HOW MOTHER’S MILK CAN HELP PRETERM INFANTS

Contemporary PEDIATRICS
Expert Clinical Advice for Today’s Pediatrician

MAY 2022 VOL. 39 | NO. 04

PRACTICE IMPROVEMENT

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Treating eating disorders in adolescents

Infectious Diseases
What illnesses are being overlooked during the pandemic?

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RSV, respiratory syncytial virus.
*According to a study of pediatric hospitalizations between 1997 and 2000.
†Surveillance data between October 2014 and April 2015. Among 1,176 RSV-hospitalized infants aged under 12 months, 851 had no reported underlying condition (prematurity was classified as an underlying condition in the study).

References:

RethinkRSV.com
For pediatric health care providers, encouraging patients to be active is of particular importance right now. After a 2-year hiatus from school and other group sports and activities, children—who by nature are wriggling, kicking, swinging, bouncing beings—can jump back into playing baseball and soccer, dancing, joining others in the sandbox, climbing jungle gyms, and more.

The American Academy of Pediatrics offers physical activity guidelines for infants, children, and adolescents. Among the highlights for these age groups:

- **Birth to 11 months**: Caregivers should place infants in settings that stimulate movement experiences and active play for short periods several times a day, as well as provide supervised “tummy time” daily while infants are awake.

- **Aged 1 to 4 years**: Young children should engage in at least 60 minutes and up to several hours of unstructured physical activity, plus at least 30 minutes of structured physical activity, each day.

- **Aged 5 to 21 years**: School-aged children, adolescents, and young adults should get at least 60 minutes of physical activity—mostly aerobic—each day, as well as engage in muscle- and bone-strengthening activity at least 3 days per week.

On a side note: Don’t forget to take care of your own physical needs, too: Refresh that gym membership; walk around the building between seeing patients. May is National Physical Fitness & Sports Month—let’s make it meaningful for all of us.
New members, plus a fond farewell

This is a very exciting time for *Contemporary Pediatrics*®—we are welcoming 4 distinguished additions to our Editorial Advisory Board (EAB):

- **Vivian Hernandez-Trujillo, MD, FAAP, FAAAAI, FACAAI**, director of the Division of Allergy & Immunology at Nicklaus Children’s Hospital in Miami, Florida, brings expertise in an important area that many clinicians address with patients daily. Her interests include allergic rhinitis, food allergy, anaphylaxis, and atopic dermatitis.

- **Jessica Peck, DNP, APRN, CPNP-PC, CNE, CNL, FAANP, FAAN**, is a clinical professor of nursing at Baylor University Louise Herrington School of Nursing in Dallas, Texas, and immediate past president of the National Association of Pediatric Nurse Practitioners. A nationally recognized antihuman trafficking advocate, Peck served as founding chair of the Alliance for Children in Trafficking (ACT) and started the ACT Advocates grassroots program, training thousands of nursing professionals at the local, state, national, and international levels to respond to human trafficking, a problem that many clinicians may not be aware could exist in their communities.

- **Rebecca A. Baum, MD**, a developmental behavioral pediatrician and clinical professor of pediatrics at the University of North Carolina School of Medicine in Chapel Hill, where she serves as chief of the Section of Development, Behavior, and Learning. She was a contributing author for our March issue, which focused on the national emergency in children’s mental health. She brings a wealth of expertise on adolescent issues that practices are encountering more often.

- **Emily Aron, MD**, is a child and family psychiatrist, Medical Director, Medstar Infant and Early Childhood Clinic, and Associate Professor of Clinical Psychiatry, Medstar Georgetown University Hospital, Division of Child and Adolescent Psychiatry, in Washington, DC.

I also want to extend a special thank-you to Harlan Gephart, MD, who is retiring after 25 years as an active EAB member. We are so grateful for his robust contributions and dedication to *Contemporary Pediatrics*®—and we wish him all the best.

Be sure to check out the must-read articles in this month’s issue:

- Practice Improvement offers an excellent guide to staying in practice and remain profitable. Written by EAB member Andrew J. Schuman, MD, this practical piece packs valuable tips for pediatricians.

- The Respiratory Disorders/Pediatric Pharmacology section report explains how messenger RNA vaccine technology is furthering the development of vaccines for influenza, respiratory syncytial virus, and other conditions.

- The Developmental Disorders section features a timely summary of what clinicians should know when treating eating disorders, which have surged throughout the pandemic.

As always, thank you for providing outstanding care to your patients during these rapidly changing times: and enjoy the warmer weather around the country! As Robin Williams said, “Spring is nature’s way of saying, ‘Let’s party.’ ”

Please stay safe and well. I welcome your suggestions, comments, and questions.

With warm regards,

Tina Q. Tan

email: titan@luriechildrens.org

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PUBLISHER’S NOTE

The editors are pleased to announce the availability of our new parent company’s continuing education activities. We’ve picked this one especially for our Contemporary Pediatrics’ readers. Go to: bit.ly/2VvBWjY

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A review of current—but limited—studies on the relationship between diet and acne uncovered evidence that some dietary factors may indeed influence acne development and treatment. The implicated factors include glycemic index, dairy content, dietary fats, and probiotics.

Results of several studies demonstrated that patients with acne who consume diets with a low glycemic load (GL) have fewer lesions than those on high-GL diets, as shown in a study of 31 young men with acne that compared a low-GL diet with a control diet. Other findings reveal that eating chocolate and confections daily is independently and highly associated with acne. In addition, results of 2 randomized controlled trials showed that, compared with a carbohydrate-dense control diet, a low-GL diet reduced the number of acne lesions.

A 3-year prospective study of more than 6000 girls found a link between acne and consumption of full-fat, low-fat, and skim milk but no association with non-milk dairy foods, chocolate, and pizza. Yet a similar study of more than 4000 boys found only a weak association between acne and skim milk, and no association with higher-fat milks. Other findings showed that consuming dairy of some sort is positively linked with acne.

Some results suggest that patients with acne may benefit from increased intake of omega-3 fatty acids or γ-linoleic acid. For example, a randomized controlled trial in 45 patients found that supplementation with these fatty acids significantly reduced the number of lesions compared with no supplementation.

Finally, in a small pilot trial in adult patients with acne, probiotics showed promise for reducing acne lesions, but more study is needed to support these early findings. It also appears that diet significantly affects the efficacy of acne treatment, with maximum absorption linked with a fasted state and no consumption of dairy.

This is an interesting review article, but my takeaway is “Who knows what to do?” Milk and chocolate are low-glycemic foods but may still increase acne. Perhaps trial and error in an individual patient is the way to go (and there certainly are good reasons besides acne prevention to limit chocolate and other sweets).

Diagnostic testing for SVT usually can be skipped

Children visiting the emergency department (ED) for management of supraventricular tachycardia (SVT) often undergo diagnostic tests, and the results almost always are normal; even when abnormal, the results are overwhelmingly clinically irrelevant. These were the chief findings of a retrospective study in patients presenting for management of SVT at a single urban tertiary care center during a 7-year period.

The mean age of the 40 patients (who had a total of 92 encounters) was 8.6 years; 50% had a history of SVT and 35% had comorbidities, most often asthma. During the study period, slightly more than half (52.5%) had 1 ED visit, 32.5% had 2 or 3, and 6 had 4 to 17.

More than two-thirds (67%) of patients underwent serologic laboratory evaluation. Eight children had an abnormality, just 1 of which was considered clinically significant enough to warrant intervention. Almost 30% of patients had chest radiography, which revealed no significant findings. Investigators concluded that routine laboratory or radiographic investigation in this population may be unwarranted, given the risk of false-positive results, patient and parent discomfort, and study cost.

For community-acquired pneumonia, 5 days of treatment proves superior to 10

Children who respond to initial treatment for outpatient community-acquired pneumonia (CAP) are better off following a 5-day strategy than a longer antibiotic course, according to investigators with a randomized placebo-controlled clinical trial. Compared with longer treatment, the shortened approach resulted not only in similar clinical responses and antibiotic-associated adverse effects (AEs) but also in reduced antibiotic exposure and resistance.

The 380 participants, who ranged in age from 6 months to 5 years and came from health care settings in 8 US cities, had nonsevere CAP, and showed early clinical improvement. On day 6 of their originally prescribed therapy, the children were divided into 2 groups and received either 5 more days of their initial antibiotic (standard course group) or 5 days of placebo (short course group). Study drugs were 80 to 100 mg/kg/day of amoxicillin or amoxicillin/clavulanate, divided twice daily, or 12 to 16 mg/kg/day of cefdinir, also divided.

The groups did not differ with regard to inadequate clinical response or persistent symptoms (experienced by < 10% of all participants) or antibiotic-associated AEs (generally mild—irritability and diarrhea). The short-course strategy was associated with significantly less likelihood of developing antibiotic-resistance, which investigators detected using DNA from throat swabs at the end of the study.

For years, 10 days of antibiotic treatment was the standard of care for most infections, but we have moved to shorter courses for many entities, such as otitis media in older children, and urinary tract infections. It looks like we can add pneumonia to the list in those rare instances in which an antibiotic is needed in the first place.


Readers of this section should know I am a big proponent of “less is more” when it comes to testing, and here is another reason. When you see a child with SVT, it usually will be sufficient to restore normal rhythm and then refer to cardiology for evaluation.

Telehealth for pediatric well visits: sometimes the best option

SUSAN J. KRESSLY, MD, FAAP

During the early part of the COVID-19 pandemic, pediatricians realized that to reach families and continue to provide preventive care, including developmental, mental health, and social determinants of health screenings, they needed to embrace telehealth and meet families where they were: at home. What can and can’t be accomplished in a virtual visit? How can health care providers address access to care through the lens of health care disparities and equity? How do payment models affect care delivery?

Whereas technology has not yet allowed us to administer vaccines virtually, many aspects of a preventive visit lend themselves well to a virtual format. The well visit is meant to be part of a continuous conversation with patients and families to anticipate, identify, and address health care needs and promote wellness in a family-centered environment. Anticipatory guidance, screenings, discussion of patient/family priorities, and coordination of care are well suited to a telehealth visit. Telehealth may offer advantages, such as the ability to assess the home environment for issues such as safety, housing, and food insecurity. In addition, physical examination technology is rapidly evolving with the use of smartphones to assess vital signs and visualize key findings.

In the meantime, to make sure patients receive the care they need, starting a visit virtually and then identifying gaps that should be closed via an in-person visit may be used in a hybrid approach. Performing screenings and the “talking” part of a well visit can be accomplished virtually; practices can then choose to use extended hours (early morning and end of day) to allow patients to come in for more accurate growth and blood pressure measurements, targeted exams, and immunizations.

As we innovate for the future, our equity lens should be at the center of our focus. We need to design tools so that the patients who have the most difficulty accessing care are assured of high-quality medical help and improved outcomes. This might include tools that don’t require a high bandwidth or personal data usage, are designed with limited technology and health literacy in mind, and are available in multiple languages. It is often difficult for families to leave essential jobs and pull children out of school or day care for an in-person visit. During the height of the pandemic, some Medicaid managed care plans found that their well visit rates actually improved with the availability of telehealth. In addition, many families expressed that they were more comfortable staying on “their turf” rather than coming to a health care facility, which changes the power paradigm of who drives the visit. We should implement workflows that give families choices to make sure their children get the care they need.

