that fewer children are in foster care now than 10 years ago is good news. However, another child in need of placement every 4 minutes surely still qualifies as an epidemic and one that reflects on fundamental failures in our society. Foster care is, if you will, a symptom of underlying social diseases: domestic and sexual abuse, drug and alcohol abuse, and, most basically of all, poverty. Certainly we need to treat the “symptom” and strengthen the foster care system so that it best meets the needs of children, but until we effectively address the ills that make foster care necessary, we are ultimately treating pain with aspirin, not eliminating its cause.

– Henry M. Adam, MD
Associate Editor, In Brief
Caliciviridae is a family of viruses that is divided into at least 5 genera, with noroviruses and sapoviruses being the 2 that are often termed human caliciviruses. The cause of a condition first described in 1929 as the “winter vomiting disease” because of its predilection for wintertime outbreaks, norovirus was initially named in 1968 as the Norwalk virus because it was discovered in Norwalk, OH. Noroviruses are single-stranded RNA viruses, with many genotypes capable of causing human disease. The primary genotypes responsible for disease in humans are G-I (~15% of cases), G-II (~85% of cases), and G-IV (<1% of cases). The viral capsid is composed of 2 primary proteins: VP1 and VP2. The P-domain can undergo antigenic drift and shift, thereby allowing immune evasion and giving the virus potential for pandemic spread.

In the United States, noroviruses are responsible for more than 50,000 hospitalizations each year and 500 to 800 deaths. With more than 1 million doctor visits annually, norovirus is now the #1 cause of pediatric gastroenteritis since the introduction of the rotavirus vaccines. Sapovirus infections have also been recognized in the past as a substantial cause of sporadic cases of acute pediatric gastroenteritis and more recently of outbreaks of diarrheal illness. Worldwide, norovirus is responsible for 685 million episodes of gastroenteritis annually, with 200 million of these cases among children younger than age 5 years. These infections lead to the deaths of an estimated 50,000 children every year, nearly all of which occur in developing countries. Periodically a pandemic strain arises and the number of deaths more than doubles. Just how often norovirus is the cause of travelers’ diarrhea is not known, but some studies indicate the incidence may be as high as 65% of cases.

Shedding of norovirus and sapovirus can be asymptomatic, most often among children, which makes closed populations (schools, child care centers, long-term care facilities, and cruise ships) particularly susceptible to the development of outbreaks. Viral transmission is most commonly fecal-oral, either directly from contaminated food or by touching surfaces harboring the virus and then from hand to mouth. Currently, in fact, norovirus is the #1 cause of foodborne illnesses in the United States. Contagious vomitus has also been the source of individual infections and several outbreaks.

Several factors contribute to the ease of norovirus spread: it has a very low infectious dose of fewer than 100 viral particles, it can live a long time on contaminated surfaces, large numbers of viral particles are excreted with infection, and shedding can persist for weeks after symptoms resolve.

Infections occur throughout the year but have an increased incidence during the cooler months. The incubation period is 12 to 48 hours, after which symptomatic patients may develop the abrupt onset of nausea and vomiting with watery diarrhea, abdominal cramps, and loss of appetite. Most typically, symptoms last for 1 to 3 days, but the very young and the elderly as well as patients weakened by underlying illness may have more prolonged illness. Beyond the gastrointestinal
tract, patients may experience fever, muscle aches, and headache. Rarely, norovirus infection has been associated with hemolytic-uremic syndrome, elevations in liver function tests, and influenza-like symptoms. Some studies have suggested a possible link between norovirus infection and the development of inflammatory bowel disease.

Several diagnostic tests can identify norovirus: a multiplex nucleic acid-based assay, an enzyme immunoassay kit, and real-time reverse transcriptase-polymerase chain reaction. These tests, however, are not widely available in clinical laboratories; they are primarily used for public health reasons rather than for the care of individual patients for whom symptoms are usually of short duration and self-resolving with supportive care.

Maintenance of hydration, either orally or intravenously, is the mainstay of treatment. Vaccines against norovirus are in the early stages of development, but for now at least, meticulous handwashing with soap and running water remains the key to prevention and is more effective than the use of alcohol gels. Within the hospital setting, regular control measures as well as contact precautions should be taken for patients admitted with norovirus infection.

