Indication for PEDIARIX

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

Important Safety Information for PEDIARIX

• Contraindications for PEDIARIX are: severe allergic reaction (eg, anaphylaxis) after a previous dose of any diphtheria toxoid-, tetanus toxoid-, pertussis-, hepatitis B-, or poliovirus-containing vaccine, or to any component of PEDIARIX; encephalopathy within 7 days of administration of a previous pertussis-containing vaccine; progressive neurologic disorders

• In clinical trials, PEDIARIX was associated with higher rates of fever relative to separately administered vaccines

• The decision to give PEDIARIX should be based on potential benefits and risks if Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, or if adverse events (ie, temperature ≥105°F, collapse or shock-like state, persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours after vaccination; seizures within 3 days after vaccination) have occurred after receipt of a pertussis-containing vaccine

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

• Syncope (fainting) can occur in association with administration of injectable vaccines. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope

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

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

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

Catch them up with the one you know: PEDIARIX

DTaP=diphtheria, tetanus, and acellular pertussis.

Important Safety Information for PEDIARIX (cont’d)

• For children at higher risk for seizures, an antipyretic may be administered at the time of vaccination with PEDIARIX
• Apnea following intramuscular vaccination has been observed in some infants born prematurely. Vaccination with PEDIARIX should be based on consideration of the individual infant’s medical status and the potential benefits and possible risks of vaccination
• In clinical trials, common adverse reactions in infants receiving PEDIARIX included injection-site reactions (pain, redness, and swelling), fever, drowsiness, irritability/fussiness, and loss of appetite
• Vaccination with PEDIARIX may not result in protection in all vaccine recipients

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

References: 1. Prescribing Information for PEDIARIX.
2. Prescribing Information for Pentacel.

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PDRJRNA200004 November 2020
Produced in USA.
PEDIARIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine)

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

1 INDICATIONS AND USAGE

PEDIARIX is indicated for active immunization against diphtheria, tetanus, pertussis, and hepatitis B. PEDIARIX contains diphtheria toxoid, tetanus toxoid, pertussis antigens, hepatitis B antigens, and poliovirus vaccine.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Shake vigorously to obtain a homogeneous, turbid, white suspension. Do not use if resuspension does not occur with vigorous shaking. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exist, the vaccine should not be administered.

Attach a sterile needle and administer intramuscularly.

The preferred administration site is the anterolateral aspect of the thigh for children younger than 1 year. In older children, the deltoid muscle is usually large enough for an intramuscular injection. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk. Gluteal injections may result in suboptimal hepatitis B immune response. Do not administer this product intravenously, intradermally, or subcutaneously.

2.2 Recommended Dose and Schedule

Immunization with PEDIARIX consists of 3 doses of 0.5 mL each by intramuscular injection at 2, 4, and 6 months of age (at intervals of 6 to 8 weeks, preferably 8 weeks). The first dose may be given as early as 6 weeks of age. Three doses of PEDIARIX constitute a primary immunization course for diphtheria, tetanus, pertussis, and poliomyelitis and the complete vaccination course for hepatitis B.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

A severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria toxoid-, tetanus toxoid-, pertussis antigen-, hepatitis B-, or poliovirus-containing vaccine or any component of this vaccine, including yeast, neomycin, and polymyxin B, is a contraindication to administration of PEDIARIX [see Description (11) of full prescribing information].

4.2 Encephalopathy

Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous dose of a pertussis-containing vaccine that is not attributable to another identifiable cause is a contraindication to administration of any pertussis-containing vaccine, including PEDIARIX.

4.3 Progressive Neurologic Disorder

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

5 WARNINGS AND PRECAUTIONS

5.1 Fever

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

5.2 Guillain-Barré Syndrome

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

5.3 Latex

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

5.4 Syncope

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

5.5 Adverse Reactions following Prior Pertussis Vaccination

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

• Temperature >39.5°C (103°F) within 48 hours not due to another identifiable cause;
• Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours;
• Persistent, inconsolable crying lasting >3 hours, occurring within 48 hours;
• Seizures with or without fever occurring within 3 days.

5.6 Children at Risk for Seizures

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

5.7 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about immunization of an infant born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination.

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. 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 comparative studies (including the German and U.S. studies described below), administration of PEDIARIX was associated with higher rates of fever relative to separately administered vaccines [see Warnings and Precautions (5.1)]. The prevalence of fever was highest on the day of vaccination and the day following intramuscular vaccine. 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 hematopoietic influenzavirus type b (Hib) conjugate vaccines (GlucoSmithKline [licensed in the United States only for booster immunization], Wyeth Pharmaceuticals Inc. [no longer licensed in the United States], Sanofi Pasteur SA [U.S.-licensed], or Merck & Co, Inc. [U.S.-licensed]) at 3, 4, and 5 months of age and for 768 infants in the control group that received separate U.S.-licensed vaccines (INFANRIX, Hib conjugate vaccine [Sanofi Pasteur SA], and oral poliovirus vaccine [OPV] [Wyeth Pharmaceuticals, Inc., no longer licensed in the United States]). In this study, information on adverse events that occurred within 30 days following vaccination was collected. More than 95% of study participants were white.

In a U.S. study, the safety of PEDIARIX administered to 673 infants was compared with the safety of separately administered INFANRIX, ENGERIX-B (Hepatitis B Vaccine [Recombinant]), and IPV (Sanofi Pasteur SA) in 335 infants. In both groups, infants received Hib conjugate vaccine (Wyeth Pharmaceuticals Inc; no longer licensed in the United States) and 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) concomitantly at separate sites. All vaccines were administered at 2, 4, and 6 months of age. Data on solicited local reactions and general adverse reactions were collected by parents using standardized diary cards for 4 consecutive days following each vaccine dose (i.e., day of vaccination and the next 3 days). Telephone follow-up was conducted 1 month and 6 months after the third vaccination to inquire about serious adverse events. At the 6-month follow-up, information also was collected on new onset of chronic 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 study are presented in Table 1. This study was powered to evaluate fever >101°F following Dose 1. The rate of fever ≥101.4°F following each dose was significantly higher in the group that received PEDIARIX compared with separately administered vaccines. Other statistically significant differences between groups in rates of fever, as well as other solicited adverse reactions, are noted in Table 1. Medical attention (a visit to or from medical personnel) for fever within 4 days following vaccination was sought in the group who received PEDIARIX for 8 infants after the first dose (1.2%), 1 infant following the second dose (0.2%), and 5 infants following the third dose (0.8%) (Table 1). Following Dose 2, medical attention for fever was sought for 2 infants (0.6%) who received separately administered vaccines (Table 1). Among infants who had a medical visit for fever within 4 days following vaccination, 9 of 14 who received PEDIARIX and 1 of 2 who received separately administered vaccines, had 1 or more diagnostic studies performed to evaluate the cause of fever.

(continued on next page)
PEDIARIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, and T-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></td>
<td>Dose 1</td>
<td>Dose 2</td>
</tr>
<tr>
<td>Locala</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>667</td>
<td>644</td>
</tr>
<tr>
<td>Pain, any</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>Pain, Grade 2 or 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain, Grade 3</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Redness, &gt;5 mm</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Redness, &gt;20 mm</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Swelling, any</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Swelling, &gt;5 mm</td>
<td>6</td>
<td>6</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>671</td>
<td>653</td>
</tr>
<tr>
<td>Drowsiness, any</td>
<td>70</td>
<td>68</td>
</tr>
<tr>
<td>Drowsiness, Grade 2 or 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness, Grade 3</td>
<td></td>
<td></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>28</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>8</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.

aWithin 4 days of vaccination defined as day of vaccination and the next 3 days.

bLocal reactions at the injection site for PEDIARIX or INFANRIX.

cRate 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 PEDIARIX] does not include 0).

dAxillary 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% [7/763]). None of these subjects had a febrile seizure, 1 had an afebrile seizure, and 1 had subdural hematoma. One subject received PEDIARIX and 1 death was reported among 2,287 (0.04%) recipients of comparator vaccines. Causes of death in the group that received PEDIARIX included 2 cases of sudden infant death syndrome (SIDS) and 1 case of each of the following: convulsive disorder, congenital immunodeficiency with sepsis, and neuroblastoma.

