LEADING VIRAL CAUSE OF BIRTH DEFECTS

Congenital Cytomegalovirus

Mothers and postpartum depression

How to prevent medical errors

Primary immunodeficiency

FRANK A. OSKI, MD,
CHILDREN’S ADVOCACY AWARD
Rami Sunallah, MD

PUZZLER
Febrile neutropenia and a hepatic mass

Not only is congenital cytomegalovirus the leading viral cause of birth defects, it is also the #1 nongenetic cause of childhood sensorineural hearing loss. —National CMV Foundation
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Rami Sunallah, MD, was working a shift in the pediatric emergency department (ED) at Clear Lake Regional Medical Center near Houston as Hurricane Harvey’s torrential rains pummeled southeast Texas. The late-August 2017 ED shift turned into 4 straight days in the hospital, caring for sick kids during and after the storm.

“I couldn’t go back home because of all the flooding, and there wasn’t anybody who could come and replace me,” he says.

On the fifth day, Sunallah left the hospital and made a quick stop to check on his newly opened private practice in League City, a Houston suburb where Sunallah, his wife, and 2 young children live. Unlike many of the nearby homes and businesses, his practice had only minor flooding. Although Sunallah’s wife was concerned that the water from flooded streets was about to enter their home during the storm, the family’s home also escaped Harvey’s wet wrath.

The sleep-deprived pediatrician checked on his family and his staff, and everybody was all right. However, when he looked around in his community, he saw that most weren’t as fortunate. Even medical centers had closed down, leaving many patients, including children and their families, scrambling to find medical care.

On the sixth day post-Harvey landfall, Sunallah and his staff decided to open the practice and offer care to anyone who needed it, free of charge.

“We basically posted a message on Facebook that whoever needs care, we’re open from 10 AM to 6 PM, or until we’re done,” he says. “We didn’t charge them, and they didn’t have to be our patients to be seen. It was just basically to make sure everybody could be taken care of.”

By 9 AM that morning, families were waiting at Sunallah’s practice. The pediatrician had arranged access to a military vehicle that could get through the flooded streets, to transport patients who needed to be hospitalized.

“We ended up transporting a couple of kids that needed to go to the hospital,” Sunallah says, “and we saw about 50 families, each with 2 or 3 kids. These are families that didn’t have any medical access for about 4 or 5 days, if not more.”

Sunallah says he and his staff saw the spectrum of maladies that day—from children with seizures who had gone without care, to skin infections, pneumonia, ear infections and more. “Honestly, I was happy with my team. They did an impressive job and everybody, at the end of the day, felt good about it,” he says.

Comfortable with really sick kids

Sunallah was well suited for the hectic schedule, triaging, and emergency care he had to provide that day.

After completing a pediatric residency at the University of Toledo, Ohio, Sunallah did a 3-year fellowship in pediatric emergency medicine at the University of Alabama at Birmingham. He completed his fellowship in 2015 and moved with his family to the
Sunallah says he thrives working in the pediatric ED, but, at age 40, doesn’t envision doing that his whole career. “I love the ED—I’m comfortable dealing with sick kids—but it’s not bad having a healthy kid every now and then,” he says.

So, in 2017, he opened a practice aimed at offering children and families the best of both worlds—private practice and emergency medicine.

One example: Sunallah’s work in private practice focuses on controlling patients’ pain with tricks and tactics he learned to manage patients’ pain in the ED.

“Studies show that not a lot of EDs pay enough attention to kids’ pain,” he says. “We do tricks basically, some kind of distraction. We make sure that whatever we’re doing—whether we give them a shot or sutures, or what-not—we take care of the pain first, and then go forward.”

Among the distractions: Shot-Blockers (Bionix; Toledo, Ohio) help dull injection-site pain when children have shots, and iPads always are a great distraction for children, according to Sunallah. “Let them play a game or watch a YouTube video. Once they’re into the game, you can do whatever you want to them, and they won’t notice,” he says.

Focus on avoiding the ED

Sunallah also focuses on helping children and families avoid going to the ED. He says children who often go to EDs or urgent-care centers because of chronic medical conditions suffer from a lack of a continuum of care.

“Kids will actually get sicker because nobody is providing the primary care to take care of them,” he says. “Instead of saying “Here’s your medicine and good luck,” we [take care of them after the urgent visit].”

His ability to keep kids out of the ED when possible goes back to his training. “As an ED doc, when sick kids come to me in the clinic, it gives me an extra push with what we need to do. For example, I do my own x-rays here at the clinic. I have my own full set of labs. Most of the kids I see in the clinic, I take care of myself, unless they need a [computed tomography (CT)] scan,” he says.

If a child needs a CT scan, Sunallah says he’ll send the family to get the scan then follow up to determine if the child needs to be admitted to the hospital or requires surgery, which still avoids the ED. “Why should the family pay an extra ED visit? I tell the hospitalist that I have a kid who needs to be admitted, and the patient goes to the floor rather than the ED,” Sunallah says.

Children who often go to EDs or urgent-care centers because of chronic medical conditions suffer from a lack of a continuum of care.

—Rami Sunallah, MD

People in the community seem to appreciate Sunallah’s approach. One patient’s mother summed it up on the League City Pediatrics’ Facebook page: “This is the pediatrician’s office you always hope that you can find for your children. They listen to your concerns and really talk in depth about possible causes and resolutions. I was blown away by the kindness of everyone there. My boys were thrilled with the play area and even happier when the staff used some nerve confusion techniques to aid with the pain of shots! No tears from shots = happy boys + thrilled mom!”

Ms. Hilton is a medical writer who has covered health and medicine for 25 years. She resides in Boca Raton, Florida. She has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.
BABY ECZEMA RELIEF BODY CREME helps prevent the incidence of flare over time with daily use\textsuperscript{1}

80\% of children remained flare-free for six months\textsuperscript{1}
Is that child with “penicillin allergy” really allergic?

Reseacchers at Wisconsin Children’s Hospital in Milwaukee found that 100 children who visited a pediatric emergency department (ED) with a reported history of penicillin allergy based on low-risk symptoms all had negative allergy testing for penicillin and all tolerated a penicillin challenge (500 mg of oral amoxicillin) without developing a severe allergic reaction. Penicillin allergy labels were removed from their hospital medical records.

In a follow-up study to this one, conducted within a year after the negative results on standard 3-tier penicillin allergy tests were reported, investigators surveyed parents and primary care practitioners (PCPs) of each child to identify care practices and any subsequent antibiotic use or adverse events related to it. They combined data from the PCP and parent surveys to identify children who received an antibiotic and calculated financial savings for patients delabeled as penicillin allergic.

About 90% of parents reported that they were aware of their child’s penicillin allergy testing results, whereas 84% of PCPs said that patient families had not notified them about the results. Indeed, about half the children still had a penicillin allergy label in the PCP medical record. Almost three-quarters of parents reported that they now would be “comfortable” or “very comfortable” if their child received a penicillin antibiotic. Those whose response was “somewhat comfortable” or “not comfortable” cited worry about a repeat allergic reaction to penicillin as the reason for their concern.

Delabeling children did change PCPs’ and other physicians’ prescription behavior, however, with a total of 46 penicillin prescriptions for 36 study participants filled during the follow-up period. Amoxicillin or penicillin was most commonly prescribed followed by azithromycin, cefdinir, and combined amoxicillin and clavulanic acid. One child developed a rash about 24 hours after starting amoxicillin and was relabeled as penicillin allergic. No child had a serious allergic reaction after reexposure to the medication.

Investigators calculated that cost savings for these 36 children totaled $1,368 and cost avoidance amounted to $1,812 in the interval since the first study (Vyles D, et al. Pediatrics. 2018;141[5]:e20173466).
**Parents are most likely to accept vaccines when you assume they will**

When you approach a parent who is hesitant about vaccinating her infant at the appropriate well-baby visits, perhaps you say something like this: “Well, we have to do some shots.” Or you might say, “How do you feel about vaccines today?” The former strategy (a “presumptive” approach) is more likely to be effective than the latter (a “participatory” approach), according to a study in parents whom a standardized survey classified as being hesitant about vaccines.

Investigators assessed the immunization status of the newborns of 73 parents when the infants reached age 8 months. Using electronic immunization records, they obtained data from 82%, 73%, and 53% of participants after the 2-, 4-, and 6-month visits, respectively.

At each time point, clinicians used a presumptive approach more often than a participatory approach (65% vs 42%, respectively, at 1 or more visits). A minority of parents brought up the subject of vaccines themselves. The presumptive format at 1 or 2 or more visits was associated with increased immunization, and that association increased along with the number of visits at which this approach was used. The participatory format at more than 2 visits was associated with significantly more underimmunization, also in a dose-response relationship (Opel DJ, et al. *Acad Pediatr*. 2018;18[4]:430-436).