During the pandemic, current fee-for-service models have rapidly exposed the problems with our health care system. If we did not need to focus on which care-delivery sites were adequately paid, we could turn our attention to delivering care in the format best suited for each situation, with consideration for family preferences. Unfortunately, no robust, value-based payment models are designed for pediatric needs. We must advocate for pediatric-specific payment models that address health promotion and illness prevention and show societal value (not simply cost savings in a short time frame, as per chronic disease/adult models). In the meantime, we need to advocate for continued payment parity of telehealth visits, including current procedural terminology codes that include well visits, and determine how to best provide care in an in-person, telehealth, or hybrid format.

Many aspects of a preventive visit lend themselves well to a virtual format.

Susan J. Kressly is a pediatrician and founding partner of Kressly Pediatrics in Sanibel, Florida. She has a financial interest in Office Practicum, which does not prevent her from giving an unbiased presentation.
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A case of progressive joint pain and rash in a 5-year-old

EMILY VARA, DO; STEFAN HANSEN, MD; AND MILEKA GILBERT, MD, PHD

A 5-year-old nonverbal boy with autism spectrum disorder and global developmental delay presented to the emergency department with bilateral lower-extremity bruising and progressive difficulty ambulating.

One month prior, he began limping, and his mother noticed a new bruise on his right heel. Two weeks later, he presented to orthopedics after developing bilateral ankle swelling and a new bruise on his left ankle. A radiograph of his left leg did not show any osseous abnormalities. Over the next several days, his symptoms progressively worsened, and he was no longer able to walk. His mother reported that he appeared in pain, except when lying in a froglike position. During this time, his mother also noticed swelling in his knees, fine bumps overlying his hair follicles, and bruising on his left calf.

Hospital course
At time of admission, the patient was noted to have petechiae, ecchymosis, and a perifollicular rash, as well as joint pain with passive range of motion—specifically, internal rota-

Presentation
A review of his symptoms included profound fatigue and “not acting like himself.” His mother denied trauma, recent travel, or other illnesses in the past month and said he did not take any medications or supplements. She reported that his aversion to certain textures and tastes led to a very poor diet, consisting of cheese crackers, corn chips, toaster pastries, pepperoni, chocolate bars, and sandwich cookies. He was no longer eating chicken nuggets, which were a staple of his diet until the past cou-
ple of months. His mother also reported that he unintentionally lost approximately 10 pounds over the past month. She denied that he had fever, mouth sores, gum bleeding, shortness of breath, rhinorrhea, emesis, blood or mucus in his stool, and abdominal pain.

Vitamin C deficiency results from a lack of dietary intake of ascorbic acid, the bioavailable form of the nutrient.

Want to read more of your colleagues’ puzzling cases? Find the whole collection at ContemporaryPediatrics.com/pediatric-puzzler
tion of his hips and extension of his knees. He had tenderness to palpation of his paraspinal muscles, most significant in his lumbar region. He did not have any appreciable joint swelling. Pain prevented him from walking. Initial laboratory findings included microcytic anemia (hemoglobin, 10.7 g/dL; mean corpuscular volume, 72.6 fl), elevated erythrocyte sedimentation rate (45 mm/h), elevated C-reactive protein (3.26 mg/dL), and elevated uric acid (7.6 mg/dL). Results were in the normal range for platelet count (421 K/mm^3), white blood cell (WBC) count (8.94 K/mm^3), liver function (aspartate aminotransferase, 24 U/L; alanine aminotransferase, 9 U/L; total bilirubin, 0.2 mg/dL; lactate dehydrogenase (LDH; 269 U/L), and prothrombin time (15 s)/activated partial thromboplastin time (28.3 s).

Rheumatology, dermatology, and hematology/oncology were consulted for further evaluation of the boy’s anemia and petechial rash. An MRI of his abdomen, pelvis, and lumbar spine was obtained to evaluate for abdominal mass, subclinical joint effusions, and another osseous source of pain and inflammation. The MRI showed abnormal enhancement of the costochondral junctions, left ischium adjacent to the triradiate cartilage, lumbar spinal processes, lumbar paraspinal musculature, and synovitis in the hips, with small hip effusions concerning for autoimmune process, vitamin deficiency, or postinfectious phenomenon. There was no infiltrative marrow disease or appreciable intra-abdominal mass.

Blood cell counts, including WBC, hemoglobin, and platelets, were normal. Pathology evaluated his peripheral smear and did not find any abnormal cell lines. The patient was noted to initially have an elevated uric acid that normalized with hydration. His LDH and total bilirubin level were normal, making hemolysis unlikely. He was noted to have a low iron level and decreased percentage of total iron-binding capacity saturation, consistent with iron deficiency anemia. Ferritin was normal and not depressed, as would be expected in iron deficiency anemia, likely due to its role as an acute phase reactant.

Given the patient’s limited dietary intake and MRI findings concerning for a vitamin deficiency, his laboratory evaluation was expanded. Serum levels of zinc (65.4 µg/dL) and lead (< 2 mcg/dL) were normal. Vitamin A (0.12 mg/L; reference range [ref], 0.2–0.5 mg/L), vitamin C (< 0.09 mg/dL; ref, 0.4–2 mg/dL), and vitamin D (25-hydroxy, 11.5 ng/mL) were low.

Dermatology was also consulted for further evaluation of perifollicular rash. On close observation using a dermatoscope, the team noted perifollicular hemorrhages with cork-screw hairs.

**Differential diagnosis**

The differential diagnosis was initially broad and can be seen in Table 1. The differential included leukemia, an abdominal mass such as neuroblastoma, transient synovitis, septic arthritis, juvenile idiopathic arthritis (JIA), myositis, Henoch-Schönlein purpura, and nutritional deficiencies. His WBC, platelet counts, and peripheral smear were reassuring and did not support leukemia as a likely

### Table 1.

**DIFFERENTIAL DIAGNOSIS: DISEASE PROCESSES ASSOCIATED WITH JOINT PAIN, JOINT SWELLING, AND RASH IN CHILDREN**

<table>
<thead>
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<th>CONDITION</th>
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<td>Hematologic</td>
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<td>Abdominal mass</td>
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<td></td>
<td>Septic arthritis</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>Juvenile idiopathic arthritis</td>
</tr>
<tr>
<td></td>
<td>Myositis</td>
</tr>
<tr>
<td></td>
<td>Leukocytoclastic vasculitis</td>
</tr>
<tr>
<td></td>
<td>Henoch-Schönlein purpura</td>
</tr>
</tbody>
</table>
diagnosis. Imaging demonstrated synovitis, which could be consistent with JIA, transient synovitis, and nutritional deficiencies, but his dermatologic findings were not consistent with JIA or transient synovitis.

The patient’s clinical findings of arthralgia, hip synovitis, and rash showing perifollicular hemorrhages with corkscrew hairs was most consistent with vitamin C deficiency, also known as scurvy.

**Scurvy/vitamin C deficiency**

Vitamin C deficiency results from a lack of dietary intake of ascorbic acid, the bioavailable form of the nutrient. Foods high in vitamin C include many fruits and vegetables, including citrus fruits, mango, papaya, kiwifruit, tomatoes, spinach, broccoli, potatoes, and Brussels sprouts. The highest vitamin C concentration occurs in the raw food source. The nutrient plays an integral role in collagen synthesis. Ascorbic acid assists in the triple-helix formation of collagen, which provides structure for blood vessels, ligaments, cartilage, bone, and skin, and aids wound repair. The body can be depleted of vitamin C stores in approximately 1 to 3 months with limited intake or poor absorption from the gut. Due to vitamin C’s effects on collagen formation, as the body becomes depleted, vessel structure weakens and risk of bleeding increases.

Historically, vitamin C deficiency was associated with situations in which people had limited or no access to a steady dietary intake of fresh fruits and vegetables. The primary example has been sailors on extended voyages, but widespread deficiency has also been associated with major famines and wars that disrupted food supplies. More recently, vitamin C deficiency has been associated with children and adults who have limited dietary intake or poor absorption.

**Presenting symptoms**

Signs of vitamin C deficiency are often multisystem, including musculoskeletal, dermatologic, and hematologic symptoms, which are initially nonspecific and gradually worsen. Increased fatigue and changes in mood are usually among the first symptoms to arise. Additional symptoms include anorexia, joint pain, joint swelling, perifollicular rash, softening of previous scars, poor wound healing, gingival swelling, and gingival bleeding. Because of the joint pain and/or swelling, some patients are thought to have a rheumatologic process, such as JIA, at presentation. Vasculitis may be on the differential because the perifollicular hemorrhages are misinterpreted as a purpuric rash. Malignancy is also typically on the differential due to presentation of anemia, joint complaints, and petechiae.

**Laboratory findings**

Because laboratory findings are not necessarily reliable, diagnosis is typically based on clinical suspicion. The most available test, the serum ascorbic acid level, is diagnostic if the result is less than 0.2 mg/dL. However, recent dietary consumption of vitamin C would alter the serum level to falsely normal levels. Additional nutritional deficiencies are common and should be evaluated for, including thiamine (B₁), pyridoxine (B₆), folic acid, cobalamin (B₁₂), and vitamin D.

Lastly, due to concern for a potential autoimmune or infectious cause of symptoms, inflammatory markers are often obtained. In vitamin C deficiency, these markers are often elevated; however, the exact mechanism for the elevation remains unclear.

**Musculoskeletal findings**

Approximately 80% of patients with vitamin C deficiency present with musculoskeletal complaints, which tend to be more prominent in pediatric patients, who can present with severe myalgias. Children may experience significant thigh pain, leading them to sit in a froglike position, legs flexed and externally rotated. Typically, patients will endorse arthralgia in the wrists, knees, and/or ankles and can develop hemarthrosis, often involving either the hips, knees, or ankles. The hemarthrosis is thought to be multifactorial and caused by damage to the synovial vessels and microfractures. Lastly, at the distal ends of the diaphysis, subperiosteal hematomas may be palpable.

Radiographic findings are typically found in the distal end of the long bones. General findings will include osteopenia and loss of trabecular bone matrix. More specific findings, which typically arise later and are not present at disease onset, include the white line of Frankel, Trümmerfeld zone “beaks,” and Wimberger ring zone. The white line of Frankel is an irregular and thickened white line at the metaphysis. The Trüm-
Approximately 80% of patients with vitamin C deficiency present with musculoskeletal complaints, which tend to be more prominent in pediatric patients.
Indication for PEDIARIX
PEDIARIX is indicated for active immunization against diphtheria, tetanus, pertussis, infection caused by all known subtypes of hepatitis B virus, and poliomyelitis. PEDIARIX is approved for use as a 3-dose series in infants born of hepatitis B surface antigen (HBsAg)-negative mothers. PEDIARIX may be given as early as 6 weeks of age through 6 years of age (prior to the 7th birthday).