Deaths
In 14 clinical trials, 5 deaths were reported among 8,088 (0.06%) recipients of PEDIARIX and 1 death was reported among 2,287 (0.04%) recipients of comparator vaccines. Causes of death in the group that received PEDIARIX included 2 cases of sudden infant death syndrome (SIDS) and 1 case of each of the following: convulsive disorder, congenital immunodeficiency with sepsis, and neuroblastoma.

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 nephropathy. 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 = 789) reported seizures. In a separate German study that evaluated the safety of INFANRIX in 22,505 infants who received 66,867 doses of INFANRIX administered as a 3-dose primary series, the rate of seizures within 7 days of vaccination with INFANRIX was 0.13 per 1,000 doses (febrile seizures 0.0 per 1,000 doses, afebrile seizures 0.13 per 1,000 doses).

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

Other Neurological Events of Interest
No cases of hypotonic-hypore sponsiveness 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 followed 1 previous dose of PEDIARIX with a 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 1991 to 2000 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 considered 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 40,000 infants who received PEDIARIX was compared with the equivalent 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 (≥100.4°F that resulted in hospitalization, an emergency department visit, or an outpatient visit) during the 4-day period following vaccination. Possible seizures and medical visits plausibly related to fever were identified by searching automated inpatient and outpatient data files. Medical record reviews of identified events were conducted to verify the occurrence of seizures or medically-attended fever. The incidence of verified seizures and medically-attended fever from this study are presented in Table 2.

(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 Controls</th>
<th>Difference (PEDIARIX–DTaP Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</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</td>
<td>7</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>(0.01, 0.04)</td>
<td></td>
<td>(0.01, 0.03)</td>
</tr>
<tr>
<td>Dose 2, Days 0-7</td>
<td>40,000</td>
<td>3</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>(0.00, 0.02)</td>
<td></td>
<td>(0.00, 0.03)</td>
</tr>
<tr>
<td>Dose 3, Days 0-7</td>
<td>40,000</td>
<td>6</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>(0.01, 0.03)</td>
<td></td>
<td>(0.00, 0.03)</td>
</tr>
<tr>
<td>Total doses</td>
<td>120,000</td>
<td>16</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>(0.00, 0.02)</td>
<td></td>
<td>(0.00, 0.02)</td>
</tr>
</tbody>
</table>

Medically-Attended Fever

|                  | N | n | % (95% CI) | N | n | % (95% CI) | % (95% CI) |
|------------------|-----------|--------------------------|-------------------------------------|
|                  | Dose 1, Days 0-3 | 7,500 | 14 | 0.19 | 7,500 | 14 | 0.19 | 0.00 |
|                  | (0.11, 0.30) | | (0.11, 0.30) | | | | |
|                  | Dose 2, Days 0-3 | 7,500 | 25 | 0.33 | 7,500 | 19 | 0.20 | 0.13 |
|                  | (0.22, 0.48) | | (0.11, 0.33) | | | | |
|                  | Dose 3, Days 0-3 | 7,500 | 21 | 0.28 | 7,500 | 19 | 0.25 | 0.03 |
|                  | (0.17, 0.43) | | (0.15, 0.39) | | | | |
|                  | Total doses | 22,500 | 68 | 0.27 | 22,500 | 48 | 0.21 | 0.05 |
|                  | (0.20, 0.34) | | (0.16, 0.28) | | | | |

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.

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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. Investigations
Abnormal liver function tests.

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

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

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

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

Vascular Disorders
Pallor, petechiae.

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS

Idiopathic thrombocytopenic purpura.
Lymphadenopathy.
Thrombocytopenia,

GASTROINTESTINAL DISORDERS

Abdominal pain.
Intussusception.
Nausea.

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

Asthenia.
Malaise.

HEPATICOBILIARY DISORDERS

Jaundice.

IMMUNE SYSTEM DISORDERS

Anaphylactic shock.
Serum sickness–like disease.

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

Arthralgia.
Arthritis.
Muscular weakness.
Myalgia.

NERVOUS SYSTEM DISORDERS

Encephalopathy.
Headache.
Meningitis.
Neuritis.
Neuropathy.
Paralysis.

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

Alopecia.
Erythema multiforme.
Lichen planus.
Pruritus.
Stevens Johnson syndrome.

vascular disorders

Vasculitis.

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

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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Well, we have made it to March, the “straddle” month. This is that pivotal moment on the calendar when we can brush off winter and finally see legitimate signs of spring, from the vernal equinox to the earliest flowerings (the dogwood and magnolia trees start blooming!). In the health care world, spring 2021 heralds another season filled with promise. Besides the offerings in this current issue of *Contemporary Pediatrics,* (from a refresher on seasonal allergies to guidelines for helping parents deal with their children’s sleep issues), we continue to expand and change on our other platforms. On Medical World News,™ our company’s 24-hour medical news channel, you can listen to interviews with *Contemporary Pediatrics*’ educational advisory board member Andrew J. Schuman, MD, as he discusses everything from nutritional best practices to the latest on coronavirus disease 2019 (COVID-19). Our podcast series, launched this past summer and available on our website, https://www.contemporarypediatrics.com, includes an engaging chat with vaccine authority Paul A. Offit, MD, on medical myths, an informative episode on ear exams and hearing loss in children, and more. Additionally, we have initiated a “Meet the Board” podcast series. Each month, a member of our advisory board will share with us thoughts on why they chose medicine as a profession and what they see as the biggest challenges for health care providers in 2021.

It is hard to believe that March 19 will be the 1-year anniversary of the first state stay-at-home order (California). Thankfully, we are in a much less vulnerable position now, due to the remarkable work of those who have provided us with vaccines, treatments, and personal protective equipment at record speed. So let those flowers bloom!

---

**Mike Hennessy Sr**
Chairman and Founder
MJH Life Sciences®

Send comments to llevine@mjhlifesciences.com
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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/3ibVix2

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in this issue MARCH 2021
Her struggles may be tied to complex ADHD. Differential diagnosis is key.

Our understanding of ADHD has evolved from that of a discrete behavioral condition to a complex neurobiologic disorder with various associated comorbidities.\(^1\)\(^4\) It is now recognized that ADHD is usually accompanied by coexisting disorders and other complicating factors that may or may not be identified and adequately treated.\(^5\) Overlapping comorbidities can obscure the many faces of ADHD, potentially standing in the way of effective treatment and successful long-term outcomes.\(^5\)

Visit TEAM-ADHD.com/DDx for a deeper dive into complex ADHD and nuances of differential diagnoses.

The road to normal

as the rollout of coronavirus disease 2019 (COVID-19) vaccines in the community increases, it is time to start thinking how we can offer these vaccines in a streamlined, effective manner. Clinical trials of COVID-19 vaccines are now being conducted in children above age 12, and we hope that a vaccine will be available for the pediatric population by the fall of 2021. With the emergence of new COVID-19 variants, questions have arisen about the current vaccines’ effectiveness against them. The estimated percentage of people that must be vaccinated to achieve herd immunity has slowly increased to 80%. This gives us some food for thought, as the pediatric population accounts for about 25% of the US population, a considerably larger portion than that of other countries.

In this month’s issue, several must-read articles:

- “Seasonal allergies: What every pediatrician needs to know” is an excellent review of current allergens, protocols for treatment, and specific things to be aware of.
- The article on the return to sports and active play of children who tested positive for COVID-19 provides excellent guidance for pediatric health care providers including what to monitor and evaluate prior to return. This is an issue that is rapidly evolving and there has been a major increase in questions as more schools return to in school learning and resume club sports and play.
- The report on sleep problems in children underscores the idea that media use can lead to a decrease in the quality and duration of sleep, especially if it occurs prior to bedtime.

As always, I recommend your comments, suggestions, and questions. Please stay safe and well.

