Nutrition

Cystic Fibrosis

GI clues for early diagnosis
in this issue

FEBRUARY 2020

nutrition
12 Gastrointestinal manifestations of cystic fibrosis: A primer for pediatricians
Addressing the gastrointestinal (GI) complications of cystic fibrosis presents a major opportunity to improve care for children with this debilitating disease.

Anna Reed, MD, MPH; Darla Shores, MD, PHD

infectious disease
10 How Lyme disease guidelines are set to change
Now that a comment period on new recommendations has closed, there may be new guidelines for antibiotic options.
Rachael Zimlich, RN, BSN

pediatric pharmacology
17 Triple combination therapy for cystic fibrosis is here!
A newly approved triple CTR modulation therapy is showing dramatic results.
Kimberly M Dickinson, MD, MPH; Shruti M Paranjape, MD

behavioral health
20 ADHD guideline update: What’s new, what’s changed
The revised clinical practice guideline addresses how to manage co-occurring psychologic and behavioral issues.
Rachael Zimlich, RN, BSN

21 Why pediatricians are the first line of care for gender-diverse children
It’s important to talk early to patients and their families about gender identity and offer referral for support.
Rachael Zimlich, RN, BSN

25 Religious exemptions to vaccination are rising
More parents are opting out of vaccinating their children for kindergarten on religious grounds.
Catherine M Radwan, Managing Editor

dermatology
26 Counsel safety and risk with tattoos and piercings
It may not be your personal choice, but be open to discussing the risks and legality of body modification.
Rachael Zimlich, RN, BSN

29 Dermcase: Boy builds a snowman, suffers swollen fingers
A 4-year-old boy presents for evaluation of painful swollen fingers after playing outdoors in the cold.
Erinolaoluwa F Aroeyi, BS, MS3

in addition
6 EDITORIAL ADVISORY BOARD
6 CHAIRMAN’S LETTER
8 JOURNAL CLUB
28 ADVERTISING INDEX

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/2vrvsN3

Contemporary Pediatrics® (Print ISSN: 0750-0562, Digital ISSN: 2150-6345) is published monthly by Multimedia Healthcare LLC, 230 W. Superior St, STE 400 Duluth, MN 55802. Subscription rates: one year $90, two years $150 in the United States & possessions, $219 for three years, $288 for five years in Canada and Mexico, all other countries $156 for one year, $228 for three years, $294 for five years, single copies $18 per issue plus $2.00 per additional copy for U.S. postage and handling. Periodicals postage paid at Duluth, MN 55804 and additional mailing offices. POSTMASTER: Please send address changes to Contemporary Pediatrics, PO Box 452, Cranbury, NJ 08518-5447, Canadian GST number: R1240135875R5. Publications Mail Agreement Number 400-50000. Return Undeliverable Canadian Addresses to: NEA Global Solutions, P.O. Box 25642, London, ON N6C 6B2, Canada. Printed in the U.S.A.

© 2020 Multimedia Medical LLC. All rights reserved. Reproduction of any portion of this publication may be reproduced in print, electronic, or mechanical including by photography, recording, or information storage and retrieval system without permission in writing from the publisher. Authorization to photocopy items for internal/educational or personal use, or the internal/educational or personal use of specific clients is granted by MJH Life Sciences for Libraries and other users registered with the Copyright Clearance Center. 222 Rosewood Dr, Danvers, MA 01923. 978-750-8400. Fax 978-646-8700 or visit http://www.copyright.com online. For uses beyond those listed above, please direct your written request to Permission Dept.

Email: permissions@mmhgroup.com

MJH Life Sciences provides certain customer contact data. If you are a customer’s name, address, physician, phone number, and other personal information. If you are not a customer of MJH Life Sciences, you may request permission to receive relevant products, services, and other information by either calling us toll-free 888-527-7008 or writing to cradwan@mmhgroup.com. You can also visit our website at: www.contemporarypediatrics.com. MJH Life Sciences does not verify any claims or other information appearing in any of the advertisements contained in the publication, and cannot take responsibility for any losses or other damages incurred by readers in reliance on such content.

Contemporary Pediatrics welcomes unsolicited manuscripts for consideration for publication. The submission guidelines, send requests to the Content Managing Editor: cradwan@mmhgroup.com. When submitting manuscript documents as well as high-resolution digital image files and other supplemental content, send all components as separate attachments to email-cradwan@mmhgroup.com. Library Access: Libraries offer online access to current and back issues of Contemporary Pediatrics through the EBSCO host database. To subscribe, call toll-free 888-927-7188. Outside the U.S., call 218-740-6477.
Professionally Recommended
Problem-Solving Products

For samples, visit:
www.summers-direct.com/samples
CHAIRMAN’S LETTER

How treatment for cystic fibrosis is changing

Cystic fibrosis (CF) is the most common lethal autosomal recessive disease among US infants, affecting 2,000 to 4,000 newborns. It is primarily thought of as a respiratory disease, but after decades of research into the pancreatic insufficiency that causes a failure to thrive in children with CF comes a new understanding of the effects of CF mutations on the entire gastrointestinal system. Authors Anna Reed, MD, MPH, and Darla Shores, MD, PHD, contribute an informative primer about the complex interplay among the components of gut physiology to help pediatricians identify and manage the gastrointestinal issues associated with CF in their young patients. Their article begins on page 12.

Also in this issue, Contemporary Pediatrics provides updates on the latest FDA-approved pharmacologic therapy for CF as well as changing guidelines for treating Lyme disease and managing attention-deficit/hyperactivity disorder. This publication is your go-to advisor for all things pediatric.

Mike Hennessy, Sr.
Chairman and Founder
MJH Life Sciences
Recommend Aquaphor® Baby as the complete solution for babies’ diaper area needs

**Prevent** Aquaphor Baby Healing Ointment
- Provides immediate protection by creating a barrier from wetness, acidity, and chaffing
- Uniquely formulated with 41% Petrolatum and 4 key ingredients that protect and soothe to help heal skin

**Treat** Aquaphor Baby Diaper Rash Cream
- 83% of patients had improvement from baseline in diaper rash and irritation by Week 1*
- Formulated with 15% Zinc Oxide, odor-free, preservative-free, and talc-free

*Data on File. ©2019 Beiersdorf Inc.

Beiersdorf
Newborn infants with tongue-tie (ankyloglossia) are more likely to have severe breastfeeding problems than infants without the condition, according to an observational study carried out in Germany in newborn mother-infant pairs. Low birth weight and prematurity also have a significant negative impact on breastfeeding, the investigation showed.

During a 10-month period, researchers enrolled 776 mother-infant pairs at a maternity unit nursery; all the infants were born after at least 35 weeks of gestation. To obtain data about the association of various factors with breastfeeding problems, investigators reviewed participants’ medical records related to pregnancy and birth; assessed infants’ frenulum using the Assessment Tool for Lingual Frenulum Function (ATLFF) score; used a breastfeeding questionnaire to explore mothers’ perception of breastfeeding; and administered a maternal pain scale as well as 2 objective breastfeeding scales to assess the effectiveness of breastfeeding.

Of total newborns, 116 (15%) had a tongue-tie, more than half of whom (55%) had breastfeeding problems compared with 42% of infants without a tongue-tie. In addition, severe breastfeeding problems were more common in newborn infants with tongue-tie than in those without it. Compared with the infants without tongue-tie, those with the condition had lower scores on the breastfeeding scales and their mothers had higher pain levels, indicating poorer latch and lower levels of milk transfer. Analysis showed that other risk factors for breastfeeding problems were no breastfeeding experience, low birth weight, prematurity, and birth by cesarean delivery.

Mothers who reported breastfeeding problems received support from a lactation consultant and, in infants with tongue-tie, a frenulotomy was performed, if indicated. Follow-up phone calls and administration of breastfeeding scales showed a significant reduction in breastfeeding problems after frenulotomy. Of the 33 infants with a clear indication for frenulotomy, those who underwent the procedure had significantly fewer breastfeeding problems after the surgery. Specifically, only 3 of 23 of the infants who had the procedure still had breastfeeding problems compared with 6 of the 10 who did not undergo a frenulotomy (Schlatter SM, et al. *Acta Paediatr.* 2019;108[12]:2214-2221).

Years ago, we didn’t clip tongue-tie because it doesn’t interfere with speech when the child is older. I agree that some children benefit but I am not convinced it is as many as reported here. Lactation support outside the hospital should reduce the number, as was demonstrated by Caloway and colleagues (Caloway C, et al. *JAMA Otolaryngol Head Neck Surg.* July 11, 2019. Epub ahead of print), who also report a surgical fee of $850 for the procedure. As more doctors (and dentists!) take up clipping tongues, we’re also going to see more complications.
Should adult criteria for prediabetes be applied to youngsters?

A study of hemoglobin A1c (HbA1c) levels that compared levels in normal-weight and obese middle schoolers found that overall distribution of HbA1c was similar in the 2 groups and that the adult-defined cutoff was seen in 2% of normal-weight youth. Based on previously published epidemiologic data, the authors concluded that in youngsters these adult prediabetes levels are highly unlikely to represent evolving diabetes and recommended that results of HbA1c screening in children “be interpreted with caution.”