**How long are new mothers at risk for postpartum depression?**

New mothers may develop postpartum depression (PPD) at any time during the first year after giving birth, an analysis of monthly depression screening data showed. Furthermore, the highest rate of positive screens—23%—occurred at 12 months postpartum.

Investigators screened 152 new mothers for PPD every month for a year after they gave birth using the 10-question Center for Epidemiological Studies Depression Scale (CES-D-10). During the study period, 49% of participants had a positive PPD screen during at least 1 month. Of those who screened positive, 17% had their first positive screen at 1 month, 8% at 2 months, and 6% at 6 months. An additional 9% of mothers had their first positive screen after 6 months.

In other words, 15% of those new mothers who screened positive did not do so until 6 to 12 months postpartum. Analysis also showed that living in a household earning $50,000 or less and having a limited education increase the risk of a positive PPD (McKean M, et al. *Clin Pediatr (Phila)*. 2018;57[6]:689-693).
Febrile neutropenia and a hepatic mass

PALAK SHAH, DO; JAMIE HARRIS, MD; MADALINA MINDRUT, MD

A 7-month-old girl presents to her pediatrician’s office with a 1-week history of fevers and upper respiratory symptoms.

History
The infant had no past medical history and her immunizations were up-to-date. She had some decreased appetite and occasional fussiness, but was otherwise acting appropriately for her age. She had normal urine output. Because of the 1-week history of fevers and rhinorrhea, the pediatrician obtained laboratory studies revealing normocytic anemia and thrombocytosis. The infant was then referred to the emergency department (ED) for further evaluation.

Physical exam
On initial presentation, the patient was febrile to 102.5°F; heart rate was 185 beats per minute; respiratory rate was 36 breaths per minute; blood pressure was 97/49 mm Hg; and oxygen saturation was 99% on room air. Physical exam revealed an active 7-month-old girl in no acute distress but found to be pale and non-jaundiced. She had a regular cardiac rate and rhythm without a murmur. Lungs were clear to auscultation bilaterally without increased work of breathing, wheezing, or crackles. Abdomen was soft, nontender, nondistended with active bowel sounds, and with no hepatosplenomegaly or palpable masses. Her remaining physical exam was appropriate for age.

Labs and hospital course
Initial laboratory results demonstrated a white blood cell (WBC) count of 9.1 K/μL; absolute neutrophil count (ANC) of 0.3 K/μL; hemoglobin of 7.8 g/dL with mean corpuscular volume (MCV) of 79.9 fL; hematocrit, 24.3%; and platelets, 633 K/μL. Comprehensive metabolic panel was normal, specifically: aspartate amino-

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transferase (AST), 23 U/L; alanine aminotransferase (ALT), 17 U/L; alkaline phosphatase, 142 U/L; and total bilirubin, 0.2 mg/dL.

Inflammatory markers were elevated with C-reactive protein (CRP) of 26.8 mg/dL and erythrocyte sedimentation rate (ESR) greater than 120 mm/h. Iron studies were: iron, 9 μg/dL; total iron binding capacity (TIBC), 114 μg/dL; iron saturation, 8%; and ferritin, 434 ng/mL, not exclusively consistent with iron-deficiency anemia. A blood culture and nasopharyngeal respiratory pathogen panel was obtained.

The patient was admitted to the general pediatric unit for febrile neutropenia and was started on cefepime for empiric bacterial antibiotic coverage. Due to potential malignancy, the patient had an abdominal ultrasound that showed a 6.4-cm hepatic mass, confirmed with an abdominal computed tomography (CT) scan (Figure 1).

**Differential diagnosis**
The patient’s main abnormal vital sign/physical exam finding was fever. She had several initial laboratory abnormalities including severe neutropenia, normocytic anemia, thrombocytosis, and elevated inflammatory markers. Also, she was found to have a nonspecific hepatic mass on imaging, although not exclusively consistent with iron-deficiency anemia. A blood culture and nasopharyngeal respiratory pathogen panel was obtained.

The patient was admitted to the general pediatric unit for febrile neutropenia and was started on cefepime for empiric bacterial antibiotic coverage. Due to potential malignancy, the patient had an abdominal ultrasound that showed a 6.4-cm hepatic mass, confirmed with an abdominal computed tomography (CT) scan (Figure 1).

**Further evaluation and diagnosis**
Febrile neutropenia can be caused by viral suppression of bone marrow function. However, given the additional abnormal findings in this patient (ie, elevated inflammatory markers and hepatic mass), timely involvement of pediatric subspecialists and further workup were needed. The Hematology/Oncology team was consulted for febrile neutropenia, anemia, and thrombocytosis with concerns for a possible oncologic etiology, and the Infectious Disease team for infectious process as the cause of her signs and symptoms.

**TABLE**

**DIFFERENTIAL DIAGNOSIS FOR LIVER MASS IN INFANTS**

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From Weinberger SE; Nakanuma Y, et al.7
The patient continued to be febrile while on cefepime. Her blood culture was negative. She was found to have enterovirus/rhinovirus on her respiratory viral polymerase chain reaction (PCR) panel, likely the source of her fever. Her remaining infectious disease workup was negative, specifically for hepatitis, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and *E histolytica*. Sepsis was ruled out given that her blood culture was negative. The child remained well appearing throughout her hospitalization and had a negative infectious disease workup.

She underwent a bone marrow biopsy that was negative for malignancy. A fine needle biopsy of the hepatic lesion was performed initially, but this was not diagnostic. Subsequently, she had an open liver biopsy, which demonstrated a right-lobe hepatic mass with pathology showing abundant mixed lymphoplasmacytic infiltrate and positive immunoglobulin (Ig) G4 plasma cells, consistent with inflammatory pseudotumor (Figure 2).

Additional laboratory studies including normal alpha-fetoprotein and beta-hCG levels were negative, but showed positive granulocyte antibodies. Genetic congenital neutropenia panel was also negative. All IG levels (IgG, IgM, and IgA) were elevated.

**Discussion**

Inflammatory pseudotumors (IPTs) are rare, benign, solitary, well-demarcated lesions caused by proliferation of inflammatory cells. Other terminology used to describe IPT includes inflammatory myofibroblastic tumor, plasma cell granuloma, fibrous histiocytoma, fibroxanthoma, and xanthogranuloma. This type of benign lesion is most commonly found in the lung, although extrapulmonary sites have been identified, including the head and neck regions, orbit, major salivary glands, submandibular glands, lymph nodes, breast, kidney, pancreas, gastrointestinal (GI) tract, liver, spleen, retroperitoneum, genitourinary tract, and soft tissue. As of 2011, fewer than 300 cases of hepatic IPT have been identified and reported. From 1971 to 2008, only 35 pediatric cases were reported with an additional 9 pediatric cases from 2009 to 2014. Increased IPT identification can be attributed to advances in medical imaging.

Because of a variety of constitutional symptoms (fever, malaise, weight loss, and fatigue) and difficulty in accurately diagnosing IPT, patients often are misdiagnosed initially with malignancy. The majority of documented IPTs are asymptomatic, incidental findings. Although extremely rare, severe lesions causing mass effect have been reported as well.

Initial laboratory studies usually are significant for elevated WBC...
count, elevated acute phase reactants such as ESR and CRP, and abnormal liver function tests (LFTs). Although uncommon, IPT can cause cytopenias affecting WBC, specifically, ANCs, hemoglobin, and/or platelets. Ultrasound, CT, MRI, and positron emission tomography (PET) imaging can demonstrate variable clinical images based on location and density of the affected lesion. If diagnosis remains unknown, patients often undergo fine-needle aspiration (FNA) or open biopsy/resection to determine a diagnosis.

Inflammatory pseudotumor typically develops secondary to an aberrant inflammatory response from a cellular insult. Histologically, when inflammatory cells are activated, various cytokines are produced and released (Figure 2). These cytokines activate neutrophils, eosinophils, lymphocytes, plasma cells, histiocytes, multinucleated giant cells, myofibroblasts, and spindle-shaped cells, leading to cellular damage and IPT formation.

Although the etiology of IPT remains unknown, several possibilities have been proposed, ranging from postinfectious to autoimmune to neoplastic causes. Inflammatory pseudotumors have been identified after postradiation therapy for malignant neoplasms. Several IPT lesions show anaplastic lymphoma kinase positivity at the tyrosine kinase locus, supporting a theory that plasma cell granulomas are low-grade mesenchymal neoplasms with a secondary inflammatory component.

Previously reported cases have not demonstrated a correlation between IPT and severe neutropenia, leading to this perplexing case. Generally, patients diagnosed with IPT do not require inpatient hospitalization and can be monitored on an outpatient basis. This patient’s diagnosis remained unknown for multiple days and was complicated by continued fevers and severe neutropenia with initial concerns for malignancy, causing her prolonged hospitalization. The persistent neutropenia was likely secondary to a combination of IPT of the liver, viral illness with enterovirus/rhinovirus, and autoimmune neutropenia. Although the etiology and long-term implications of this patient’s IPT and neutropenia remain unknown, the concomitant presentation suggested a potential association between the two.