Important Safety Information for PEDIARIX
• Contraindications for PEDIARIX are: severe allergic reaction (eg, anaphylaxis) after a previous dose of any diphtheria toxoid-, tetanus toxoid-, pertussis-, hepatitis B-, or poliovirus-containing vaccine, or to any component of PEDIARIX; encephalopathy within 7 days of administration of a previous pertussis-containing vaccine; progressive neurologic disorders
• In clinical trials, PEDIARIX was associated with higher rates of fever relative to separately administered vaccines
• The decision to give PEDIARIX should be based on potential benefits and risks if Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, or if adverse events (ie, temperature ≥105°F, collapse or shock-like state, persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours after vaccination; seizures within 3 days after vaccination) have occurred after receipt of a pertussis-containing vaccine
• The tip caps of the prefilled syringes contain natural rubber latex, which may cause allergic reactions
• Syncope (fainting) can occur in association with administration of injectable vaccines. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope

Learn more at DosingPEDIARIX.com
PEDIARIX has the broadest combination DTaP vaccine age indication\textsuperscript{1,2,3}

PEDIARIX gives you time to catch up appropriate patients who fell behind schedule\textsuperscript{1}

- Pentacel and Vaxelis are indicated to the 5\textsuperscript{th} birthday\textsuperscript{2,3}
- The recommended PEDIARIX dosing interval is 6 to 8 weeks, preferably 8 weeks\textsuperscript{1}
- Three doses of PEDIARIX constitute a primary immunization course for diphtheria, tetanus, pertussis, poliomyelitis and complete the vaccination course for hepatitis B\textsuperscript{1}
- Data are not available on the safety and effectiveness of PEDIARIX following 1 or more doses of a DTaP vaccine from a different manufacturer\textsuperscript{1}

Important Safety Information for PEDIARIX (cont’d)

- For children at higher risk for seizures, an antipyretic may be administered at the time of vaccination with PEDIARIX

- Apnea following intramuscular vaccination has been observed in some infants born prematurely. Vaccination with PEDIARIX should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination

- In clinical trials, common adverse reactions in infants receiving PEDIARIX included injection-site reactions (pain, redness, and swelling), fever, drowsiness, irritability/fussiness, and loss of appetite

- Vaccination with PEDIARIX may not result in protection in all vaccine recipients

Please see Important Safety Information for PEDIARIX and Brief Summary of full Prescribing Information for PEDIARIX following this ad.


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BRIEF SUMMARY

PEDIARIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine)

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

1 INSTRUCTIONS AND USAGE

PEDIARIX is indicated for active immunization against diphtheria, tetanus, pertussis, infection caused by known subtypes of hepatitis B virus, and poliovirus. PEDIARIX is approved for use as a 3-dose series in infants born of hepatitis B surface antigen (HBsAg)-negative mothers. PEDIARIX may be given as early as 6 weeks of age through 6 years of age (prior to the 7th birthday).

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Shake vigorously to obtain a homogeneous, turbid, white suspension. Do not use if resuspension does not occur with vigorous shaking. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered. Attach a sterile needle and administer intramuscularly. The preferred administration site is the anterolateral aspect of the thigh for children younger than 1 year. In older children, the deltoid muscle is usually large enough for an intramuscular injection. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk. Gluteal injections may result in suboptimal hepatitis B immune response.

Do not administer this product intravenously, intradermally, or subcutaneously.

2.2 Recommended Dose and Schedule

Immunization (while administered concomitantly at separate sites). All vaccines were licensed in the United States) and 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) concomitantly at separate sites. All vaccines were licensed in the United States except for OPV.

11. of full prescribing information

1.3 Progressive Neurologic Disorder

Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy, is a contraindication to administration of any pertussis-containing vaccine, including PEDIARIX. PEDIARIX should not be administered to individuals with such conditions unless the neurologic status is clarified and stabilized.

5 WARNINGS AND PRECAUTIONS

5.1 Fever

In clinical trials, administration of PEDIARIX in infants was associated with higher rates of fever relative to separately administered vaccines [see Adverse Reactions (6.1)].

5.2 Guillain-Barré Syndrome

If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give PEDIARIX or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks.

5.3 Latex

The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions.

5.4 Syncpe

Syncpe (fainting) can occur in association with administration of injectable vaccines, including PEDIARIX. Syncpe can be accompanied by transient neurological symptoms, such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncpe.

5.5 Adverse Reactions following Prior Pertussis Vaccination

If any of the following reactions occur in temporal relation to receipt of a vaccine containing a pertussis component, the decision to give any pertussis-containing vaccine, including PEDIARIX, should be based on careful consideration of the potential benefits and possible risks:

- Temperature >38.5°C (101.3°F) within 48 hours not due to another identifiable cause;
- Collapse or shock-like state (hypotonic-hyposesisive episode) within 48 hours;
- Persistent, inconsolable crying lasting >3 hours, occurring within 48 hours;
- Seizures with or without fever occurring within 3 days.

5.6 Children at Risk for Seizures

For children at higher risk for seizures than the general population, an appropriate antipyretic may be administered at the time of vaccination with a vaccine containing a pertussis component, including PEDIARIX, and for the ensuing 24 hours to reduce the possibility of post-vaccination fever.

5.7 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about the administration of PEDIARIX or any vaccine containing a pertussis component, including PEDIARIX, to infants born prematurely should be based on consideration of the individual infant’s medical status and the potential benefits and possible risks of vaccination.

5.8 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

A total of 23,649 doses of PEDIARIX have been administered to 8,088 infants who received 1 or more doses as part of the 3-dose series during 14 clinical studies. Common adverse reactions that occurred in ≥25% of subjects following any dose of PEDIARIX included local injection site reactions (pain, redness, and swelling), fever, drowsiness, irritability/tussiness, and loss of appetite. In comparative studies (including the German and U.S. studies described below), administration of PEDIARIX was associated with higher rates of fever relative to separately administered vaccines [see Warnings and Precautions (5.1)]. The prevalence of fever within 3 days of vaccination and the day following vaccination was more than 96% of episodes of fever resolved within the 4-day period following vaccination (i.e., the period including the day of vaccination and the next 3 days).

In the largest of the 14 studies conducted in Germany, safety data were available for 4,666 infants who received PEDIARIX administered concomitantly at separate sites with 1 of 4 Haemophilus influenzae type b (Hib) conjugate vaccines (GliaxoSmithKline [licensed in the United States only for booster immunization], Wyeth Pharmaceuticals Inc. [no longer licensed in the United States], Sanofi Pasteur SA [U.S.-licensed], or Merck & Co. Inc. [U.S.-licensed]) at 3, 4, and 5 months of age and for 768 infants in the control group that received separate U.S.-licensed vaccines (INFANRIX, Hib conjugate vaccine [Sanofi Pasteur SA], and oral poliovirus vaccine [OPV] [Wyeth Pharmaceuticals Inc., no longer licensed in the United States]). In this study, information on adverse events that occurred within 30 days following vaccination was collected. More than 95% of study participants were white.

In a U.S. study, the safety of PEDIARIX administered to 673 infants was compared with the safety of separately administered INFANRIX, ENGERIX-B [Hepatitis B Vaccine (Recombinant)], and IPV (Sanofi Pasteur SA) in 335 infants. In both groups, infants received Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the United States) and 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) concomitantly at separate sites. All vaccines were administered at 2, 4, and 6 months of age. Data on solicited local reactions and general adverse reactions were collected by parents using standardized diary cards for 4 consecutive days following each vaccine dose (i.e., day of vaccination and the next 3 days). Telephone follow-up was conducted 1 month and 6 months after the third vaccination to inquire about serious adverse events. At the 6-month follow-up, information also was collected on new onset of chronic illness. A total of 638 subjects who received PEDIARIX and 313 subjects who received INFANRIX, ENGERIX-B, and IPV completed the 6-month follow-up. Among subjects in both study groups combined, 69% were white, 18% were Hispanic, 7% were black, 3% were Oriental, and 3% were of other racial/ethnic groups.

Solicited Adverse Reactions

Data on solicited local reactions and general adverse reactions from the U.S. safety study are presented in Table 1. This study was powered to evaluate fever >101.3°F following Dose 1. The rate of fever >101.3°F following each dose was significantly higher in the group that received PEDIARIX compared with separately administered vaccines. Other statistically significant differences between groups in rates of fever, as well as other solicited adverse reactions, are noted in Table 1. Medical attention (a visit to or from medical personnel) for fever within 4 days following vaccination was sought in the group who received PEDIARIX for 8 infants after the first dose (1.2%), 1 infant following the second dose (0.2%), and 5 infants following the third dose (0.8%) (Table 1). Following Dose 2, medical attention for fever was sought for 2 infants (0.6%) who received separately administered vaccines (Table 1). Among infants who had a medical visit for fever within 4 days following vaccination, 9 of 14 who received PEDIARIX and 1 of 2 who received separately administered vaccines, had 1 or more diagnostic studies performed to evaluate the cause of fever.

(continued on next page)
Adverse Reaction | PEDIARIX, Hib Vaccine, & PCV7 | INFANRIX, ENGERIX-B, IPV, Hib Conjugate Vaccine, & PCV7
---|---|---
Local Adverse Reaction | Dose 1 | Dose 2 | Dose 3 | Dose 1 | Dose 2 | Dose 3
Pain, any | 671 | 653 | 648 | 335 | 323 | 315
Pain, Grade 2 or 3 | 36 | 36 | 31 | 32 | 30 | 30
Pain, Grade 3 | 12 | 11 | 11 | 9 | 9 | 9
Redness, any | 25 | 37 | 40 | 18 | 33 | 39
Redness, >5 mm | 6 | 10 | 13 | 2 | 6 | 7
Redness, >20 mm | 1 | 1 | 1 | 0 | 0 | 0
Swelling, any | 17 | 27 | 29 | 10 | 20 | 25
Swelling, >5 mm | 6 | 10 | 9 | 2 | 5 | 4
Swelling, >20 mm | 2 | 3 | 3 | 1 | 0 | 1

General

Adverse Reaction | Dose 1 | Dose 2 | Dose 3
---|---|---|---
Drowsiness, any | 57 | 52 | 41 | 54 | 48 | 38
Drowsiness, Grade 2 or 3 | 16 | 14 | 11 | 18 | 12 | 11
Drowsiness, Grade 3 | 3 | 1 | 1 | 1 | 2 | 1
Irritability/Fussiness, any | 61 | 65 | 61 | 62 | 62 | 57
Irritability/Fussiness, Grade 2 or 3 | 20 | 28 | 25 | 19 | 21 | 19
Irritability/Fussiness, Grade 3 | 3 | 4 | 4 | 3 | 3 | 3
Loss of appetite, any | 30 | 31 | 26 | 28 | 27 | 24
Loss of appetite, Grade 2 or 3 | 7 | 8 | 8 | 6 | 5 | 3
Loss of appetite, Grade 3 | 1 | 0 | 0 | 1 | 0 | 0

Deaths

In 14 clinical trials, 5 deaths were reported among 8,088 (0.06%) recipients of PEDIARIX and 1 death was reported among 2,287 (0.04%) recipients of comparator vaccines. Causes of death in the group that received PEDIARIX included 2 cases of Sudden Infant Death Syndrome (SIDS) and 1 case of each of the following: convulsive disorder, congenital immunodeficiency with sepsis, and neuroblastoma. One case of SIDS was reported in the comparator group. The rate of SIDS among all recipients of PEDIARIX across the 14 trials was 0.25/1,000 infants (reported rate of SIDS in Germany in the latter part of the 1990s was 0.71/1,000 newborns). The reported rate of SIDS in the United States from 1990 to 1994 was 1.2/1,000 live births. By chance alone, some cases of SIDS can be expected to follow receipt of pertussis-containing vaccines.

Onset of Chronic Illnesses

In the U.S. safety study in which all subjects received concomitant Hib and pneumococcal conjugate vaccines, 21 subjects (3%) who received PEDIARIX and 14 subjects (4%) who received INFANRIX, ENGERIX-B, and IPV reported new onset of a chronic illness during the period from 1 to 6 months following the last dose of study vaccines. Among the chronic illnesses reported in the subjects who received PEDIARIX, there were 4 cases of asthma and 1 case each of diabetes mellitus and chronic neutropenia. There were 4 cases of asthma in subjects who received INFANRIX, ENGERIX-B, and IPV.