The trial looked at 8814 normal-weight and obese youngsters (4603 and 4211 in each group, respectively) aged from 11 years to 15 years. For most participants, HbA1c assessments were conducted in either sixth or eighth grade and at both times for some. Although mean HbA1c was higher in obese youth compared with those of normal weight, overall HbA1c was similar in the 2 groups, with 2 of every 100 normal-weight youngsters having a level in the prediabetes range. However, normal-weight black children had significantly higher HbA1c levels than other participants, with 7.1% in the prediabetes range compared with 1.3% of Hispanic children and 0.1% of white children (Kelsey MM, et al. J Pediatr. 2020;216:232-235).

Virtual reality education reduces the stress of chest radiography

Children who received virtual reality (VR) education before undergoing chest radiography showed lower levels of stress during the procedure than their peers who did not receive the VR exposure, a randomized trial in 99 children found.

Participants were divided into a VR group and a control group. Those in the VR group experienced a 360°, 3-dimensional environment featuring a 3-minute video that explained the procedure, took them into a radiography room, showed them how to position themselves in front of a radiography machine, and encouraged taking a deep breath and being cooperative. The control group was given the usual simple verbal instructions for chest radiography.

During the chest radiography, investigators measured children’s stress and anxiety using a scale that assessed behaviors such as crying, clinging, fear, restraint, and screaming. A score of >5 was considered “more distressed” and <5 considered “less distressed.” The number of less-distressed children was significantly higher in the VR group than in the control group (38 vs 26, respectively), and the degree of stress and anxiety in the VR group also was significantly lower. Whereas only 16.3% of the VR group needed parental presence, 36% of the control group expressed this need. Virtual reality education was also associated with improved parental satisfaction and reduced procedural time (Han SH, et al. JAMA Pediatr. 2019;173[11]:1026-1031).

I chose this study to show that I do not consider all electronics to be bad for children, when used properly. This clever creation is the sort of brief, targeted intervention that can take advantage of the undoubted attraction video has for children.
How Lyme disease guidelines for antibiotics are set to change

Now that a comment period on new recommendations has closed, there may be new guidelines for antibiotic options.

RACHAEL ZIMLICH, RN, BSN

The guidelines for diagnosing and treating Lyme disease may soon be changing, although pediatricians aren’t expected to readily adopt all the recommendations.

Last September, the comment period closed on a new set of guidelines for the prevention, diagnosis, and treatment of Lyme disease. The guidelines have several updates, but one of the primary changes is the recommendation to use doxycycline for treatment of Lyme disease infection and as prophylaxis after a high-risk tick bite—even in children. Pediatrists, however, are not used to using doxycycline in children due to concerns about damage and staining to teeth, and the authors of the guidelines anticipate pediatricians will hesitate to adopt the change, opting instead to continue prescribing other antibiotics.

Paul G. Auwaerter, MD, president of the Infectious Diseases Society of America, a Sherrilyn and Ken Fisher professor of Medicine at the Johns Hopkins University School of Medicine in Baltimore, Maryland, and co-author of the guidance, says the guidelines were drafted by a panel from the Infectious Diseases Society of America, the American Academy of Neurology, and the American College of Rheumatology, with input from a number of other organizations and experts. There is no word yet on when final recommendations will be published.

Lyme disease is found in 3 expanding regions of the United States, according to the proposed guidelines—the northeast states from Virginia to eastern Canada, the upper Midwest, and northern California. Presence of a rash is still a hallmark sign of infection following a tick bite, according to the report. The rash associated with Lyme disease—erythema migrans—is present in roughly 80% of cases and its presence is enough to warrant initiation of treatment for Lyme disease, according to the guidance. Blood testing is generally not recommended, as only about 33% of patients will have detectable antibodies along with the erythema migrans rash.

The recommendations also do not suggest performing any testing on the ticks. Identifying the tick and examining whether it is engorged, indicating more prolonged attachment and feeding time, is more helpful, according to the guideline. This is because *Borrelia burgdorferi*, the primary bacteria that causes Lyme disease, is found in a tick’s midgut and is only activated some time after the tick attaches to a host and begins to feed. The bacteria must first migrate from the midgut to the mouth of the tick and then pass to human hosts by reflux through the tick’s salivary glands during feeding. Generally, ticks must feed for more than 36 to 48 hours to pass the bacteria to its host, although infection may occur sooner.

Testing and treatment
The infection process for Lyme disease is clinically complex, with a wide range for the latent period after exposure and before an infection presents. Symptoms of Lyme infec-
fection may include localized skin lesions at the site of the bite, neuropathy, meningitis, cardiac conduction problems, and arthritis. Manifestations can occur as early as a few days after a tick bite to as late as several months after.

Serum antibody testing is highly sensitive and the first-line method of testing for Lyme disease, according to the guidance, although false negative results may occur early in the infection process as a detectable antibody response may take some time to develop. Therefore, testing isn’t always recommended, particularly for patients who are asymptomatic.

Lyme disease is treated with antimicrobials including doxycycline, penicillin, amoxicillin, cefuroxime, ceftriaxone, and azithromycin. Oral antibiotics are usually sufficient and preferred, according to the guidance, but there are some indications in which intravenous antibiotics may be used.

One of the major changes in the proposed guidelines is the recommendation to use doxycycline in children aged younger than 8 years. Previously, doxycycline was not recommended for use in children over concerns about tooth enamel damage and discoloration. The new guidelines, however, dismiss this concern and note instead that doxycycline is effective against more than one tick-borne disease and can be given for children with broader manifestations. It is also the only oral option that is effective against Lyme meningitis outside of parenteral options, which carry additional risks.

However, the guideline authors note that amoxicillin may still be more frequently used in pediatric patients simply because it is more commonly used in pediatric practice. The dosing for doxycycline is 4.4 mg/kg—maximum dose 200 mg—for children. The proposed recommendations also include postexposure prophylaxis of a single dose of doxycycline for pediatric patients when an engorged tick has been removed. It is recommended only to use prophylactic antibiotic therapy within 72 hours of removing an identified, high-risk tick exposure, according to the guidelines. This includes bites from identified Ixodes ticks; bites that occur in highly endemic areas for B burgdorferi-infected ticks; and when ticks are engorged and attached for more than 36 hours.

**Prevention is Key**

The safest bet is to prevent tick exposure and Lyme disease infection from the start. The proposal lists physical barriers such as protective clothing that is light in color to see ticks, special cleaning techniques when ticks are found on clothes, and treating pets. Repellents with N,N-diethyl-meta-toluamide (DEET), picaridin; 380 ethyl-3-(N-n-butyl-N-acetyl) aminopropionate (IR3535), oil of lemon eucalyptus, or permethrin 381 are strongly recommended, with the authors noting that there is no evidence to support the efficacy of botanical agents or essential oils in repelling ticks. Concerns have been raised about the safety of products containing DEET. However, the proposed guidelines state that there are actually very low rates of adverse effects with products containing DEET as long as they are used as labeled.

The guidelines also make suggestions on tick removal, recommending against burning attached ticks or using chemicals or petroleum products for removal. Instead, the guidance suggests removing ticks mechanically with a clean tweezer inserted between the tick’s body and the host’s skin.

**In Summary**

There is still more research to be done, and official recommendations and clinical guidance won’t be issued until after comments are reviewed and considered. Whereas the guidelines cover a lot of specifics, there is also a lot of room for additional research, Auwaerter says.

“We still have questions and are advocating for more research into tick-borne diseases. In the meantime, we are updating the Lyme disease guidelines to promote safe, effective, proven treatment,” Auwaerter says. “The guidelines use the best available evidence to guide decisions regarding diagnosis and treatment of B burgdorferi infections.”

**Comments?** E-mail them to cradwan@mmhgroup.com

**Reference**


**Ms Zimlich** is a freelance writer in Cleveland, Ohio. She writes regularly for *Contemporary Pediatrics* and sister publications *Managed Healthcare Executive* and *Medical Economics*. She has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

Continue reading on page 25

Religious exemptions to vaccinations are rising amid stricter state policies.
Gastrointestinal manifestations of cystic fibrosis
A primer for pediatricians

Significant improvements in cystic fibrosis (CF) care have focused primarily on the pulmonary system, but addressing the gastrointestinal (GI) complications of CF presents a major opportunity for improvement in disease management.

Anna Reed, MD, MPH
Darla Shores, MD, PhD

Cystic fibrosis (CF) is the most common lethal autosomal recessive disease in the United States, occurring in 2000 to 4000 newborns. It is caused by one of the more than 2000 mutations of the CF transmembrane conductance regulator (CFTR). Although most of its morbidity and mortality stems from pulmonary decline, it was first recognized in 1938 as a cause of severe failure to thrive in infants due to characteristic pancreatic insufficiency. Decades later, we are starting to understand the full implication of the effects CFTR mutations on the entirety of the gastrointestinal (GI) system (Table 1). The CFTR transports chloride and bicarbonate across the apical surface of epithelial cells in the respiratory and GI tracts. Mutations are classified as I to VI, with I to III being the most severe. Mutations result in abnormal structure, synthesis, and/or function of the CFTR protein.

