Celiac Disease
What every pediatrician needs to know
PEDIARIX
A VACCINE WITH A HISTORY OF SUPPLY RELIABILITY

For more information, please visit ThinkPEDIARIX.com

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

For more information, please visit ThinkPEDIARIX.com
In 17 years, PEDIARIX has never had a supply shortage\textsuperscript{1,2}

Other manufacturers had primary series DTaP or pediatric HepB vaccine shortages that lasted a year or more.\textsuperscript{3,4,*} In fact,

• GSK distributed millions of additional doses to cover the 3 DTaP-containing vaccine shortages and the global pediatric HepB shortage to help reduce negative impact\textsuperscript{2}

• Shortages ranged from approximately 365 days to 940 days.\textsuperscript{3,4}

Continue your DTaP immunization routine without interruption with PEDIARIX\textsuperscript{†}

DTaP=diphtheria, tetanus, and acellular pertussis; HepB=hepatitis B.

*Data as of May 2020. Shortages of vaccines were identified by the Center for Biologics Evaluation and Research (CBER) within the Food and Drug Administration. CBER works closely with the manufacturer to voluntarily obtain accurate information.

†Data are not available on the safety and effectiveness of using PEDIARIX following one or more doses of a DTaP vaccine from a different manufacturer.

Important Safety Information for PEDIARIX (cont’d)

• 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 Brief Summary of Prescribing Information for PEDIARIX following this ad.

5.6 Children at Risk for Seizures

For children at higher risk for seizures than the general population, an appropriate anticonvulsant 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 prematurely. Decisions about whether to administer an intramuscular injection, 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 23,849 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. 3.0% 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/fussiness, and loss of appetite. In clinical trials (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 was highest on the day of vaccination and the day following vaccination. 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 (GiaxoSmithKline [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 (INFIIX, 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 convulsions and illnesses. 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 studies are presented in Table 1. This study was conducted as part of a larger study to assess the complete vaccination course for diphtheria, tetanus, and poliomyelitis and the complete vaccination course for hepatitis B. 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 convulsions and illnesses. 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.

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Deaths
In 14 clinical trials, 5 deaths were reported among 8,088 (0.06%) recipients of

Table 1: Percentage of Infants with Solicited Local and General Adverse
Reactions within 4 Days of Vaccinations at 2, 4, and 6 Months of Age
with PEDIARIX Administered Concomitantly with Hib Conjugate Vaccine
and 7-Valent Pneumococcal Conjugate Vaccine (PCV7) or with Separate
Concomitant Administration of INFANRIX, ENGERIX-B, IPV, Hib Conjugate
Vaccine, and PCV7 (Modified Intent-to-Treat Cohort).

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>PEDIARIX, Hib Vaccine, &amp; PCV7</th>
<th>INFANRIX, ENGERIX-B, IPV, Hib Vaccine, &amp; PCV7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locala</td>
<td>Dose 1</td>
<td>Dose 2</td>
</tr>
<tr>
<td>n</td>
<td>671</td>
<td>663</td>
</tr>
<tr>
<td>Pain, any</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Pain, Grade 2 or 3</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Pain, Grade 3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Redness, any</td>
<td>25</td>
<td>37</td>
</tr>
<tr>
<td>Redness, &gt;5 mm</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Redness, &gt;20 mm</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Swelling, any</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>Swelling, &gt;5 mm</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Swelling, &gt;20 mm</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>667</td>
<td>644</td>
</tr>
<tr>
<td>Fever, &gt;100.4°F</td>
<td>28</td>
<td>39</td>
</tr>
<tr>
<td>Fever, &gt;101.3°F</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Fever, &gt;102.2°F</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Fever, &gt;103.1°F</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fever, M.A.</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Drowsiness, any</td>
<td>57</td>
<td>52</td>
</tr>
<tr>
<td>Drowsiness, Grade 2 or 3</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Drowsiness, Grade 3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Irritability/Fussiness, any</td>
<td>61</td>
<td>65</td>
</tr>
<tr>
<td>Irritability/Fussiness, Grade 2 or 3</td>
<td>20</td>
<td>28e</td>
</tr>
<tr>
<td>Irritability/Fussiness, Grade 3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Loss of appetite, any</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Loss of appetite, Grade 2 or 3</td>
<td>7</td>
<td>8e</td>
</tr>
<tr>
<td>Loss of appetite, Grade 3</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the
United States); PCV7 (Wyeth Pharmaceuticals Inc.); IPV (Sanofi Pasteur SA).
Modified intent-to-treat cohort = All vaccinated subjects for whom safety data were
available.

n = Number of infants for whom at least 1 symptom sheet was completed; for
fever, numbers exclude missing temperature recordings or tympanic
measurements. M.A. = Medically attended (a visit to or from medical personnel).
Grade 2 defined as sufficiently discomforting to interfere with daily activities.
Grade 3 defined as preventing normal daily activities. Within 4 days of vaccination
defined as day of vaccination and the next 3 days. Local reactions at the injection
site for PEDIARIX or INFANRIX. Rate significantly higher in the group that received
PEDIARIX compared with separately administered vaccines (P-value < 0.05 [2-sided
Fisher Exact test] or the 95% CI on the difference between groups [Separate minus
PEDARIX] does not include 0). "Axillary temperatures increased by 1°C and oral
temperatures increased by 0.5°C to derive equivalent rectal temperature.

Serious Adverse Events
Within 30 days following any dose of vaccine in the U.S. safety study in which
all subjects received concomitant Hib and pneumococcal conjugate vaccines, 7
serious adverse events were reported in 7 subjects (1% [7/673]) who received
PEDIARIX (1 case each of pyrexia, gastronenteritis, and culture-negative clinical
sepsis and 4 cases of bronchiolitis) and 5 serious adverse events were reported in
4 subjects (1% [4/335]) who received INFANRIX, ENGERIX-B, and IPV (ureteropelvic
junction obstruction and testicular atrophy in 1 subject and 3 cases of bronchiolitis).

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 = 4,668) 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 febrile
and afebrile seizures, and 1 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 = 768) reported seizures. In a separate German study that
evaluated the safety of INFANRIX in 27,952 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 0.15 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 PEDIARIX 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 Doses 1-3, a random sample
of 5% of infants who received PEDIARIX was co-enrolled; this sample was not
enrolled for the remaining 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 febrile
episodes 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.