Inflammatory pseudotumor can be a manifestation of IgG4-related disease, an immune-mediated condition characterized by lymphoplasmacytic infiltration with a predominance of IgG4-positive plasma cells, frequent elevation of serum IgG4, and a dramatic response to glucocorticoids, if administered. Initially, this patient had elevated serum IgG4 levels, which normalized over time, and liver pathology was positive for IgG4 plasma cells. Given these laboratory and pathology findings, the patient’s IPT appeared to be consistent with the lymphoplasmacytic subtype. Although glucocorticoids are found to be effective, this patient did not receive steroids because of her improved fever curve and continued hemodynamic stability throughout her hospitalization.

In most instances of postinfectious neutropenia, particularly with viral infections, neutropenia is transient and rarely results in superimposed bacterial infections. Other viral infections known to cause mild to moderate neutropenia include influenza A and B, respiratory syncytial virus (RSV), and parvovirus. Measles, rubella, and varicella more commonly cause leukopenia with mild neutropenia and lymphopenia. Viruses leading to greater immune suppression include EBV, CMV, human herpesvirus-6 (HHV-6), hepatitis, and human immunodeficiency virus (HIV), which can cause more superimposed bacterial infections.

Previous reports have demonstrated improvements in neutropenia in 3 to 8 days. However, the patient in this case remained persistently neutropenic throughout her hospital course. Prolonged fevers and neutropenia always raise concern for possible sepsis. Luckily, she was diagnosed with enterovirus/rhinovirus without secondary infectious etiologies.

Autoimmune neutropenia (AIN),
caused by granulocyte-specific antibodies, is commonly diagnosed between ages 7 to 9 months. Patients often are incidentally diagnosed when laboratory studies are obtained for other reasons with an initial ANC ranging from 0.5 to 1.0 K/μL. Diagnosing AIN can be challenging because of difficulties in detecting autoantibodies, and AIN is most commonly diagnosed with the indirect granulocyte immunofluorescence test (indirect-GIFT) or the granulocyte agglutination test (GAT). This patient underwent testing and was found to have positive granulocyte antibodies with chronic neutropenia, thereby diagnosing her with a component of autoimmune neutropenia. Treatment typically includes close monitoring with spontaneous remission and disappearance of autoantibodies.

Patients with recurrent or severe infections or those undergoing surgical procedures often receive granulocyte colony-stimulating factor (G-CSF), also known as filgrastim. Escalating therapy for refractory cases include intravenous immunoglobulin (IVIG), corticosteroids, or monoclonal antibodies. Although the patient in this case did not have a severe viral infection, she remained persistently neutropenic without improvement, leading to the decision to start treatment with G-CSF.

Among the few reported cases of IPT, even fewer have been associated with neutropenia. Cojean and colleagues describe a patient with severe congenital neutropenia concurrently diagnosed with IPT through positron emission tomography (PET) imaging, which occurred after an unsuccessful response to G-CSF in anticipation of bone marrow transplantation (BMT). As IPT has not been consistently associated with neutropenia, a plausible connection could be neutropenic patients becoming more susceptible to developing IPT after recovery from a cellular insult secondary to an infection. Although rare, it is important to consider IPT when there are concerns for a mass with or without significant neutropenia, as this lesion does not always require inpatient hospitalization, medications, or surgical intervention.

First-line treatment for IPT includes outpatient monitoring with serial imaging, frequent ultrasounds, and repeat laboratory studies.

Treatments options
Treatment options are usually conservative but can require surgical resection if no clinical improvement is observed. First-line treatment for IPT includes outpatient monitoring with serial imaging, frequent ultrasounds, and repeat laboratory studies. If IPT continues to persist, patients often undergo full surgical resection. After surgical intervention, most cases of IPT do not recur. Nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics also have been utilized with varying responses. If an IgG4-related disease is suspected, glucocorticoids can help with tumor regression.

Patient outcome
During her 19-day hospitalization, the patient’s neutropenia continued and the decision was made to start G-CSF. She was discharged once she was no longer febrile with improvement in her ANC, anemia, thrombocytosis, and inflammatory markers. Because of the location and size of her hepatic lesion, she was not a candidate for a complete resection at the time of her biopsy. She continued conservative treatment with serial imaging and repeat laboratory studies.

Initially, she was receiving serial abdominal ultrasounds monthly, then extended to bimonthly with an abdominal MRI scan demonstrating complete regression of the hepatic IPT 9 months after the initial diagnosis (Figure 3). Luckily, this patient had spontaneous regression and did not require surgical resection of her IPT. She remained on G-CSF for 4 months as outpatient therapy with improvement in chronic neutropenia. Repeat Ig levels also normalized. Overall, her clinical course improved significantly with regression of her IPT and normalization of abnormal laboratory studies.

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Dr. Shah is a graduating pediatric resident at Advocate Children’s Hospital, Park Ridge, Illinois. Dr. Harris is a graduating pediatric resident, Advocate Children’s Hospital, Park Ridge, Illinois. Dr. Mindrut is a pediatric hospitalist, Advocate Children’s Hospital, Park Ridge, Illinois. The authors have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

For references, go to ContemporaryPediatrics.com/puzzler-0718
The advent of the congenital Zika virus epidemic in 2016 focused considerable and well-deserved attention on the recognition and prevention of this infection. Even as this tragedy continues to unfold, however, the ongoing problem of congenital cytomegalovirus (cCMV) infection deserves similar scrutiny. This article provides an overview of the impact of cCMV on pediatric practice, with an emphasis on evolving concepts in maternal and newborn screening, counseling and education, diagnosis in the newborn, and medical management of children with CMV infection.

**How common is cCMV infection?**

Congenital infections with CMV are common and appear to be underrecognized. In the United States, the Centers for Disease Control and Prevention has estimated an overall birth prevalence of 0.65%.\(^1\) Congenital infections are even more prevalent in the developing world, with estimates of rates as high as 6.5% in some populations.\(^2\)

In the United States, this corresponds to more than 25,000 newborns every year with cCMV. Considerable variation also has been seen in birth prevalence based on maternal age, race, socioeconomic status, and the entire spectrum of the social determinants of health.\(^3\) Rates of cCMV are highest in black infants, making cCMV an example of a disease reflecting health disparities nationally.\(^4\)\(^-\)\(^6\)

To put this all in perspective, as of June 2016, there had been 7830 suspected cases of congenital Zika syndrome reported to the Brazilian Ministry of Health.\(^7\) The largest total of US cases of congenital infection with another teratogenic virus, rubella, was in 1969, when 57,686 cases were reported.\(^8\)

Thus, the total number of cases of cCMV in this country (and globally) far exceeds the cases of congenital Zika syndrome and is similar in scope to the magnitude of congenital rubella syndrome observed in the developing world, with estimates of rates as high as 6.5% in some populations.\(^2\)
Given the high prevalence of cCMV, why isn’t it more commonly recognized by clinicians? One important issue is the lack of knowledge and awareness not only among the lay public but also among healthcare providers, including obstetricians and pediatricians. Women of childbearing age in particular lack knowledge about the risks associated with cCMV. Transmission of CMV requires exposure to infectious body fluids including urine, saliva, blood, and breast milk. Women who have children in group daycare are at particular risk because CMV shedding rates are high in infants and toddlers attending daycare centers. Toddlers bring CMV home from the daycare center and expose their susceptible parents to the virus, resulting in infections that often are asymptomatic or minimally symptomatic but can lead to congenital transmission if that child’s mother is pregnant. Surveys have shown that women are less well informed about cCMV than they are about neural tube defects, fetal alcohol syndrome, Down syndrome, and toxoplasmosis, even though all these threats to healthy pregnancy are less common than CMV. Thus, there is a great unmet need for programs that can increase the public’s familiarity with cCMV.

Another major challenge that diminishes overall awareness of cCMV is the recognition that the majority of infants with cCMV (85%-90%) are asymptomatic at birth. In the 10% to 15% of infants who do have signs or symptoms at birth, clinical manifestations may include growth retardation, petechiae, hepatospllenomegaly, microcephaly, jaundice, seizures, and rashes (Table 1). Symptomatic infants are more likely to have long-term neurodevelopmental sequelae, including mental retardation, seizure disorders, cerebral palsy, sensorineural hearing loss (SNHL), microcephaly, and learning disabilities. Of these sequelae, SNHL is the most common.

It is important to keep in perspective that asymptomatic cCMV is not innocuous. Asymptomatic infection can portend long-term risk, particularly as it relates to SNHL. Approximately 22% to 65% of children with symptomatic disease at birth and 6% to 23% of children with asymptomatic cCMV infection will have SNHL following cCMV infection. Also of note is that SNHL caused by cCMV infection may not be present at birth and will not be noticeable until later in childhood.