Newborn screening detects trypsinogen, a protein released from the pancreas during the process of its destruction in utero. However, there are false negative results or cases where the specimen is unacceptable, or not received, and there is no appropriate follow-up. As 60% of infants are born with pancreatic insufficiency and another 30% will develop insufficiency in the next 3 years, and as GI, pancreatic, and hepatic manifestations are the most common initial manifestations of CF, before pulmonary manifestations become apparent, clinicians should have a low threshold for obtaining additional testing if CF is suspected.

Nutrition
Achieving optimal growth in early life correlates with fewer pulmonary exacerbations and fewer hospitalizations. Infants with...
Children with CF should be seen monthly to monitor proper growth and then every 3 months for routine care. Patients with suboptimal growth should be seen more frequently.

Children with CF require 110% to 200% of normal caloric intake to achieve normal growth. In general, the goal body mass index (BMI) is the 50th percentile for age, or the 50th percentile weight-for-length in children aged younger than 2 years. In instances where BMI offers a poor reflection of nutritional status, such as hepatomegaly or ascites, mid-arm circumference serves as an alternative measure. Attainment of nutritional goals involves adequate caloric intake, supplementation with fat-soluble vitamins (A, D, E, K), and pancreatic enzyme replacement therapy (PERT) under the guidance of a CF-trained nutritionist.

In addition to BMI, stunted height must be screened for, as height also correlates with lung function. There are multiple causes of stunting in CF (Table 2). A chronic inflammatory state makes insulin-like growth factor 1 (IGF1) less responsive to growth hormone. In addition, CF-related diabetes (CFRD), a unique form of diabetes specific to CF, can lead to growth failure.

Zinc deficiency from malabsorption and sodium deficiency related to CFTR dysfunction also can contribute to poor growth. Serum sodium may be normal despite depleted body sodium. A urine sodium to creatinine ratio can be measured. Cystic Fibrosis Foundation (CFF) guidelines emphasize sodium supplementation from infancy onward and with exercise. Zinc supplementation can be instituted empirically if a child is failing to thrive.

Due to fat malabsorption and dysregulation of fatty acid metabolism, patients with CF frequently have essential fatty acid deficiency (EFAD), which contributes to poor growth and can lead to immune system compromise, dermatitis, alopecia, and thrombocytopenia.

In young children, picky eating can lead to inadequate weight gain. Although often a behavioral issue, underlying pathology from eosinophilic or celiac disease can manifest as picky eating, so these should be considered. All patients and families should be screened for food insecurity.

Attainment of nutritional goals is important. If a child is failing to meet goals, early discussions around invasive interventions such as nasogastric, gastrostomy, gastrojejunal, or jejunal tubes should be undertaken, as families may need time to become comfortable with these ideas.

**Gastrointestinal issues**

**PANCREATIC INSUFFICIENCY**
Sixty percent of newborns with CF are born with complete pancreatic insufficiency (PI), and another 25% develop it by age 1 year. A baseline fecal elastase should be obtained in the neonatal period to assess for pancreatic sufficiency. Patients can develop PI at any time without early symptoms to indicate change. Annual monitoring with fecal elastase is recommended. A decrease in fecal elastase precedes steatorrhea. Steatorrhea develops only after lipase output falls below 10%. Fecal elastase can be falsely positive in watery stool and in severe nutritional depletion. In the latter case, testing should be repeated once nutritional repletion is addressed.

Pancreatic enzyme replacement therapy is critical to nutrient absorption and growth. It is important to optimize the timing of enzymes when the child is actively eating or immediately after, not prior to meals. Schools may need additional information about proper medication timing.

**DYSMOTILITY: MECONIUM ILEUS (MI), INTUSSUSCEPTION, CONSTIPATION, AND DISTAL INTESTINAL OBSTRUCTION SYNDROME (DIOS)**
Children with CF have an altered in-

**TABLE 1 GI MANIFESTATIONS OF CFTR MUTATIONS**

<table>
<thead>
<tr>
<th>Pancreatic exocrine insufficiency</th>
<th>Microgallbladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal cholestasis</td>
<td>Gallbladder hypokinesis and cholelithiasis</td>
</tr>
<tr>
<td>Meconium ileus</td>
<td>Hepatic steatosis</td>
</tr>
<tr>
<td>Gastroesophageal and duodenogastric reflux</td>
<td>Focal biliary cirrhosis</td>
</tr>
<tr>
<td>Small intestinal bacterial overgrowth</td>
<td>Multilobular cirrhosis</td>
</tr>
<tr>
<td>Dysmotility</td>
<td>Liver failure</td>
</tr>
<tr>
<td>Constipation</td>
<td>Celiac disease—increased frequency</td>
</tr>
<tr>
<td>Rectal prolapse</td>
<td>Crohn disease—increased frequency</td>
</tr>
<tr>
<td>Distal intestinal obstruction syndrome</td>
<td>Esophageal cancer</td>
</tr>
<tr>
<td>Pancreatitis in pancreatic sufficient patients</td>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td>Pancreatic endocrine insufficiency and CF-related diabetes</td>
<td>Colon cancer</td>
</tr>
</tbody>
</table>

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; GI, gastrointestinal. Author created.
Traluminal intestinal environment. Gut microbiome changes in CF are already detected at 15 days of life. Breastfeeding can help promote diversity but does not eliminate all the issues related to CFTR dysfunction. This CFTR dysfunction leads to a dehydrated intestinal mucin layer and inspissated secretions. Decreased pancreatic bicarbonate secretion changes pH, and together with overexposure to acid reducers and antibiotics results in altered gut microbiota with diminished diversity, which can mimic a Crohn-like microbiome. The diminished diversity can lead to overgrowth of bacteria, impairing the enteric nervous system and contributing to slowed motility and stagnation.

In the neonatal period this manifests as meconium ileus (MI), occurring in up to 25% of neonates with CF. Meconium ileus develops in utero and is characterized by thick meconium in the terminal ileum. Whereas MI may resolve on its own, it frequently presents with signs and symptoms of small bowel obstruction (SBO), such as vomiting, abdominal distention, and failure to pass meconium, and also can lead to microcolon. The patient’s X-rays will show dilated loops of bowel, sometimes with fluid levels and “soap bubbles” in the area of the meconium. Treatment is supportive with intravenous fluids and nasogastric decompression and includes surgical consultation. Hyperosmolar enema administration under fluoroscopy can dislodge meconium in 30% to 80%, although with risk of perforation it should be performed by an experienced radiologist. Up to 50% of cases of MI can be complicated by prenatal or segmental volvulus, ischemic necrosis, perforation, and intestinal atresia. All infants with MI should have an evaluation for CF. If the sweat test and trypsinogen are negative, infants should be referred for genetic testing.

Thickened intestinal secretions also predispose children with CF to intussusception, which has a prevalence of 1% and is most commonly ileocolonic. It is more common in older children with CF, contrary to healthy children. It may be the presenting complaint of undiagnosed CF. Persistent constipation is also prevalent in this population. As a result, almost a quarter of CF patients have experienced rectal prolapse. Prolapse is rarely the initial presentation of CF, so consider other diagnoses (ie, Hirschsprung disease) first in the absence of other symptoms. However, with recurrent prolapse associated with diarrhea, evaluation for CF is warranted. Constipation must be differentiated from DIOS, which can present with acute right lower quadrant pain and signs and symptoms of SBO (Figure).

Distal intestinal obstruction syndrome is most common in older adolescents with a prevalence of 10% to 15.8%. The greatest risk factor is prior DIOS. In constipation, stool and gas accumulate gradually in the colon with or without colonic dilatation. Nonstimulant laxatives (ie, polyethylene glycol) are most commonly used for treatment of constipation and prevention of DIOS. Patients may require admission for nasogastric administration of the large volumes that are often needed (20-40 mL/kg/h) until effluent is clear. A gastrografin enema can be performed by a radiologist for treatment of DIOS.

If DIOS is refractory to standard treatments, alternate diagnoses should be considered, such as intermittent intussusception, ileal Crohn disease, or appendicitis. In CF, appendicitis mimics DIOS due to its atypical presentation with classic symptoms frequently absent. Interestingly, appendicitis occurs in 1% to 2% of children with CF compared with 7% of the non-CF population, likely because of the frequent use of antibiotics in CF. However, due to confusion with DIOS, perforation is more common.

Reflux
Sixty-seven percent of children with
CF have reflux on impedance monitoring. Reflux is attributed to a variety of factors, including delayed gastric emptying; impaired gut motility; increased intra-abdominal pressure from coughing; effects of respiratory medications on the lower esophageal sphincter (LES) pressure; inherently decreased LES basal tone; hyperinflation of lungs with increased transdiaphragmatic pressure; abnormal esophageal peristalsis; postural drainage techniques in infants; and a high fat diet.14 Acid reducers increase the pH of refluxate but may not necessarily affect frequency of episodes of reflux unless the reflux is so severe that acid exposure has impaired the LES. Acid reducers should not be used indefinitely as they have been associated with small intestinal bacterial overgrowth and an increased risk of respiratory infections.