(continued on next page)
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</th>
<th>Difference (PEDIARIX–DTaP Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N  n   % (95% CI)</td>
<td>N  n   % (95% CI)</td>
<td>% (95% CI)</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   7  0.02 (0.01, 0.04)</td>
<td>39,232 6  0.02 (0.01, 0.03)</td>
<td>0.00 (-0.02, 0.02)</td>
</tr>
<tr>
<td>Dose 2, Days 0-7</td>
<td>40,000   3  0.01 (0.00, 0.02)</td>
<td>37,405 4  0.01 (0.00, 0.03)</td>
<td>0.00 (-0.02, 0.01)</td>
</tr>
<tr>
<td>Dose 3, Days 0-7</td>
<td>40,000   6  0.02 (0.01, 0.03)</td>
<td>40,000 5  0.01 (0.00, 0.03)</td>
<td>0.00 (-0.01, 0.02)</td>
</tr>
<tr>
<td>Total doses</td>
<td>120,000 16 0.01 (0.01, 0.02)</td>
<td>116,637 15 0.01 (0.01, 0.02)</td>
<td>0.00 (-0.01, 0.01)</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 14 0.19 (0.11, 0.30)</td>
<td>7,500 14 0.19 (0.11, 0.30)</td>
<td>0.00 (-0.14, 0.14)</td>
</tr>
<tr>
<td>Dose 2, Days 0-3</td>
<td>7,500 25 0.33 (0.22, 0.48)</td>
<td>7,500 15 0.20 (0.11, 0.33)</td>
<td>0.13 (-0.03, 0.30)</td>
</tr>
<tr>
<td>Dose 3, Days 0-3</td>
<td>7,500 21 0.28 (0.17, 0.43)</td>
<td>7,500 19 0.25 (0.15, 0.39)</td>
<td>0.03 (-0.14, 0.19)</td>
</tr>
<tr>
<td>Total doses</td>
<td>22,500 60 0.27 (0.20, 0.34)</td>
<td>22,500 48 0.21 (0.16, 0.28)</td>
<td>0.05 (-0.01, 0.14)</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 have been identified during postapproval use of 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.

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

Immune System Disorders
- Anaphylactic reaction, anaphylactoid reaction, hypersensitivity

Infections and Infestations
- Upper respiratory tract infection

Musculoskeletal and Connective Tissue Disorders
- Abdominal pain, b intussusception, a,b nausea, b

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

6.5 Postmarketing Spontaneous Reports for INFANRIX Compared with Historical Controls

8 Days of Vaccination and Medically-Attended Fever within 4 Days of Vaccination with INFANRIX Compared with Historical Controls

<table>
<thead>
<tr>
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<td>40,000   6  0.02 (0.01, 0.03)</td>
<td>40,000 5  0.01 (0.00, 0.03)</td>
<td>0.00 (-0.01, 0.02)</td>
</tr>
<tr>
<td>Total doses</td>
<td>120,000 16 0.01 (0.01, 0.02)</td>
<td>116,637 15 0.01 (0.01, 0.02)</td>
<td>0.00 (-0.01, 0.01)</td>
</tr>
</tbody>
</table>

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

Immune 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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Greetings!

As the COVID-19 pandemic surges again across the country and new restrictions, travel bans, and stay-at-home orders are implemented, the specter of “COVID-19 fatigue” becomes increasingly apparent. As we all continue to work to provide the most comprehensive and compassionate care to our patients, it is important to remember to care for ourselves. As cliché as it sounds, self-care and wellness are now more important than ever. I was recently reminded of this while attending a very busy inpatient infectious diseases service with a number of severely ill patients, including those with COVID-19-associated multisystem inflammatory syndrome in children. Working long hours with very sick patients day in and day out, getting little sleep, not taking time to eat, putting everyone else’s needs before your own personal needs, in addition to juggling other responsibilities is not sustainable or healthy. In the midst of the chaos, a friend reminded me that I cannot provide the level of care to my patients that I am accustomed to if I don’t take care of myself. Incorporating moments during the day to recharge helps to build resilience and allows one to work through challenges. As Mary Holloway said, “Resilience is knowing that you are the only one that has the power and the responsibility to pick yourself up.”

As we move deep into the winter season, please stay safe and well. And as always, I welcome your suggestions, comments, and questions.

With warmest regards,
Tina
Tina Q Tan, MD, FAAP, FIDSA, FPIDS
Editor-in-Chief
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in this issue
Our understanding of ADHD is evolving; there is an emerging recognition that more needs to be done\(^1\)\(^2\)\(^3\)

- More than 6 million US children and adolescents have ADHD—1 in every 10 school-aged child\(^1\)

New clinical practice guidelines have been issued for the first time in nearly a decade\(^2\)\(^3\)

The American Academy of Pediatrics (AAP) released updated guidelines\(^2\)
- These include screening for emotional or behavioral, developmental, and physical conditions\(^2\)

The Society for Developmental & Behavioral Pediatrics (SDBP) introduced their first-ever clinical practice guideline\(^3\)
- It emphasizes that clinicians with specialized expertise should initiate a comprehensive assessment and develop an interprofessional, multimodal treatment plan for any child/adolescent with suspected or diagnosed complex ADHD\(^3\)

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...And a healthy new year!

It seems extraordinary that it is already December, when so much of this year has felt like a blur. Over the past 9 months, the COVID-19 cloud has taxed both pediatricians and their patients, making the promise of a new year (and a fresh start) that more alluring. A look at the results of this year’s Issues & Attitudes survey, sent out to pediatric health care workers each September, presented a clear snapshot of how challenging the pandemic has been. Your responses to questions about a COVID vaccine, should one become available, could not have been more timely: As this issue was going to press, Pfizer, Moderna, and AstraZeneca all reported COVID-19 vaccine candidates (with high efficacy rates) were very close to coming to market. We will continue to inform you of all news regarding the progression of COVID-19 vaccines, along with all other updates and information pertinent to your work as a pediatric health care provider. (For those of you who may not be aware, Medical World News, our 24-hour online program for health care professionals, can be tuned into through the Contemporary Pediatrics website, under the “media” tab.)

Enjoy this last issue of Contemporary Pediatrics from 2020, and I hope you are planning for a joyous, healthy and safe holiday season. Happy New Year!
Though physicians sometimes empirically prescribe acid inhibitors for infant distress, nonacid reflux causes at least as much—and perhaps more—pain and distress in infants than acid reflux, according to a study in 62 children with persistent unexplained fussiness or distress and a median age of 3.5 months.

The prospective study included all children aged younger than 24 months referred to a European hospital for 24-hour multiple intraluminal impedance-pH (MII-pH) monitoring because of recurrent unexplained inconsolable distress thought to be a symptom of gastroesophageal reflux (GER). In addition to the monitoring, parents filled in a symptom diary and the Face, Legs, Activity, Cry, Consolability (FLACC) scale, a measurement for assessing pain in infants and young children. The scale ranges from 0 to 10 with 0 representing “relaxed and comfortable” and 7-10 “severe discomfort/pain.” Investigators then analyzed the FLACC scores in relation to the presence or absence, duration, chemical composition, and esophageal extension of GER episodes.

During the MII-pH monitoring, 452 episodes of distress were recorded, which parents scored with the FLACC scale. The number of episodes ranged from 1 to 32 per child, with a mean of 7.3. Fewer than half of the episodes (48%) were associated with GER. When associated with symptoms, GER occurred significantly more often before an episode of distress than it did simultaneously or after such an episode.

The median FLACC score did not differ significantly between the distress episodes that were associated with GER and those that did not. Overall, 361 (80%) distress episodes were in patients with an acid reflux index <7% and 91 (20%) in those with a pathologic acid reflux index. Episodes of distress associated with nonacid reflux presented a significantly higher FLACC than those with acid content (FLACC 6 vs 5). In addition, the median FLACC value was significantly lower in the 12 (19%) infants with a pathologic reflux index compared with the 50 infants (81%) with a normal reflux index (Salvatore S, et al. J Pediatr Gastroenterol Nutr. 2020;71[4]:465-469).