**COMMENT:** In the age of probiotics and prebiotics, monoclonal antibodies, fifth-generation antimicrobials, stem cell transplants, even fecal transplants, how ironic that our best defense against norovirus is running water and soap! Is it comic or tragic that our best tools against malaria (and, for that matter, Zika) remain bug spray and mosquito netting? Yes, to paraphrase Frost, the world is lovely, dark and deep, but we have promises to keep, and miles to go before we sleep.

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

---

**ANSWER KEY FOR DECEMBER 2016 PEDIATRICS IN REVIEW**

### 2017 AAP CME SCHEDULE

**The Best CME/CPD* for the Best Pediatric Care**

<table>
<thead>
<tr>
<th>JANUARY</th>
<th>FEBRUARY</th>
<th>MARCH</th>
<th>APRIL</th>
<th>MAY</th>
<th>JUNE</th>
</tr>
</thead>
</table>
| January 20-22  
Clinical Pediatric Hospital Medicine  
Tempe, AZ | February 2-5  
Practical Pediatrics CME Course  
Copper Mountain, CO | March 4-8  
PREP® The Course  
St. Petersburg, FL | April 7-9  
Leadership Development Conference  
St. Petersburg, FL | May 6-9  
Pedicatric Academic Societies Annual Meeting (PAS)  
San Francisco, CA | June 23-25  
Practical Pediatrics CME Course  
San Diego, CA |
| February 9-12  
Practical Care of the Adolescent & Young Adult  
Anaheim, CA | | March 24-26  
Practical Pediatrics CME Course  
Orlando, FL | | | |

<table>
<thead>
<tr>
<th>JULY</th>
<th>AUGUST</th>
<th>SEPTEMBER</th>
<th>OCTOBER</th>
<th>NOVEMBER</th>
<th>DECEMBER</th>
</tr>
</thead>
</table>
| July 27-30  
PREP®:ID  
A Comprehensive Update of Pediatric Infectious Diseases and Antimicrobial Therapy  
Dallas, TX | August 19-23  
PREP® The Course  
Portland, OR | September 1-3  
Labor Day Weekend Practical Pediatrics CME Course  
Philadelphia, PA | November 3-5  
Practical Pediatrics CME Course  
Tucson, AZ | December 1-3  
Practical Pediatrics CME Course  
San Antonio, TX | |
| | | September 16-19, 2017  
National Conference & Exhibition  
Chicago, IL | | | |
| | | September 15  
Pre-conference Session | | | |

### Practical Pediatrics CME Courses

Designed for pediatricians, family physicians, nurse practitioners, and physician assistants caring for children, Practical Pediatrics CME Courses feature nationally prominent faculty presenting topics that highlight current issues in pediatrics.

### PREP® The Course

An intensive review and update of pediatrics featuring course content based on the content specifications issued by the American Board of Pediatrics (ABP) for Maintenance of Certification™ (MOC). The course features a variety of educational formats to meet different learning styles, including lectures, case-based sessions, faculty panels, visual diagnosis, pre-/post-course self-assessment, and hot topics.

### Subspecialty/Section CME Courses

Appropriate for the pediatric subspecialist or the general pediatrician with a particular interest in the topic.

### National Conference & Exhibition

Home to the largest pediatric technical exhibit, the National Conference showcases the latest products and services, as well as AAP educational and professional resources and programs. From hot-topic plenary sessions to interactive, hands-on workshops, this conference will offer you every opportunity to enhance your clinical skills.

---

**The Self-Assessment portion of many of these live CME activities is approved through the AAP MOC Portfolio Program for 10 points by the American Board of Pediatrics for MOC Part 2.**

**Continuing Medical Education**

The American Academy of Pediatrics (AAP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. These activities have been approved for **AMA PRA Category 1 Credit™**.

*Continuing Professional Development.
MOC | CME | BOARD REVIEW

Stay current in pediatric hematology-oncology with the online self-assessment program that delivers clinically relevant, peer-reviewed questions, in-depth discussions of preferred answers and references for further study – all mapped to the ABP subspecialty content specifications. PREP® Hematology-Oncology provides a comprehensive review and the opportunity to grow your knowledge.