Altered motility also results in duodenogastroesophageal reflux, as demonstrated by increased bile in the stomachs of children with CF.14 Bile salts are an irritant and airway exposure correlates with worse lung disease. Erythromycin, which improves gastric emptying on scintigraphy in patients with CF, may offer benefit.

**MICROBIOME CHANGES: SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO), CLOSTRIDIUM DIFFICILE**

Small intestinal bacterial overgrowth (SIBO) can present with abdominal pain, bloating, and diarrhea as well as nutrient malabsorption.15 Providers should have a high index of suspicion for this diagnosis and treat empirically as the breath tests used in other populations are difficult to interpret in CF. Diagnosis should be under the guidance of a gastroenterologist.

Patients with CF have risk factors for acquisition of *Clostridium difficile* infections, including recurrent antibiotics use, hospitalization, dysbiosis, and acid reducer use. Asymptomatic carriage rates in CF are 22% to 55%.12 Diarrhea is uncommon. The presentation is often fulminant disease with rapid progression to toxic megacolon.

**HEPATOBILIARY**

Cholestasis is the earliest and most common manifestation of CF liver disease (CFLD), which is a diagnosis of exclusion. Cystic fibrosis liver disease is seen in 6% of infants with CF, but up to 25% of those with meconium ileus.3 Clinically, these findings can be confused with biliary atresia, which should be ruled out urgently. Infants with cholestasis benefit from a formula rich in medium-chain triglycerides, which do not require bile acids or micellar formation for absorption. Currently, there is no evidence supporting the routine use of ursodiol in CF.16 Cholestasis exacerbates fat-soluble vitamin malabsorption and leads to osteopenia, due to deficiency of vitamins D and K.15

Bone density scans are part of routine monitoring.

Gallbladder disease occurs in up to 50% of children with CF.8 In addition to microgallbladder, gallbladder hypokinesis is common as well. This predisposes patients to gallbladder stasis, which can lead to gallstones, with a prevalence up to 25%, including neonates. The evaluation and treatment are the same as for the general population and should be undertaken early in anticipation of progressive pulmonary operative risk over time. Biliary scintigraphy should be considered to evaluate emptying of the cystic duct, as bile duct strictures are not uncommon. Patients with biliary strictures are also at increased risk of cholangiocarcinoma.

Hepatic steatosis has a prevalence of 23% to 70% at any age.1 It is likely multifactorial, resulting from malnutrition; CFTR dysfunction; deficiencies of choline, carnitine, essential fatty acids; or poorly controlled CFRD.7 Other non–CF-related conditions also can result in steatosis. These patients should be referred to Gastroenterology.

Transient elevations of liver enzymes and gamma-glutamyl transferase (GGT) are exceedingly common and do not predict chronic liver disease.1,17 Elevations should be followed every 1 to 2 weeks until resolved or stable. Abnormalities persisting beyond 6 months should be evaluated with complete abdominal ultrasound with liver vascular duplex and referral to Gastroenterology. Hepatosplenomegaly should prompt earlier referral. Standard evaluation for chronic elevation of transaminases includes consideration of infectious hepatitis, drug-induced liver disease (from modulators, antibiotics, etc.), autoimmune hepatitis, Wilson disease, alpha-1-antitrypsin

---

**TABLE 2 CAUSES OF STUNTING IN CYSTIC FIBROSIS**

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic inflammation</td>
</tr>
<tr>
<td>Zinc deficiency</td>
</tr>
<tr>
<td>Sodium deficiency</td>
</tr>
<tr>
<td>Essential fatty acid deficiency (EFAD)</td>
</tr>
<tr>
<td>Undiagnosed celiac disease</td>
</tr>
<tr>
<td>Undiagnosed Crohn disease</td>
</tr>
</tbody>
</table>

Author created.
Cystic fibrosis liver disease is the 3rd-leading cause of death in CF following lung disease and transplant complications, and constitutes 2.5% of mortality in CF. Incidence increases every year from birth reaching 32% by age 25 years and then levels out. There is a higher prevalence among males, those homozygous for F508del, and those with a history of meconium ileus. Synthetic function is usually preserved. Cystic fibrosis liver disease is thought to be a consequence of bile ductule inspissation that starts out as focal biliary cirrhosis with ductule inspissation and a nodular liver on exam. Five percent to 10% of patients have multilobular cirrhosis with areas of focal biliary cirrhosis with progression to multilobular cirrhosis and a nodular liver on exam. Five percent to 10% of patients have multilobular cirrhosis before adolescence. The most significant consequence of CFLD is progression to portal hypertension, which can lead to varices and hypersplenism. Regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in this context due to resultant thrombocytopenia. Varices are treated with banding, and transjugular intrahepatic portosystemic shunt is considered with recurrent bleeding as bridge to liver transplantation.

Development of ascites is an ominous sign usually accompanied by a decline in nutrition and lung function. Signs of impending liver failure include declining platelets, hypoalbuminemia, elevated international normalized ratio (INR), and hypoglycemia. Hepatopulmonary syndrome is a rare but serious complication with a 5-year survival rate of 23%.

**TABLE 3**
**RIGHT LOWER QUADRANT PAIN IN CYSTIC FIBROSIS**

- DIOS
- Intussusception
- Appendicitis
- Constipation
- Crohn disease
- Kidney stones
- Gynecologic/Testicular process

**ABDOMINAL PAIN**
In healthy children, the frequency of occasional abdominal pain is about 11%. In contrast, 50% to 60% of children with CF report chronic abdominal pain. This is a major issue for quality of life, leading to sleep disruption, restriction of activities, and contributing to anxiety and depression. Functional abdominal pain is common due to visceral hyperalgesia and amplification of pain attributed to the stress of being chronically ill. Additional considerations include gastritis (due to frequent use of steroids or NSAIDs), pancreatitis (among patients who have pancreatic sufficiency), and postoperative complications, such as adhesions or strictures following abdominal surgery. Right upper quadrant or epigastric pain should alert a provider to the possibility of cholelithiasis.

There is a 3-fold increased prevalence of celiac disease in CF, but it often goes unrecognized. However, CF alone can result in a falsely elevated anti-tissue transglutaminase (tTG) immunoglobulin A (IgA), as it is an acute phase reactant. Thus, endoscopic evaluation is necessary to confirm celiac disease.

Right lower quadrant pain can be due to appendicitis, DIOS, intussusception, or Crohn disease, which is 17 times more prevalent in CF than the general population (Table 3). As in children without CF, intermittent abdominal pain can be due to undiagnosed malrotation with intermittent volvulus. In particular, infants with CF are at higher risk of volvulus in absence of malrotation due to inspissation of meconium. Fat malabsorption increases the risk of oxalate kidney stones. Gynecologic or testicular issues also should be remembered in the appropriate clinical settings.

**Conclusion**
Significant improvements in CF have focused primarily on the pulmonary system with less attention given to the gastrointestinal complications. Effects of CFTR mutations on the gastrointestinal system are beginning to be better appreciated. The complex interplay between electrolytes, enzymes, microbiota, and the various other components of gut physiology requires further research. Gastrointestinal symptoms contribute substantially to morbidity in CF and represent a major opportunity for improvement in the care of these patients. A multidisciplinary team of pediatricians, pulmonologists, gastroenterologists, respiratory therapists, nutritionists, pharmacists, and physical therapists who appreciate the complexity of this disease and recognize the importance of the holistic approach in patients’ care can make a significant difference in these children’s life expectancy and quality of life.

---

**COMMENTS?** E-mail them to cradwan@mmhgroup.com

**For references, go to ContemporaryPediatrics.com/GI-manifestations-in-CF**

**Dr Reed** reports receiving a Cystic Fibrosis Foundation second-year clinical fellows’ grant. **Dr Shores** has nothing to disclose.
Cystic fibrosis (CF) is an autosomal recessive genetic disorder characterized by chronic and progressive obstructive lung disease, sinusitis, pancreatic exocrine insufficiency leading to malabsorption and malnutrition, liver disease, and CF-related diabetes mellitus. The disease affects approximately 30,000 individuals in the United States and 70,000 persons worldwide. The care of individuals with CF has evolved significantly since it was first described in 1938. Earlier diagnosis through universal newborn screening, therapies to improve lung health and prevent exacerbations, a focus on optimization of nutritional status, aggressive treatment of chronic respiratory infections, and lung transplantation all have led to significant improvements in overall survival, with the current predicted median survival of 47.4 years.