Seizures

In the German safety study over the entire study period, 6 subjects in the group that received PEDIARIX (n = 4,666) reported seizures. Two of these subjects had a febrile seizure, 1 of whom also developed afebrile seizures. The remaining 4 subjects had afebrile seizures, including 2 with infantile spasms. Two subjects reported seizures within 7 days following vaccination (1 subject had both afebrile and afebrile seizures, and another subject had afebrile seizures), corresponding to a rate of 0.22 seizures per 1,000 doses (febrile seizures 0.07 per 1,000 doses, afebrile seizures 0.14 per 1,000 doses). No subject who received concomitant INFANRIX, Hib vaccine, and OPV (n = 769) reported seizures. In a separate German study that evaluated the safety of INFANRIX in 22,505 infants who received 66,867 doses of INFANRIX administered as a 3-dose primary series, the rate of seizures within 7 days of vaccination with INFANRIX was 0.13 per 1,000 doses (febrile seizures 0.0 per 1,000 doses, afebrile seizures 0.13 per 1,000 doses).

Over the entire study period in the U.S. safety study in which all subjects received concomitant Hib and pneumococcal conjugate vaccines, 4 subjects in the group that received PEDIARIX (n = 673) reported seizures. Three of these subjects had a febrile seizure and 1 had an afebrile seizure. Over the entire study period, 2 subjects in the group that received INFANRIX, ENGERIX-B, and IPV (n = 335) reported febrile seizures. There were no afebrile seizures in this group. No subject in either study group had seizures within 7 days following vaccination.

Other Neurological Events of Interest

No cases of hypotonic-hyporesponsiveness or encephalopathy were reported in either the German or U.S. safety studies.

Safety of PEDIARIX after a Previous Dose of Hepatitis B Vaccine

Limited data are available on the safety of administering PEDIARIX after a previous dose of hepatitis B vaccine. In 2 separate studies, 160 Moldovan infants and 96 U.S. infants, respectively, received 3 doses of PEDIARIX following 1 previous dose of hepatitis B vaccine. Neither study was designed to detect significant differences in rates of adverse events associated with PEDIARIX administered after a previous dose of hepatitis B vaccine compared with PEDIARIX administered without a previous dose of hepatitis B vaccine.

6.2 Postmarketing Safety Surveillance Study

In a safety surveillance study conducted at a health maintenance organization in the United States, infants who received 1 or more doses of hepatitis B vaccine from approximately mid-2003 through mid-2005 were compared with age-, gender-, and area-matched historical controls who received 1 or more doses of separately administered U.S.-licensed DTaP vaccine from 2002 through approximately mid-2003. Only infants who received 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) concomitantly with PEDIARIX or DTaP vaccine were included in the cohorts. Other U.S.-licensed vaccines were administered according to routine practices at the study sites, but concomitant administration with PEDIARIX or DTaP was not a criterion for inclusion in the cohorts. A birth dose of hepatitis B vaccine had been administered routinely to infants in the historical DTaP control cohort, but not to infants who received PEDIARIX. For each of DTaP, PEDIARIX, and INFANRIX, a birth dose of hepatitis B vaccine was given to infants who were vaccinated with the historical DTaP control cohort for the incidence of seizures (with or without fever) during the 8-day period following vaccination. For each dose, random samples of 7,500 infants in each cohort were also compared for the incidence of medically-attended fever (fever ≥100.4°F that resulted in hospitalization, an emergency department visit, or an outpatient visit) during the 4-day period following vaccination. Possible seizures and medical visits plausibly related to fever were identified by searching automated inpatient and outpatient data files. Medical record reviews of identified events were conducted to verify the occurrence of seizures or medically-attended fever. The incidence of verified seizures and medically-attended fever from this study are presented in Table 2.
Black Idiopathic thrombocytopenic purpura, a,b lymphadenopathy, a thrombocytopenia. a,b

Blood and Lymphatic System Disorders
Anaphylactic shock, b serum sickness–like disease. b

Musculoskeletal and Connective Tissue Disorders
Arthralgia, b arthritis, b muscular weakness, b myalgia, b

Nervous System Disorders
Encephalopathy, a headache, a meningitis, a neuritis, a neuropathy, a paralysis. b

Skin and Subcutaneous Tissue Disorders
Alopecia, b erythema multiforme, b lichen planus, b pruritus, a,b Stevens Johnson syndrome, a

Vascular Disorders
Vasculitis. b

*Following INFANRIX (licensed in the United States in 1997).
*Following ENGERIX-B (licensed in the United States in 1989).

7.1 Concomitant Vaccine Administration

Immunologic responses following concomitant administration of PEDIARIX, Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the U.S.), and 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) were evaluated in a clinical trial [see Clinical Studies (14.3) of full prescribing information].

7.2 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to PEDIARIX.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and effectiveness of PEDIARIX were established in the age group 6 weeks through 6 months on the basis of clinical studies [see Adverse Reactions (6.1), Clinical Studies (14.1, 14.2) of full prescribing information]. Safety and effectiveness of PEDIARIX in the age group 7 months through 6 years are supported by evidence in infants aged 6 weeks through 6 months. Safety and effectiveness of PEDIARIX in infants younger than 6 weeks and children aged 7 to 16 years have not been evaluated.

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PORJRNA210001 February 2021
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Table 2: Percentage of Infants with Seizures (with or without Fever) within 8 Days of Vaccination and Medically-Attended Fever within 4 Days of Vaccination with PEDIARIX Compared with Historical Controls

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>PEDIARIX</th>
<th>Historical DTaP Controls</th>
<th>Difference (PEDIARIX–DTaP Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n % (95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>All Seizures (with or without fever)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 1, Days 0-7</td>
<td>40,000</td>
<td>7</td>
<td>0.02 (0.01, 0.04)</td>
</tr>
<tr>
<td>Dose 2, Days 0-7</td>
<td>40,000</td>
<td>3</td>
<td>0.01 (0.00, 0.02)</td>
</tr>
<tr>
<td>Dose 3, Days 0-7</td>
<td>40,000</td>
<td>6</td>
<td>0.02 (0.01, 0.03)</td>
</tr>
<tr>
<td>Total doses</td>
<td>120,000</td>
<td>16</td>
<td>0.01 (0.01, 0.02)</td>
</tr>
<tr>
<td>Medically-Attended Fever*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 1, Days 0-3</td>
<td>7,500</td>
<td>14</td>
<td>0.19 (0.11, 0.30)</td>
</tr>
<tr>
<td>Dose 2, Days 0-3</td>
<td>7,500</td>
<td>25</td>
<td>0.33 (0.22, 0.48)</td>
</tr>
<tr>
<td>Dose 3, Days 0-3</td>
<td>7,500</td>
<td>21</td>
<td>0.28 (0.17, 0.43)</td>
</tr>
<tr>
<td>Total doses</td>
<td>22,500</td>
<td>60</td>
<td>0.27 (0.20, 0.34)</td>
</tr>
</tbody>
</table>

DTaP – any U.S.-licensed DTaP vaccine. Infants received 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) concomitantly with each dose of PEDIARIX or DTaP. Other U.S.-licensed vaccines were administered according to routine practices at the study sites.

N = Number of subjects in the given cohort.

n = Number of subjects with reactions reported in the given cohort.

*Medically-attended fever defined as fever ≥100.4°F that resulted in hospitalization, an emergency department visit, or an outpatient visit.

6.3 Postmarketing Spontaneous Reports for PEDIARIX

In addition to reports in clinical trials for PEDIARIX, the following adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Cardiac Disorders
Cyanosis.

Gastrointestinal Disorders
Diarrhea, vomiting.

General Disorders and Administration Site Conditions
Fatigue, injection site cellulitis, injection site induration, injection site itching, injection site nodule/lump, injection site reaction, injection site vesicles, injection site warmth, limb pain, limb swelling.

Immunologic Disorders
Anaphylactic reaction, anaphylactoid reaction, hypersensitivity.

Infections and Infestations
Upper respiratory tract infection.

Investigations
Abnormal liver function tests.

Nervous System Disorders
Bulging fontanelle, depressed level of consciousness, encephalitis, hypotonia, hypotonic-hyporesponsive episode, lethargy, somnolence, syncope.

Psychiatric Disorders
Crying, insomnia, nervousness, restlessness, screaming, unusual crying.

Respiratory, Thoracic, and Mediastinal Disorders
Apnea, cough, dyspnea.

Skin and Subcutaneous Tissue Disorders
Angioedema, erythema, rash, urticaria.

Vascular Disorders
Pallor, petechiae.

6.4 Postmarketing Spontaneous Reports for INFANRIX and/or ENGERIX-B

The following adverse reactions have been identified during postapproval use of INFANRIX and/or ENGERIX-B in children younger than 7 years but not already reported for PEDIARIX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Blood and Lymphatic System Disorders
Idiopathic thrombocytopenic purpura, a,b lymphadenopathy, a thrombocytopenia, a,b

Gastrointestinal Disorders
Abdominal pain, a intussusception, a,b nausea, a,b

General Disorders and Administration Site Conditions
Anaphylactic shock, b serum sickness–like disease, b

Musculoskeletal and Connective Tissue Disorders
Arthralgia, a arthritis, b muscular weakness, b myalgia, b

Nervous System Disorders
Encephalopathy, a headache, a meningitis, a neuritis, a neuropathy, a paralysis, a

Skin and Subcutaneous Tissue Disorders
Alopecia, a erythema multiforme, b lichen planus, b pruritus, a,b Stevens Johnson syndrome, a

Vascular Disorders
Vasculitis, a,b

a,b Following INFANRIX (licensed in the United States in 1997).

a,b Following ENGERIX-B (licensed in the United States in 1989).
Dengue virus, measles, TBI and TB disease: Are they being overlooked because of the pandemic?

DONNA HALLAS, PHD, CPNP, PPCNP-BC, PMHS, FAANP, FAAN

What infections besides COVID-19 should be on pediatric health care providers’ radar?

The COVID-19 pandemic has taught health care providers a lot: how quickly a virus can spread globally, how unprepared we were to respond to a pandemic, and how rapidly science and technology could evolve to make a safe and effective vaccine, as well as that many people are vaccine hesitant or refusers and that individuals and groups resisting public health safety measures (eg, masking, social distancing) could prolong a pandemic with repetitive surges. Most importantly, we have learned that it is critical to be more than a step ahead of future infectious diseases by analyzing and responding to emerging data both in the United States and globally. This article reviews infectious diseases that may have taken a back seat in the news since March 2020 and how they affect the daily lives of children and adolescents all around the world.

Dengue virus

The Dengue virus (DENV) is a major public health problem in the tropics and subtropics and is endemic in the US territories of Puerto Rico, the US Virgin Islands, and American Samoa.1 As Americans begin to travel and the United States welcomes global visitors, pediatric providers must consider who may be exposed to 1 of the 4 known DENVs and the presenting symptoms (Table1–7). An individual can be infected with the 4 serotypes over time. Long-term immunity is achieved for an individual who contracted a homologous DENV, but this protection does not last more than 3 months if an individual is infected with a different serotype. Evidence has shown that a person who sustains a second infection is more likely to develop severe dengue compared with those experiencing the first or a third or fourth illness.2 DENV is most often transmitted to a human through the bite of an infected mosquito (Aedes aegypti).1 The incubation period is 3 to 14 days before symptom onset. Infected individuals can transmit DENV to mosquitoes 1 to 2 days before symptoms develop and during the 7-day viral illness.1

During the Ebola outbreak, it was critical when taking a patient’s history to ask anyone presenting with fever about recent travel. To diagnose a DENV illness, providers must continue the practice of asking about recent travel globally and within the endemic areas in the US territories. Dengvaxia, a Dengue vaccine, is now approved by the US Food and Drug Administration and is listed on the 2022 US immunization schedule for individuals aged 9 to 16.
years. However, the vaccine can be administered only if prevaccination laboratory testing reveals confirmed evidence of a previous DENV infection. It is contraindicated to administer the Dengvaxia vaccine to children who are seronegative because that action would place them at high risk of hospitalization and severe dengue illness.