What comes with an annual subscription to PREP Hematology-Oncology?

- Clinically relevant cases with multimedia aids and references.
- Instant feedback and PREP® Pearls for further study.
- Easy-to-read, case-based questions with clear, succinct explanations all mapped to American Board of Pediatrics (ABP) content specifications.

2017 Rates:

- AAP Non-Member ....................... $260
- AAP Member.......................... $210
- AAP Subspecialty Section Member ...... $190

Learn more and order at shopAAP shop.aap.org/2017-PREP-Hematology-Oncology or by calling 866/843-2271.

PREP Hematology-Oncology is approved for 20 points of MOC Part 2 credit by the American Board of Pediatrics (ABP) through the AAP MOC Portfolio program.*

What Subscribers Say About PREP Hematology-Oncology...

“Two of these vignettes corresponded with recent patient encounters that I have dealt with in the past year. It was nice to see that other physicians in the field are thinking about similar issues.”

For a FREE trial of PREP Hematology-Oncology, visit prep_trials.courses.aap.org.

*All approved activities must be completed by the MOC Credit Approval End Date. All deadlines and MOC point values should be confirmed on the ABP’s Activity Catalog within each physician’s ABP Portfolio.

All pricing and specifications presented are subject to change without notice.
NEW 2nd Edition!
American Academy of Pediatrics
Textbook of Pediatric Care, 2nd Edition

The landmark guide to pediatric medicine—updated and streamlined for today’s clinicians and students

Highlighting the numerous advances across the full span of pediatrics, the new second edition of AAP Textbook of Pediatric Care provides a complete update of this premier clinical reference, including signs and symptoms, behavioral health, care of healthy and high-risk infants, adolescent health, critical situations, practice management, ethical and legal concerns, and much more.

Hardcover with eBook Access, June 2016—3,192 pages

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®
A 17-month-old Girl With Persistent Cough

Nicholas Potisek, MD,* Laura N. Shashy, MD*

*Department of Pediatrics, Wake Forest School of Medicine, Winston-Salem, NC.

PRESENTATION

A 17-month-old girl with a past medical history of birth at 31 weeks’ gestation and several episodes of bronchodilator-responsive wheezing is transferred for management of a pneumothorax. One month ago, she was diagnosed with influenza A based on a dry cough. The patient refused to take oseltamivir and her cough persisted. Over the past 2 to 3 days, the cough has worsened in frequency and developed a “wet” quality. Recently, several of the coughing episodes were associated with nonbloody, nonbilious posttussive emesis. While waiting to be seen by her primary pediatrician today, she developed back swelling, which prompted more immediate evaluation.

Other than recent symptoms of rhinorrhea, the remainder of her review of systems is negative. Throughout this illness, she has continued normal voiding and stool patterns as well as normal levels of activity.

As noted previously, the girl was born at 31 weeks’ gestation via cesarean delivery due to eclampsia. She did not require endotracheal intubation but received supplemental oxygen for 2 weeks. Her immunizations are up to date. She is small for her age and has reached developmental milestones. Currently, she is prescribed beclomethasone dipropionate twice daily and albuterol as needed for previous wheezing and coughing episodes. She has never been hospitalized. Family history includes asthma in her father.

On physical examination, her rectal temperature is 100.8°F (38.2°C), heart rate is 123 beats per minute, respiratory rate is 18 breaths per minute, blood pressure is 96/78 mm Hg, and oxygen saturation is 99% on 4 L/min of supplemental oxygen via nasal cannula. Her weight is 8 kg (3rd percentile). She appears well-nourished, is in no apparent distress, and is breathing comfortably. Posterior lung auscultation reveals diffuse crackles along both lung fields. Cardiac auscultation reveals a crunching sound during systole. There are no murmurs, gallops, or rubs. The skin on her back is raised, and soft-tissue crepitus is audible with palpation over nearly her entire back. The remainder of the physical examination findings are within normal parameters.

The diagnosis is confirmed after review of her chest radiographs in the context of her physical examination findings.