The fluctuating and (in many cases) delayed nature of cCMV-associated SNHL means that the majority of cases will be missed by routine newborn hearing screening. This provides a compelling rationale for universal CMV screening for all newborn infants. Such universal screening could create an opportunity to provide any infant (even asymptomatic babies) with known cCMV with serial, regular audiologic assessment to facilitate early intervention for those infants demonstrating evidence of SNHL.

**When and how to test for cCMV**

The cornerstone of diagnosis of cCMV is based on virology, not serology. Although the term “TORCH titers” (toxoplasmosis; other diseases including HIV, syphilis, and measles; rubella; cytomegalovirus; herpes simplex) is unfortunately still used in clinical practice, this nomenclature should be abandoned because antibody studies are rarely useful in the workup and management of congenital viral infections. The traditional gold standard for diagnosis of cCMV has been demonstration of vi-
Case study: Cytomegalovirus (CMV)

**Cytomegalovirus (CMV)**

US children born with or developing long-term medical conditions each year

- **CMV**: 5500
- Fetal Alcohol Syndrome: 5000
- Down Syndrome: 4000
- Spina Bifida: 3000
- HIV/AIDS: 200

Women’s awareness of these diseases

- CMV: 98%
- Fetal Alcohol Syndrome: 97%
- Down Syndrome: 83%
- Spina Bifida: 76%
- HIV/AIDS: 14%

From National CMV Foundation (www.nationalCMV.org)

Cytomegalovirus (CMV) is a common viral infection, with the majority of cases occurring in the United States. CMV is a common cause of congenital infections, and it can have significant long-term medical consequences. The chart above illustrates the prevalence of CMV and other conditions in US children born with or developing long-term medical conditions each year.

**85% to 90% of infants with cCMV are asymptomatic at birth.**

Studies have shown that most infants with CMV are asymptomatic at birth, with the majority of cases occurring in the United States. The chart above highlights the prevalence of CMV and other conditions in US children born with or developing long-term medical conditions each year.

**CMV by culture in specimens of saliva, urine, or blood obtained from the infected newborn.** Few diagnostic laboratories offer culture today, however, and virologic diagnosis is now more commonly predicated on identification of viral DNA by polymerase chain reaction (PCR) assay. A PCR of urine or saliva is equally definitive in making the diagnosis of cCMV. Most experts recommend obtaining blood PCR for CMV DNA in addition to urine and saliva samples. The finding of CMV immunoglobulin (Ig) G antibodies is not informative because it neither confirms that an infant has congenital CMV (as transplacental transfer of IgG can occur without bona fide infection) nor excludes the possibility of cCMV infection (as late gestation transmission can occur from mother to fetus prior to appearance of IgG antibodies). Evaluation of neonatal serum for IgM antibodies can be useful, but the test is relatively insensitive and should not be relied on to confirm or exclude the diagnosis.

One critically important element to consider in the diagnosis of congenital CMV is the timing of obtaining specimens for definitive testing. It is imperative that diagnostic specimens be obtained in the first 21 days of life and preferably in the first 14 days of life. This is because shedding of CMV in infants aged older than 21 days may reflect perinatal transmission, most commonly from breastfeeding.

Although breast milk-acquired infections are generally of no clinical importance in term babies, this mode of acquisition can complicate the evaluation for cCMV infection. This is a particular concern for infants who fail the newborn hearing screen, and requires audiologic referral to investigate for possible etiologies of SNHL. In this setting, infants are often aged older than 3 weeks when they present to an audiologist for diagnostic evaluation. Under these circumstances, a positive urine or saliva PCR for CMV DNA must be interpreted cautiously because a positive result could reflect postnatal acquisition and may have nothing to do with an infant’s hearing loss.

Once diagnostic virology has confirmed the diagnosis, other ancillary studies are important in the evaluation of cCMV. The pattern of laboratory abnormalities, if present, is valuable in defining whether an infant has symptomatic or asymptomatic congenital infection. A complete blood count and differential leukocyte count is important, given that thrombocytopenia in the neonate stands out as a predictive biomarker for an increased risk of neurodevelopmental sequelae.

Liver function tests, including assessment for cholestasis, are useful. Imaging studies are a key component of the evaluation. Head ultrasound is recommended in the neonatal period and has excellent sensitivity for demonstrating periventricular calcifications, structural lesions, and ventriculomegaly. Ophthalmologic evaluation is warranted in all proven cases of cCMV. Serial audiologic assessment is essential, including brainstem auditory evoked responses, in the setting of proven cCMV.

Until universal cCMV screening becomes implemented, which infants require diagnostic evaluation for cCMV infection? Certainly, any infant with signs and symptoms suggestive of cCMV warrants virologic evaluation. If CMVs is demonstrated, additional studies may be undertaken as outlined earlier. The notion that cCMV is asymptomatic in 85% to 90% of cases, however, may substantially underestimate the frequency of subtle clinical manifestations of infection, because more detailed diagnos-
tic evaluation may not be performed in infants who appear to be unaffected. Newborns who demonstrated prenatal ultrasonographic abnormalities, such as intrauterine growth retardation, central nervous system (CNS) anomalies, and, in particular, echogenic bowel, should be tested for cCMV in the newborn period. Infants with a small-for-gestational-age presentation or infants born to women who have histologic evidence of placental abnormalities at birth also should be tested for cCMV. The diagnosis of cCMV should be considered in infants with unexplained premature birth because there appears to be a higher CMV birth prevalence in premature infants. Finally, for any newborn whose result is “refer” on the newborn hearing screen, consideration should be given to performing CMV testing prior to hospital discharge.

Although only a small percentage of infants who do not pass the newborn hearing screen actually have hearing loss, there is an enrichment for cCMV in this group of infants. Moreover, as previously noted, obtaining a diagnostic specimen for CMV in the immediate newborn period eliminates the diagnostic uncertainty intrinsic to the finding of viral shedding in an infant aged older than 21 days undergoing audiological evaluation. Therefore, I recommend that if an infant does not pass the newborn hearing screen, testing for congenital CMV should be performed immediately in the newborn nursery.

When and how to treat cCMV infections

Which infants require treatment for cCMV infection? Currently, treatment is reserved for infants with symptomatic congenital infection; that is, infants with obvious signs (by clinical assessment, laboratory studies, or imaging abnormalities) of disease at birth. Infants with symptomatic disease including the CNS are probably the highest-priority candidates for treatment. This includes infants with microcephaly; radiographic abnormalities consistent with cCMV CNS disease (ventriculomegaly, intracerebral calcifications, periventricular echogenicity, cortical or cerebellar malformations); abnormal cerebrospinal fluid (CSF) indices for age; chorioretinitis; SNHL; or the detection of CMV DNA in CSF.

Infants with clinical evidence of cCMV who have clear-cut symptomatic disease, even without CNS involvement, also should be offered therapy given that the risk of long-term neurodevelopmental sequelae is high. This includes infants with thrombocytopenia, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, hepatitis (raised transaminases or bilirubin), or other signs of infection. Those infants who have isolated SNHL with no other clinical manifestation of infection and those with asymptomatic congenital infection are not currently considered candidates for antiviral therapy, however, although the potential benefits of treatment are being evaluated in several active clinical trials and consultation with an expert is recommended.

Treatment, when indicated, should consist of oral valganciclovir suspension. The suggested dose is 16 mg/kg orally twice daily. In infants unable to tolerate oral therapy, intravenous therapy with ganciclovir can be considered. Treatment should be commenced in the first month of life. The finding of CMV by PCR or culture in urine, saliva, or blood in an infant aged older than 21 days cannot be presumed to be diagnostic of cCMV infection because breastfed babies, as noted above, may acquire infection postnatally. This confounds the interpretation of diagnostic studies in infants who have clinical features of congenital infection.

### TABLE 2
**SUGGESTED DIAGNOSTIC STUDIES IN EVALUATION AND WORKUP OF cCMV INFECTION**

<table>
<thead>
<tr>
<th>Laboratory and radiographic evaluation</th>
<th>Subspecialty consultants</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Complete blood count, platelet count, differential leukocyte count</td>
<td>- Audiology (auditory-evoked response studies)</td>
</tr>
<tr>
<td>- Hepatic panel (transaminases, bilirubin)</td>
<td>- Otolaryngology</td>
</tr>
<tr>
<td>- CMV DNA PCR (blood, urine, saliva)</td>
<td>- Child neurology</td>
</tr>
<tr>
<td>- Placental histopathology (if available)</td>
<td>- Developmental specialist</td>
</tr>
<tr>
<td>- Head ultrasound (screening test; consider follow-up MRI)</td>
<td>- Ophthalmology</td>
</tr>
<tr>
<td></td>
<td>- Physical therapy/ Occupational therapy</td>
</tr>
<tr>
<td></td>
<td>- Pediatric infectious diseases</td>
</tr>
</tbody>
</table>

Abbreviations: CMV, cytomegalovirus; cCMV, congenital cytomegalovirus; DNA, deoxyribonucleic acid; MRI, magnetic resonance imaging; PCR, polymerase chain reaction. Modified from Swanson EC, et al.¹⁶
The author’s research laboratory (www.cmvscreening.org/) will perform CMV DNA PCR on saved, archived newborn dried blood spots if available (routinely obtained in the course of normal newborn care and retained in most states), with permission of the infant’s family and the respective state health department. Clinicians interested in this service can contact the lab for further discussion. In some cases, the test helps resolve the question of whether an infant was born with cCMV infection.18,19

Active clinical studies are also examining whether delayed initiation of antiviral therapy (ie, beyond age 1 month) is beneficial. These studies, in particular, are being pursued in infants with previously unexplained SNHL that is recognized later in infancy or early childhood to be attributed to cCMV. Again, consultation with a pediatric infectious disease specialist is recommended in this circumstance.