With warmest regards,
Tina

The Clinical Pharmacologist’s Notebook

contributing editors

Bernard A. Cohen, MD Section Editor for Dermcase, Professor of Pediatrics and Dermatology, Johns Hopkins University School of Medicine, Baltimore, Maryland

Jon Matthew Farber, MD Section Editor for Journal Club, pediatrician, ALL Pediatrics, Woodbridge, Virginia

Carlton K. K. Lee, PharmD, MPH, FASHP, FPPAG Section Editor for The Clinical Pharmacologist’s Notebook, Pediatric Clinical Pharmacy Specialist, Department of Pharmacy, and Associate Professor, Department of Pediatrics, Johns Hopkins Medical Institutions, Baltimore, Maryland

Nina L. Alfiari, MD, MS Instructor of Pediatrics, Feinberg School of Medicine, Northwestern University.


Amin J. Barakat, MD, FAAP

Pediatrician for Children’s Physicians, Omaha, Nebraska, assistant clinical professor, Creighton University Medical School, Omaha, Co-editor for SOID (Section of Infectious Diseases) newsletter, CODe (Committee on Development) member for AAP

Jane M. Carnazzo MD, FAAP Clinical Professor of Pediatrics Emeritus, University of Washington School of Medicine, Seattle, Washington

Michael S. Jellinek, MD

Clinical Professor of Psychiatry and of Pediatrics, Harvard Medical School, Boston, Massachusetts

Rana F. Hamdy, MD, MPH, MSCE

Assistant Professor of Pediatrics, George Washington University School of Medicine and Health Sciences; Pediatric Infectious Diseases Attending, Director, Antimicrobial Stewardship Program, Associate Fellowship Program Director, Children’s National Hospital, Washington, DC.

Andrew J. Schuman, MD

Clinical Assistant Professor of Pediatrics, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire

Candice Jones, MD

Board-certified general pediatrician in group practice in Orlando, Florida, former National Health Service Corps Scholar, AAP member, spokesperson and author

Steven M. Selbst, MD

Professor of Pediatrics, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, Pennsylvania, Attending Physician, Pediatric Emergency Medicine, Nemours/Alfred I duPont Hospital for Children, Wilmington, Delaware

Donna Hallas, PhD, CPNP, PPCNP-BC, PMHS, FAAN

Clinical Professor, New York University Meyers College of Nursing, and Director, Pediatric Nurse Practitioner Program, New York, New York

W. Christopher Golden, MD

Associate Professor of Pediatrics Neonatologist, Division of Neonatology Medical Director, Newborn Nursery Director, Pediatrics Core Clerkship, Johns Hopkins University School of Medicine, Baltimore, Maryland

Jane M. Carnazzo MD, FAAP

Dr Farber’s journal club

BY MARIAN FREEDMAN
KEY TAKES ON MUST-READ STUDIES

Lung ultrasound: A useful tool for investigating bronchiolitis

Investigators found a significant correlation between clinical severity score and LUS score, as well as a positive correlation between LUS score and days of hospitalization. In addition, patients with higher LUS scores were most likely to require oxygen therapy. LUS findings were lung B-lines, subpleural consolidation, and abnormalities of the pleural line. Lung B-lines, in particular confluent B-lines, were most frequently seen in LUS posterior projection. Subpleural consolidations were present in 54 infants, most often the multiple forms or consolidation. Finally, 13 infants had pleural line abnormalities. In comparing CXR and LUS results, investigators noted a concordance in findings of subpleural lung consolidations as well as a significant correlation between abnormalities of the pleural line and air trapping.

Once again, the ultrasound demonstrates that it can provide a valuable diagnostic tool in a number of areas, whose advantages include its ability to be used at the bedside and being radiation free. However, before you get too excited about the idea of using this routinely in children with bronchiolitis, look at the next abstract.


THOUGHTS FROM DR FARBER

Once again, the ultrasound demonstrates that it can provide a valuable diagnostic tool in a number of areas, whose advantages include its ability to be used at the bedside and being radiation free. However, before you get too excited about the idea of using this routinely in children with bronchiolitis, look at the next abstract.


Dr Farber, section editor for Journal Club, is a pediatrician in Woodbridge, Virginia. Ms Freedman is a freelance medical editor and writer in New Jersey. The editors have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of these articles.
A case report illustrates the importance of carefully evaluating the diagnosis when laboratory results do not match up with clinical signs and symptoms. It describes how results of a complete blood count for a girl aged 5 years, whose parents were concerned about her short stature, confirmed a diagnosis of thrombocytopenia. However, the child had no personal or family history of bleeding diathesis, and the blood test revealed many small platelet clumps, which were highly suggestive of ethylenediaminetetraacetic acid (EDTA)-dependent pseudothrombocytopenia. A new blood sample was divided into an EDTA microtainer and a citrate container for immediate testing. Small platelet clumps again were seen in the EDTA but not in the citrate sample. This and other blood sample findings supported the diagnosis of EDTA-dependent pseudothrombocytopenia. This condition is a laboratory artifact caused by the presence of antiplatelet antibodies in the patient’s serum.

Senior staff and nurses, but not residents, can diagnose respiratory syncytial virus (RSV) infection based on cough sound as accurately as bedside tests. However, they can’t outperform the gold-standard diagnostic test—multiplex ligation-dependent probe amplification (MLPA)—according to the results of a Netherlands study. During a 3-month period, parents of children aged younger than 1 year who were admitted to the pediatric ward because of airway complaints recorded their child’s cough sounds with their smartphone. Investigators then linked these audio fragments to the viral agents found via MLPA analysis. They inserted 16 cough fragments representing 4 different viral pathogens (RSV, influenza, human metapneumovirus, and rhinovirus) into a questionnaire presented to 32 pediatric nurses, 16 residents, and 16 senior staff members. Respondents were asked to classify each cough (as wet, dry, or other), specify features of the so-called typical RSV cough, and indicate whether the cough was or was not caused by RSV.

Participants showed no consistency in describing the coughs, making it impossible to specify features of a so-called typical RSV cough. Influenza was most easily distinguished from RSV, whereas RSV itself most often was identified as RSV. On average, senior staff correctly identified 3.8 of 5 of the RSV coughs, with 37.5% identifying all coughs correctly, demonstrating a mean sensitivity of 76.2%. Nurses did nearly as well, correctly identifying 3.7 of 5 RSV coughs, with 34.4% achieving 100% accuracy, corresponding to a mean sensitivity of 73.1%. Residents, whose average work experience was 2.1 years, fared worse than senior staff and nurses in identifying the coughs (mean sensitivity, 51.3%), and investigators determined that they needed at least 3.5 years of working experience to reach the same level of detection as their more experienced colleagues. Compared with bedside tests, senior staff and nurses performed as well at detecting patients with RSV based on cough sound, but could not validly distinguish RSV from other pathogens. Investigators therefore concluded that diagnosis based on cough sounds could not replace MLPA analysis.

Can you really diagnose RSV based on how the cough sounds? Senior staff and nurses, but not residents, can diagnose respiratory syncytial virus (RSV) infection based on cough sound as accurately as bedside tests. However, they can’t outperform the gold-standard diagnostic test—multiplex ligation-dependent probe amplification (MLPA)—according to the results of a Netherlands study. During a 3-month period, parents of children aged younger than 1 year who were admitted to the pediatric ward because of airway complaints recorded their child’s cough sounds with their smartphone. Investigators then linked these audio fragments to the viral agents found via MLPA analysis. They inserted 16 cough fragments representing 4 different viral pathogens (RSV, influenza, human metapneumovirus, and rhinovirus) into a questionnaire presented to 32 pediatric nurses, 16 residents, and 16 senior staff members. Respondents were asked to classify each cough (as wet, dry, or other), specify features of the so-called typical RSV cough, and indicate whether the cough was or was not caused by RSV.

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I got a different takeaway from this. Although it is rarely necessary to diagnose RSV infections specifically in outpatients, this study shows that experienced pediatricians can do this quite well without any testing, and without even auscultating the lungs for wheezing. If you also look at the child to see how ill he or she appears, which should enhance accuracy, these findings suggest that televisits for diagnosing bronchiolitis in infants are not far-fetched.