**Measles**

In 2019, there were 1282 confirmed cases of measles in 31 states. There were 2 primary reasons for US outbreaks: In 2019, the number of people who contracted measles abroad increased; then, upon their return to the United States, these individuals spread the virus in communities that had low measles vaccination rates. In 2020 and 2021, the number of reported measles cases in the United States dropped significantly to 13 and 49, respectively; thus far, in 2022, 3 cases have been reported.

Two factors may account for the 2020 and 2021 decreases. These data may represent the effect of the COVID-19 pandemic on measles transmission in the United States—fewer families traveled overseas as the pandemic surged throughout this country. Also, many elementary and secondary schools were closed in 2020; when they reopened in 2021, masks and social distancing were in place. Thus, these factors may have significantly reduced children and unvaccinated families from contracting and spreading the measles virus.

These data provide evidence that pediatric providers should reach out to parents whose children need the measles-mumps-rubella (MMR) vaccine, citing 2 influential factors: (1) Many states have removed school mask mandates, putting unvaccinated children at risk of contracting measles. Parents should be reminded that measles spreads through direct contact with an infected person or airborne transmission (via coughing or sneezing) up to 4 days before rash onset and for 4 days after the rash erupts. (2) Timely measles vaccination will protect children who may be traveling to parts of the world where measles is endemic.

The World Health Organization (WHO) reported that measles remains a problem in developing countries, especially in parts of Africa and Asia. The WHO also reported that in 2018, more than 140,000 people—mostly children less than 5 years old—died from measles, with more than 95% of these deaths occurring in countries that have low-income populations and weak health care systems. The MMR vaccine saves lives. All health care providers should proactively encourage parents to vaccinate their children.

**Pediatric tuberculosis**

A diagnosis of pediatric tuberculosis (TB), for either latent TB (referred to as tuberculosis infection [TBI]) or TB disease (active TB), is made for patients aged less than 15 years who have either a positive tuberculin skin test or a positive interferon-
The COVID-19 pandemic has taught us how quickly a virus can spread globally, and how unprepared we were.

Adults who have the TB bacterium, Mycobacterium tuberculosis, spread the organism via airborne transmission by coughing, speaking, or singing. However, children with pediatric TB do not spread the organism as readily as adults, because pediatric TB is less infectious than the adult form. Children younger than 4 years are at the highest risk of progressing from TBI to TB disease, with data showing a risk of 40% to 50% for infants less than 1 year old and 25% for 1- to 2-year-olds. However, children with a diagnosis of TBI who receive drug therapy and whose parents adhere to the regimen have a 90% reduced risk of developing TB disease. Adolescents older than 12 years have a risk of progression to adult-type TB disease. Children and adolescents who are immunocompromised also have a high risk of disease progression.

In 2021, the clinical practice guidance for treatment of latent TB and TB disease was revised. Children older than 2 years may be treated with once-weekly isoniazid-rifapentine for 12 weeks. Additional regimens include 4 months of rifapentine or 9 months of daily isoniazid. Parents often prefer shorter courses, resulting in more children completing a full course.

For TB disease, children can be treated with several anti-TB medications for 4, 6, or 9 months, based on the selection of the drug therapy believed to be most effective for the child and for parental adherence. Providers need to be aware that the Centers for Disease Control and Prevention does not recommend the 4-month rifapentine-moxifloxacin TB regimen for children younger than 12 years. Best practices for pediatric providers include consulting a TB expert prior to beginning the treatment course, based on the available data showing that young children have a high risk of developing life-threatening TB disease.

Conclusions

Pediatric health care providers are on the frontlines for identifying infectious diseases and, to prevent poor outcomes, must react quickly to diagnose and treat cases in children and adolescents. The COVID-19 pandemic public health measures—masking, social distancing, and limited social contact among children and adolescents—have reduced the prevalence of other infectious diseases. As public health policies begin to change and global travel resumes, pediatric providers must remain astutely aware of the potentially devastating effects of emerging infectious diseases and newer ones that may affect US and global pediatric populations.

REFERENCES

The business of being a pediatrician

ANDREW J. SCHUMAN, MD

Primary care providers enjoy caring for their patients, but a practice is also a business and must be profitable. Here’s what you should know.

Although many primary care providers (PCPs) enjoy the freedom of managing their own offices, the number of physician-owned practices is slowly declining. Results of a 2020 American Medical Association (AMA) survey of 3500 PCPs showed that 49.1% of those surveyed worked in physician-owned practices, down from 54% in a 2018 AMA survey. Respondents gave the following chief reasons for abandoning private practice:

- Many feared that, as medical practice grows more complicated, health care reform will drive more physicians out of practice.
- Most doctors saw joining a hospital or health system organization as a way to safeguard salaries, at least for the near future.
- More than half of doctors cited electronic health record (EHR) requirements as a main reason for leaving private practice.

Pediatricians become employed by institutions because they believe that by joining a large medical organization, they will be assured of consistent pay and patient visits. However, as employees, they also give up their autonomy. This means using the EHR chosen by the institution and following policies established by managers. Pediatricians may be able to express their opinions and influence decisions, but, unlike with private practice, change comes slowly, and policies are often reactive rather than proactive.

The following suggestions will help independent pediatric practices thrive in an era of uncertainty, pandemics, and health care reform. The good news: The need for PCPs is expected to increase over the next few years, and those who provide quality care will be in the best position to negotiate lucrative contracts with insurance companies.

Focus on the essentials

First and foremost, a practice needs a good office manager to ensure that revenues are maximized and patients and staff are happy, as well as keep a sharp eye on changes in the community that will affect a practice. The manager is the go-to person for patient or staff issues and works with the managing physician to oversee the well-being of the practice. Their skill set includes coding, familiarity with EHRs, experience in negotiating insurance contracts and accounts payable, and management of human resources. The office manager will lead and conduct regular meetings with all staff and business meetings with providers.

Cash flow is the lifeblood of any practice. If insurance companies delay payments or the practice has a slow month or 2, a decline in cash flow may threaten viability. Using an effective billing service or employing experienced coders and billers can optimize cash flow. Electronic claims should be submitted within 7 days of service for a busy practice and posted within 2 or 3 days of receipt; patient bills should be generated within a week of posting. Paper claims can significantly prolong the collection process and should be avoided.

Co-payments and monies owed the practice should be collected at the time of service. Offering discounts for cash or check payments...
might be appreciated by patients while avoiding credit card fees. Patient eligibility should always be verified via the insurance company’s website—this usually takes less than 2 minutes.

Many practices have parents or patients sign an agreement enabling the practice to charge a credit card for their portion of the bill once insurance company has processed the submitted claim.

Billing services can be outsourced, but the vendor will collect a percentage of payments or a charge per claim processed (or a hybrid), even if the bill is not paid. Many pediatricians prefer to keep billing and collections in-house so they can monitor cash flow and react to problems sooner rather than later.

Finally, a practice should consider rewarding the office manager with productivity bonuses for increasing practice revenue or averting disasters. Additionally, coders and billers should be paid well and perhaps given incentives for hitting collection benchmarks.

Do your due diligence on denied claims
Pediatricians should never be reluctant to challenge denied claims for charges they feel are appropriate. Not infrequently, insurance companies fail to make payments for new services that a practice offers, such as photo screeners for visual screening. Attaching American Academy of Pediatrics (AAP) policy statements that support appeal letters can be helpful. The LISTSERV run by the AAP’s Section on Administration and Practice Management is a great resource for researching related issues.

Some pediatricians are not aware that they can charge for both a well visit and a sick visit when coders use modifiers correctly and provide notes to document services. This can be done when, during a well visit, a patient is discovered to have an ear infection, a sore throat, or pneumonia or a new significant problem (eg, blood in stool, palpitations) is discussed requiring further evaluation.

A substantial cash reserve can keep a practice running for months should collections or productivity decline. If having a large amount of cash on hand is not possible, an established line of credit can be used in times of need and paid off in times of plenty.

Improve efficiency
Pediatricians need to scrutinize workflow to optimize daily patient throughput. This means simplifying the check-in process by shortening patient intake or registration questionnaires, mailing new-patient registration forms or using patient portals, and using secure email or online services to remind patients of appointments. Technological devices, especially photoscreeners and otoacoustic emissions automated hearing screeners, can improve office-based care and screening, as can in-office diagnostic tools such as rapid strep and influenza tests and testing for lead, respiratory syncytial virus, and COVID-19.

Workflow practices should maximize quality time with patients so pediatricians can reinforce recommendations. Staff should take vital signs in examination rooms, as well as document the chief complaint and update the medication and problem list, so providers can focus on patient care rather than deal with electronic housekeeping. To increase office efficiency, all examination rooms should be equipped with computers running the EHR and printers so that health forms can be handed directly to the patient’s caregiver before exiting.

It is important for pediatricians to offer telehealth services to facilitate patient access. Consider using telehealth even for well visits.

Optimize coding, billing, and collection
Learning coding for pediatric services is crucial. (To read about the most recent coding updates for pediatric health care providers, visit bit.ly/3qWU9ja.) Simply understanding
The nuances of documenting to support the level of service provided will improve a pediatrician’s bottom line and ability to survive any insurance company audit. Physicians tend to undercode office visits. For example, 99214 visits are generally reimbursed $30 to $50 more than 99213 visits; 99214 visits require moderate medical decision-making and should be considered when seeing patients presenting with the following:

- At least 1 chronic illness with mild exacerbation, progression, or adverse effects of treatment (eg, asthma exacerbation, attention-deficit/hyperactivity disorder, not responding to medication)
- 2 or more stable chronic illnesses (eg, asthma, enuresis)
- An undiagnosed new problem with uncertain prognosis (eg, blood in stool)
- Acute illness with systemic symptoms (eg, pyelonephritis, pneumonitis, colitis)
- Acute complicated injury (eg, head injury with brief loss of consciousness)
- A condition that requires prescription drug management (eg, urinary tract infection, streptococcal pharyngitis)

**Rein in overhead**

Practices can take many measures to reduce expenses. EHRs are extremely expensive, so practices should not hesitate to compare systems and make cost-effective changes. Patient portals can dramatically reduce overhead by saving postage and time by automating many of the tedious processes that can occupy much of a medical staff’s time. Most portals facilitate bill payment via the portal itself.

The costs of high-price items (eg, photoscreeners, copier) can be reduced through leasing agreements, which allow keeping up with the latest and greatest technologies—devices often become obsolete after a few years. Scribes or voice-recognition dictation software can save time in documenting office notes.

A strict no-show policy will help reduce the number of missed appointments. Another consideration: charging patients after the first missed appointment and discharging those who are frequent abusers.

Additionally, employing the right staff to meet office needs keeps costs down. For example, nurses should not be hired to perform duties that medical assistants can easily do. With the appropriate number of staff, everyone is busy but not stressed and overworked. Group purchasing services such as Physicians’ Alliance of America and Physicians’ Buying Group offer members discounted rates on frequently bought items such as table paper, syringes, and needles.

**Monitor key indicators**

Keeping tabs on key performance indicators helps ensure a practice is functioning optimally. The Physicians Computer Company (PCC) provided current data for this article (see Table) regarding pediatric practice benchmarks, derived from over 1000 pediatric providers using the PCC EHR and practice management/billing suite. The table shows average performance benchmarks as well as those for the top 10% performers using the PCC system.