Acid reflux is often blamed, incorrectly, for fussiness in infants. I have commented previously on the risk of anti-reflux medicines (Contemporary Pediatrics Journal Club, June 2020). I am not advocating for pH probes in fussy children, but rather for innocuous treatments that support parents through the fussy period.
Acetaminophen is not the best choice for fever in asthmatics

Children with asthma who use a nonsteroidal anti-inflammatory drug (NSAID) during a respiratory infection or no antipyretic at all have a lower risk of experiencing an asthma exacerbation (AE) than asthmatics who use acetaminophen. These were the findings of an analysis of data from a national database in Taiwan related to more than 27,000 children with asthma who had at least one episode of respiratory infection and a similar number of age-and sex-matched non-asthmatic children with respiratory infection who served as controls.

Participants were divided into 3 groups: acetaminophen use, NSAID cyclooxygenase-1 (COX-1) use, and no antipyretic use. Overall, asthmatic patients used antipyretics less often than controls (48.5% vs 55.5%) with antipyretic users in the asthmatic group tending to be older than nonusers (9.3 vs 7.8 years).

Investigators compared the rate of AE occurrence within the first 7 days after diagnosis of respiratory infection among the groups and analyzed the risk of AE with adjustments for age, gender, and urbanization level. The overall rate of AE within 7 days of a single respiratory infection episode was low—about 0.14%, with no observable difference in rate between those who used antipyretics and those who did not. The risk of AE was highest in those who took acetaminophen (Chung R-S, et al. Science Direct. 2020; Epub ahead of print).

Because of the potential adverse effects of aspirin in children with asthma, some pediatricians avoid using NSAIDs in these children. This study suggests that acetaminophen may be a worse option. However, the risk is very low, so if acetaminophen is your preferred antipyretic in a given child (and I do support making miserable children feel better), use it.

Prefilled pen may be a better way to deliver methotrexate to children with JIA

When methotrexate (MTX) is administered to patients with juvenile idiopathic arthritis (JIA) using a prefilled pen, the procedure is associated with less pain and fewer side effects than when a conventional prefilled syringe is used, according to a study conducted at a pediatric rheumatology center in Poland.

The 23 patients with JIA, who ranged from 2 to 18 years of age (mean age, 11.7 years) were receiving subcutaneous MTX therapy using a prefilled syringe at the start of the study.

After completing a questionnaire evaluating their experience with this device, they began a 1-month period of using the prefilled pen and then completed the same questionnaire to document their experience with the new delivery system. Participants also indicated their overall preference for the pen or syringe. Caregivers completed these questionnaires when they, not the patients themselves, administered the MTX.

Almost 83% of patients or caregivers preferred the prefilled pen to the syringe for administering MTX, citing it as easier to use despite having considerably more experience with the syringe. Moreover, injection with the prefilled pen was considered less painful than with the prefilled syringe. Finally, side effects of MTX were less pronounced after treatment with the prefilled pen, particularly with regard to nausea, vomiting, and abdominal pain (Roszkiewicz, J, et al. Pediatr Rheumatol. 2020; Epub ahead of print).

I am in favor of anything that reduces pain safely. In the near future, more children will be receiving injections of biologics for conditions such as Crohn’s disease, lupus, and asthma. We will see if the pen proves mightier than the syringe.
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A case of acute psychosis that will make your head spin

ANGIE BUTTIGIEG, MD, AND POLIANA DA SILVA, MD

Due to acute onset neuropsychiatric symptoms of unknown etiology, the patient was initially admitted to the pediatric intensive care unit for close monitoring. Initial differential diagnosis was broad given the patient’s new-onset severe neuropsychiatric symptoms (Table 1). Bacterial or viral meningitis/encephalitis may present similarly, and upper respiratory symptoms may precede presentation, as was the case in our patient. However, these patients also typically present with fever and nuchal rigidity, neither of which were present in our patient. Other infectious etiologies include HIV, syphilis, Bartonella, and Lyme disease. Toxic ingestion, especially of alcohol, ketamine, phencyclidine, or organophosphates can cause new onset agitation; however, symptoms typically do not last as long as they did in our patient.
Endocrine and metabolic derangements are also known to cause neuropsychosis. Neoplastic disorder, either primary or secondary, as well as paraneoplastic syndromes can present with focal neurologic signs and/or neuropsychiatric symptoms. Rheumatologic disorders, including lupus, may also present with psychiatric symptoms, though our patient had no other stigmata typical of lupus. Entities that cause inflammation of the central nervous system, such as autoimmune encephalitis (eg, anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis and acute disseminated encephalomyelitis) can present with a similar constellation of symptoms as our patient and must also be considered. Primary psychiatric disease should be a diagnosis of exclusion once all organic causes are ruled out or considered sooner if the patient has a known psychiatric history.

One week after discharge, CSF studies returned positive for anti-NMDAR and anti-MOG antibodies.

Examination and Testing
Video EEG at our institution did not demonstrate evidence of seizures. Head computed tomography (CT) on admission showed hypofunction in bilateral thalami, though more on the right side as compared to the left side. Magnetic resonance imaging (MRI), magnetic resonance angiogram, and magnetic resonance venography were done given concern for vasculitis and significant for hyperintensity flair in the medial thalami/massa intermedia. Urine toxicology screen was negative. A lumbar puncture showed a high opening pressure and cerebrospinal fluid (CSF) pleocytosis with white blood cells of 26, suggesting infectious versus autoimmune processes. Further infectious work-up, including a complete blood count, procalcitonin, meningitis/encephalitis panel, antistreptolysin O (ASO) titer, group A streptococcus direct DNA probe, rapid plasma reagin (RPR), Epstein-Barr virus, Lyme disease titers, HIV, quantiferon gold, Bartonella antibodies, and herpes simplex virus (HSV) antibodies were all negative. Rheumatologic work-up, including erythrocyte sedimentation rate, c-reactive protein, antinuclear antibody, anti-ds DNA, C3, C4, proteinase-3 antibody, myeloperoxidase antibody, and centromere antibody were unremarkable. A comprehensive metabolic panel, lactic acid, ammonia, thyroid stimulating hormone (TSH), free T4, vitamin B1, ceruloplasmin, and copper studies did not demonstrate a toxic or metabolic cause. A CT abdomen and pelvis was done to rule out an oncologic process and was within normal limits. Alpha-fetoprotein was normal. An autoimmune and paraneoplastic panel was sent from the CSF, however results were not available during the patient’s hospital admission.

Diagnosis
Laboratory evaluation was largely unremarkable, except for slight CSF pleocytosis. This, along with the CT and MRI findings and the clinical picture of waxing and waning aggression, agitation, and insomnia was concerning for autoimmune encephalitis. One week after discharge, CSF studies returned positive for anti-NMDAR and anti-MOG antibodies.

Patient outcome
Given concern for anti-NMDAR encephalitis and known poorer prognosis with delay in treatment, our patient was presumptively treated with high-dose steroids and intravenous immune globulin (IVIG). He did not demonstrate improvement in his neuropsychiatric symptoms with this treatment, and continued to require daily lorazepam for agita-

### TABLE 1

**DIFFERENTIAL DIAGNOSIS**

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Toxic or Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial meningitis</td>
<td>Drug ingestion (alcohol, ketamine, PCP, organophosphates)</td>
</tr>
<tr>
<td>Viral encephalitis</td>
<td>Carbon monoxide</td>
</tr>
<tr>
<td>Prion disease</td>
<td>Thyroid dysfunction (eg, Hashimoto’s thyroiditis)</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Wilson’s disease</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Neuroleptic malignant syndrome</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Neoplastic</th>
<th>Autoimmune or Inflammatory disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary CNS neoplasm</td>
<td>Acute disseminated encephalomyelitis (ADEM)</td>
</tr>
<tr>
<td>Secondary (eg, metastatic) CNS neoplasm</td>
<td>Anti-NMDAR encephalitis</td>
</tr>
<tr>
<td>Paraneoplastic syndrome</td>
<td>Systemic Lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>Autoimmune vasculitis (ie, Wegner)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary psychiatric disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar disorder</td>
</tr>
<tr>
<td>Primary schizophrenia</td>
</tr>
</tbody>
</table>

DECEMBER 2020 | CONTEMPORARYPEDIATRICS.COM 15
tion. The patient was subsequently treated with rituximab with clinical improvement.