Making a diagnosis when labs and clinical findings don’t correlate A case report illustrates the importance of carefully evaluating the diagnosis when laboratory results do not match up with clinical signs and symptoms. It describes how results of a complete blood count for a girl aged 5 years, whose parents were concerned about her short stature, confirmed a diagnosis of thrombocytopenia. However, the child had no personal or family history of bleeding diathesis, and the blood test revealed many small platelet clumps, which were highly suggestive of ethylenediaminetetraacetic acid (EDTA)-dependent pseudothrombocytopenia. A new blood sample was divided into an EDTA microtainer and a citrate container for immediate testing. Small platelet clumps again were seen in the EDTA but not in the citrate sample. This and other blood sample findings supported the diagnosis of EDTA-dependent pseudothrombocytopenia. This condition is a laboratory artifact caused by the presence of antiplatelet antibodies in the patient’s serum.

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Thoughts from Dr Farber

Remember this pearl should this situation ever come up. More importantly, no matter how much faith you may put in lab testing, remember that an unexpected finding does not automatically mean you missed something on your history and examination; the error may lie in the technology.

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INTRODUCING A

Therapeutic OTC Eczema Regimen

Complement your therapeutic approach by recommending clinically proven solutions for Eczema-prone skin

NEW Eucerin® Baby Eczema Relief Cream Body Wash

- Statistically significant improvement in itching (55%), erythema (46%), and dryness (44%) at Week 1 vs baseline
d- 2% Colloidal Oatmeal*, Ceramide NP, gentle cleansing system
d- Gentle, non-foaming body wash

Eucerin Baby Eczema Relief Cream

- 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

* A skin protectant
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A 17-year-old boy with a history of anxiety was transported from a juvenile detention center for altered mental status, including hallucinations and agitation.

Four days prior, he had arrived at the center in his usual state of health. Upon arrival, he was placed in a solitary isolation room due to a pending coronavirus disease 2019 (COVID-19) test. Three days later he was found to be diaphoretic with visual hallucinations, paranoia (asking to change rooms, describing “snipers on the roof”), physical agitation, and bizarre behavior, including attempting to drink out of the toilet bowl.

He was then taken to a community emergency department (ED), where he had a normal noncontrast head computed tomography (CT) scan. There he received lorazepam, diphenhydramine, and haloperidol, after which he became less physically agitated but remained significantly altered. He was then transferred to our tertiary care children’s hospital.

It was difficult to obtain an initial medical history from the patient due to his altered mental status. He did admit to some substance use, including alcohol, marijuana, and benzodiazepines, prior to detention. His grandmother, with whom he lived, had also found a “green pill” in the house, which she could not identify and had flushed down the toilet. She also reported that her grandson had been anxious but otherwise well prior to entering the juvenile detention center. According to his grandmother, and staff at the juvenile detention center, he had not had any known fevers, headache, blurry vision, gait instability, head trauma, or loss of consciousness. His family history was notable for depression, anxiety, and substance use disorders.

Initial testing
Initial laboratory evaluation demonstrated normal serum electrolytes and tests of renal function, with elevated serum aspartate aminotransferase/alanine aminotransferase levels of 143/43 u/L with normal serum ammonia. His complete blood count displayed a mildly elevated white blood cell count (11 K/uL) with 71.9% neutrophils; inflammatory markers were normal. A serum drug screen was negative for alcohol, acetaminophen, and salicylates. A urine immunoassay drug screen was positive for cannabinoids but otherwise negative, including for amphetamines, benzodiazepines, cocaine, and opiates. A broad serologic laboratory work-up extremity being handcuffed to the bed. His mental status was alert and oriented to self and place (he was unsure of the date). It was notable for describing seeing “virtual currency,” hearing “things through his AirPods” even when he was not using them, and tangential thought content without pressured speech. In sleep, he was observed to have frequent bilateral upper extremity myoclonic jerking and unintelligible utterances. Sleep appeared to be fragmented into 15- to 20-minute segments.

Want to read more of your colleagues’ puzzling cases?
Find the whole collection at ContemporaryPediatrics.com/pediatric-puzzler
TABLE
DIFFERENTIAL DIAGNOSIS OF PSYCHOSIS

<table>
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<th>PRIMARY PATHOLOGY BY SYSTEM</th>
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<td>Drugs/toxicants</td>
<td>Drug toxicity (marijuana and synthetic cannabinoids, hallucinogens, sympathomimetics, opioids, sedatives, barbiturates, anticholinergics)</td>
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<td>Drug withdrawal (alcohol, benzodiazepines)</td>
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<td>Serotonin syndrome</td>
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<td>Other toxicants (toxic alcohols, carbon monoxide, cyanide, heavy metals, etc)</td>
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<tr>
<td>Psychiatric</td>
<td>Schizophrenia, schizoaffective disorder, schizopreniform disorders</td>
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<td></td>
<td>Delusional disorder</td>
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<td>Brief psychotic disorder</td>
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<td>Schizotypal personality disorder</td>
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<td>Major depressive disorder or bipolar disorder with psychotic features</td>
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<td>Autoimmune/inflammatory</td>
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<td>Anti-NMDA receptor encephalitis (or other autoimmune encephalitis)</td>
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<td>Neurologic</td>
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<td>CNS space-occupying lesion</td>
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<td>Postictal psychosis</td>
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<td>Infectious</td>
<td>Bacterial, viral, or rickettsial meningitis/encephalitis</td>
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<td>Sepsis or other systemic infections</td>
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<td>Syphilis</td>
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<td>Organ failure</td>
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<td>Metabolic derangements</td>
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<td></td>
<td>Nutritional deficiencies (vitamin B12, folate, thiamine—Wernicke encephalopathy)</td>
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<td>Endocrine disturbances</td>
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<td>Hypercarbia/hypoxemia</td>
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<td>Inborn errors of metabolism (acute intermittent porphyria, Wilson disease)</td>
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<td>Hypo- and hyperglycemia</td>
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NMDA, N-methyl-D-aspartate. CNS, central nervous system

was sent, which included an autoimmune encephalitis panel, oligoclonal bands, antinuclear antibody (ANA), rheumatoid factor (RF), copper, ceruloplasmin, vitamin B12/folate, thyroid-stimulating hormone (TSH), and rapid plasma regain (RPR)/HIV. A lumbar puncture and empiric antimicrobials were deferred given lack of infectious signs or symptoms.

The patient was given empiric thiamine for possible Wernicke encephalopathy.

Diagnostic test results
Video electroencephalogram (EEG) and brain magnetic resonance imaging were performed and were normal. The autoimmune encephalitis panel, oligoclonal bands, ANA, RF, copper, ceruloplasmin, B12/folate, TSH, and RPR/HIV returned negative.

Further history: The key to the diagnosis
On hospital day 2, the patient’s mother disclosed that the patient had previously informed her of 3 to 4 months of daily alprazolam use, as much as 2 to 3 “xanny bars” per day, which he was obtaining from friends or via social media. In light of the clinical history of acute onset diaphoresis, psychosis, sleep abnormalities, psychomotor agitation, and hypertension in the setting of recent incarceration, and a history of regular benzodiazepine use, his presentation was felt to be most consistent with alprazolam withdrawal.

Hospital course
A trial of alprazolam was administered to see if it would reverse the presumed withdrawal symptoms. After serial 1-mg alprazolam doses (total, 3 mg over 4 hours), the patient had a return of normal mental status and significant subjective improvement in perceptual disturbances, without sedation. Of note, a “xanny bar” is a 2-mg dose formulation of alprazolam; the patient had complete resolution of symptoms with a dosage comparable to what he had report-
A CLOSER LOOK AT DIAGNOSIS
The differential diagnosis for a teenager with altered mental status is extensive (Table). The diagnoses considered most likely are:

**Frontal lobe epilepsy**
Frontal lobe epilepsy can have highly variable presentations, including perceptual disturbances, focal motor seizures, and automatisms. Sleep-related hypermotor epilepsy is a relatively newly defined condition consisting of brief (<2 min) hypermotor events (kinetic kicking, cycling of legs; often associated with vocalizations) with abrupt onset and offset, usually occurring in sleep. Peak onset occurs during childhood and adolescence, and seizures can occur many times per night. Seizures may not be captured on interictal and ictal scalp EEG; video EEG is often required for the diagnosis. 1

Seizure clusters or status epilepticus is also more common in frontal lobe seizures, and there may be some preserved consciousness during episodes.