Practitioners should take a realistic look at their financial and practice metrics and ask themselves if they are seeing as many patients as they did 2 years ago. Is the practice growing or shrinking in terms of enrolled patients? Is overhead rising? Practices that are not thriving might consider merging with others in the area. Larger practices offer advantages in controlling costs, negotiating contracts with insurance companies, and centralizing billing and computer operations.

While we cannot be certain what a medical practice will look like next year or in 10 years, pediatricians can take solace in the fact that they take care of a very special group of patients.

**Comments?** Email them to llevine@mjhlifesciences.com

Andrew Schuman is section editor for Practice Improvement and a member of the Contemporary Pediatrics® Editorial Advisory Board.

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**TABLE. PEDIATRIC PRACTICE BENCHMARKS AS OF NOVEMBER 2021**

<table>
<thead>
<tr>
<th></th>
<th>Average</th>
<th>Top 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No-show Rate</td>
<td>4.6%</td>
<td>1%</td>
</tr>
<tr>
<td>Visits coded as 99214 or higher</td>
<td>35%</td>
<td>61%</td>
</tr>
<tr>
<td>A/R days</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>A/R 60-90 days</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>RVUs per visit</td>
<td>2.92</td>
<td>3.73</td>
</tr>
<tr>
<td>Revenue per visit</td>
<td>$158</td>
<td>$208</td>
</tr>
</tbody>
</table>

Source: Physician Computer Company. Used with permission.

A/R, accounts receivable; RVU, relative value unit; A/R 60-90 days, total A/R that is 60 to 90 days old; AR days, length of time required to collect money owed.

To read about the impact of COVID-19 on medical practices, go to ContemporaryPediatrics.com/business-of-being-a-pediatrician
mRNA vaccine technology update

LAUREN BISCALDI

Multiple pharmaceutical companies are investigating the application of mRNA technology to develop vaccines that treat and prevent multiple conditions, from influenza to cancer and beyond.

Moderna, Pfizer, and Boehringer Ingelheim are among the pharmaceutical companies investigating the applicability of messenger RNA (mRNA) vaccines to treat and prevent other conditions. In addition to a vaccine for HIV, mRNA is being explored as a potential vehicle to create vaccines for several other conditions.1

Influenza

An mRNA influenza vaccine has the potential to improve on the current flu vaccine paradigm. Three mRNA flu vaccines began phase 1 clinical trials in 2020.

Together, Sanofi and Translate Bio are investigating a monovalent flu vaccine candidate for the hemagglutinin protein of the A/H3N2 strain of the influenza virus.2 When the A/H3N2 strain is most dominant, flu activity may be more severe, particularly among at-risk groups, such as older adults and younger children.

Pfizer’s phase 1 trial (NCT05052697)3 is evaluating the response to their mRNA flu vaccine candidate in a group of healthy adults between 65 and 85 years across the United States. Participants will randomly receive 1 of 4 dose levels of the company’s monovalent vaccine candidate (A or B strain of the virus); 1 of 4 dose levels of the bivalent candidate (A and B strains of the virus); the quadrivalent candidate; or a currently approved quadrivalent flu vaccine.

In July 2020, Moderna announced the dosing of the first participants in a phase 1/2 study of mRNA-1010, a quadrivalent flu vaccine candidate4 to evaluate the safety and immunogenicity of 3 levels of doses of the vaccine targeting hemagglutinin surface proteins from 4 World Health Organization–recommended influenza strains. Moderna is also investigating an mRNA candidate (mRNA-1073) combining vaccines for COVID-19 and the flu.5

Respiratory syncytial virus

Previous investigations into a vaccine for respiratory syncytial virus (RSV) have been unsuccessful, with early candidates ultimately strengthening rather than protecting against the disease.6 Moderna is now studying mRNA-1345,7 an RSV vaccine candidate that uses the same lipid nanoparticle as their COVID-19 vaccine. In late 2021, the company announced interim data7 from a phase 1 trial (NCT04528719) evaluating the tolerability and reactogenicity of mRNA-1345 in groups of participants between 18 and 49 years, 65 and 79 years, and 12 and 59 months. Results showed that at 1 month post vaccination, 50-μg and 100-μg doses were “generally well tolerated” in the study’s cohort of younger adults.

Cytomegalovirus

Moderna’s cytomegalovirus (CMV) vaccine candidate,8 mRNA-1647, combines 6 mRNAs into 1 vaccine aimed at protecting against CMV—a significant unmet need, according to a company press release. CDC estimates suggest 1 in 200 babies are born with CMV, 1 of 5 of whom will experience “devastating sequelae,” such as hearing loss, seizures, and blindness, as well as potential complications later in life.9

The phase 3 CMVictory study (NCT05085366) will evaluate safety and efficacy of mRNA-1647 against primary CMV infection in women between 16 and 40 years. Investigators are aiming to enroll 8000 participants (6900 of childbearing age) across 150 global sites.

Epstein-Barr virus

In January 2022, Moderna announced the dosing of the first candidate in the company’s phase 1 Eclipse study (NCT05164094) of mRNA-1189, an Epstein-Barr virus (EBV) vaccine candidate. EBV affects millions of adolescents globally.

The goal of mRNA-1189 is to prevent EBV-induced infectious mononucleosis and potentially EBV infection itself.

CONTINUED ON PAGE 42

From our sister publication, Drug Topics®
Innovations that deliver

There’s only one SMOFlipid and it’s now approved for patients at every age and stage

SMOFlipid is the FIRST and ONLY 4-oil lipid injectable emulsion indicated for pediatric patients, including term and preterm neonates, who require parenteral nutrition (PN). Its expanded indication is yet another example of Fresenius Kabi’s commitment to delivering a balance of nutrition to PN patients of all ages.

Learn more about SMOFlipid at: www.FreseniusKabiNutrition.com/deliver

SMOFlipid is indicated in adult and pediatric patients, including term and preterm neonates, as a source of calories and essential fatty acids for parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated. Contraindications: Known hypersensitivity to fish, egg, soybean, or peanut protein, or to any of the active ingredients or inactive ingredients in SMOFlipid. Severe disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglycerides > 1,000 mg/dL).

Please see Brief Summary of Prescribing Information for SMOFlipid on the reverse side.
SMOFLIPID (lipid injectable emulsion), for intravenous use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This brief summary does not include all the information needed to use SMOFlipid safely and effectively. For more information about prescribing information for intravenous use at www.freseniuskabinutrition.com.

INDICATIONS AND USAGE

SMOFlipid is indicated in adult and pediatric patients, including term and preterm neonates, as a source of calories and essential fatty acids for parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated.

DOSAGE AND ADMINISTRATION

The recommended daily dosage for adults is 1 to 2 g/kg per day and should not exceed 2.5 g/kg per day. Pediatric dosage in Table 1, and do not exceed an infusion rate of 0.15 g/kg/hour.

Table 1: Recommended Pediatric Dosage

<table>
<thead>
<tr>
<th>Pediatric Age Group</th>
<th>Initial Dose</th>
<th>Maximum Dose</th>
<th>Duration of Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 2 years of age (including preterm and term neonates)*</td>
<td>0.5 to 1 g/kg/day</td>
<td>3 g/kg/day</td>
<td>20 to 24 hours for preterm and term neonates 12 to 24 hours for patients 1 month to 2 years</td>
</tr>
<tr>
<td>2 to &lt;4 years of age</td>
<td>1 to 2 g/kg/day</td>
<td>3 g/kg/day</td>
<td>12 to 24 hours</td>
</tr>
<tr>
<td>4 to &lt;12 years of age</td>
<td>1 to 2 g/kg/day</td>
<td>2.5 g/kg/day</td>
<td>12 to 24 hours</td>
</tr>
<tr>
<td>12 to 17 years of age</td>
<td>1 to 2 g/kg/day</td>
<td>2.5 g/kg/day</td>
<td>12 to 24 hours</td>
</tr>
</tbody>
</table>

* The neonatal period is defined as including term, post-term, and preterm newborns. The neonatal period for term and post-term infants is the day of birth plus 27 days. For preterm infants, the neonatal period is defined as the day of birth through the expected age of delivery plus 27 days (i.e., 44 weeks post-maternal age).

CONTRAINDICATIONS

- Known hypersensitivity to fish, egg, soybean, or peanut protein, or to any of the active ingredients or inactive ingredients in SMOFlipid.

- Severe disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglycerides >1,000 mg/dL).

WARNINGS AND PRECAUTIONS

- Risk of Parenteral Nutrient-Related Liver Disease (PNALD): SMOFlipid, as a triglyceride-based lipid emulsion, can contain triglycerides in a ratio that may increase the potential for PNALD. In rare cases, PTDL may be caused by intravenous lipid emulsions containing soybean oil, particularly those over 30% soy and/or containing high concentrations of highly unsaturated fatty acids. PNALD, also known as post-hepatic steatosis of the liver, can be associated with prolonged hospital stays and increased mortality. The incidence of PNALD appears to be higher with lipid emulsions containing soybean oil than with those containing medium-chain triglycerides.

- Deaths in preterm neonates: Deaths in preterm neonates after infusion of lipid injectable emulsions containing only soybean oil have been reported in the medical literature. Allopathic findings in these preterm neonates include elevated plasma triglycerides, increased hepatic stellate cell activation, and perivascular fat deposition. Premature and small-for-gestational-age neonates have poor clearance of intravenous lipid emulsion and increased free fatty acid plasma levels after infusions. Plasma lipid and fatty acid levels should be continuously monitored when administering intravenous lipid emulsions. Monitor patients receiving SMOFlipid for signs and symptoms of possible PNALD.

- Hypersensitivity Reactions: SMOFlipid contains soybean oil, fish oil, and egg phospholipids, which may cause hypersensitivity reactions. Cross reactions have been observed between soybean and peanut SMOFlipid. SMOFlipid contains soybean and peanut proteins that have been heat-treated, but may still cause a reaction in patients with known hypersensitivity to soybean, peanut, or any of the active or inactive ingredients in SMOFlipid. If a hypersensitivity reaction occurs, stop infusion of SMOFlipid immediately and initiate appropriate treatment and supportive measures.

- Infecctious Complications: SMOFlipid is not a substitute for standard infection prevention and control. SMOFlipid may support microbial growth and is an independent risk factor for the development of catheter-related bloodstream infections. To decrease the risk of infectious complications, ensure aseptic technique is used for catheter placement, catheter maintenance, and preparation and administration of SMOFlipid. Monitor for signs and symptoms of infection including fever and chills, as well as laboratory test results that might indicate infection (including leukocytosis and hyperglycemia). Perform frequent checks of the intravenous catheter insertion site for edema, redness, and discharge.

- Fat Overload Syndrome: This is a rare condition that has been reported with intravenous lipid emulsions, and is characterized by a sudden deterioration in the patient’s condition (e.g., fever, anemia, leukopenia, thrombocytopenia, coagulation disorders, hypoglycemia, hypernatremia, deteriorating liver function, and coagulopathy) resulting from intravenous lipid emulsions that contain soybean, peanut protein, or to any of the active or inactive ingredients in SMOFlipid. If a hypoglycemia reaction occurs, stop infusion of SMOFlipid immediately and initiate appropriate treatment and supportive measures.

- Pregnancy and Lactation: Administration of the recommended dose of SMOFlipid is not expected to result in fetal harm or to cause male or female reproductive toxicity in preclinical studies. No adequate and well-controlled studies have been conducted with SMOFlipid in pregnant women; therefore, SMOFlipid use in pregnant women should be considered only when clearly needed. SMOFlipid is not expected to cause harm to the nursing mother, based on the available evidence of safety in preclinical studies. SMOFlipid use has not been studied in breastfeeding mothers and it is unknown if SMOFlipid is excreted in breast milk. Administration of SMOFlipid to breastfeeding mothers is not recommended.