Cystic fibrosis results from deleterious genetic variants in the CFTR gene, which encodes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The CFTR gene was first discovered in 1989, and different mutations in the CFTR gene result in functional changes to the CFTR protein, grouped into 6 distinct classes (Figure 1). The different defects in CFTR protein lead to absent or malfunctioning chloride channels in apical membranes of the lung surface and glandular epithelium causing mucus to be thick and sticky, and resulting in chronic cough and lung infections, bronchiectasis, chronic sinusitis, pancreatic and liver dysfunction, as well as reduced fertility. Whereas there are more than 2000 different disease-causing mutations, approximately 90% of individuals with CF have at least 1 copy of F508del, the most common CFTR mutation.4,5

The ability to identify CFTR gene mutations has allowed for the development of therapies that target the basic genetic defects that cause the disease, known as CFTR modulator therapies. These therapies allow patients to receive treatments tailored to their individual mutations and have contributed greatly to improvements in quality of life, overall health, and survival. This article discusses the evolution of CFTR modulator therapies, with a focus on the most recently approved therapy—elexacaftor/tezacaftor/ivacaftor (Trikafta).

Current CF modulator therapies

POTENTIATOR

Ivacaftor (Kalydeco): In 2012, the first modulator, ivacaftor, was approved by the US Food and Drug Administration (FDA) for the treatment of CF. Ivacaftor is known as a potentiator therapy because it binds to the defective CFTR protein at the cell surface and helps to keep chloride channels open so that chloride is better able to flow through the surface of the cell. It was initially approved exclusively for individuals with the G551D mutation, the third most common mutation (approximately 5% of the CF population). Through in vitro testing and clinical trials, the
FDA has now expanded approval to 38 mutations, allowing individuals with lower prevalence mutations to benefit from modulator therapies. Ivacaftor is approved for use in individuals aged 6 months and older. Long-term studies have shown that ivacaftor use is associated with reduced mortality and rates of lung transplantation.7

**POTENTIATOR-CORRECTOR COMBINATION**

Lumacaftor/ivacaftor (Orkambi) is a combination therapy FDA-approved for individuals aged 2 years and older with 2 F508del copies. Approximately 44% of individuals with CF are homozygous for this mutation.1 Lumacaftor is known as a corrector therapy, working to increase the amount of CFTR protein that reaches the surface of cells. When used in conjunction with ivacaftor, there is significant improvement in the amount of chloride that can flow through the CFTR protein, which ultimately leads to clinical improvements in lung function (measured in percentage of predicted forced expiratory volume (ppFEV1), and a decrease in pulmonary exacerbations and need for intravenous antibiotic treatment, as well as improvements in nutritional status.6 Notably, respiratory adverse effects such as dyspnea and chest tightness have been reported with initiation of lumacaftor/ivacaftor, but it is generally well tolerated.9

Tezacaftor/ivacaftor (Symdeko) is an improved combination therapy FDA-approved for individuals aged 6 years and older with 2 copies of F508del or individuals with 1 of 26 other specified mutations. Tezacaftor/ivacaftor has been associated with improvements in lung function and lower rates of pulmonary exacerbations with a low rate of discontinuation attributed to adverse effects.10 Additionally, there are fewer drug-drug interactions than lumacaftor/ivacaftor, avoiding the need for temporary discontinuation due to other therapies, such as antifungals and oral contraceptives.

**TRIPLE COMBINATION OR “NEXT-GENERATION” MODULATOR**

Elexacaftor/tezacaftor/ivacaftor (Trikafta): Although CFTR modulator therapy has revolutionized CF care, individuals with certain heterozygous F508del genotypes were un-

---

**FIGURE 1 CFTR MUTATIONS**

<table>
<thead>
<tr>
<th>CLASS</th>
<th>DESCRIPTION</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No functional CFTR created.</td>
<td>GS42X, W1282X, R553X</td>
</tr>
<tr>
<td>II</td>
<td>CFTR protein is created, but misfolded, keeping it from reaching the cell surface.</td>
<td>F508del, N1303K, I507del</td>
</tr>
<tr>
<td>III</td>
<td>CFTR protein is created and reaches cell surface, but does not function properly.</td>
<td>G551D, S549N, V520F</td>
</tr>
<tr>
<td>IV</td>
<td>The opening in the CFTR protein ion channel is faulty.</td>
<td>R117H, D1152H, R347P</td>
</tr>
<tr>
<td>V</td>
<td>CFTR is created in insufficient quantities.</td>
<td>3849+10kbC-&gt;T, 2789+5G-&gt;A, A455E</td>
</tr>
</tbody>
</table>

SOURCE OF DATA: Cystic fibrosis patients under care at CF Foundation-accredited care centers in the United States, who consented to have their data entered. Adapted from: CFTR Modulator Therapies; http://www.cff.org/Life-With-CF/Treatments-and-Therapies/Medications/CFTR-Modulator-Therapies/#section2. Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator. Cystic Fibrosis Foundation Patient Registry; 2017 Annual Data Report; Bethesda, Maryland. ©2018 Cystic Fibrosis Foundation. Used with permission.
able to receive these highly effective modulator therapies. In October 2019, the FDA approved the use of a triple-combination therapy for individuals aged 12 years and older with at least 1 F508del mutation. This twice-daily therapy, administered as 2 tablets in the morning and 1 in the evening, will allow nearly 90% of individuals with CF to benefit from highly effective CFTR modulator therapy that targets the underlying cause of disease.

Trikafta has been shown in clinical trials to result in dramatic improvement in key clinical disease measures. Individuals receiving Trikafta demonstrated a mean treatment difference of almost 14% in ppFEV₁ at week 4 of therapy compared with placebo and an increase in 10% compared with treatment with tezacaftor/ivacaftor.¹¹ Lung function improvement was sustained through 24 weeks of treatment. Individuals receiving Trikafta experienced a lower annualized rate of pulmonary exacerbations, including those requiring hospitalization or intravenous antibiotics, as well as sustained improvements in body mass index. Importantly, there was also a significant improvement in patient-reported quality of life, as measured by the Cystic Fibrosis Questionnaire-revised.¹²

Trikafta has been shown to be safe with potentially fewer adverse effects noted than with prior modulators. Notable drug-drug interactions include antifungal medications, certain antibiotics (such as rifampin or rifabutin), several seizure medications, and St. John’s wort. Similar to all CFTR modulators, Trikafta should be administered with fatty foods to help improve absorption. Quarterly monitoring of liver function testing in the first year of treatment and annual eye examinations are recommended to monitor for gastrointestinal (GI) complications, as well as the possibility of cataracts.

Summary

These CFTR modulators have heralded a new era of personalized medicine and life-prolonging therapies for an increased number of individuals with CF (Figure 2). Studies are now under way to assess the long-term effects of Trikafta as well as the possibility of simplifying daily treatment burden. As of the 2018 Cystic Fibrosis Foundation Patient Registry report, more than 50% of individuals living with CF are aged older than 18 years and the median life expectancy continues to rise.¹³

There is hope that CFTR modulators will help to continue to improve median life expectancy. Nevertheless, it is important to note that these therapies do not reverse existing disease, and approximately 10% of individuals presently do not qualify for any of the available CFTR modulator therapies based on their genotypes.¹⁴ The availability of mutation-specific modulators has brought new hope to individuals with CF and their families, but the search continues to find modulator therapies to benefit all individuals with all CFTR mutations.¹⁵

NOTE FROM DR. LEE  The Cystic Fibrosis (CF) Foundation’s partnership with the pharmaceutical industry has significantly impacted patients with this lethal disorder by making CFTR-modifying drugs available. We look forward to the anticipated positive outcomes on morbidity and mortality for CF. Partnerships with pharma may serve as the way to accelerate the development of medicines for other diseases where therapies are limited and/or less effective.

—Carlton Lee, PHARMD, MPH, FASHP, FPPAG

For references, go to ContemporaryPediatrics.com/CFTR-modulator-triple-therapy
ADHD guideline update: What’s new, what’s changed

The revised clinical practice guideline advises how to manage co-occurring psychologic and behavioral issues.

RACHAEL ZIMLICH, RN, BSN

Attention-deficit/hyperactivity disorder (ADHD) is a lifelong disorder, commonly occurring in tandem with other problems, and the American Academy of Pediatrics (AAP) is recognizing this issue and how clinicians can tackle it with a guideline update.

The update to the clinical practice guidelines is the first since 2011, and changes focus on the evaluation, diagnosis, and treatment of ADHD in children aged 4 to 18 years. Although there are no major changes to how ADHD is managed, the guidelines highlight the need to address issues that the child may be experiencing outside of ADHD, such as learning and language disorders, anxiety, depression, and autism.

“Pediatricians need to be able to diagnose and treat preschool and school age children and adolescents with ADHD and at least screen them for most common co-occurring conditions including learning and language disorders, opposition defiant disorder, anxiety, depression, and exposure to trauma,” says Mark Wolraich, MD, FAAP.

Wolraich is the CMRI/Shaun Walters Professor of Pediatrics, chief of the Section of Developmental and Behavioral Pediatrics, and director of the Child Study Center at Oklahoma University Health Sciences Center in Oklahoma City. He was one of the lead authors of the guidelines and serves as chair of the AAP’s Subcommittee on Children and Adolescents with Attention-deficit/hyperactivity disorder.