Our patient was admitted for 16 days and discharged home with mild cognitive delays but no activity restrictions. After discharge, the patient had close follow-up with neurology and hematology/oncology, including a 2nd dose of rituximab and a repeat MRI that showed interval complete resolution of previously identified T2-weighted-fluid-attenuated inversion recovery hyperintensity within pulvinar region of bilateral thalami. He was given a 504 plan for additional time in academic activities, however reports not using it and is earning B’s in school.

In addition, the neuropsychiatric team evaluated the patient in order to delineate sequelae of neurocognitive deficits due to encephalitis. His first evaluation was approximately 3 months after discharge and showed weaknesses in sustained visual attention, auditory memory, and visual memory. There were also concerns regarding impulse control. The neuropsychiatric team conducted a follow up evaluation about 7 months later. Our patient demonstrated significant improvement, specifically in attention, concentration, and memory domains of the evaluation. He also exhibited improved self-control during testing.

Discussion

The NMDA is a glutamate-gated ion channel critical for multiple central nervous system (CNS) functions including processes underlying learning, memory and neuroplasticity. Anti-NMDAR encephalitis is an autoimmune disorder with IgG antibodies against the NR1 and NR2 subunit of the NMDA receptor. The presenting symptoms of anti-NMDAR encephalitis are quite broad, but usually evolve in stages including a prodrome of fever, headaches and viral-like symptoms. Days to weeks after this prodromal phase begins the onset of psychiatric and behavioral problems, including personality and behavioral changes, autonomic and cognitive dysfunction, and finally neurologic decompensation leading to insomnia, seizures, altered levels of consciousness, and breathing or autonomic instability.

In multiple studies, it was shown that the condition, when identified, affects predominantly females (up to 80% of females vs males). Age ranges from 18-35 years, with 40% of patients aged younger than 18 years.

This disorder is a leading cause of encephalitis in young patients, with up to 4% of patients with encephalitis having NMDAR antibodies. In women aged older than 18 years, the majority will have the presence of an underlying tumor, such as teratoma of the ovary, however in children, this is uncommon.

Diagnosis of anti-NMDAR encephalitis is made by identification of NMDAR antibodies in the CSF or serum. First line therapy is typically high dose corticosteroids. Second line therapy includes IVIG and/or plasma exchange. Other attempted therapies include rituximab, azathioprine, and cyclophosphamide. If a neoplasm is found, treatment includes surgical excision of neoplasm, if possible.

Anti-NMDAR encephalitis is the second leading cause of immune-mediated encephalitis, after acute disseminated encephalomyelitis. Despite the prevalence of the condition, anti-NMDAR encephalitis is an overlooked diagnosis. Timely diagnosis and treatment of anti-NMDAR encephalitis should be considered early on in patients presenting with new onset of altered mental status of unknown etiology. Anti-NMDAR encephalitis is a complex syndrome, with a severe disease course and broad differential diagnosis. Mortality can be up to 25%, whereas many other patients are left with cognitive deficits that may affect education, work, or social life. However, with early recognition and aggressive treatment, prognosis remains good with most cases (up to 75%) making a full recovery or only having mild disability, as was demonstrated in our patient.

Comments? E-mail them to llevine@mjlifesciences.com

For references and images, go to ContemporaryPediatrics.com/puzzler-1220

Dr Buttigieg is a pediatric hospital medicine fellow at Mount Sinai Kravis Children’s Hospital, New York, New York.

Dr Da Silva is a pediatric resident at Newark Beth Israel Medical Center, Newark, New Jersey.

The authors have nothing to disclose.
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**SOFIA* SARS ANTIGEN FIA IS AVAILABLE FOR SALE IN THE USA UNDER EMERGENCY USE AUTHORIZATION FOR SOFIA 2 AND SOFIA
A new diagnostic paradigm for celiac disease

Since the middle of the 20th century and into the 21st century, the incidence of celiac disease has been rising significantly throughout the Western world. Here is what you need to know about this autoimmune condition.

JOCELYN SILVESTER, MD

Celiac disease (CD) is an autoimmune disease in which a reaction to gluten consumption damages the small intestine. With a steadily increasing global prevalence of close to 1%, public awareness of CD and gluten-related disorders has grown considerably over the last few decades.

Celiac disease is more common in children with the following risk factors:
- A family member with CD or dermatitis herpetiformis
- Type 1 diabetes
- Down syndrome or Turner syndrome
- Autoimmune thyroid disease

Celiac disease can be challenging to diagnose as patients may present with gastrointestinal and/or extraintestinal symptoms, and many are apparently asymptomatic. Furthermore, there is a poor correlation between gastrointestinal damage and symptoms.

Timely diagnosis of CD and optimization of nutrition is particularly important in childhood to prevent irreversible complications such as short stature and osteoporosis. All individuals with untreated CD are at risk for long-term complications, whether or not they present with symptoms.

COMMON SIGNS/SYMPTOMS OF PEDIATRIC CD INCLUDE:

- Chronic or intermittent diarrhea
- Chronic constipation not responding to usual treatment
- Chronic abdominal pain
- Abdominal distension
- Recurrent nausea or vomiting
- Weight loss or failure to thrive
- Stunted growth or short stature
- Delayed puberty
- Iron-deficiency anemia
- Irritability and behavioral issues
- Headaches
- Arthritis/arthralgia
- Dental enamel defects
- Recurrent aphthous stomatitis
- Elevated aminotransaminases

With the growing prevalence of CD and the heterogeneous, often non-specific nature of symptoms, many patients remain untreated and diagnosis may be delayed by several years. Currently, it is estimated that 43% of the CD population remains undiagnosed. Like many autoimmune diseases, the exact trigger of CD is unknown; however, the genet-
Celiac risk factors (HLA-DQ2/DQ8) are well defined. Additional environmental factors including infant-feeding practices, gastrointestinal infections, and the intestinal microbiome may all play a role.

Whatever the cause, when the body’s immune system mounts an attack against the “invasion” of gluten, the reaction damages the villi: slight hair-like projections that line the small intestine. This damage prevents the villi from performing the function of absorbing vitamins, minerals, and other nutrients, which means the celiac patient cannot get enough nutritional value from the food they’re eating. This can be especially disruptive to normal growth and development in children.

Left unchecked, chronic intestinal inflammation and malabsorption from CD can cause a host of complications, including:

- Malnutrition
- Bone fractures
- Infertility and miscarriage (in adults)
- Lactose intolerance
- Cancer, especially intestinal lymphoma and small bowel cancers
- Cardiac disease (myocarditis, cardiomyopathy)
- Neuropsychiatric disease

All of these comorbidities represent an enormous human toll, as well as an expensive strain on the health care system.