Our patient’s history of alterations in perception and abnormal movements and vocalizations in sleep could be consistent with frontal lobe seizures. However, his acute onset psychosis, agitation and diaphoresis, persistent autonomic instability between episodes, and lack of automatisms disfavored seizures.

**First onset primary psychosis**
The first episode of a primary psychosis occurs most commonly in late adolescence and early adulthood. A primary psychosis can consist of hallucinations, delusions, disorganized thoughts, and agitation, without intact reality testing. These symptoms are typically associated with prodromal symptoms, including decreased functioning, subclinical psychotic symptoms, and negative symptoms, such as a blunted affect, apathy, and decreased speech and thought content. A history of substance use is associated with a higher risk of developing a primary psychosis in patients with prodromal symptoms; there is also known association with mood disorders, including depression and anxiety. 2

Our patient had a personal and family history of substance use and anxiety, placing him at higher risk of developing a primary psychotic disorder. However, his lack of other prodromal symptoms made this seem less likely.

**Benzodiazepine withdrawal**
Abrupt cessation of regular benzodiazepine use can precipitate a withdrawal syndrome. This can include tremors, anxiety, autonomic instability, psychomotor agitation, and, less commonly, perceptual disturbances and psychosis, as well as life-threatening seizures. Time of onset can vary depending on the half-life of the benzodiazepines, ranging from 24 to 48 hours in benzodiazepines with short half-lives (alprazolam, lorazepam), and up to several weeks in those with longer half-lives (clonazepam, diazepam). Alprazolam withdrawal in particular is associated with more severe withdrawal syndromes, with more prominent features of psychosis, sleep disturbance, and anxiety compared to other benzodiazepines, even in the setting of short-term (~1 week) use. 3 Risk of seizure may occur regardless of the severity of other withdrawal symptoms.

Our patient had a history of substance abuse, including benzodiazepines, prior to his detention. His drug screen showed only cannabinoids, but we still considered withdrawal from benzodiazepine.

Discussion
The use of benzodiazepines, although prevalent among adults (12.6% in recent estimates, highest among ages 50-65 years), is presumably less common in the pediatric population; however, relevant data are sparse. Notably, younger adults (ages 18-25 years) have higher rates of benzodiazepine misuse despite lower rates of overall use. Younger adults or adolescents (18-24 and 13-17 years of age, respectively) are more likely to use alprazolam than diazepam without a medical purpose. 4,5 Alprazolam in particular has a higher misuse liability compared with other benzodiazepines, and is associated with more severe withdrawal syndromes, including delirium, psychosis, and even catatonia. 6,7

The diagnosis of benzodiazepine withdrawal must be made clinically in order to provide timely treatment. In the setting of a substance use history, particularly with a trigger for abrupt cessation of use such as placement in a detention facility, and without other clear organic etiologies, the constellation of abrupt onset of autonomic...
Although latent tuberculosis is the result of an immune system preventing the causative bacterium from becoming active, tuberculosis remains the world’s most deadly infectious disease. Clinicians currently use two methods of screening: the tuberculin skin test and the interferon gamma release assay. How does each measure up to standards of testing for children?

In this Contemporary Pediatrics® podcast, Dr. Anna Mandalakas discusses applications and efficacy of each test, including a 2020 study on predictive values; as well as the importance of proper specimen handling, impacts on testing outcomes in immunocompromised populations, and sensible criteria for retesting patients.

Go to: contemporarypediatrics.com/tb-kids
This young man was at risk of potentially life-threatening consequences of withdrawal while in physical and social isolation.
The mother of a 4-month-old patient is concerned that her son is not yet sleeping through the night. This is not uncommon for a young baby; the mother needs to return to work soon and is worried about being able to do her job effectively. He is on a regular feeding schedule at this point, but wakes up several times throughout the night, and sometimes it is difficult to get him back to sleep. She is wondering if there is something else she should be doing to help him sleep more consistently through the night. She has been reading about different methods of sleep training, and would like your input on which, if any, might be the most effective.

How much sleep is enough sleep

Getting enough sleep each day is critical to children’s health. The National Sleep Foundation maintains that babies, children, and teenagers need more sleep per day than adults to support mental and physical growth.1 Sleep deprivation has been shown to result in increased weight, restricted cognitive and motor development, slowed growth, affected cardiometabolic health, increased sedentary behavior, and more injuries.2 Rather than address all of these connections to sleep deprivation, this article focuses solely on the negative effects of insufficient sleep on behavioral and emotional regulation in children and teenagers. Despite the potential severity of sleep deprivation, parents as well as practitioners are nonetheless unsure of the amount of sleep children need.

The American Academy of Sleep Medicine (AASM) published pediatric sleep recommendations in 2016, and the American Academy of Pediatrics (AAP) endorsed these guidelines.3,4 The AASM recommends that in a 24-hour period, including naps, infants aged 4 to 12 months should sleep 12 to 16 hours; children aged 1 to 2 years should sleep 11 to 14 hours; those aged 3 to 5 years, 10 to 13 hours; those aged 6 to 12 years, 9 to 12 hours; and teenagers aged 13 to 18 years, 8 to 10 hours.5 The AAP supports these recommendations.6 The National Sleep Foundation makes similar recommendations, which are summarized in Table 1.

Factors that can inhibit sleep

Despite clear guidelines for sleep duration in children, most children get 30 to 90 minutes less sleep than recommended in a 24-hour period.5 Conditions that can interfere with adequate sleep in children include mental health conditions, such as attention-deficit/hyperactivity disorder (ADHD), anxiety, and depression. Separation anxiety, nighttime fears, and nightmares can interfere with sleep in younger children. Additionally, restless leg syndrome, insomnia, and sleep apnea are conditions which may affect sleep quality and quantity in children as well.7 Media use can also lead to decreased duration and quality of sleep. A meta-analysis of 20 studies around the world, including a total of 125,198 children, found a correlation between media use near bedtime and decreased number of hours of sleep.8 The risk of not getting enough sleep was twice that in children and adolescents using media prior to bedtime compared with those

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SHARI SCHRACK, CRNP; JENNIFER SEIDENBERG, MD

Jennifer Seidenberg, MD
is assistant professor and board-certified pediatrician at the The Pennsylvania State University College of Medicine University Park Regional Campus, State College, Pennsylvania.

Shari Schrack, CRNP,
is a certified nurse practitioner at Penn State Health Medical Group, State College, Pennsylvania.

The authors have nothing to disclose.
not using media before bedtime. Interestingly, having access to a media device in bedrooms is associated with inadequate sleep even if the device is not in active use. Researchers show that 72% of children aged 6 to 17 years have at least 1 electronic device that is left in their bedroom overnight, and 39% report leaving a television on all night.

Other risk factors for insufficient sleep include female gender, non-White race, disadvantaged socioeconomic status, and doing homework in the morning hours prior to school. A lack of a consistent bedtime routine in all ages can lead to insufficient sleep, and many families of preschoolers fail to adhere to their stated bedtime routines.

### Table 2: Illustrates Contributive Factors Related to Insufficient Sleep

<table>
<thead>
<tr>
<th>Age Range</th>
<th>American Academy of Pediatrics</th>
<th>American Academy of Sleep Medicine</th>
<th>The National Sleep Foundation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 months</td>
<td>N/A</td>
<td>12-16 hours of sleep</td>
<td>14-17 hours of sleep May be appropriate, 11-19 hours</td>
</tr>
<tr>
<td>4-12 months</td>
<td>12-16 hours of sleep</td>
<td>12-16 hours of sleep</td>
<td>12-15 hours (4-11 months of age) May be appropriate 10-18 hours</td>
</tr>
<tr>
<td>1-2 years</td>
<td>11-14 hours</td>
<td>11-14 hours</td>
<td>11-14 hours May be appropriate, 9-16 hours</td>
</tr>
<tr>
<td>3-5 years</td>
<td>10-13 hours</td>
<td>10-13 hours</td>
<td>10-13 hours May be appropriate, 8-14 hours</td>
</tr>
<tr>
<td>6-12 years</td>
<td>9-12 hours</td>
<td>9-12 hours</td>
<td>9-11 hours (children 6-13 years) May be appropriate, 7-12 hours</td>
</tr>
<tr>
<td>13-18 years</td>
<td>8-10 hours</td>
<td>8-10 hours</td>
<td>8-10 hours (teenagers 14-17 years) May be appropriate, 7-11 hours</td>
</tr>
<tr>
<td>18-25 years</td>
<td>N/A</td>
<td>N/A</td>
<td>7-9 hours May be appropriate, 6-11 hours</td>
</tr>
</tbody>
</table>

The problem of insufficient sleep in children and adolescents is likely best addressed in a multifactorial manner. Although adjusting school start times has been an effective social intervention, educating caregivers and health care providers also is necessary. Children whose parents enforce sleep-related rules, such as having a specified bedtime and limiting electronics and caffeine use, sleep on average 0.6 to 1.1 hours longer than children in homes where these rules are not present or enforced.