- Pediatric Use: SMOFlipid is not recommended for use in pediatric patients, including term and preterm neonates. Use of SMOFlipid in neonates is supported by evidence from short-term (i.e., 1 to 4-week) studies, and one study following neonates beyond 4 weeks (see Clinical Studies, (14)). Use of SMOFlipid in older pediatric patients is not supported by evidence from a short-term (i.e., <28 days) study in pediatric patients 28 days to 12 years of age and additional evidence from studies in adults (see Clinical Studies, (14)). The most common adverse reactions in SMOFlipid-treated pediatric patients were anemia, vomiting, gamma-glutamyltransferase elevation, increased triglycerides, and PNALD. Deaths in preterm infants after infusion of lipid injectable emulsions containing only soybean oil have been reported in the medical literature (see Warnings and Precautions (5.9); Adverse Reactions (6.1)). Monitor pediatric patients for laboratory parameters to screen for evidence of PNALD. Infants receiving prolonged treatment with SMOFlipid may be at risk for aluminum toxicity (see Warnings and Precautions (5.8)).

USE IN SPECIFIC POPULATIONS

- Pregnancy: There are no adequate and well-controlled studies in pregnant women. Use of SMOFlipid in pregnant women is expected to result in fetal harm or to cause male or female reproductive toxicity in preclinical studies. SMOFlipid use in pregnant women is not recommended. SMOFlipid use has not been studied in breastfeeding mothers and it is unknown if SMOFlipid is excreted in breast milk. Administration of SMOFlipid to breastfeeding mothers is not recommended.

- Pediatric: Use SMOFlipid in pediatric patients, including term and preterm neonates. Use of SMOFlipid in neonates is supported by evidence from short-term (i.e., 1 to 4-week) studies, and one study following neonates beyond 4 weeks (see Clinical Studies, (14)). Use of SMOFlipid in older pediatric patients is not supported by evidence from a short-term (i.e., <28 days) study in pediatric patients 28 days to 12 years of age and additional evidence from studies in adults (see Clinical Studies, (14)). The most common adverse reactions in SMOFlipid-treated pediatric patients were anemia, vomiting, gamma-glutamyltransferase elevation, increased triglycerides, and PNALD. Deaths in preterm infants after infusion of lipid injectable emulsions containing only soybean oil have been reported in the medical literature (see Warnings and Precautions (5.9); Adverse Reactions (6.1)). Monitor pediatric patients for laboratory parameters to screen for evidence of PNALD. Infants receiving prolonged treatment with SMOFlipid may be at risk for aluminum toxicity (see Warnings and Precautions (5.8)).

OVERDOSAGE

In an overdose situation, sedation may occur. Stop the SMOFlipid infusion until triglyceride levels have normalized and symptoms have subsided. The effects are usually reversible by stopping the lipid infusion. If medically appropriate, further intervention may be indicated. Lipids are not dialyzable from plasma.

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Assessment and treatment of eating disorders in adolescents

JASMINE M. REESE, MD, MPH

Pediatric health care providers understand that eating disorders are not lifestyle choices but life-threatening mental health conditions.

Among patients of all ages, anorexia nervosa (AN) has the second-highest mortality rate of all mental health conditions, after substance abuse. Both suicide and the physical effects of nutritional deficit are implicated. Mortality rates for other eating disorders, including bulimia and binge eating disorder, though lower than for anorexia, are still considerably higher than average.

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) defines 4 categories of eating disorders: AN, bulimia nervosa (BN), binge eating disorder (BED), and avoidant/restrictive food intake disorder, along with several noted as “other” or “atypical disorders.”

Table 1 summarizes the diagnostic criteria for these categories. Body weight is among the diagnostic criteria for AN only; these patients may be underweight, within normal range, or overweight.

**Prevalence**

Analyses of prevalence vary widely in their findings. One meta-analysis found lifetime prevalence of AN from 1.7% to 3.6% for female patients and 0.1% for male patients; lifetime prevalence of BN for female patients was about 2.1%. BED, with reported prevalence rates of approximately 2% to 4%, is almost as common among male as female patients.

Among adolescents aged 13 to 18 years, one study found prevalence rates of 0.3% for AN, 0.9% for BN, and 1.6% for BED.

Long characterized as affecting primarily affluent White adolescent girls, eating disorders now affect people from lower socioeconomic groups, members of non-White ethnic groups, preteen children, and boys. LGBTQIA+ young people may be at particular risk.

During the early months of the COVID-19 pandemic, hospitalizations for eating disorders doubled, and patients reported significant increases in unhealthy behaviors.

**Screening**

Caregiver reports about a child’s weight or eating habits or clinical observation of unexpected weight changes are likely to alert the pediatrician to the possibility of an eating disorder. Routinely charting patients’ weight and height on a graph can help physicians immediately identify a possible problem.

Screening instruments for eating disorders are more practical for use in eating disorder centers than in most primary care settings. An alternative is a set of questions known as SCOFF:

**S** Do you make yourself sick because you feel uncomfortably full?

**C** Do you worry you have lost control over how much you eat?

**O** Have you recently lost more than one stone (14 lb) in a 3-month period? (Stones is a British measurement.)

**F** Do you believe yourself to be fat when others say you are too thin?

**F** Would you say that food dominates your life?

Although the originators of SCOFF suggest that 2 or more yeses warrant further assessment, health care providers (HCPs) may want to follow up with even 1 affirmative answer.
History
Secrecy and denial characterize eating disorders. Patients should be questioned alone, away from their caregivers, to encourage honesty. Questions should be specific and pointed—not just “Do you exercise?” but “What kinds of exercise do you do? How many times per week? For how many minutes? How many [miles, reps, laps]?” Similarly, a detailed 24-hour diet history should be taken. Does the patient count calories, carbohydrates, fats, or other nutrients or ever eat in secret?

Other categories of questions include the following:

- **Body image:** “What is your ideal weight? How much of the day do you spend thinking about food or your body?”

---

### TABLE 1
**SUMMARY OF MAIN DSM-5 EATING DISORDERS**

<table>
<thead>
<tr>
<th>DSM-5 DIAGNOSIS</th>
<th>SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anorexia nervosa (AN)</strong></td>
<td>- Restriction of energy intake leading to significantly lower-than-expected body weight</td>
</tr>
<tr>
<td></td>
<td>- Intense fear of gaining weight or becoming fat or persistent behavior that interferes with weight gain</td>
</tr>
<tr>
<td></td>
<td>- Disturbance in how one’s body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of current low body weight</td>
</tr>
<tr>
<td></td>
<td>- Two types: restrictive and binge eating/purging</td>
</tr>
</tbody>
</table>

| **Bulimia nervosa (BN)**         | - Recurrent episodes of binge eating, defined by both of the following:   |
|                                  |   - Eating, in a discrete period, more food than most individuals would eat under similar circumstances |
|                                  |   - Feeling a lack of control over eating during the episode             |
|                                  | - Recurrent inappropriate compensatory behaviors to prevent weight gain (self-induced vomiting, laxatives, diuretics, fasting, excessive exercise) |
|                                  | - Bingeing and compensatory behaviors occurring at least once a week for 3 months |
|                                  | - Self-evaluation unduly influenced by body shape and weight             |

| **Binge eating disorder**        | - Recurrent episodes of binge eating, as defined as for BN                |
|                                  | - Binge-eating episodes associated with 3 or more of the following:     |
|                                  |   - Eating much more rapidly than normal                                 |
|                                  |   - Eating until uncomfortably full                                     |
|                                  |   - Eating large amounts when not hungry                                |
|                                  |   - Eating alone because embarrassed by how much one is eating          |
|                                  |   - Feeling disgusted with oneself, depressed, or very guilty afterward  |
|                                  | - Marked distress regarding binge eating                                 |
|                                  | - At least weekly episodes for 3 months                                 |
|                                  | - No association with recurrent use of inappropriate compensatory behaviors |

| **Avoidant/resistant food intake disorder** | - Eating or feeding disturbance with persistent failure to meet appropriate nutritional and/or energy needs associated with 1 or more of the following: |
|                                            |   - Significant weight loss or failure to achieve expected weight gain   |
|                                            |   - Significant nutritional deficiency                                   |
|                                            |   - Dependence on enteral feeding or oral nutritional supplements        |
|                                            |   - Marked interference with psychosocial functioning                    |
|                                            | - Not better explained by lack of available food or an associated culturally sanctioned practice |
|                                            | - Does not occur during AN or BN; no evidence of body weight or shape disturbance |
|                                            | - Not attributable to concurrent medical condition or better explained by another mental disorder |

*DSM-5, Diagnostic and Statistical Manual of Mental Disorders.*

CONTINUED ON PAGE 36
orders. Heart health is a significant factor, so the physician may order an electrocardiogram (ECG). Bradycardia is the most common arrhythmia and finding in patients with AN. Clinicians may be inclined to attribute a low heart rate to an “athletic heart,” but bradycardia due to starvation is a potentially lethal condition.

Laboratory tests rule out diabetes, thyroid disease, anemia, and other physical causes and also document the extent of physical damage. Checking electrolytes is important. One of the most important tests is the phosphorus level. Medical complications can include depleted adenosine triphosphate, which affects cardiac function and can lead to sudden death.12,13

Emergency hospitalization
Patients with AN, in particular, may be in immediate danger of severe complications. Presence of any one of the following symptoms indicates the need for immediate medical hospitalization for refeeding.2,4,14
- Heart rate less than 50 beats per minute (bpm) while awake; less than 45 bpm while asleep
- Systolic pressure less than 90/45 mm Hg
- Orthostatic changes: decrease in blood pressure of more than 20 mm Hg systolic or 10 mm Hg diastolic; heart rate increase of more than 20 bpm
- ECG abnormalities: Prolonged corrected QT interval or other arrhythmia
- Syncope
- Temperature less than 96°F (35.6°C)
- Electrolyte abnormalities
- Uncontrollable binge eating and purging
- Dehydration
- Suicide risk
- Less than 75% of expected body weight
- Failed outpatient management
- Acute weight loss and food refusal

Communication
Today’s young people typically know what anorexia and bulimia are. When asked screening questions, the patient understands what the clinician is getting at but is likely to be in denial.

Education can start during the screening interview: “Here’s what concerns me when you tell me these things. You’re taking in less energy than your body is expending, and that’s affecting your physical health. Your blood pressure is low. I’m worried that you could pass out while you’re playing your sport or driving.” Sharing weight numbers or commenting on the patient’s thinness may backfire because the patient is likely to view alarming weight loss as a positive development.

In contrast, weight trends, particularly charted on a graph, can help the HCP communicate the seriousness of the problem to the caregivers. Clinicians should share conclusions from the history and the physical exam with patients and caregivers separately and then bring them together to talk about next steps. Both patients and caregivers need to understand, for example, that a broad array of tests is necessary because disordered eating affects a broad array of body systems.

If it is safe to send the patient home, the practitioner can enlist the caregivers to start addressing the eating disorder. Patients who are severely malnourished or underweight or have severe restricting or purging behaviors may need to stop exercise until they have developed a healthier relationship with food. Parents may need to take the lead on preparing meals and monitor consumption.