Updated testing recommendations

Historically, the cornerstone of CD diagnosis has been a duodenal biopsy with histological analysis. Now serological tests are available, each with a role to play: tissue transglutaminase-IgA (tTG IgA), total IgA, endomysial IgA (anti-EMA), and IgG-based tests.

Given the time-consuming, expensive, and invasive nature of duodenal histology, there has been increased focus on finding the most efficient algorithm and omitting duodenal histology in patients who fulfill other CD diagnostic criteria.

Recently, both the American Gastroenterological Association (AGA) and the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) released updated guidelines for diagnosing CD. Both reports were based on available published evidence and emphasize that the diagnosis should be made by a specialist (eg, gastroenterologist).

The pediatric testing algorithm

For pediatricians managing patients with symptoms of CD or an affected first degree relative, the recommended diagnostic approach is to begin with an initial test for total serum IgA in addition to a test for serum antitissue transglutaminase IgA antibo-
ies (tTG IgA) as the child continues to consume a gluten-containing diet. This is the most clinically and cost-effective screening method. All patients with elevated serum tTG IgA should be referred to a pediatric gastroenterologist for additional testing to confirm the diagnosis of CD (see Table).

A GFD should be continued until the diagnosis is confirmed, as diagnostic testing is less reliable on a GFD. The degree of tTG IgA elevation is somewhat proportionate to the likelihood of CD, such that those with very high tTG IgA levels (>10 times the upper normal limit) may not require a duodenal biopsy for their pediatric gastroenterologist to confirm the diagnosis if the more specific anti-endomysial IgA (EMA IgA) test is also positive (see Figure A).

In these cases, the guidelines give the option to omit duodenal histology. Proceeding with a no-biopsy approach should be decided on a case-by-case basis with informed discussion among the caregivers, pediatric gastroenterologist, pediatrician, and child. In practice, this strategy may reduce the need for gastroscopy with biopsy by 30-50%. Pediatric patients aged younger than 2 to 3 years may have a less robust presence of IgA rendering tTG IgA testing less efficient. In these cases, pediatricians may choose to test for IgG deamidated gliadin antibodies (anti-DGP IgG) in addition to the recommended tTG IgA (see Figure A). Performing both tTG IgA and DGP IgG may increase diagnostic sensitivity as some patients with CD have DGP IgG antibodies but not tTG IgA antibodies.

Other relevant, specific markers for CD are anti-endomysial antibodies (anti-EMA). Testing for anti-EMA is labor-intensive and expensive, and should be used as a confirmatory test, particularly if the non-biopsy algorithm proposed in the most recent 2020 clinical practice update is being considered (see Figure A).

**COMMENTS?** E-mail them to llevine@mjhlifesciences.com

For references, go to ContemporaryPediatrics.com/new-paradigm-celiac-disease

### TABLE

<table>
<thead>
<tr>
<th>SYMPTOMATIC** (INTESTINAL OR EXTRAINTESTINAL MANIFESTATIONS) OR HIGH-RISK* (REGARDLESS OF SYMPTOMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCREENING</strong></td>
</tr>
<tr>
<td>Primary care</td>
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<tr>
<td>Gluten-containing diet</td>
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<tr>
<td>Glutens</td>
</tr>
<tr>
<td>Symptomatic</td>
</tr>
<tr>
<td><strong>DIAGNOSIS</strong></td>
</tr>
<tr>
<td>Gastroenterologist</td>
</tr>
<tr>
<td>Continue gluten</td>
</tr>
<tr>
<td>Very High tTG IgA &gt;10x ULN</td>
</tr>
<tr>
<td>EMA IgA Positive</td>
</tr>
<tr>
<td>EMA IgA Negative</td>
</tr>
<tr>
<td>Gluten-free diet</td>
</tr>
<tr>
<td>High tTG IgA &lt;10x ULN</td>
</tr>
<tr>
<td>Biopsy Positive</td>
</tr>
<tr>
<td>Biopsy Negative</td>
</tr>
<tr>
<td>Specialist – refer to Figure C in reference below</td>
</tr>
<tr>
<td>Low suspicion of CD</td>
</tr>
<tr>
<td>Low suspicion of CD</td>
</tr>
</tbody>
</table>

*High-Risk (including asymptomatic) |

- First degree relatives with celiac disease
- Type 1 diabetes
- Autoimmune thyroid disease
- Trisomy 21
- Turner Syndrome
- HLA-DQ2/DQ8 testing

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Will the COVID-19 cloud change pediatric medicine forever?

With the United States still in the throes of a pandemic, nearly 400 pediatric health care providers share their struggles in getting patients back to the office, advocating for a COVID-19 vaccine, and working their way toward optimism in the face of the biggest health care challenge of their lives.

LOIS LEVINE, EDITOR

What a difference a year makes. Last year, when Contemporary Pediatrics put out its annual issues and attitudes survey, 57% of respondents said they were feeling less optimistic about their ability to provide adequate care for patients (which was, by the way a 13% jump from 2013). This year, that percentage rose even more, to 60%, a notable majority. But although the reasons around the pessimism remained the same in both 2013 and 2019 (insufficient time with patients, inadequate reimbursement, and health care reform), this year—no surprise—the top reason was concerns about adequately treating patients with COVID-19 and multisystem inflammatory syndrome in children (MIS-C). That was followed by inadequate insurance reimbursement and not enough time with patients. Interesting too, is that those who answered they were more optimistic (only 9%), felt that way because of new tech tools (38%), good relationships with local specialists that they refer patients to (34%), and having more treatment options for COVID-19/MIS-C (24%). (Editor’s note: this survey went out in September, when treatments like remdesivir and convalescent plasma had been approved by the US Food and Drug Administration for use of COVID-19).

If a reliable and safe vaccine for COVID-19/MIS-C came on the market for both adults and children, would you encourage your patients to get it?

- Yes: 74%
- No: 3%
- Not Sure: 23%

How many of your patients do you think would be hesitant to get a COVID-19/MIS-C vaccine that has been judged to be safe and effective?

- Most: 28%
- Some: 70%
- None: 2%
In 2019, when asked what the top 2 challenges to their practice were, 45% of health care providers said transitioning to electronic health records (EHRs) and dealing with insurance (42%) were the greatest obstacles. This year, EHRs were not even mentioned in the top 5 reasons, taking a back seat to lack of patients due to issues around COVID-19/MIS-C, which 60% of respondents gave as the biggest challenge, followed by compensation (36%), dealing with insurance (28%), not having effective treatments for COVID-19 and MIS-C (20%), and vaccine hesitancy (20%). Also not surprising was that more than 40% of respondents reported that their work level had decreased over the year, (compared to only 10% claiming that the year prior), another sober indication of how the pandemic has affected patient traffic in pediatric offices around the United States.

In regards to vaccine hesitancy, 70% of respondents said that they believe that some of their patients would be hesitant to get a COVID-19/MIS-C vaccine, even one that had been judged safe and effective; 28% thought most would be hesitant, and only 2% thought that none would be wary of a vaccine on the market. Considering the recent news about 3 vaccines that might soon be available to the public, this hesitancy is worrisome indeed.

The good news here: The pediatric medical community continues to stand behind its scientists. A whopping 74% of you would encourage your patients to get a vaccine, if a reliable and safe one came on the market to combat the pandemic. Only 23% of respondents were unsure, and 3% would advise not getting a vaccine at all.