Evidence of benefit conferred by therapy with oral valganciclovir was demonstrated in a randomized, placebo-controlled trial that showed a statistically significant benefit of treatment in symptomatic neonates.20 All symptomatic cytomegalovirus-infected neonates received valganciclovir for 6 weeks and were then randomized to receive either placebo or additional valganciclovir treatment to complete a 6-month course. Neonates receiving 6 months of valganciclovir had an increased likelihood of improved hearing at 24 months versus those who received only 6 weeks of valganciclovir treatment (followed by placebo). Importantly, neurodevelopmental outcomes also were improved with therapy. Based on these data, antiviral therapy with valganciclovir should be considered in all infants with symptomatic cCMV infection.

Laboratory monitoring is essential in infants treated with valganciclovir. Treatment is associated with neutropenia, and absolute neutrophil counts should be followed weekly for 6 to 8 weeks, then monthly for the duration of therapy. Transaminases should be followed monthly throughout therapy. For infants with drug-induced neutropenia, although there are no consensus management guidelines on this issue, therapy with granulocyte colony-stimulating factor (G-CSF) can be offered as needed. This allows many infants to complete a full 6-month course of treatment.

Many parents and clinicians become invested in their commitment to finish a 6-month course of therapy, and G-CSF can safely enable this. The author also recommends that audologic testing be done at 3-month intervals for the first 3 years of life in all cases of cCMV, irrespective of whether symptoms are present at birth or whether the infant is treated with valganciclovir, and, at a minimum, annually thereafter through adolescence (ages 10 to 19 years).

Serial developmental assessments, beginning at the first year of life, are helpful in some children with symptomatic cCMV disease, as is additional neuroimaging. Because some infants with cCMV with evolving SNHL are or become candidates for cochlear implantation, brain magnetic resonance imaging (MRI) can be considered at the same time that temporal bone MRI is performed prior to implant placement.

Treatment and monitoring of cCMV involves much more than just antiviral therapy and monitoring for drug tox-
It requires a coordinated, team-based approach including, in many instances, specialists in ophthalmology, audiology, otolaryngology, neurology, developmental pediatrics, occupational and physical therapy, orthopaedic surgeons, psychiatrists, and pediatric infectious disease specialists. The pediatrician can play a central role in coordinating and managing the multidisciplinary evaluations required for many of these infants.

Finally, the infant with cCMV can and should receive routine childhood immunizations, including infants on antiviral therapy, given that there is no evidence such infants have overarching immune deficiencies or problems handling live-virus vaccines.

Why newborn CMV screening?
Infants with asymptomatic cCMV are at risk for long-term sequelae, in particular SNHL. Thus, there has been considerable interest in universal newborn CMV screening, and, in particular, the question of whether cCMV should be added to the Recommended Uniform Screening Panel (RUSP; www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html), which is recommended for all newborns.

Two major issues have so far precluded adding cCMV to the RUSP panel. First, it is not yet clear what constitutes the optimal specimen for newborn screening for CMV infection. Performing PCR for CMV DNA on the dried newborn blood spot would, in principle, represent an ideal strategy given that it is obtained routinely in the nursery. Therefore, using the blood spot for this purpose would obviate the need for procuring additional samples for CMV testing. However, a multicenter cCMV screening study of blood spot PCR demonstrated suboptimal sensitivity. Alternative approaches could include PCR testing of saliva or urine samples, but the cost associated with obtaining such samples in all newborns may be prohibitive.

Second, in contrast to most newborn screening tests (which are typically performed to identify uniformly serious and even life-threatening conditions), cCMV screening will identify many infants who are destined to have a normal clinical outcome. On the other hand, advocates for universal cCMV screening point out that even asymptomatic congenitally infected infants are at risk for development of SNHL, even if they pass the newborn hearing screen, and that identification of such infants is not only capable of improving their clinical outcomes but is also cost-effective. Further study is required to resolve this issue.

A compromise that has emerged in some states is “targeted screening,”...
that is, testing for cCMV in all infants who fail the newborn hearing screen. Such programs will miss the majority of cases of cCMV but will facilitate timely diagnosis and early intervention for many infants who could benefit from intervention.\textsuperscript{24} An exciting development has been the engagement of state legislative bodies across the United States addressing the issue of targeted screening. Several bills have been passed in recent years that variably mandate targeted screening and/or require state health departments to provide educational resources, aimed in particular at healthcare providers and young women of childbearing age, about the problem of cCMV infection (Figure).

For example, a CMV knowledge and awareness bill, the Vivian Act, is currently under consideration by the state of Minnesota House of Representatives (www.house.leg.state.mn.us/members/pressrelease.asp?pressid=28204&party=2&memid=15434). It is hoped that these measures can address the substantial and disconcerting knowledge deficit that exists, among both the lay public and physicians, regarding the risks of acquiring CMV infections during pregnancy.\textsuperscript{9,25}

The future: CMV vaccines
Ultimately, prevention of cCMV will most likely require the development and implementation of an effective vaccine. Several CMV vaccine platforms have been developed and assessed in preclinical models, and in phase 1 and phase 2 human studies.\textsuperscript{27} The best-studied candidate to date, a purified and adjuvanted recombinant vaccine against the immunodominant glycoprotein B present in the CMV viral envelope, has demonstrated efficacy ranging from 43% to 50% in preventing primary CMV infection in young women.\textsuperscript{28,29}

Many questions remain about how a CMV vaccine would be used in clinical practice. Should a CMV vaccine be given universally to young children toward the goal of universal coverage (“herd” immunity), using a paradigm that was successful for vaccine-mediated protection against congenital rubella syndrome? Or, should a vaccine selectively target young women (and young men) of childbearing age to enhance protection during the childbearing years? Should serologic screening be performed before the administration of vaccine to young women, knowing that the greatest risk for disability in infants occurs in the context of primary maternal infection during pregnancy? Or, should all women be vaccinated prior to pregnancy, irrespective of CMV serology results, given that it is becoming clear that CMV “immune” women can become reinfected with new strains during pregnancy that can result in congenital transmission? Although reinfection probably results in fewer sequelae than does primary maternal infection during pregnancy,\textsuperscript{10} a strong case can be made for universal immunization of women of childbearing age, since “boosting” natural immunity may prove useful in preventing reinfections.

In conclusion
Regardless of how these questions play out, these are exciting times with encouraging prospects ahead for solving the problem of cCMV. The combination effects of increased awareness, evolution of newborn screening programs, and development and deployment of an effective vaccine should synergize on the near horizon to give clinicians the solutions for this common, underrecognized, and disabling infection in newborns.

RESOURCES FOR PEDIATRICIANS AND PARENTS ABOUT CMV
Awareness flyers to help clinicians educate parents and pregnant women about cytomegalovirus (CMV), the leading viral cause of birth defects, are available for downloading and distribution in both English and Spanish versions. Many more resources are available on the website. www.nationalCMV.org

For references, go to ContemporaryPediatrics.com/congenital-cytomegalovirus
Primary immunodeficiency
When recurrent infections signal something more

For all patients with recurrent infections, early detection and treatment are critical to avoid the life-altering adverse effects of an underlying, untreated immunodeficiency disorder.

MARY BETH NIERENGARTEN, MA

When children present with recurrent infections, treatment of the specific infection is typically paramount in the clinician’s mind. Although obviously necessary, such focus on resolving the infection may distract from considering an underlying condition, such as allergies or immunodeficiencies, that may be occasioning the recurrent infections.

“Some immunodeficiency disorders are not picked up as early as they might be because pediatricians are so focused on treating, for example, an ear infection from crisis to crisis with antibiotics that they may not get at the real cause, which might be an immunodeficiency,” says Stuart L. Abramson, MD, PhD, FAAP, director, Allergy/Immunology Services, Shannon Medical Center/Shannon Clinic, San Angelo, Texas.

It is estimated that primary immunodeficiencies (PIs) occur in about 1:2000 live births.¹ Unlike secondary immunodeficiencies that occur in connection with other conditions (for example, viral infections, malignancies, or malnutrition), PIs are inherited disorders affecting the functioning of the immune system. Children and adults with PIs are predisposed to infection, autoimmune disease and aberrant inflammatory response, and malignancy.