DIAGNOSIS

Review of the chest radiographs revealed extensive subcutaneous and mediastinal emphysema (Figs 1 and 2). The patient’s physical examination and chest radiograph findings were consistent with a diagnosis of spontaneous pneumomediastinum (SPM) or mediastinal emphysema. Because of her recent episodes of forceful...
vomiting, an esophagram was obtained to ensure the SPM was not due to a spontaneous esophageal rupture. The esophagram was negative for any evidence of esophageal rupture or perforation. The patient’s SPM was suspected to be related to her worsening cough or recent vomiting.

Discussion

SPM is defined as the presence of air in the mediastinum without a recent history of mechanical ventilation, thoracic surgical procedures, or chest trauma. There is a bimodal peak incidence of SPM occurring in children ages 6 months to 3 years and again in children ages 13 to 17 years. Most SPM cases are encountered during the adolescent period. The incidence of SPM is estimated to range from 1 in 800 to 1 in 40,000 hospital emergency department visits per year.

Diagnosis of SPM is based on physical examination and radiographic imaging. Additional evaluation with laboratory studies is often unnecessary but may reveal a moderately elevated neutrophil count if a bronchopulmonary infection is suspected as the underlying cause of SPM. Common physical examination findings with SPM include subcutaneous emphysema and the Hamman sign. Subcutaneous emphysema can be appreciated with palpation of the skin; touching affected areas reveals a crackling of the skin underneath the fingertip. The extent of subcutaneous emphysema should be assessed with careful inspection of the neck and back. The Hamman sign is a classic physical examination finding of SPM that refers to a crunching, rasping sound that is synchronous with the heartbeat. It is heard over the precordium and sometimes at a distance from the chest in mediastinal emphysema. Clinically, older children may report chest pain, dysphagia, or dyspnea along with the previously noted physical examination findings. If SPM is not severe, children often appear well and have no vital sign abnormalities.

Evidence of mediastinal air on the frontal chest radiograph is diagnostic of pneumomediastinum. Both frontal and lateral chest radiographs are useful in identifying radiographic signs associated with SPM and evaluating for any potential complications. Pneumomediastinum may appear as a vertical lucent streak along the left side, outlining the mediastinal pleura, pulmonary artery, and aortic arch due to a collection of air or gas along the superior left lateral aspect of the heart and medial to the parietal pleura. Several radiographic signs found in SPM include the thymic spinnaker sail sign (angel wing sign), the continuous diaphragm sign, and the ring-around-the-artery sign. The thymic spinnaker sail sign is often seen in neonates and refers to lifting of the thymus off the heart border by air trapped between the cardiac thymic fascia and parietal pleura, giving the appearance of spinnaker sails on chest radiograph. The continuous diaphragm sign represents air along the superior surface of the diaphragm, separating it from the pericardium, and is best seen on a frontal chest radiograph. The ring-around-the-artery sign is seen on the lateral chest radiograph as a lucent ring around the right pulmonary artery. Additional radiographic findings can include subcutaneous air extending superiority into the neck and retropharyngeal soft tissues or thoracic hyperinflation in a patient with a past medical history of asthma.

Pneumothorax may occur with pneumomediastinum and should not be overlooked on chest radiograph. Because of similar appearances on imaging, pneumomediastinum

Figure 1. Frontal radiograph showing subcutaneous emphysema along the back (blue arrow), mediastinal emphysema along the heart border (red arrow), and continuous diaphragm sign (green arrow).

Figure 2. Lateral radiograph showing retrosternal subcutaneous emphysema (green arrow) and subcutaneous emphysema along the back (blue arrow).
Spontaneous pneumomediastinum (SPM) is an uncommon diagnosis in young children and should be suspected in a patient presenting with severe coughing or vomiting episodes with physical examination findings of subcutaneous emphysema or a Hamman sign.

Frontal and lateral chest radiographs can confirm the diagnosis of SPM and often demonstrate common radiographic signs. SPM is frequently confused with a pneumothorax; obtaining a lateral decubitus radiograph can help differentiate these two conditions.

Although the differential diagnosis for SPM is limited, clinicians should consider esophageal perforation if the patient’s history is consistent with this diagnosis.

SPM is typically a benign condition that resolves within 2 weeks. Severe pneumothorax and pneumopericardium are uncommon complications that may occur with SPM.

Summary
Suggested Readings