Base diagnoses on DSM-5

One major change in the new guidelines is that the diagnoses are now based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) with the changes that children aged 17 years and older require fewer behaviors to make a diagnosis and the symptoms need to be manifest before the age of 12 years instead of 7 years, Wolraich says. The guidelines also stress the need to identify co-morbidities in children with ADHD.

“There is greater emphasis on the need to consider ADHD a chronic condition emphasizing the need for developing a medical home that includes communication between the key players, families, teachers, mental health consultants, and the primary care practice.”
—MARK WOLRAICH, MD, FAAP

Clinicians should manage ADHD in an ongoing manner as they would for other chronic conditions, the guideline notes, following the principles of the chronic care model and the medical home.

A historical perspective report published alongside the guidelines illustrates the need for careful manage-
Whereas hormone prescribing for transgender or gender diverse children and teenagers may be a specialty, primary care pediatricians are often the first-line provider families turn to for support and guidance. Ryan Pasternak, MD, MPH, associate professor of Clinical Pediatrics and division head of General Ambulatory Pediatrics and Adolescent Medicine, Louisiana State University Health School of Medicine, New Orleans, Louisiana, led a session titled “Tips to improve primary care for transgender youth,” at the 2019 American Academy of Pediatrics (AAP) National Conference and Exhibition in New Orleans that discussed the role of pediatricians in providing first-line care to this often marginalized population. “Think about the needs of those patients. It seems more and more likely that our primary care providers are providing the first line of care,” he says. “I think we want to address gender diverse or transgender patients in primary care settings, and need to think about what is involved to provide good primary care to those patients, including identification and initial evaluations, specialty, and referral care.”

Up to 2.7% of children and teenagers identify as gender diverse or transgender, with recent studies showing much higher percent-

Why pediatricians are the first line of care for gender-diverse children

It’s important to be able to talk to patients and families about differences in gender identity and offer an early referral for specialized support.

RACHAEL ZIMLICH, RN, BSN

Whereas hormone prescribing for transgender or gender diverse children and teenagers may be a specialty, primary care pediatricians are often the first-line provider families turn to for support and guidance. Ryan Pasternak, MD, MPH, associate professor of Clinical Pediatrics and division head of General Ambulatory Pediatrics and Adolescent Medicine, Louisiana State University Health School of Medicine, New Orleans, Louisiana, led a session titled “Tips to improve primary care for transgender youth,” at the 2019 American Academy of Pediatrics (AAP) National Conference and Exhibition in New Orleans that discussed the role of pediatricians in providing first-line care to this often marginalized population. “Think about the needs of those patients. It seems more and more likely that our primary care providers are providing the first line of care,” he says. “I think we want to address gender diverse or transgender patients in primary care settings, and need to think about what is involved to provide good primary care to those patients, including identification and initial evaluations, specialty, and referral care.”

Up to 2.7% of children and teenagers identify as gender diverse or transgender, with recent studies showing much higher percent-

Whereas hormone prescribing for transgender or gender diverse children and teenagers may be a specialty, primary care pediatricians are often the first-line provider families turn to for support and guidance. Ryan Pasternak, MD, MPH, associate professor of Clinical Pediatrics and division head of General Ambulatory Pediatrics and Adolescent Medicine, Louisiana State University Health School of Medicine, New Orleans, Louisiana, led a session titled “Tips to improve primary care for transgender youth,” at the 2019 American Academy of Pediatrics (AAP) National Conference and Exhibition in New Orleans that discussed the role of pediatricians in providing first-line care to this often marginalized population. “Think about the needs of those patients. It seems more and more likely that our primary care providers are providing the first line of care,” he says. “I think we want to address gender diverse or transgender patients in primary care settings, and need to think about what is involved to provide good primary care to those patients, including identification and initial evaluations, specialty, and referral care.”

Up to 2.7% of children and teenagers identify as gender diverse or transgender, with recent studies showing much higher percent-

## Why pediatricians are the first line of care for gender-diverse children

It’s important to be able to talk to patients and families about differences in gender identity and offer an early referral for specialized support.

RACHAEL ZIMLICH, RN, BSN

Whereas hormone prescribing for transgender or gender diverse children and teenagers may be a specialty, primary care pediatricians are often the first-line provider families turn to for support and guidance. Ryan Pasternak, MD, MPH, associate professor of Clinical Pediatrics and division head of General Ambulatory Pediatrics and Adolescent Medicine, Louisiana State University Health School of Medicine, New Orleans, Louisiana, led a session titled “Tips to improve primary care for transgender youth,” at the 2019 American Academy of Pediatrics (AAP) National Conference and Exhibition in New Orleans that discussed the role of pediatricians in providing first-line care to this often marginalized population. “Think about the needs of those patients. It seems more and more likely that our primary care providers are providing the first line of care,” he says. “I think we want to address gender diverse or transgender patients in primary care settings, and need to think about what is involved to provide good primary care to those patients, including identification and initial evaluations, specialty, and referral care.”

Up to 2.7% of children and teenagers identify as gender diverse or transgender, with recent studies showing much higher percent-

## Why pediatricians are the first line of care for gender-diverse children

It’s important to be able to talk to patients and families about differences in gender identity and offer an early referral for specialized support.

RACHAEL ZIMLICH, RN, BSN

Whereas hormone prescribing for transgender or gender diverse children and teenagers may be a specialty, primary care pediatricians are often the first-line provider families turn to for support and guidance. Ryan Pasternak, MD, MPH, associate professor of Clinical Pediatrics and division head of General Ambulatory Pediatrics and Adolescent Medicine, Louisiana State University Health School of Medicine, New Orleans, Louisiana, led a session titled “Tips to improve primary care for transgender youth,” at the 2019 American Academy of Pediatrics (AAP) National Conference and Exhibition in New Orleans that discussed the role of pediatricians in providing first-line care to this often marginalized population. “Think about the needs of those patients. It seems more and more likely that our primary care providers are providing the first line of care,” he says. “I think we want to address gender diverse or transgender patients in primary care settings, and need to think about what is involved to provide good primary care to those patients, including identification and initial evaluations, specialty, and referral care.”

Up to 2.7% of children and teenagers identify as gender diverse or transgender, with recent studies showing much higher percent-

Whereas hormone prescribing for transgender or gender diverse children and teenagers may be a specialty, primary care pediatricians are often the first-line provider families turn to for support and guidance. Ryan Pasternak, MD, MPH, associate professor of Clinical Pediatrics and division head of General Ambulatory Pediatrics and Adolescent Medicine, Louisiana State University Health School of Medicine, New Orleans, Louisiana, led a session titled “Tips to improve primary care for transgender youth,” at the 2019 American Academy of Pediatrics (AAP) National Conference and Exhibition in New Orleans that discussed the role of pediatricians in providing first-line care to this often marginalized population. “Think about the needs of those patients. It seems more and more likely that our primary care providers are providing the first line of care,” he says. “I think we want to address gender diverse or transgender patients in primary care settings, and need to think about what is involved to provide good primary care to those patients, including identification and initial evaluations, specialty, and referral care.”

Up to 2.7% of children and teenagers identify as gender diverse or transgender, with recent studies showing much higher percent-

Whereas hormone prescribing for transgender or gender diverse children and teenagers may be a specialty, primary care pediatricians are often the first-line provider families turn to for support and guidance. Ryan Pasternak, MD, MPH, associate professor of Clinical Pediatrics and division head of General Ambulatory Pediatrics and Adolescent Medicine, Louisiana State University Health School of Medicine, New Orleans, Louisiana, led a session titled “Tips to improve primary care for transgender youth,” at the 2019 American Academy of Pediatrics (AAP) National Conference and Exhibition in New Orleans that discussed the role of pediatricians in providing first-line care to this often marginalized population. “Think about the needs of those patients. It seems more and more likely that our primary care providers are providing the first line of care,” he says. “I think we want to address gender diverse or transgender patients in primary care settings, and need to think about what is involved to provide good primary care to those patients, including identification and initial evaluations, specialty, and referral care.”

Up to 2.7% of children and teenagers identify as gender diverse or transgender, with recent studies showing much higher percent-

Whereas hormone prescribing for transgender or gender diverse children and teenagers may be a specialty, primary care pediatricians are often the first-line provider families turn to for support and guidance. Ryan Pasternak, MD, MPH, associate professor of Clinical Pediatrics and division head of General Ambulatory Pediatrics and Adolescent Medicine, Louisiana State University Health School of Medicine, New Orleans, Louisiana, led a session titled “Tips to improve primary care for transgender youth,” at the 2019 American Academy of Pediatrics (AAP) National Conference and Exhibition in New Orleans that discussed the role of pediatricians in providing first-line care to this often marginalized population. “Think about the needs of those patients. It seems more and more likely that our primary care providers are providing the first line of care,” he says. “I think we want to address gender diverse or transgender patients in primary care settings, and need to think about what is involved to provide good primary care to those patients, including identification and initial evaluations, specialty, and referral care.”

Up to 2.7% of children and teenagers identify as gender diverse or transgender, with recent studies showing much higher percent-

**REFERENCES**


mental health

ages than in the past, he adds. This means that there may be up to 100 gender-non-conforming patients in a 2500-to-5000-patient practice.