1:2000 ratio of primary immunodeficiencies to live births.¹

A key presenting feature of all immunodeficiency disorders is an increased susceptibility to infection. Therefore, children who present with frequent infections should be on the clinician’s radar as potentially having...
### TABLE 1

<table>
<thead>
<tr>
<th>PRIMARY IMMUNODEFICIENCY DISORDERS BY TYPE OF CELL DEFECT</th>
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<tbody>
<tr>
<td>DISORDERS</td>
</tr>
<tr>
<td><strong>B-CELL DISORDERS (COMMON)</strong></td>
</tr>
<tr>
<td>Selective IgA deficiency</td>
</tr>
<tr>
<td>IgG2 subclass/selective deficiency</td>
</tr>
<tr>
<td>Transient hypogammaglobulinemia of infancy</td>
</tr>
<tr>
<td><strong>B-CELL DISORDERS (UNCOMMON)</strong></td>
</tr>
<tr>
<td>X-linked agammaglobulinemia (XLA)</td>
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<tr>
<td>Common variable immunodeficiency (CVID)</td>
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<tr>
<td><strong>T-CELL DISORDERS (COMMON)</strong></td>
</tr>
<tr>
<td>DiGeorge anomaly (partial)</td>
</tr>
<tr>
<td><strong>T-CELL DISORDERS (UNCOMMON)</strong></td>
</tr>
<tr>
<td>DiGeorge anomaly (complete)</td>
</tr>
<tr>
<td><strong>SEVERE COMBINED IMMUNODEFICIENCIES (UNCOMMON)</strong></td>
</tr>
<tr>
<td>Severe combined immunodeficiency (SCID)</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td>Leukocyte adhesion deficiency</td>
</tr>
<tr>
<td>Complement component disorders (uncommon)</td>
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</tbody>
</table>

Abbreviations: IgA, immunoglobulin A; IgG, immunoglobulin G.
From Abramson SL. 3
immunodeficiency disorders. This is the first step in recognizing and managing what could be a life-altering condition if not caught and treated early. Early diagnosis and treatment are critical to preventing or reducing the significant morbidity and mortality that can result if PIs are left undiagnosed and untreated.2

“Chance favors the prepared mind,” says Abramson, quoting the French scientist Louis Pasteur. “If you don’t think about it, you aren’t going to make the diagnosis and help these patients. So just thinking about the problem, being alert to the early warning signs, and getting the proper testing and referral can make all the difference.”

In a presentation at the 2017 American Academy of Pediatrics (AAP) meeting in Chicago, Illinois, titled “Recurrent infections: Is it immunodeficiency?” Abramson discussed the warning signs suggestive of a PI, a stepwise approach to making the diagnosis, and management issues in the care of children with PI disorders.3

**Warning signs**
Abramson opened his talk with a description of the different types of immunodeficiency disorders, focusing specifically on PI disorders. All PIs stem from the failure of one or more of the body’s defensive mechanisms to properly function. The type of PI depends on the specific defect of the immune system—whether it is characterized by a humoral (antibody) deficiency, cellular deficiency, or a combination of both humoral and cellular deficiencies.1

Fifty percent of PIs are primary B-cell disorders: both more common PIs (eg, selective immunoglobulin A [IgA] deficiency disorders) and uncommon PIs (eg, X-linked agammaglobulinemia). Other types of PIs are categorized as combined B-cell and T-cell immunodeficiencies (20%), phagocyte immunodeficiencies (18%), T-cell immunodeficiencies (10%), and complement immunodeficiencies (2%).1 Abramson provided a brief description of several common and uncommon PIs and their clinical presentations (Table 1).

To help clinicians recognize when a child may have a PI, Abramson referred to a quick checklist of 10 warning signs developed by the Jeffrey Modell Foundation.2 As noted in Table 2, a child who presents with 2 or more of these warning signs should undergo further assessment to make the differential diagnosis. Some of these symptoms also may indicate an underlying undiagnosed and untreated allergy, so making the correct diagnosis is crucial.

Abramson emphasized the importance of pediatricians knowing these 10 warning signs because “they are often the first line of defense in terms of picking up these patients and getting them to the proper specialists.”

**About 75% of PIs can be diagnosed by obtaining a complete blood count and quantitative immunoglobulin levels (stage 1).**

—Stuart L. Abramson, MD, PhD, FAAP

**Early diagnosis, treatment are critical**
Diagnosis of a PI disorder is based on a stepwise approach involving 4 stages. Table 3 lists the stepwise approach to diagnosis recommend-
ed by the Jeffrey Modell Centers Network. Abramson said that most PIs (about 75%) can be diagnosed by obtaining a complete blood count (CBC) and quantitative immunoglobulin levels (stage 1).

If either test is abnormal, he emphasized, it is important to repeat the test to ensure that the first reading was not a lab error and that the positive test truly reflects a persistent problem.

“Unless you get a follow-up test, for example, of an initial test that showed either a low or high white blood cell count, you don’t know whether the blood cell count has normalized,” Abramson said. “In the case of a very low lymphocyte count that remains low, that could be indicative of a cellular immunodeficiency and not just a viral infection.”

“Viral infections can lower the white blood count, but if it doesn’t go away, it may be a persistent cellular deficiency,” he reiterated.

If a positive test persists after repeat testing, further diagnosis is indicated. For any diagnosis required after stage 1, Abramson suggests pediatricians consider referral to an allergist or immunologist for further workup. In addition to a potential diagnosis of a PI, some of these children with recurrent infections (eg, recurrent otitis) may have an underlying allergy that needs to be diagnosed or ruled out to make the correct differential diagnosis.

Following this stepwise diagnostic approach and referring children to specialists when warranted are critical to ensuring an accurate and early diagnosis.

“Early diagnosis is very important for some of these disorders because if the patient goes for a long period of time with recurrent infections, this can sometimes cause more chronic problems,” said Abramson, citing the potential for, among other conditions, the development of bronchiectasis if the underlying PI goes undetected and untreated.

In addition, Abramson said that early detection is critical for children who have a severe PI because they can be candidates for bone marrow transplantation. These children typically have an immunodeficiency that poses serious, life-threatening outcomes if immune reconstitution is not achieved. “If you wait too long and the infection becomes too difficult to treat or becomes chronic, it’s much riskier to do a bone marrow transplant because you have to immunosuppress the patient as you don’t want them to develop a graft-versus-host reaction,” he said. Characteristics for transplantation for PI disorder are listed in Table 4.

Currently, most children diagnosed with PI disorders are treated with immunoglobulin therapies that can be delivered either intravenously in the clinic or subcutaneously at home.

### Table 3

<table>
<thead>
<tr>
<th>STAGE 1</th>
<th>History and physical exam, including height and weight</th>
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<tbody>
<tr>
<td></td>
<td>Complete blood count and differential</td>
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<tr>
<td></td>
<td>Quantitative immunoglobulin levels IgG, IgM, IgA, related to age</td>
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<tr>
<td>STAGE 2</td>
<td>Specific antibody responses (tetanus, diphtheria)</td>
</tr>
<tr>
<td></td>
<td>Response to pneumococcal vaccine (before and after) for children aged 3 y and older</td>
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<td></td>
<td>IgG subclass analysis</td>
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<tr>
<td>STAGE 3</td>
<td>Candida and tetanus skin tests</td>
</tr>
<tr>
<td></td>
<td>Lymphocyte surface markers CD3, CD4, CD8, CD19, CD16, CD56</td>
</tr>
<tr>
<td></td>
<td>Mononuclear lymphocyte proliferation studies, using mitogen and antigen stimulation</td>
</tr>
<tr>
<td>STAGE 4</td>
<td>Complement screening CH50, C3, C4</td>
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<tr>
<td></td>
<td>Enzyme measurements (adenosine deaminase, purine nucleoside phosphorylase)</td>
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<td></td>
<td>Phagocyte studies (surface glycoproteins, mobility, phagocytosis)</td>
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<tr>
<td></td>
<td>Natural killer cytotoxicity studies</td>
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<tr>
<td></td>
<td>Further complement studies AH50</td>
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<td></td>
<td>Neointertin to test antibody production</td>
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<tr>
<td></td>
<td>Other surface/cyttoplasmic production</td>
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<tr>
<td></td>
<td>Cytokine receptor studies</td>
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<tr>
<td></td>
<td>Family/genetic studiesa</td>
</tr>
</tbody>
</table>

*Dr. Stuart Abramson does not recommend genetic testing for everyone with suspected immunodeficiency. If testing is sought, he recommends consultation with a specialist.

Abbreviation: IG, immunoglobulin.

From: Modell V, et al.2 Available at: http://downloads.info4pi.org/pdfs/Physician-Algorithm--2-.pdf
Clinical Feature

Intravenous Immunoglobulin Therapy. For some children, subcutaneous therapy at home may be a better option. When compared with intravenous therapy, the benefits of subcutaneous therapy include improved quality of life, lower costs, and lower systemic adverse effects. However, disadvantages may include the need for more frequent treatments and local reactions at infusion sites.