On another encouraging note, pediatric providers are riding the tech tidal wave in ways they never have before. The fact that EHRs didn’t even make the list of challenges this year suggests that they are now a way of life. Furthermore, more than 70% of respondents said they were doing more telehealth than previous years.

Once we can see our way out of the pandemic, what changes will be permanent as a result of living and working under the COVID-19 cloud? We can’t wait to hear from you to tell us.
Every physician has likely committed a medical error at some time.1 Fortunately, most medical errors are minor, and many do not reach the patient. However, a recent study suggested that medical errors are the third leading cause of death in the United States.2 In a study of internal medicine trainees, 45% reported being involved in a serious medical error.3 In a survey of practicing physicians, 10.5% reported they were involved in a major medical error during the prior 3 months.4 Provider burnout has been linked to medical errors. Medical errors often lead to burnout, and the reverse is also probable.5,6,7

The Emergency Department (ED) is a high-risk area where medical errors are likely. This is, in part, because the ED is often extremely busy with multiple ill or complicated patients. Emergency clinicians often must make rapid decisions in a chaotic environment, so the chance for error is high. This is not entirely unique to the ED. Pediatricians in office practice may find their office fits this mold on many days!) Many errors in pediatric emergency medicine relate to physician fatigue. Others relate to frequent distractions that are prevalent in the ED setting. In one study,8 attending physicians and nurses were followed in a level 1 trauma center. It was noted that physicians were interrupted 10 times within an hour, and nurses were interrupted 12 times in an hour. These providers performed between 1-8 other activities before returning to the original task. They were interrupted by phones, pagers, other staff members. It is easy to see how errors can result from these frequent disruptions. In some cases, ED providers commit cognitive errors, perhaps because of “premature closure.” That is, the clinician fixes on a diagnosis early on and ignores other findings that could lead to a different diagnosis.

In many cases, errors result from poor communication. In the ED it is obviously crucial for staff to work as a cohesive team. Certainly, ED providers must communicate well with nursing staff, and consultants. Numerous errors result when there is a breakdown in this communication. In fact, the Joint Commission notes that communication issues are the third leading cause of sentinel events.9 Likewise, ED providers must communicate well with patients and families to obtain an accurate history and develop a management plan together.

Although this seems obvious, it is not guaranteed. In one interesting study10 involving 2 teaching hospitals in Michigan, patients were asked about 4 domains soon after their ED visit:

1. Do you understand your diagnosis?
2. Do you understand what was done for you in the ED?
3. Do you know what you are supposed to do after your ED visit (discharge instructions).
4. Do you understand what symptoms should prompt you to return to the ED?

### TABLE 1 COMMON CAUSES OF MEDICAL ERROR in pediatric emergency medicine/office practice
- Physician fatigue
- Physician burnout
- Frequent distractions/interruptions
- Poor communication with patients/families, staff, consultants
- Failure to monitor patients
- Need for rapid decisions in busy environment
- Cognitive errors due to premature closure
CASE 1
A 15-year-old boy presented to the ED with the complaint of chest pain for 1 week. He reported that he was hit over his ribs on the right side of his chest when playing football a week ago. His pain, described as achy and stabbing, worsened in the past few days. It was worse with walking and for one day, he had difficulty climbing the stairs. He was short of breath at times and had mild dizziness with standing. He had no fever, no vomiting or diarrhea, no cough or rhinorrhea. Physical examination revealed temperature 100.9°F, heart rate 78 beats per minute (up to 106 beats per minute when standing), respiration 24/minute, blood pressure 128/84 (124/92 standing). He was alert and talkative and in no distress. He had mild tenderness over his sternum. Cardiac exam was normal. Lungs were clear. Abdomen was benign. His exam was otherwise unremarkable.

A chest x-ray showed clear lungs; the heart was noted to be "top normal" in size. (see radiograph Figure 1). An electrocardiogram had ‘non-specific’

findings such as ST elevation in some leads and borderline prolonged QT interval.

The patient received ibuprofen for his pain, and intravenous saline because it was thought he may be dehydrated. His vital signs remained unchanged after the fluids. A cardiologist was consulted by phone. The cardiologist believed the patient had musculoskeletal pain, and he did not need immediate cardiology evaluation. The patient was discharged to home. About 8 hours later, he collapsed and died. Myocarditis was found on autopsy.

Teaching points: In retrospect, the diagnosis of myocarditis is obvious. The patient had classic findings: chest pain for several days, worsening with exertion and leading to shortness of breath. He also had a low-grade fever in the ED, that seems to have been ignored by the cardiologist who was consulted. Myocarditis can be a difficult diagnosis, and in many cases the patient is evaluated multiple times before myocarditis is considered.11

Chest pain associated with fever is concerning. If pneumonia is ruled out, consider myocarditis as the etiology for pain. Chest pain with exertion is concerning for a cardiac etiology rather than musculoskeletal pain, which should improve over time, not worsen. Pay attention to the vital signs! If the patient continues to have tachycardia (or dizziness) with standing, after intravenous fluids, perhaps there is cardiac insufficiency rather than dehydration.
CASE 2
A 5-year-old girl presented to the ED with persistent vomiting. She was seen by her pediatrician who obtained a rapid throat swab that was positive for Group A Streptococcus. She also had an abdominal radiograph that showed constipation. She was referred to the ED because her emesis had a foul odor. It smelled of ‘fecal material.’ In the ED, it was noted that she had been vomiting intermittently for about 3 months, but had 8–9 episodes today. Her emesis was ‘greenish-brown’ and there was no blood in her stool. She had crampy abdominal pain. Physical exam revealed temperature 98.9°F, heart rate 96 beats per minute, respiratory rate 20/minute, blood pressure 106/66. She was alert, well-nourished, with an injected pharynx. Her chest was clear; abdomen was soft and unremarkable.

The patient was given an enema and was able to tolerate oral fluids. She was discharged to home with a diagnosis of constipation, and strep throat. The next day, she had a generalized seizure and was brought back to the hospital. A computed tomography (CT) scan of her brain was promptly obtained and showed a large brain tumor. The child expired the next day.

**Teaching points:** Vomiting has many etiologies. Viral gastroenteritis is perhaps the most common etiology. However, when a child has vomiting without diarrhea, other conditions must be considered. Vomiting is sometimes associated with strep pharyngitis, and perhaps the clinicians in this case were misled by the rapid test of the pharynx. Constipation is unlikely to cause persistent vomiting—it is wise to look for another etiology before concluding that constipation is the culprit. Diabetic ketoacidosis and pneumonia are other possibilities, but unlikely in the case above. A viral infection, gastritis without diarrhea, is possible. However, clinicians must also consider an intracranial cause for vomiting, such as a brain tumor. In this case, a neurologic exam was not even documented in the medical record. Her history of prolonged vomiting over several months was apparently ignored.

CASE 3
A 2-year-old girl was bitten by a dog. She presented to the ED with extensive facial wounds. A plastic surgeon was consulted, and the face lacerations were meticulously repaired. She was discharged to home. She returned to the ED a few days later because of frequent vomiting and low-grade fever. A head CT scan was obtained and showed a brain abscess. With careful inspection, it was noted there was a defect in the patient’s skull. The dog’s tooth had apparently penetrated the child’s skull, leading to intracranial infection. The skull defect was not noted under the toddler’s extensive hair and thus it was not cleaned or addressed at the initial visit.