“The prevailing idea is that it is less stigmatized and there is better awareness,” Pasternak says of the increase. “There is more visibility in the media and culturally for non-conforming persons. Being able to hold someone up as a role model and identify them makes it more acceptable to children and adolescents. It also gives them a term to use for how they feel.”

Gender identity begins very early
Patients often say they felt different about their gender from younger ages, but didn’t know how to describe themselves until they heard the terms transgender or gender diverse. They are understanding more how to talk about their feelings, he says. For pediatricians, it’s important to be able to talk to patients and families about differences in gender identity, and offer an early referral for more specialized support. Referral may be to an endocrinologist, adolescent medicine specialist, or other interdisciplinary care for support of social transition, puberty blocking medication, or hormonal transition.

Most patients have consistency in gender identity by the early school years, he says, and it can create conflict if they recognize a difference between their gender and both their physical sex or others’ expectations of them based on their sex assigned at birth.

“Ask patients how they feel about themselves and how they identify,” Pasternak suggests. “If we don’t ask, we’re unlikely to find out answers to any of these questions.”

Parents can provide information about gender development, but some patients may not be in living in environments that are supportive. In these cases, pediatricians consistently discussing gender during well visits is key.

“Maybe children did express themselves, but they had a negative response and limited these expressions. . . . Many patients may present initially with depression or anxiety later,” Pasternak says. “Just try and continually engage the child and the family.”

Pediatricians can provide support when there are conflicts within families, and should assess for anxiety, suicidality, and substance abuse in patients who don’t have support or acceptance of their gender identity or expression. Sometimes, patients are only able to talk about their gender later in adolescence, and have gone without support or guidance, he says.

Listen to your patients
It’s important to start assessments and discussion early, he says, before problems arise from not recognizing the child’s needs. While some may question assessing this too early, Pasternak argues that trusting in the concerns of patients and parents in regard to gender should be no different than other concerns.

“It’s important to understand just how early gender identity occurs,” he says. “Trust your patients and what their parents say.”

That being said, there is an aspect of experimentation and curiosity in child development, and it’s important not to jump to conclusions. Playing with certain toys or wearing certain clothing that isn’t stereotypical for a traditional binary gender doesn’t necessarily mean a child is transgender, he adds.

“The other side of it is not overreacting or jumping to conclusions because a patient may express themselves in a way that may not be in line with a culture’s traditional gender expression,” Pasternak says. “It’s really about their gender and how they see themselves, and that’s a whole different domain.”

The Genderbread Person is a helpful resource for pediatricians in discussing gender identity, he says, but the important part is to remain open-minded and supportive of questions and concerns from both patients and parents.

“Try to just be very mindful of the individual differences and hearing the patient and family as much as you can, and work with them to address their needs,” Pasternak says.

Ms Zimlich is a freelance writer in Cleveland, Ohio. She writes regularly for Contemporary Pediatrics and sister publications Managed Healthcare Executive and Medical Economics. She has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

COMMENTS? E-mail them to cradwan@mmhgroup.com
Minority children face more ED visits for asthma

A study investigates the prevalence of asthma in minority groups and how often they turn to the emergency department (ED) for management.

MINORITY CHILDREN FACE MORE ED VISITS FOR ASTHMA

Minority children are more likely to have asthma and to need their condition managed in the emergency department (ED), according to a recent report.

Published in the Journal of Asthma, the study sought to identify which racial subgroups have the highest prevalence of asthma and ED utilization for the condition. The goal is to use this data to identify possible interventions to prevent asthma exacerbations and reduce disparities across population types.

“We were among the first studies to look at the effect of asthma management in relation to having an ED visit, specifically in terms of preventative medication use, having taken an asthma management course, or having an asthma action plan,” says Audrey Urquhart, MPH, a clinical research coordinator at the Children’s Hospital of Philadelphia (Pennsylvania) PolicyLab and lead author of the report. “Using national level data allowed us to compare across racial/ethnic groups.”

Minority children have a higher prevalence of asthma than white children, and also used emergency services for their asthma at higher rates, according to the report. Most research previously has focused on white and black populations, but this study investigated other racial groups and sought to answer additional questions about these patients’ asthma management and preventive practices.

Asthma prevalence

The study reviewed data collected between 2013 and 2015 from the National Health Interview Survey. A total of 3336 patients aged between 2 and 17 years—58.7% of them boys—were identified as having asthma. Prevalence was documented by racial subgroup, highlighting disparities in ED visits over a period of 1 year.

The study found that asthma prevalence was highest in Puerto Rican children at 21.2%, followed by 14.5% in non-Hispanic black children, 8.5% in other Hispanic children, 8.2% in non-Hispanic white children, 7.5% in Mexican American children, and 7.1% in other non-Hispanic children. In comparison non-Hispanic white children to the other subgroups, there were significantly higher odds of ED visits for asthma management occurring in most minority subgroups, the report notes. The highest risk for visiting an ED for asthma management was found in Hispanic children, followed by Puerto Rican, Mexican American, and non-Hispanic black...
children, the report notes. Other non-Hispanic children was the only sub-group that did not have a higher risk than non-Hispanic white children of visiting the ED for asthma.

The study did not take into account environmental factors involved in asthma prevalence or ED visits, and the authors identified this as an area for future study. Additionally, Urquhart notes that the continuing existence of disparities between racial subgroups are multifactorial and likely relate to a complex interplay between medical and social factors.

“Whereas this study did not uncover a specific intervention, our results highlighting these disparities continue to stimulate the need for both clinical research in this area to understand the casual mechanisms and, in parallel, a continued expansion of evidenced-informed policies to mitigate these disparities in children today,” says Urquhart.

Not one thing will fix this problem, she notes, but pediatricians can still help.

“There is no one-sized-fits-all solution for disparities in childhood asthma,” Urquhart says. “I encourage clinicians to continue working to not only treat the physical symptoms of asthma but also collaborate with other healthcare professions to connect children living with chronic illness and who have complex social needs with community-available resources that benefit their health and their family.”

COMMENTS? E-mail them to cradwan@mmhgroup.com

Ms Zimlich is a freelance writer in Cleveland, Ohio. She writes regularly for Contemporary Pediatrics and sister publications Managed Healthcare Executive and Medical Economics. She has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

REFERENCE

Religious exemptions to vaccination are rising amid stricter state policies

As state policies on vaccination before kindergarten eliminate exemptions for personal beliefs, parents claim more exemptions on religious grounds.

Catherine M Radwan, Managing Editor

States that allow exemptions to vaccinations for children based upon personal or religious beliefs of the parents report a significant rise in kindergartners with religious exemptions during the 2017-2018 school year compared with the 2011-2012 school year, and a new study has determined that the elimination of personal belief exemptions may be responsible for the increase.

The study, published recently in Pediatrics, analyzed data on exemptions for children starting kindergarten from 2011 to 2018 from the Centers for Disease Control and Prevention. Researchers performed a cross-sectional, retrospective, state-level analysis of state estimates of the proportion of children with medical and religious/personal belief exemptions as well as the proportion of kindergartners who were up-to-date on recommended vaccinations including measles/mumps/rubella, diphtheria/tetanus/acellular pertussis, and varicella, and calculated the proportion of kindergartners with religious vaccine exemptions for each state year, adjusting for the strength of each state’s exemption policies.

In unadjusted analyses, states with religious and personal belief exemptions had a significantly lower mean proportion of kindergartners with religious exemptions (0.41%; 95% confidence interval [CI], 0.28%-0.53%) compared with states with religious exemptions only (1.63%; 95% CI, 1.30%-1.97%). In adjusted analyses, states with religious and personal belief exemptions were one-fourth as likely to have kindergartners with religious exemptions compared with states with religious exemptions only (risk ratio, 0.25%; 95% CI, 0.16-0.38).

"State-level religious exemption rates appear to be a function of personal belief exemption availability, decreasing significantly when states offer a personal belief exemption alternative." —Williams JTB, et al.¹

As likely to have kindergartners with religious exemptions compared with states with religious exemptions only (risk ratio, 0.25%; 95% CI, 0.16-0.38).

Using the 2011-2012 reference year, states were more likely to have kindergartners with religious exemptions during the 2017-2018 school year (P=0.4). This finding held for states with easy, medium, or difficult exemption policies.

The researchers say their study demonstrates how vaccine exemption policies influence state-reported vaccine exemption data. "State-level religious exemption rates appear to be a function of personal belief exemption availability, decreasing significantly when states offer a personal belief exemption alternative," they write.

However, the study authors note that the increase in exemptions based on religious beliefs is curious because it is accompanied by a simultaneous decrease in Americans’ declarations of religious affiliations. All major religions support vaccination, they write, and fewer Americans say they are religious, yet exemptions based on religious belief have increased as of the 2017-2018 school year.

The authors suggest that researchers and policymakers work together to reconsider the nature and purpose of religious exemption laws “to determine how best to balance a respect for religious liberty with the need to protect public health.”

Comments? E-mail them to cradwan@mmhgroup.com

Reference

Counsel safety and risk with tattoos and piercings

Even if it’s not your personal choice, pediatricians need to know how to talk to patients and parents about body art.