Establishing good sleep hygiene should start in the early infancy, as many infants 4 months of age older can self-soothe and sleep through the night without a feeding. Research findings support behavioral inter-
interventions for decreasing bedtime resistance and night awakenings. Investigators have studied various methods, such as unmodified extinction (ie, crying it out), graduated extinction (intermittent soothing without picking the child up), faded bedtime (starting bedtime when the child is sleepy then gradually making bedtime earlier), and scheduled awakenings, but there is no clear consensus as to which is the most effective. The goal of all sleep training is to enable the child to self-soothe, and sleep independently, and provide them with positive sleep associations. Positive sleep associations such as holding a stuffed animal or a blanket, help a child fall asleep independently of a caregiver. Negative sleep associations such as holding a stuffed animal or a blanket, help a child fall asleep independently of a caregiver. Negative sleep associations are actions a caregiver takes to help the child fall asleep, and should be avoided. These can include rocking, singing, bouncing, or feeding, and do not teach the infant to self-soothe. External sleep associations consist of the sleep environment itself, such as ambient room temperature, white noise, darkness, and so on, and caregivers should modify them to promote sleep.²

Consistent routines are important throughout childhood, and should be implemented at bedtime to promote healthy sleep behaviors.² In young children, a simple bedtime routine could include brushing their teeth, reading a book, then going to bed (with or without a bath).⁸ Such a routine provides structure for children, as well as bonding time with caregivers. Children should not have media in their bedrooms during sleep hours and caregivers should restrict its use, focusing on unplugged time with family an hour prior to bedtime.⁶ Children should avoid active play and exercise near bedtime, and omit or limit caffeine.

All well-child visits should include sleep-habit discussions, as well as visits when patients present with concerns such as fatigue, inattention, or psychological or behavioral issues. Difficulty waking in the morning, napping for longer intervals or unplanned napping, irritability, depressed mood, inattention, and difficulties at school may indicate insufficient sleep.¹² Afternoon naps longer than 20 minutes can signal inadequate sleep and may delay bedtime, which can contribute to abnormal regulation of the circadian rhythm.¹² Keeping a diary of sleep habits may identify clues to potential causes of insufficient sleep. Practitioners can consider a sleep study if there are ongoing concerns, but the majority of sleep concerns can be addressed with a thorough history and physical.

In the earlier scenario with the mother of the 4-month old infant, it is important to look at the baby’s growth charts and ask about the feeding schedule. If he is growing appropriately, and nighttime nursings are brief, encourage sleep training. Sleep training at this age can set a baby up for successful sleeping as he ages, and help his mother have adequate sleep as well.

According to a recent survey done by the AASM, more than half of parents (57%) with school-aged children say they have a child or teenager who does not get enough sleep on school nights.¹³ For children of all ages, ensuring adequate sleep hygiene is necessary for maintaining their health and well-being, especially behavioral and emotional health. The importance of sleep quality and quantity in children and adolescents in behavioral and emotional regulation is well documented. Educating caregivers regarding the importance of sleep training and bedtime routines in infants and young children can help to establish healthy sleep patterns at an early age. For adolescents, good sleep hygiene practices and later school start times can help improve mood and emotional regulation, and decrease disciplinary issues.

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

**TABLE 2**

<table>
<thead>
<tr>
<th>Contributors to Insufficient Sleep by Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0-4 years</strong></td>
</tr>
<tr>
<td>poor sleep hygiene</td>
</tr>
<tr>
<td>obstructed sleep apnea</td>
</tr>
<tr>
<td>5-14 years</td>
</tr>
<tr>
<td>screen time</td>
</tr>
<tr>
<td>overscheduling</td>
</tr>
<tr>
<td>mental health disorders</td>
</tr>
<tr>
<td>12-18 years</td>
</tr>
</tbody>
</table>

*GERD can happen at any age, but it is more likely to affect sleep in infants
**Attention-deficit/hyperactivity disorder

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## Developmental Health

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For references, go to ContemporaryPediatrics.com/effects-of-insufficient-sleep

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For more information, please visit ContemporaryPediatrics.com.
It’s springtime, which means flowers are blooming and children sneezing. Here’s a quick refresher on seasonal allergy diagnoses and prescriptions.

CANDICE JONES MD, FAAP; AND LAKIEA WRIGHT, MD, MAT, MPH

During the spring, exposure to pollen can trigger a range of symptoms in the nose, eyes, throat, lungs, or skin. Patients may refer to these spring allergy symptoms as hay fever. The classic presentation includes rhinorrhea, nasal congestion, sneezing, and/or nasal itching which are characteristic of allergic rhinitis, or watery itching eyes which are characteristic of allergic conjunctivitis.1 In addition, patients may present with cough secondary to postnasal drip or cough equivalent asthma, as allergens including pollen are common triggers for asthma.2 Finally, patients may present with a sore throat from post-nasal drip or oral itching from pollen food allergy syndrome due to cross reactivity between pollen and food.3

Patients with spring allergies may have common physical exam findings:
- clear nasal discharge
- pale, boggy nasal mucosa
- turbinate hypertrophy
- adenoid facies (mouth breathing)
- allergic shinners (dark circles around the eyes)
- allergic salute (habit of wiping or rubbing the nose)
- allergic crease (dark line at the bend of the nose)
- rash around the eyes due to rubbing (periorbital atopic dermatitis)1,4,5

Allergic rhinitis is the most common cause of chronic nasal congestion affecting 7.2% of US children annually. According to a 2014 National Health Interview Survey, 5.2 million children reported hay fever in the past 12 months.6

Children with certain risk factors are more likely to have allergic rhinitis. These include a family history of atopy, and other allergic diseases such as asthma and atopic dermatitis.1,7

Allergic rhinitis symptoms can be triggered by one or more allergens. When the body is exposed to a substance it perceives as foreign,
such as pollen, it responds by producing specific immunoglobulin E (IgE) antibodies. The antigen or allergen binds to the antibodies that cross link on allergy cells, such as mast cells, releasing chemical mediators such as histamine. Histamine triggers symptoms, including sneezing and a runny, itchy nose.1

There are generally 3 pollen seasons, which vary based on the climate in which the patient lives. Spring is significant for tree pollen, including birch, cedar, cottonwood, and pine. However, in late spring, grasses, such as Timothy, Johnson, and rye, begin to pollinate. Toward the end of summer, ragweed pollen appears and continues into fall, along with outdoor molds. Environmental irritants, among them cigarette smoke, perfumes, diesel exhaust, and cleaning products, can also trigger nasal symptoms.8-13

Diagnosis
The diagnosis of allergic rhinitis is largely based on clinical history and physical exam. However, when patients do not improve with over-the-counter medication, the diagnosis is uncertain or the allergic trigger needs to be identified for targeted environmental mitigation, allergy testing is recommended. Specific IgE allergy testing, a blood sample or skin prick, helps aid in the diagnosis of allergies. A diagnostic algorithm for rhinitis is presented in Figure 1.1

The diagnosis of allergic rhinitis accounts for the timing, frequency or duration, and severity of symptoms. Classifying the disease is important to guide its management. Allergic rhinitis classified by severity of symptoms is divided into mild and moderate/severe. Mild allergic rhinitis does not interfere with the patient’s quality of life.3 But moderate/severe allergic rhinitis has symptoms severe enough to decrease quality of life, such as disordered sleep, impaired daily activities, and missed school and work days.7 Results from recent studies suggest that poorly controlled allergic rhinitis can negatively affect academic performance.15