**Teaching points:** When an injured child arrives, clinicians often focus on the most obvious injury, or perhaps the most impressive. It is wise to examine the rest of the child first. No one will miss the dramatic wound, so a careful look elsewhere is advised before devoting attention to the noticeable face laceration. Also, consider that when a big dog attacks a little child, the jaws of the animal can likely encompass a large area of the child. Look for a second wound!

CASE 4
A 2-year-old boy presented to the ED with the complaint of “something in his nose.” Despite multiple attempts, the physician’s assistant and the physician were unable to remove a foreign body. In fact, they were not able to clearly visualize the foreign body, believing it was deeply embedded in the nostril. The providers recommended that the child see a specialist in the next few days. When the child was evaluated by an otolaryngologist, a radiograph was obtained. (Figure 2). The rim of the metallic foreign body is evidence that it is a ‘button battery’. This child had a complicated course with perforation of the nasal septum, and he required extensive surgery.

**Teaching points:** Button batteries in the nose, ears, or esophagus can cause extensive burns and tissue necrosis in a short period of time. It is important to visualize a foreign body in these locations. A plastic bead can likely wait for the specialist appointment; a button battery cannot. It is wise to consider a radiograph to identify the presumed foreign body if it cannot be seen on physical examination.

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Empiric selection of lipid emulsion in hospitalized infants

BETHANY SHARPLESS CHALK, PHARMD, BCPPS; MATTHEW A BUENDIA, MD

Aqueous parenteral nutrition (PN) provides intravenous carbohydrates, electrolytes, amino acids, and minerals to meet nutritional needs when modes of enteral nutrition are compromised. Although caloric requirements can be achieved with carbohydrates and proteins alone, patients may suffer complications including essential fatty acid deficiency, developmental issues, growth restriction, and dermatitis in the absence of fat provision.

Fats are critical sources of energy and structural components of cell membranes, as well as precursors to cellular pathways and immune responses. Intravenous lipid emulsions (ILEs) are an essential component of PN, especially in preterm and very low birth infants. Intravenous lipid emulsions have revolutionized the management of infants with gastrointestinal (GI) anomalies and diagnoses such as intestinal failure, allowing nutritional support for intestinal growth and adaptation to occur, as well as a bridge for patients with contraindications to enteral feeding. However, prolonged PN use still increases the risk of infection and intestinal failure associated liver disease (IFALD), which contribute significantly to infant mortality. Furthermore, it has been suggested certain intravenous lipid emulsions contribute to the pathogenesis of IFALD.

In the United States, the most common empiric ILEs, such as Intralipid, contain 100% soybean oil, rich in omega-6 polyunsaturated fatty acids (PUFA). An alternative lipid formulation that is gaining prevalence is SMOFlipid, composed of 30% soybean oil, 30% medium chain triglycerides, 25% olive oil, and 15% fish oil. Intralipid and SMOFlipid share a similar dosing strategy, with patients typically receiving a maximum of 3 grams/kg/day, (the same total calories from fat). And, Omegaven, a 100% fish oil-based ILE, is approved specifically for reversal of IFALD by the US Food and Drug Administration, but not indicated for empiric therapy in parenterally fed infants. With new evidence, the current standard of care of providing exclusive soybean-based lipid emulsions initially to all infants come into question.

The pathogenesis of IFALD is multifactorial, and there has been extensive research reviewing the role of ILEs contributing to inflammation. Traditional soybean oil-based lipids are high in PUFA, precursors of pro-inflammatory eicosanoids. The high amounts of omega-6 PUFA have a large linoleic acid component which leads to arachidonic acid, a substrate for interleukin-6, platelet activating factor, and tumor necrosis factor-alpha, which are all implicated as pro-inflammatory factors. This pro-inflammatory state leads to potentially increased lipid peroxidation, oxidative stress and inflammation, and in turn cholestasis and hepatitis. Alternative ILEs that contain fish oil have rich sources of omega-3 fatty acids shown to have anti-inflammatory properties. Omega-3 fatty acids are precursors for prostaglandins, leukotrienes and factors promoting resolution of inflammation. Low ratios of omega-6 to omega-3 fatty acids, as seen in SMOFlipid have been shown to be correlate with lower proinflammatory markers, suggesting the potential for less inflammation and cellular damage.
As the evidence suggests, there is benefit in using SMOFlipid in infants with GI reasons for prolonged PN use, there is understandably interest in empiric use in preterm neonates, who are likely to require prolonged PN. Tomits and colleagues conducted one of the first randomized controlled trials of SMOFlipid versus Intralipid initiated in the first week of life in 60 preterm neonates (born < 34 weeks gestational age). The authors investigated the impact of each lipid on triglyceride levels and relative change in weight in the first 8 days of lipid therapy, which were both similar between groups. This study found no difference in total bilirubin between study entry and conclusion, but did not report direct bilirubin. The authors reported a significant difference between the gamma glutamyltransferase (GGT) at study entry and end between groups. In the Intralipid group, GGT increased between day zero and study end, whereas in the SMOFlipid group, GGT actually decreased from day zero to the final measurement. Although this study did not directly address measures of IFALD, it demonstrated the tolerability of SMOFlipid in preterm neonates was not significantly different than Intralipid, which is relevant as hypertriglyceridermia is a noteworthy adverse effect requiring monitoring. Following this, Rayaan et al addressed a similar patient population as the prior study, preterm neonates born at <34 weeks gestation who were expected to require a minimum of 7 days of PN. The primary outcome focused on triglyceride values, which were not significantly different between groups. In addition, this study reported the direct bilirubin values following exposure of 8 days of study lipid, and found that the mean direct bilirubin the Intralipid group was significantly higher than that of the SMOFlipid group (mean SD): 0.75 (0.42) mg/dL vs 0.6 (0.34) mg/dL). Among these patients, the authors similarly concluded that SMOFlipid was well tolerated and had a favorable impact on conjugated bilirubin.

The remaining available literature for use of SMOFlipid empirically in preterm neonates is retrospective, most commonly evaluating outcomes before and after an institutional policy change to utilize SMOFlipid in all preterm neonates. Choudhary et al retrospectively reviewed 222 patients who were born at <32 weeks gestation who required ILEs for > 14 days. The authors investigated the impact of the practice change from empiric Intralipid to empiric SMOFlipid on mortality and major neonatal morbidities. There were no significant differences in mortality or the majority of morbidities, including IFALD. The SMOFlipid group did have greater weight at 36 weeks corrected gestational age as well as a greater change in weight (a mean difference of each of about 125 g). Different from other studies, the authors found comparable hepatic outcomes with SMOFlipid use. Together though, the favorable growth outcomes may someday associate with long-term benefits in developmental outcomes.

A retrospective study of 1297 very low birth weight preterm neonates was conducted by Torgalkar and colleagues to evaluate the impact of SMOFlipid versus Intralipid on mortality prior to discharge and major morbidities. No significant differences were observed in mortality or morbidity outcomes. Time to regain birth weight was shorter in the SMOF group, and reduced rates of lipid interruptions, retinopathy of prematurity, and osteopenia of prematurity were observed. SMOFlipid was significantly associated with lower odds of lipid interruptions, retinopathy of prematurity, osteopenia of prematurity as well as neonatal cholestasis (odds ratio (0.69, 95% CI 0.51-0.95)). Although this retrospective analysis was not designed to demonstrate causality, this evaluation indicates that there is benefit of empiric SMOFlipid use in very low birth weight neonates.