RACHAEL ZIMLICH, RN, BSN

Tattoos and piercings aren’t decreasing in popularity among young adults, and it’s up to parents and pediatricians to guide them to safe body modification choices.

If you ask most people aged younger than 18 years if they want a tattoo or piercing, most will say yes, and that they are just waiting until they are old enough to legally get one, says Cora Collette Breuner, MD, MPH, a clinician in the Division of Adolescent Medicine, Orthopedics, and Sports Medicine at Seattle Children’s Hospital and a professor of Pediatrics at the University of Washington School of Medicine, Seattle.

Maybe it’s the teenagers today or maybe it’s an increasing acceptance of body art and modification in younger generations—either way, it’s increasingly important to talk to children and teenagers about tattoos and piercings and how to safely make choices about both, says Breuner, who discussed the this and more in the session titled “To the point: Talking to patients and parents about tattooing and piercing,” presented at the 2019 American Academy of Pediatrics (AAP) National Conference and Exhibition in New Orleans, Louisiana.

Breuner, who helped draft the AAP’s guidance on adolescent and young adult tattoos, piercing, and scarification in 2017, says tattoos and piercings are something pediatricians need to start talking about in well-child visits. Demographics play a role, as adolescent tattoos and piercing are strictly against the law in some states but permitted with parental permission.

"Be open minded. Recognize that although you might not in your own personal purview agree, we are the ones people will turn to with questions."

—CORA COLLETTE BRUENER, MD, MPH

in others. A major issue to discuss and one of the biggest concerns people have with tattoos and piercings, Breuner says, is infection risk. It’s difficult to know what the infection rate secondary to body art is because infections are not always documented in medical records as related to tattoos and piercings, she says. What’s important to know is that most clinicians and parents don’t realize how sterile most tattoo parlors are, but it’s still good to check out local establishments.

“What I tell people when I talk about this is to make sure the parlor is clean, and that they’re using sterile equipment and sterile gloves,” Breuner says. The circumstances under which a parlor will perform a tattoo or piercing is also important. “I counsel providers to tell parents and teenagers that it’s okay to ask someone if they will tattoo someone who is high or drunk—and don’t let them if they do.”

Another safety consideration to educate parents and patients about is immunizations, she adds. Tetanus and hepatitis A and B vaccines should be up-to-date, Breuner says, and clinicians should also take some time to discuss tattoo and piercing placement. Generational differences of opinions aside, considering an adolescent’s future goals and whether a workplace will be accepting of body art is important, as are other health issues. Pregnancy and breastfeeding should be discussed in terms of being aware that navel piercings will stretch during pregnancy, and that hardware must be removed before breastfeeding, Breuner says. In terms of healing and the care of new body art, she says the
Major criterion:
- Localized erythema and swelling involving acral skin sites (body protrusions such as finger tips, knuckles, elbows, knees, etc.) for more than 24 hours.

Minor criteria:
- Occurs or exacerbates during colder months (between November and March).
- Dermal edema with superficial and deep perivascular lymphocytic infiltrate without features of lupus erythematosus on histopathology.
- Response to conservative management—warming and drying of affected areas.

Management
Patients with pernio usually have good response to conservative management such as rewarming, drying, and, if tolerable, massaging affected areas. Smoking cessation is encouraged due to its known effects on vasculature. Topical steroids including triamcinolone may be used locally to reduce itching and inflammation and promote faster resolution of lesions. A thorough history is important to elucidate habits that led to inadequate warmth, and patients should be encouraged parents to do a field trip with their young adult,” Breuner says. “Be open minded. Recognize that although you might not in your own personal purview agree or have enough knowledge, we are the ones people will turn to with questions.”

**Comments?** E-mail them to cradwan@mmhgroup.com

---

**Dermcase** continued from page 29

**TABLE**

**DIFFERENTIAL DIAGNOSIS OF SWOLLEN FINGERS**

- Panniculitis
- Acrocyanosis
- Pernio
- Raynaud’s phenomenon
- Frostbite

Author created.

**Patient outcome**
The patient in this case was treated with topical triamcinolone 0.1% ointment sparingly twice daily for 5 days, and swollen areas were gently massaged and protected from cold. He was counseled to use warm protective clothing while playing outdoors, particularly on wet, cold days.

**Comments?** E-mail them to cradwan@mmhgroup.com

---

Ms Zimlich is a freelance writer in Cleveland, Ohio. She writes regularly for *Contemporary Pediatrics* and sister publications *Managed Healthcare Executive* and *Medical Economics*. She has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

---

**Authors**

Ms Araoye is a third-year medical student at Johns Hopkins University School of Medicine, Baltimore, Maryland.

Dr Cohen, section editor for Dermcase, is professor of Pediatrics and of Dermatology, Johns Hopkins University School of Medicine, Baltimore. The author and section editor have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article. Vignettes are based on real cases that have been modified to allow the author and editor to focus on key teaching points. Images also may be edited or substituted for teaching purposes.

For references, go to ContemporaryPediatrics.com/dermcase-0220

---

**CNTPED0220_025-027_Derm.indd 27**

1/28/20 8:27 AM
Pediatric Equipment Bargains

www.medicaldevicedepot.com
Tools for Increased Reimbursement and Office Efficiency at Discount Prices

MA 1 Handheld Audiometer
List Price: $715.00
Our Price: $640.00
You save $75.00!

Welch Allyn Spot Vision Screener
List Price: $7,600.00
Our Price: $6,597.00
You save $1,003.00!

Hausmann Pediatric Exam Table (Digital Scale)
List Price: $2,829.00
Our Price: $2,191.00
You save $638.00!

Eucerin
www.eucerinus.com

Summers Laboratories
www.sumlab.com

Reach your target audience. Our audience.
Contact me today to place your ad.
Joanna Shippoli
National Account Manager, Healthcare Careers
(440) 891-2615 • jshippoli@mmhgroup.com

Advertising Index

BEIERSDORF
Aquaphor.................................................................7
www.aquaphorus.com/aquaphor-baby-healing-ointment/
Eucerin.................................................................CV4
www.eucerinus.com

MEDICAL DEVICE DEPOT
.................................................................28
www.medicaldevicedepot.com

MERCK
Nexplanon.............................................................CV2-3
www.nexplanon.com

REES PHARMACEUTICAL COMPANY
Reese’s Pinworm................................................24
www.reesespinworm.com

SUMMERS LABORATORIES
..............5
www.sumlab.com

Contact us today to place your ad.
Joanna Shippoli
National Account Manager, Healthcare Careers
(440) 891-2615 • jshippoli@mmhgroup.com

---

Boost Your Revenue
Allergy Testing and Treatment - for the Non Allergist
Concentration, National Average $150
Studies show 80% of patients that have allergies. We provide a comprehensive program where we will not perform the allergy test (CLIA Test). Test on 2 minutes and apply 18 minutes for results. Some patients relying on OTC drugs is a service.

CALL to ORDER: 877-646-3300
www.medicaldevicedepot.com
A 4-year-old boy presents for evaluation with painful swollen fingers on both hands that erupted after he made a snowman with his siblings following a snowstorm. He complains that they are itchy and painful.

**Discussion**

Pernio, also known as chilblains, is a localized response to a nonfreezing cold, damp environment. The lesion in perniosis has been described as an erythematous or purplish swelling typically on proximal digits (fingers and toes), nose, or ears accompanied by pain, itchiness, and burning sensation (Figure). It also can appear on the calves and thighs, and lesions might ulcerate or form blisters. It commonly affects children and women, particularly those with low body mass index.1,2

Pernio is thought to occur because of abnormal cutaneous arteriolar vasoconstriction in reaction to cold temperatures leading to reduced blood flow. Further loss of heat is facilitated by increased conduction in humid conditions compared with dry air. Although not pathognomonic for pernio, histopathology will show edema of papillary dermis and a perivascular mononuclear and lymphocytic cell infiltrate with necrotic keratinocytes and a lymphocytic vasculitis.2,3

Pernio may be confused with more serious disorders such as leukocytoclastic vasculitis, lupus erythematosus, cryoglobulinemia, and cutaneous thromboembolism. Consequently, the range of possible diagnoses (Table) may lead to an unnecessary, intensive, and expensive workup consisting of multiple blood tests and skin biopsy. In 2014, a study from the Mayo Clinic proposed diagnostic criteria to guide clinicians in identifying patients with pernio before considering collagen vascular disorders and other cold triggered dermatoses. The diagnostic tool included fulfillment of the major criterion and at least 1 minor criterion.4

**FIGURE** The patient experienced erythematous swelling of the fingers after prolonged exposure to cold.
FLARES AREN’T GOING TO PREVENT THEMSELVES

DAILY USE OF ECZEMA RELIEF BODY CREAM REDUCES THE INCIDENCE OF FLARE AND INCREASES THE TIME-TO-FLARE RECURRENCE

44% reduction in risk of flare in pediatric subjects

4 out of 5 children remained flare-free for six months¹

Steroid-free | Fragrance-free