Summary

Children presenting with recurrent infections may have underlying immunodeficiency disorders. Pediatricians should be alert to the warning signs indicating the potential for a PI disorder. Diagnosis includes a stepwise approach that begins with analysis of a CBC and quantitative immunoglobulin levels. If the results are positive after repeat testing, children should be referred to a specialist for further workup.

For most children diagnosed with a PI disorder, intravenous or subcutaneous immunoglobulin therapy is the standard treatment if specific antibody production is deficient. Bone marrow transplantation is indicated for children with severe PI disorders. For all patients, early detection and treatment are critical to avoid long-term adverse effects of an untreated PI disorder.

**TABLE 4**

**CONSIDERATIONS FOR TRANSPLANTATION**

- Early intervention is preferable before chronic illness or disability sets in.
- For hematopoietic stem cell transplantation, matched-related donor is better than matched-unrelated (registry) donor. For some smaller patients (<10 kg), cord blood stem cell therapy may be possible.
- Study protocols, including gene therapy, can be found at www.clinicaltrials.gov

**TABLE 5**

**STANDARD INTRAVENOUS IMMUNOGLOBULIN THERAPY FOR PATIENTS WITH ANTIBODY DEFICIENCY**

- Dose of 400-600 mg/kg/infusion, every 4 wk
- Adjust doses and/or interval (possibly to every 2-3 wk) depending on clinical response.
- Consider a trough level of pretreatment level +300 mg/dL for patients starting with higher serum IgG level.
- Follow clinical response, not just the numbers.
- Consider subcutaneous therapy to eliminate trough levels.

Abbreviation: IgG, immunoglobulin G.

From Abramson SL.3

**CONTEMPORARY VIDEO EXCLUSIVE**

Dr. Bobby Lazzara discusses a recent review published online in Cochrane that looked at the effectiveness of human papillomavirus (HPV) vaccine for preventing development of precancer or cancer of the cervix in girls and women.

ContemporaryPediatrics.com/video-HPV-vaccine
Prevent medical errors in your practice

Diagnostic and medication errors frequently occur in pediatric practices, but even minor medical errors can be prevented by creating a culture of safety.

DANIEL R NEUSPIEL, MD, MPH, FAAP; ANDREW J SCHUMAN, MD, FAAP

It is important for pediatricians to be aware that medical errors are frequent occurrences in pediatric practice. To safeguard our patients, we must implement an effective system to identify errors, as well as develop a strategy to prevent them.

The Institute of Medicine (IOM, now known as the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine) published the monograph To Err is Human in 1999, alerting the medical community that medical errors were common in medical practice. According to the IOM report, “at least 44,000 people and perhaps as many as 98,000 people die in hospitals each year as a result of medical errors that could have been prevented.”

The IOM monograph described and detailed the types of errors seen in the hospital environment. These included:

1. Diagnostic errors resulting from a failure to employ indicated tests or failure to act on the results of such tests.
2. Treatment errors in the performance of a procedure or administering of a treatment including medications, or inappropriate care.
3. Preventive errors, including failure to provide prophylactic treatment or inadequate follow-up to treatment.

The IOM report indicated that effective reporting systems needed to be implemented in healthcare facilities in order to reduce medical errors.

Magnitude of the problem

Whereas errors are common in the inpatient setting, the number of pediatric hospitalizations pales in comparison with the number of pediatric ambulatory visits each year. In 2015, the Agency for Healthcare Research and Quality (AHRQ) reported 5.6 million pediatric hospitalizations in the United States, while the Centers for Disease Control and Prevention (CDC) reported 125 million ambulatory pediatric visits that year.

The 2003 Learning from Errors in Ambulatory Pediatrics (LEAP) study conducted by the AHRQ and the American Academy of Pediatrics (AAP) Pediatric Research in Office Setting Network produced interesting data relating to the incidence of errors occurring in the ambulatory pediatric setting. In the 4-month data collection period from 14 sites, 136 errors were identified. Error types were: 37% medical treatment, 22% patient identification, 15% preventive care, 13% diagnostic testing, and 8% patient communication.

Practice-based safety team

One of the authors of this article, Daniel Neuspiel, MD, initiated a quality improvement project in 2008 for Myers Park Pediatrics, an affiliate of the Levine Children’s Hospital of Carolinas Medical Center in Charlotte, North Carolina. The project established a safety team that included front office staff, medical providers, nursing staff, and administrative personnel. The team developed a nonpu-
nitive reporting system to identify errors in need of evaluation, using the reporting form in Figure 1. The team met monthly to review reports of errors, and recommended interventions that would prevent future errors.

Errors were defined as “any event in the patient’s care which did not go as intended with either potential or real harm.” Over a 30-month period from 2008 to 2010, 216 errors were reported. These included errors in office administration (94); communication (40); medication or immunizations (45); and lab or diagnostic testing (37). The team used a problem-solving system called root cause analysis to look at the potential causes of the errors. The analysis technique utilizes a cause-and-effect diagram to identify problems and propose solutions (Figure 2). Examples of common ambulatory pediatric practice errors along with solutions are shown in Table 1.

**Medical errors in pediatric practice**

Children are at higher risk than many adults for medical errors because they have medical dosages based on weight, limited ability to communicate symptoms when young, and often their care is fragmented, provided by not only their primary care physicians, but by varying caregivers, specialists, and providers that are seen in walk-in clinics and emergency departments.

According to the Physician Insurers Association of America, from 2003 to 2012, errors in diagnosis accounted for 828 closed pediatric cases with an average indemnity of $414,455; medication errors accounted for 113 closed cases with an average indemnity of $207,916.

The most frequent medical error type in pediatric practice is the diagnostic error. Children are at higher risk for diagnostic errors due to the difficulty in eliciting their symptoms, particularly in infants and toddlers. Another frequent source of error is medication administration, especially home medication use. Children are at particular risk due to mistakes in measurement of liquid medications, multiple caregivers responsible for medication

### FIGURE 1 AMBULATORY PEDIATRICS REPORTING FORM

**TABLE 1 EXAMPLES OF MEDICAL ERRORS AND CORRECTIVE ACTIONS**

<table>
<thead>
<tr>
<th>ERROR TYPE</th>
<th>EXAMPLE</th>
<th>ROOT CAUSE ADDRESSED</th>
<th>INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meds/Vaccines</td>
<td>Wrong vaccine given to patient</td>
<td>Nurse distractions</td>
<td>Standing orders</td>
</tr>
<tr>
<td>Administration</td>
<td>Patient not given appointment at recommended time</td>
<td>Restrictive appointment types</td>
<td>Eliminate barriers in offering appointments</td>
</tr>
<tr>
<td>Communication</td>
<td>Delay due to patient missed in waiting room</td>
<td>Chaotic waiting area</td>
<td>Redesign waiting area</td>
</tr>
<tr>
<td>Lab/Diagnosis</td>
<td>Lab specimen unlabeled, not run</td>
<td>Specimens labeled separate from collection</td>
<td>Label all specimens in exam room</td>
</tr>
</tbody>
</table>

Author created.
administration, adolescents who are self-medicating without adult supervision, and other factors.

**REducing Diagnostic Errors**
Diagnostic errors are problematic in that solutions may require radical changes in our healthcare system. According to the National Academies’ monograph *Improving Diagnosis in Health Care,* solutions may include more reliance on clinical decision support tools, utilizing teamwork more effectively, and improving healthcare education to sharpen diagnostic acumen. The monograph further suggested developing a nationwide reporting and liability system that supports the diagnostic process and designing a payment and care delivery model that encourages, rather than delays, patient visits.

**ReducIng MedicatIOn Errors**
According to a systematic review, as many as 10% of all pediatric medication orders result in a medication error. This topic was reviewed by author Andrew Schuman, MD, in the October 2017 issue of *Contemporary Pediatrics* (see “Safety first: How to avoid missteps when prescribing medications,” October 2017, page 38).

Providers can take a variety of steps to avoid prescribing errors (Table 2). You can distribute dosing charts to parents for over-the-counter medication and reinforce their use with verbal instructions. Providers must confirm the patient’s weight prior to writing a prescription and make sure the weight-based dose does not exceed the adult dose. In addition, prescriptions must indicate the exact dosage strength and the volume of medication to administer. Other measures that can reduce errors are using pediatric computerized order-entry systems and standing-order sets when available, and having an appropriate measuring device dispensed along with the medication. Having caregivers explain back to you how they will administer the medication (teach-back) and show you how they will measure it (show-back) are
practice improvement

There are a variety of common errors, other than diagnostic and medical errors, in medical practice that have been identified. Treating the wrong patient error is reduced by using 2 identifiers to confirm that the correct patient is being treated. Time-outs are appropriate means to reduce errors in the surgical suite. In the practice environment, electronic health records (EHRs) are often a cause of error as it is an easy matter to write the wrong note on the wrong patient and subsequently generate incorrect prescriptions. This common error can be avoided (but not eliminated) when providers take the time to confirm—twice—that they are in the correct record before writing prescriptions or documenting a visit. To make sure patients understand your recommendations, it is always a good idea to provide written instructions and have parents repeat instructions to you.