Treatment
Eating disorders are mental health
conditions. In addition to helping families with practical matters such as meal plans, the pediatrician must link the patient and family with mental health support. Treatment of eating disorders requires a care team consisting of, at minimum, 3 professionals:

- The HCP arranges care and assesses medical status.
- A dietitian works with the patient and family to determine goal weight and provide an individualized nutrition plan.
- A mental health therapist guides family-based therapy, a first-line mental health treatment with established effectiveness.2,31 Cognitive behavioral therapy or dialectical behavioral therapy may also be used.

Psychotropic medications are indicated for comorbid mood disorders. The FDA has approved fluoxetine for treating BN.2 Otherwise, evidence on the use of medications to treat eating disorders is mixed and often based on studies in adults.2

Treatment goals, beyond any medical stabilization requiring immediate hospitalization, are to restore the patient to a healthy weight; restore healthy eating patterns; treat physical complications; address dysfunctional thoughts, feelings, and beliefs; address affect and behavioral regulation; enlist family support; and prevent relapse.

Medical concerns associated with the first stages of recovery include refeeding syndrome and hypermetabolism.30 Refeeding syndrome can occur when nutrients, especially carbohydrates, are reintroduced after starvation. The delivery of glucose leads to increased insulin and rapid uptake of glucose and electrolytes. Low serum concentrations cause fluid retention; nausea or diarrhea may result from adaptation of atrophied gut mucosa and impaired pancreatic function; carbon dioxide production and oxygen consumption increase. Health professionals should introduce nutrition slowly, monitor electrolytes closely and supplement when indicated, and monitor weight intake and outputs.36

The mechanisms of hypermetabolism are less well understood, but an increase in metabolism during refeeding makes weight gain difficult. Patients may require at least 3000 to 4000 calories a day to meet minimum weight gain goals. The effect can last for months, but metabolism does eventually stabilize.36

Outpatient treatment consisting of an hour a week of mental health therapy and regular pediatric visits is beneficial only for patients whose condition has been caught early—typically, before any weight change. Most patients need more support. Treatment options include the following:

- Intensive outpatient program: 3 to 5 hours, 3 to 5 days per week
- Partial hospitalization: 6 to 10 hours, 5 to 7 days per week
- Residential treatment: 24-hour supervision

Pediatric practices should have a regularly updated list of treatment centers that includes treatment models, specializations, and patient populations. Most centers work with a few insurers, which rarely include public insurance programs. Insurers often cover less treatment time or intensity than is clinically indicated.

Families are often reluctant to send their child away for treatment. If residential treatment is indicated and a bed is available, HCPs can talk with the parents about the severity of the disease and how much more likely the child is to recover with 24-hour support.

Caregivers are the key to the success of any mode of treatment. The family’s trusted pediatric health care provider is in a unique position to enlist their support. HCPs can reassure caregivers that, although their child’s illness is serious, a team of professionals will partner with them to address the problem.

For references, go to ContemporaryPediatrics.com/assessment-treatment-eating-disorders

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<td><strong>PHYSICAL EXAMINATION FOR EATING DISORDERS</strong></td>
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<td><strong>Skin</strong></td>
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Adapted from Hornberger et al.2
Extremely preterm infants can benefit from their mother’s milk

Feeding infants mother’s milk may improve poor postnatal growth and prevent morbidities.

Thanks to medical advances, extremely preterm babies are increasingly likely to survive. However, these newborns require additional care to prevent complications such as retinopathy of prematurity and bronchopulmonary dysplasia, along with poorer postnatal growth.

A recent investigation looked into whether using a mother’s own milk rather than pasteurized donor milk leads to lower rates of morbidity. The investigators examined exposure to both kinds of milk from birth until 32 weeks’ postmenstrual age in extremely preterm infants who were born between 2004 and 2007. Primary outcomes were a change in z score from birth to 32 weeks’ postmenstrual age for weight, length, and head circumference; secondary outcomes were the incidence of bronchopulmonary dysplasia and retinopathy of prematurity.

The Swedish population-based cohort included 453 infants, with an average gestational age of 25.4 weeks. The investigators found no links between donor milk and growth outcomes or morbidities or between mother’s milk and bronchopulmonary dysplasia outcomes. However, the mother’s milk was positively linked to weight and head circumference, and the association remained significant in multivariable models. Furthermore, each daily increase of 10 mL/kg of mother’s own milk during the study period yielded an increase in z score units of 0.02 (95% CI, 0.01-0.03; \( P < .001 \)) for weight and 0.02 (95% CI, 0.00 to –0.04, \( P = .049 \)) for head circumference. Although the association did not carry through to adjusted analyses, a higher intake of mother’s own milk also had a significant link with a lower probability of any form of retinopathy or severe retinopathy.

The investigators concluded that increasing the intake of mother’s own milk—not donor milk or formula—was linked to improved head circumference growth and postnatal weight gain from birth until 32 weeks’ postmenstrual age in extremely preterm infants. They urged clinicians to use any intervention to encourage early intake of mother’s milk.

The American Academy of Pediatrics recently published *High Five Discipline: Positive Parenting for Happy, Healthy, Well-Behaved Kids*. Candice Jones, MD, is the author of the book, a board-certified general pediatrician in group practice in Orlando, Florida, and a member of the Editorial Advisory Board of *Contemporary Pediatrics*. In this interview, she shares lessons that both pediatricians and parents can use, including the difference between positive and negative parenting and how to handle the tumultuous teenage years.

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For U.S. Healthcare Professionals
What’s the diagnosis?
The diagnosis is seborrheic dermatitis, sometimes called cradle cap when it appears on the scalp. This chronic inflammatory skin condition is present worldwide and affects all age groups and sexes equally. It is a common disorder, and the diagnosis is usually made clinically.

Infants and young children tend to have mild disease that lasts 4 to 6 weeks but can persist up to a year. In infants, it presents with erythema and thick, patchy, white or yellow scales, sometimes with crust on the scalp and intertriginous areas including the axilla, retroauricular creases, and diaper area, in the first few months of life (Figure). On the face, it appears on the central and lower forehead, eyelids, cheeks, and nasolabial folds.¹

Seborrheic dermatitis also tends to occur in adolescents, affecting 2% to 5% of that population and appearing as an itchy, scaly rash on the scalp, face, presternal area, and skinfolds.² On darker-pigmented children, postinflammatory hypopigmentation may persist for several weeks to months after clearing with treatment.³

The cause of seborrheic dermatitis is not known but has been attributed to androgens that pass from mother to baby during pregnancy. In newborns and infants, androgens stimulate the growth of sebaceous glands that might drive the process. The yeast Malassezia can be found in higher concentrations on patients who have seborrheic dermatitis compared with controls and who may have an inflammatory reaction.²

The differential diagnosis includes psoriasis, atopic dermatitis, contact dermatitis, Langerhans cell histiocytosis, and acrodermatitis enteropathica or nutritional deficiency.²⁴

In young children, psoriasis usually starts in the diaper area and is well delineated. In infants, seborrheic dermatitis and atopic dermatitis can look very similar. The best way to distinguish them is by location and the presence of intense itching in atopy. Both conditions can cause a red, scaly scalp. The rash of seborrheic dermatitis generally involves the skinfolds and diaper area, which are usually spared in atopic dermatitis. Atopic dermatitis often appears on the face, shins, forearms, and other exposed areas that infants can scratch. Contact dermatitis is often seen on the face or diaper area and is itchy. Langerhans cell histiocytosis presents with persistent hemorrhagic, crusted, atrophic, and/or scaly patches that can be anywhere but tend to appear...
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DERMATOLOGY

CONTINUED FROM PAGE 40

in the skin creases.

Infantile seborrheic dermatitis often resolves on its own in a few months. Treatment options for persistent and/or symptomatic lesions include low-potency topical steroids (eg, hydrocortisone 1% ointment); topical calcineurin inhibitors (eg, pimecrolimus cream for > 3 months of age, tacrolimus ointment for > 2 years of age); topical antifungal creams, ointments, or shampoos (eg, ketoconazole, selenium sulfide); and mild keratolytic agents (eg, urea 10%-20%). Oil preparations such as mineral oil can soften and unloosen the scale, making it easier to separate from the hair and scalp. For areas that are not as sensitive as the face or intertriginous areas, a higher-potency topical steroid can be used sparingly for a short course; antifungals can be relied on for long-term therapy. Other medicated shampoos and treatments include ingredients such as zinc pyrithione, coal tar, and ciclopirox olamine. For severe cases, oral antifungals are sometimes used.5 6

The findings of 1 review of multiple, randomized, controlled trials showed that ketoconazole, ciclopirox olamine, and steroids had similar effective results, but the antifungals showed fewer adverse effects. Moreover, the antifungals showed comparable efficacy.7 For this 6-week-old patient, the parents were instructed to massage the infant’s scalp with mineral oil to loosen the scale before washing with ketoconazole shampoo daily. Over the following 2 weeks, the rash resolved, and the infant subsequently remained clear.

COMMENTS?
Email them to llevine@mjhlifesciences.com

Sherry G. Cohen is a family nurse practitioner in Baltimore, Maryland. She has nothing to disclose.

RESPIRATORY DISORDERS/PHARMACOLOGY

mRNA Vaccine Technology Update CONTINUED FROM PAGE 27

Cancer

Cancer vaccines are being studied both alone and in combination with chemotherapy and immunotherapy. Some of these vaccines are personalized1—created for individual patients based on their tumor samples; others target the proteins found in cancer cells more globally.1

BioNTech and Regeneron Pharmaceuticals are currently collaborating on an mRNA cancer vaccine for advanced melanoma.2 The vaccine, BNT111, is currently in a phase 2 clinical trial (NCT04526899). In late 2021, BioNTech was granted an FDA fast track designation based on “available preclinical and clinical data showing the potential of BNT111 to overcome current limitations in the treatment of inoperable therapy-resistant advanced-stage melanoma,” according to a press release.3

BioNTech is also collaborating with investigators at the University Medical Center Groningen in the Netherlands in the phase 1 OLIVIA clinical trial (NCT04163094)5 to evaluate the W_ova1 mRNA vaccine in combination with neoadjuvant chemotherapy for ovarian cancer. The first-in-human study is estimated to be completed in 2023.

Boehringer Ingelheim, CureVac, and Ludwig Cancer Research have joined forces to study mRNA vaccine BI 1361849 (CV9202), a self-adjuvanting mRNA-based immunotherapeutic cancer vaccine to “mobilize the immune system” to fight tumors.4 It contains 6 mRNAs coded for 6 different antigens commonly expressed in non–small cell lung cancer (NSCLC).4 It is being investigated in a phase 1/2 clinical trial (NCT03164772)5 as a combination treatment with durvalumab or durvalumab plus tremelimumab for NSCLC.

Moderna is studying at least 3 mRNA vaccines for cancer in clinical trials, 2 of which are personalized. KEYNOTE-942 (NCT03897881) is studying mRNA-4157 as an adjuvant therapy to pembrolizumab in patients with high-risk melanoma.6 KEYNOTE-603 (NCT03313778) is studying the safety, tolerability, and immunogenicity of mRNA-4157 in patients with solid tumors, both alone in those with resected solid tumors and in combination with pembrolizumab in those with unresectable solid tumors.7

A third Moderna vaccine—mRNA-5671/V941—is in a phase 1 study (NCT03948763)8 as both a monotherapy and in combination with pembrolizumab to target a specific cancer cell protein found in NSCLC, colorectal cancer, and pancreatic cancer.8

COMMENTS? Email them to llevine@mjhlifesciences.com

For references, go to ContemporaryPediatrics.com/dermcase-0522

Sherry G. Cohen is a family nurse practitioner in Baltimore, Maryland. She has nothing to disclose.
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