Further, it is important to note that approximately 30% to 50% of patients with chronic rhinitis may have a combination of allergic and nonallergic rhinitis, referred to as mixed rhinitis.5,10 Timely diagnosis and optimal management of allergic rhinitis is important to prevent complications, such as sinusitis, ear infections, chronic effusion, chronic headache, halitosis, dental problems, and sleep disturbances.1

Allergic rhinitis classified by severity of symptoms is divided into mild and moderate/severe. Mild allergic rhinitis does not interfere with the patient’s quality of life.3 But moderate/severe allergic rhinitis has symptoms severe enough to decrease quality of life, such as disordered sleep, impaired daily activities, and missed school and work days.7 Results from recent studies suggest that poorly controlled allergic rhinitis can negatively affect academic performance.15
respiratory

COVID-19 and environmental allergies

Sometimes it can be hard to tell the difference between allergies and viral illnesses, including coronavirus disease 2019 (COVID-19) infection. Many symptoms, such as nasal congestion, runny nose, cough, and headache, overlap, as illustrated in the National Center for Immunization and Respiratory Diseases’ Venn diagram (Figure 2). Therefore, it is crucial to keep COVID-19 infection high on the differential and to consider testing the patient.

Management

PHARMACOLOGIC THERAPIES

Managing allergic rhinitis and environmental allergies involves a 2-fold approach: pharmacologic therapies and environmental mitigation strategies. As exposure to allergens in sensitized individuals promotes inflammation, using medications to treat symptoms and mitigating exposure to allergens are very important. For treatment of seasonal allergy symptoms, initiating treatment with intranasal steroids and/or oral antihistamines is recommended 1 to 2 weeks prior to the start of the season; this should be continued throughout the season. The primary treatment for allergic rhinitis is intranasal steroids. However, they may not be tolerated in young children. Long-acting, non-sedating oral antihistamines (cetirizine, levocetirizine, fexofenadine, or loratadine) may be used in combination with or without intranasal steroids. An antihistamine or mast cell stabilizer eye drops, such as olopatadine or inhaled corticosteroids, are the mainstay of treatment for allergic asthma but therapy may need to be adjusted as outlined in the National Institutes of Health’s National Asthma Education and Prevention Program guidelines.

Treatment of pollen food allergy syndrome entails avoiding the “fresh” form of culprit food(s) referenced in Figure 3, or other strategies such as peeling the skin or eating the cooked version. These strategies are typically tolerated.

NATURAL REMEDIES AND COMPLEMENTARY AND ALTERNATIVE MEDICINE

Many patients inquire about the use of natural remedies in the treatment of allergic rhinitis and allergic conjunctivitis. Rinsing the nasal passages with over-the-counter saline in a squeeze bottle or a neti pot, for example, can be effective as a means of washing away the allergens and mucus to help reduce symptoms. Using humidifiers to treat nasal congestion is generally not recommended because it creates an environment...
which promotes the proliferation of dust mites and molds. Acupuncture has not been commonly used in the pediatric population, but findings from small studies suggest it may be beneficial in the treatment of allergic rhinitis. Natural remedies for the treatment of allergic conjunctivitis include applying a cold compress to the eyes or using refrigerated artificial tears to remove allergens.

**ENVIRONMENTAL MITIGATION STRATEGIES**

The majority of individuals with allergy symptoms are allergic to more than one allergen. Exposure to allergens should be minimized because there is a symptom threshold and reducing exposure lowers the risk of symptom exacerbation. For example, a patient may be sensitized to dust mites, mold, and animal dander with minimal symptoms year-round; however, in spring, exposure to birch pollen may cause exacerbations because they have reached their symptom threshold due to cumulative exposure to allergens and tree pollen, and thus “tip them over the edge.”

Pollens are microscopic and may be deposited on skin, hair, and clothing. Therefore, showering after coming in from outdoors is recommended. Trees tend to release the most pollen from 5 am to 9 am. Therefore, trying to minimize outdoor activities during the early morning hours may be helpful. Keeping windows closed in the car and home and wearing a mask with a small particle filter can also reduce pollen exposure. Figure 4 lists environmental mitigation strategies for common environmental allergens.

**IMMUNOTHERAPY**

Subcutaneous and sublingual are 2 types of immunotherapy available for aeroallergens. Subcutaneous immunotherapy works by introducing small amounts of allergen(s) in escalating doses until a maintenance dose is reached that helps to desensitize allergy cells. Typically, the patient receives a maintenance dose monthly for 3 to 5 years under the supervision of a physician. In recent years, there have been few new allergy medications. In 2014, sublingual immunotherapy tablets were approved for grass (ages 5-65 years) and ragweed (ages 18-65 years) polLens. In 2017, a dust mite sublingual tablet was approved for use in adults. Sublingual tablets are not widely used in the pediatric population. One major barrier is the limited insurance coverage for these tablets. However, sublingual tablets may be used more frequently in the future as more children are formally diagnosed with common environmental allergens based on clinical history and confirmed with (blood sample or skin prick) allergy testing, and a more convenient home-based form of immunotherapy is desired.

**When to refer patients to an allergist**

If the patient does not improve with over-the-counter medications and there is evidence of sensitization to common environmental allergens on testing, consider referring to them to an allergist. Additionally, for patients who are atopic, a referral to an allergist to determine whether they are a candidate for allergen immunotherapy may be beneficial. Allergen immunotherapy is approved for the treatment of allergic rhinitis and asthma. For atopic patients with allergic rhinitis without preexisting asthma, subcutaneous allergen immunotherapy is indicated for the primary prevention of asthma.

**Conclusion**

Spring allergies are common in the pediatric population. Recognizing signs or symptoms, classifying the disease and implementing a 2-fold management approach is key to quality of life for patients. Although pediatricians manage most cases of allergic rhinitis in children, knowing when to refer to an allergist is important.

**For references, go to**

ContemporaryPediatrics.com/seasonal-allergies

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**FIGURE 4 Strategies for Environmental Mitigation**

**POLLEN**
- Trees, Grasses, Weeds
- Close windows (car & home)
- Shower
- Remove & wash clothing

**PET DANDER**
- Dog and Cat
- Wash hands after handling pets
- Bathe pets regularly
- Vacuum carpets & rugs regularly
- Use HEPA Filter

**DUST MITE**
- Use hypoallergenic encasings for pillows and mattress
- Vacuum carpets & rugs weekly
- Wash bedding weekly

**MOLD**
- Repair leaks
- Use dehumidifier
- Drain rainwater away from home

**COCKROACH AND MOUSE**
- Tightly tie trash cans
- Sweep up crumbs
- Use cockroach bait
- Use mousetraps
- Seal holes and cracks
The coronavirus disease 2019 (COVID-19) pandemic has had a major impact on our delivery of health care. It has also affected economic systems, global politics, and our quality of life, especially for children and particularly those involved in sports. In the United States alone, over 35 million children and adolescents participate in athletic endeavors, and social distancing requirements and the immediate halting of large gatherings has negatively affected their physical and psychological health. With the return to school, sporting events are resuming under the watchful eyes of local or state governments, which often seek guidance from medical organizations, sporting bodies, and the Centers for Disease Control and Prevention in formulating regulations. We propose the following recommendations for the safe return of children to all athletic participation (including gym class and heavy chores), after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, to assist pediatricians and primary care providers (PCPs) in making the safest decisions for their patients.

Pediatric COVID-19 rarely results in severe systemic problems such as myocardial injury, arrhythmias, kidney failure, or stroke. However, effects on the cardiovascular system have been reported in children who are positive for SARS-CoV-2,1–4 which may occur as part of multisystem inflammatory syndrome in children (MIS-C).5–9 Pediatricians also have seen many of these effects even in children with no overt symptoms,10 the majority of which present weeks after the acute infection when the children would have completed quarantine and resumed sports.11,12 Post COVID-19, the risk of developing serious complications such as MIS-C or cardiac complications such as myocarditis, arrhythmias, and heart failure is a cause of concern for the athlete, their parents, physicians, school boards, and sports licensing groups.