**Build a culture of safety**
The Myers Park Pediatric Error Reduction Project, described above, created a safety model that will work in most ambulatory pediatric settings. One needs to acknowledge that errors are frequent occurrences in pediatric practices. However, errors can be reduced and prevented by creating a multidisciplinary safety team.

Nonpunitive reporting improves the detection of even minor errors. The team meets regularly to review reporting forms, discuss errors, and develop solutions that are tested. If successful, these processes become office policy, but if unsuccessful they are reevaluated.

By implementing these few measures, you will create a safer environment for your practice and your patients and cultivate a “culture of safety.”

**Dr Neuspiel** is professor emeritus of Pediatrics, Atrium Health (formerly Carolinas HealthCare System), Charlotte, North Carolina. He has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

**Dr Schuman**, section editor for Practice Improvement and Peds v2.0, and Editorial Advisory Board member of Contemporary Pediatrics, is clinical assistant professor of Pediatrics, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire. He is CEO of Medgizmos.com, a medical technology review site for primary care physicians.

For references, go to ContemporaryPediatrics.com/ prevent-medical-errors

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**TABLE 2 HOW TO REDUCE MEDICATION ERRORS**

Here are 12 tips to help avoid hazardous missteps when prescribing medications for children:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Confirm that the patient’s weight is correct, write weight on each order written, and make sure that weight-based dose does not exceed the adult dose.</td>
</tr>
<tr>
<td>2</td>
<td>Ensure that calculations are correct.</td>
</tr>
<tr>
<td>3</td>
<td>Induce dose and volume of medication when appropriate and specify the exact dosage strength to be used.</td>
</tr>
<tr>
<td>4</td>
<td>Write intravenous fluid orders clearly, ensuring that additives are quantified per liter and rates noted per hour.</td>
</tr>
<tr>
<td>5</td>
<td>Write out all instructions rather than using abbreviations, and make instructions specific.</td>
</tr>
<tr>
<td>6</td>
<td>Avoid use of a terminal zero to the right of the decimal point to minimize 10-fold dosing errors (ie, use 5 milliliters rather than 5.0 milliliters).</td>
</tr>
<tr>
<td>7</td>
<td>Use a zero to the left of a dose less than 1 to avoid 10-fold dosing errors (ie, use 0.1 milliliters rather than .1 milliliters).</td>
</tr>
<tr>
<td>8</td>
<td>Do not abbreviate drug names, use generic medication names rather than trade names, and spell out dosage units rather than using abbreviations.</td>
</tr>
<tr>
<td>9</td>
<td>Use computerized order entry systems and standing order sets when available.</td>
</tr>
<tr>
<td>10</td>
<td>When prescribing outpatient medications, always ask the pharmacist to dispense an appropriate measuring device.</td>
</tr>
<tr>
<td>11</td>
<td>Avoid use of verbal orders when possible.</td>
</tr>
<tr>
<td>12</td>
<td>Recommend that nurses and pharmacists always check medication calculations.</td>
</tr>
</tbody>
</table>

From Stucky ER, et al.6
medications, and pregnancy have been suggested as precipitators of LS, in the majority of patients triggering or causal factors are never found. It is thought that genetics and the environment contribute to the pathogenesis. The prevailing hypothesis is that genetic mosaicism provides the underlying substrate of LS. Early in development, a somatic mutation predisposes certain keratinocyte lineages to a currently unknown environmental insult. Basal keratinocytes present antigens from these unidentified environmental triggers to CD8+ T cells, leading to autoimmunity. Additional support for a genetic component comes from the fact that up to 85% of patients have a personal or family history of atopy.

Differential diagnosis
In young children presenting with abrupt onset of erythematous papules in a Blaschkoid distribution, other linear lichenoid eruptions must be considered, such as linear lichen planus, lichenoid nitidus, lichenoid splanonnosis, Gianotti-Crosti syndrome, chronic graft-versus-host disease, and frictional lichenoid eruption. The absence of pruritus, koebnerization, oral lesions, and systemic manifestations and the presence of postinflammatory hypopigmentation and nail dystrophy favor the diagnosis of LS.

Diagnosis is clinical, and biopsy is usually not necessary because LS is self-limited and histopathology is nonspecific with features of both eczema and lichen planus. However, for lesions that persist for longer than a year, a skin biopsy may be performed to differentiate LS from inflammatory linear epidermal nevi. This is important because one-third of patients with epidermal nevi have involvement of other organ systems, and there is a slight risk of malignant transformation. The classic biopsy finding in LS is a perivascular inflammatory infiltrate that is superficial and deep.

Management
Because of the high likelihood of spontaneous regression, therapy is not required. The benign course of this dermatosis should be stressed to the parents. If treatment is desired because of pruritus or cosmesis, topical corticosteroids may be used. Some studies have shown these treatments hasten resolution, but this finding has not been consistently borne out.

Patient outcome
A clinical diagnosis was made in this patient’s case with no further workup required. The family was reassured by the natural history of the illness. At a 6-month follow-up, the boy’s lesions had disappeared with only residual hypopigmentation.

Dr Abubucker is a PGY-1 preliminary medicine resident at the University of Hawaii, Honolulu, Hawaii. Dr Cohen, section editor for Dermcase, is professor of Pediatrics and Dermatology, Johns Hopkins University School of Medicine, Baltimore, Maryland. The author and section editor have nothing to disclose in regard to affiliations with or financial interests in any part of this article. Vignettes are based on real cases that have been modified to allow the author and editor to focus on key teaching points. Images also may be edited or substituted for teaching purposes.

85% of patients with lichen striatus have a personal or family history of atopy.

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For references, go to ContemporaryPediatrics.com/dermcase-0718

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Boy’s white patches could be a pigmentary disorder
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Boy with red bumps all in a row

SOMYA ABUBUCKER, MD

The worried mother of an 11-year-old boy arrives at the office for evaluation of an asymptomatic bumpy rash that appeared suddenly in his right groin a month ago, and that now has extended all the way down to his right ankle.

FIGURE The patient’s bumpy rash extended from his groin to ankle.

Clinical presentation and epidemiology

Lichen striatus (LS) is an uncommon, benign, self-limited papular eruption that follows the lines of Blaschko. It is a condition found most commonly in young children and that favors females.1,2 Three morphological patterns are described: typical lichen striatus, lichen striatus albus, and nail lichen striatus.3 Nail lichen striatus is the least common. It occurs almost exclusively in children, and is usually restricted to a single nail.1 Lichen striatus albus is characterized by hypopigmented lesions. By far the most common morphology is typical lichen striatus, in which crops of tiny 1- to 2-mm scaly erythematous or flesh-colored flat-topped papules appear abruptly without any known trigger. The lesions are usually solitary and unilateral and most commonly involve the limbs.4 The patient is typically asymptomatic, but a minority may complain of pruritus.1 The eruption reaches maximum development over a few weeks and then self-resolves in 6 to 24 months. The long-term sequela is postinflammatory hypopigmentation, which is seen more commonly in dark-complexioned individuals.1,2

Etiology

Although viral infections, trauma, hypersensitivity reactions, vaccines,
It’s okay to be silly during a visit (e.g., trying to find where a child hid his or her belly button), as long as there are no serious health problems and it fits your style and the child’s. This is particularly effective with children aged between 3 and 6 years.

Similarly, when an older child comes in with mild poison ivy, besides asking them how many leaves poison ivy has, I ask what it feels like. The correct answer, of course, is that you are not supposed to know what it feels like.

Along these lines, I carry some simple magic tricks in my bag, which can be done even by a clumsy person (or, in current medicalese, a person with dyspraxia) such as myself.

If you see something, say something. If the 2-year-old is chugging down a bottle of milk during a visit for fever, advise the parents that the bottle should be given up once the child is well.

Infants do not have sleep problems; parents do. I have never had an infant complain that his parents woke him up at night to feed him, and he wanted them to stop. Presenting it this way will show the parents that, if they want their older infant to sleep through the night, they will have to be the ones to bring this about.

Many parents are concerned that their normal child may have something wrong with him or her, or that they are doing something wrong, when the problem is actually due to the child’s temperament. I explain this as a matter of the child’s style, and that it is a question of personality, not pathology. There are many useful books on the subject for parents, but my shorthand description is that many children are either cats or dogs. The former, for example, are usually quieter, less demanding, and harder to read as to mood. The latter tend to be more intense, more engaging, and it is much easier to tell if they are happy/sad/excited.

Jon Matthew Farber, MD, is a pediatrician in Woodbridge, Virginia. He has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

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