With new evidence, the standard of care of providing exclusive soybean-based lipid emulsions to infants come into question.

In summary, there is some literature support for the use of empiric SMOFlipid in preterm neonates on hepatic outcomes. It is promising that infants in the SMOFlipid groups did not experience poorer growth outcomes than the standard-of-care groups. Although SMOFlipid has been approved by the FDA for adults, it has not yet been granted for infants. Previous systematic reviews evaluating lipid emulsions for infants have been inconclusive in determining added benefits, likely due to lack of highly powered data and specific patient inclusion criteria.

Consideration of patient-specific characteristics that were most associated with benefit in studies is a reasonable starting point when assessing infant SMOFlipid use, particularly in preterm neonates that are anticipated to require PN for a prolonged period (>4 weeks), regardless of a GI diagnosis.

COMMENTS? E-mail them to llevine@mjhifesciences.com

To read the complete article and for references, go to ContemporaryPediatrics.com/ILEs
Judging the efficacy of anti-bullying programs

Bullying is a far too common problem in childhood. A meta-analysis examines the effectiveness of anti-bullying interventions.

MIRANDA HESTER, EDITOR

Sadly, bullying is a fact of life for many children. Fortunately, anti-bullying interventions have been developed to tackle the problem. A meta-analysis in *JAMA Pediatrics* looks at whether the programs had a positive impact.

The researchers did a search through ERIC, PsycInfo, and Ovid MEDLINE databases using 3 sets of search terms to find randomized clinical trials that assessed anti-bullying. The outcomes looked at the impact of anti-bullying intervention on 8 variable categories including bullying exposure, mental health issues, and overall bullying.

Investigators found 69 randomized clinical trials which totaled 111,659 participants. The average age of participants in the intervention group was 11.1 years (10.8 years in the control group). Overall, anti-bullying interventions were found to be effective in reducing bullying (effect size [ES], −0.150; 95% CI, −0.191 to −0.109) as well as improving mental health problems (ES, −0.205; 95% CI, −0.277 to −0.133) at the study’s end point, with population impact numbers for universal interventions meant to target the total population of 147 (95% CI, 113-213) and 107 (95% CI, 73-173), respectively. The investigators concluded that overall the impact of anti-bullying intervention was substantial.

Examining the relationship of nitrogen dioxide and obesity on asthma outcomes

A look at the relationship between nitrogen dioxide, asthma symptoms, and BMI.

Nitrogen dioxide is a common air pollutant and can be found in elevated levels in metropolitan areas due to traffic congestion. Air pollutants have been shown to impact the development of asthma in childhood. A report examines the relationship between nitrogen dioxide and asthma symptoms and morbidity by body mass index (BMI) category as well as the impact of the asthma symptoms.

The researchers used the School Inner-City Asthma Study, which enrolled students aged 4 to 13 years who had asthma and attended 37 inner-city schools. Following enrollment into the study, asthma symptoms, lung function, pulmonary inflammation, and morbidity were watched through the next academic year. Classroom nitrogen dioxide data were collected twice per year.

There were 271 students included in the analyses and the cohort was predominantly Black and Hispanic. In the cohort, 50% of the children were normal weight (5-84th body mass index percentile); 15% were overweight (≥85-94th body mass index percentile); and 35% obese (≥95th body mass index percentile).

The researchers concluded that children who have an obese BMI seem more vulnerable to the effects of classroom exposure to nitrogen dioxide and the impact on asthma symptoms. Targeting indoor levels of nitrogen dioxide in schools could help improve asthma outcomes for children who are obese.
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Segmental form of mosaic neurofibromatosis 1

Hasina Maredia, MD

**The Case**

A healthy 16-year-old girl presented with asymptomatic lesions she had at birth. Examination revealed a 15 cm well-demarcated light brown hyperpigmented background patch localized to the right inguinal skin-fold and, within it, café-au-lait macules and patches, greater than 1.5 cm, with diffuse freckling (Figure 1).

**Etiology/epidemiology**

NF1 is the most common form of neurofibromatosis, with an estimated prevalence of 1 in 4500, although the mosaic form has a prevalence of 1 in 36,000-40,000, but is likely to be underreported.1 The skin condition MNF1 occurs after microdeletion mutations in the NF1 gene during embryonic development. Skin involvement can range from a narrow segment to half of the body in either symmetrical or asymmetrical distribution, depending on the timing of the mutation and the cell lines affected.2

**Clinical Findings**

Patients with MNF1 may meet the diagnostic criteria for NF1, but their findings occur in more localized areas as in our patient. Diagnosis is made using the National Institutes of Health criteria based on the presence of at least 2 clinical findings, of which our patient has 6 or more café-au-lait macules or patches (greater than 0.5 cm in children or 1.5 cm in adults) and freckling in the inguinal crease.1 However, children with only 3-5 café-au-lait lesions could also be affected by MNF1, though these cases are often underreported. For this presentation, the natural progression of MNF1 is similar to that of NF1, with patients first presenting with café-au-lait lesions, followed by freckling. A classic sign seen in our patient is a subtle hyperpigmented background patch in the affected area. Other diagnostic criteria include 2 or more neurofibromas or one plexiform neurofibroma, two or more Lisch nodules, optic glioma, bony dysplasia, or a first-degree relative with NF1. When they arise, neurofibromas are usually seen in adulthood.

Complications seen in NF1 include hypertelorism, macrocephaly, short stature, and thorax abnormalities, as well as learning disabilities, ophthalmologic and orthopedic issues, and increased risk of certain malignancies.1,3 However, among MNF1 with localized skin involvement, complications are more rare, but have been reported to occur, especially with larger involvement of the skin, though not necessarily in the same location as skin involvement.1

**Differential diagnosis**

About 10% of the general population has 1 to 2 café-au-lait lesions, which can be normal.3 Other important differential diagnoses include syndromes...
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associated with café-au-lait macules (NF2, legius syndrome, McCune-Albright syndrome, and multiple familial café-au-lait), conditions associated with pigmented macules (Peutz-Jeghers syndrome, LEOPARD syndrome, neurocutaneous melanosis), and other conditions causing tumor or localized overgrowth (lipo-omatosis, fibromatoses, speckled lentiginous segmental eruption).³

Management
There are no specific guidelines for management of patients with MNF1 as there are for NF1.¹ It is important for pediatricians to recognize MNF1 as it is likely underdiagnosed. Patients should be advised of lower risk of complications compared to NF1, but be aware that complications and gonadal involvement are possible.¹ It has thus been recommended that MFN1 patients undergo a complete physical exam and global assessment as well as consider genetic counseling as well.¹⁻⁴

Patients with MNF1 can be reassured that, although the involved area can evolve in appearance during childhood, new lesions or spreading of the lesions would not be expected to occur on other areas in adulthood.

Patient Outcome
Our patient is growing and developing normally, has a normal eye exam, and has no signs of systemic NF1.¹

COMMENTS? E-mail them to llevine@mjlifesciences.com

For references, go to ContemporaryPediatrics.com/dermcase-1220

Dr Maredia is a resident at Massachusetts General Hospital. The author has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in this article.
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• Gentle, non-foaming body wash

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• 44% reduction in risk of flare
• 4 out of 5 children remained flare free for 6 months
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Steroid-free • Fragrance-free • Dye-free • Paraben-free • Noncomedogenic

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