Children who are positive for SARS-CoV-2, even those who are asymptomatic, are at risk for developing myocardial injury. Previous reports illustrated that exercise in patients who are positive for COVID-19 can increase viral replication within the cardiac muscle. This leads to structural damage to the heart, directly resulting in ventricular dysfunction, arrhythmias, and, in rare cases, sudden death.1 To date, the risk of pediatric patients positive for SARS-CoV-2 developing myocardial damage is unknown, but it has been reported.1–4 However, data are not available to present a calculated risk number for myocardial injury in these patients. This risk of myocarditis, although rare, is a concern, and hence the need for guidance from medical societies and

Devyni Chowdhury, MD, MHA, FACC, FAAP

Susannah Briskin, MD, FAAP

Christopher Snyder, MD, FACC, FAAP

The authors have nothing to disclose.
In this **gradual return-to-play for all COVID-19+ individuals** protocol, we recommend a minimum 7-day progression to monitor for the development of any signs or symptoms of cardiac issues or significant fatigue. Consider extending the progression for longer than 7 days for any individual who has a prolonged course of fatigue or any pulmonary or cardiac issues during their recovery. A sample 7-day progression, adapted from Elliott et al.16

<table>
<thead>
<tr>
<th>STAGE 1</th>
<th>STAGE 2</th>
<th>STAGE 3</th>
<th>STAGE 4</th>
<th>STAGE 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAYS 1 AND 2</strong></td>
<td><strong>DAY 3</strong></td>
<td><strong>DAY 4</strong></td>
<td><strong>DAYS 5 AND 6</strong></td>
<td><strong>DAY 7</strong></td>
</tr>
<tr>
<td>15 minutes or less of light activity at an intensity of 70% or less maximum heart rate (HR); no resistance training. Patient can walk, jog, and use a stationary bike.</td>
<td>30 minutes or less of simple sports movements at an intensity of 80% or less maximum HR; no resistance training. Running, sport-specific drills are permitted.</td>
<td>45 minutes or less of complex sports movements at an intensity of 80% or less maximum HR. Patient may begin light resistance training (low weights, high reps).</td>
<td>Stage 4 (days 5 and 6) – 60 minutes of normal sports activity at an intensity of 80% or less maximum HR</td>
<td></td>
</tr>
<tr>
<td>Return to full sports activity, clearance for full competition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional testing

The electrocardiogram (ECG) used in this situation is a screening tool for myocardial injury. It has low sensitivity and an unknown specificity; however, it is readily available to health care providers. It is important to seek accurate, age-appropriate interpretation by a physician familiar with interpreting the subtleties of the pediatric ECG. Findings that should raise concerns of myocardial injury include any dysrhythmia, tachycardia, conduction delays, ST or T wave changes not including early repolarization, and low-voltage QRS complexes.14 As we illustrate in the Table, a patient with an abnormal ECG should be referred to a pediatric cardiologist for further evaluation. Further noninvasive testing includes a 24-hour Holter monitor and an exercise stress test; both of these detect arrhythmias during vigorous activity.

Many pediatric patients who are...
Infectious disease

**TABLE**

**PEdiATRIcIAN’S APPROACH TO A SARS-COV-2-POSITIVE CHILD**

<table>
<thead>
<tr>
<th>Symptom Category</th>
<th>Asymptomatic</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>None (no fever, cough, diarrhea/loss of taste)</td>
<td>Fever for &lt;3 days, aches and pains, mild gastrointestinal illness</td>
<td>Fever &gt;100.4°F for &gt;4 days, chills, cough, dyspnea, body aches, persistent chest pain, palpitations</td>
<td>Severe respiratory symptoms or MIS-C or heart failure/myocarditis requiring inpatient management, +/- need of ventilator</td>
</tr>
<tr>
<td>Exercise (graded return)</td>
<td>10 days of no intense exercise since the positive test</td>
<td>10 days of no intense exercise since the positive test and a minimum of 24 hours of symptom-free period off fever-reducing medications</td>
<td>10 days-4 weeks* of no intense exercise since the positive test and a minimum of 10 days of symptom-free period off fever-reducing medications</td>
<td>3-6 months of no intense exercise as per AHA myocarditis return to play guidelines</td>
</tr>
<tr>
<td>12 lead ECG</td>
<td>ECG(+/-)*</td>
<td>ECG(+++)**</td>
<td>ECG(+++)***</td>
<td></td>
</tr>
<tr>
<td>Doctor visit prior to return to play for clearance</td>
<td>PCP</td>
<td>PCP</td>
<td>PCP/pediatric cardiology</td>
<td>Pediatric cardiology consult</td>
</tr>
<tr>
<td>Referral to pediatric cardiology</td>
<td>If abnormal ECG or PPE or physical examination</td>
<td>If abnormal ECG or PPE or physical examination</td>
<td>If abnormal ECG or PPE or physical examination</td>
<td>Pediatric cardiology consult (inpatient) and outpatient follow-up</td>
</tr>
</tbody>
</table>

AHA, American Heart Association; ECG, electrocardiogram; MIS-C, multisystem inflammatory syndrome in children; PCP, primary care provider; PPE, preparticipation physical examination; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

* maybe indicated; ** likely indicated; *** definitely indicated.

* Depending on symptoms and findings on additional testing.

Proposed guidelines in accordance with the latest AAP COVID-19 interim guidance: Return to sports.18

Positive for COVID-19 and who have severe symptoms, particularly those with MIS-C, will undergo an echocardiogram (ECHO) during their acute hospitalization.1 An ECHO assesses cardiac function and looks for evidence of fluid around the heart and leakage from any of the heart valves. It can also evaluate the proximal coronary arteries for dilation. If there is continued suspicion of myocardial involvement from the patient’s history, physical examination, or any of the other testing, advanced imaging with a cardiac magnetic resonance imaging may be performed. This highly specialized test can show changes in the heart muscle even months after the illness.

Biomarkers, such as troponin I, are indicators of myocardial involvement and when elevated often indicate myocardial injury.15 Routine testing for biomarkers in all children positive for SARS-CoV-2 is not required; such tests are used only if there is high clinical concern of cardiac involvement. In this age group, physicians must exercise caution when interpreting this test; biomarker elevation alone cannot constitute a diagnosis of myocardial injury as biomarkers can be elevated in patients after vigorous exercise or local trauma.

**Approach to the return to play**

The Table shows our recommendations for an approach for PCPs to provide patient clearance for a safe return to play.

To facilitate the safe return to sports, despite the lack of data, we recommend that all patients who are SARS-CoV-2-positive refrain from exercise for a minimum of 10 days after the positive test result. Those who are asymptomatic or have mild symptoms (≤3 days of fever, aches, and pains; mild gastrointestinal illness) may begin a gradual return after 10 days in quarantine; a minimum time of 24 hours, symptom-free period off fever-reducing medications has passed; and they have been cleared by a physician.

For those with moderate symptoms (fever >100.4°F for 4 or more days; chills, cough, dyspnea, body aches, persistent chest pain, or palpitations), consider their having a 12 lead ECG prior to returning to
athletic activities. In a child who is SARS-CoV-2 positive, a normal ECG suggests that direct cardiac involvement is less likely. The PCP can give clearance to a patient for a gradual, safe return to sports after 10 days in quarantine and a minimum of 10 symptom-free days have passed while they are off fever-reducing medicine. After returning to sports, patients should be monitored for presence of symptoms and, if required, be re-evaluated by their physician. Pediatric patients who are hospitalized due to moderate-severe COVID-19 or MIS-C and/or have overt symptoms of myocarditis or heart failure should be treated according to existing guidelines of the American Heart Association and the American College of Cardiology for myocarditis.17 We note that COVID-19–related myocardial injury may be different from the typical viral myocarditis referred to in the guidelines, but in the absence of data, this approach is prudent. This may include a halt on all exercise for up to 3 to 6 months, depending on the individual pediatric patient. A pediatric cardiologist should evaluate these patients to further assist with guidance regarding their return to sports.

Our proposed guidelines are in accordance with the latest American Academy of Pediatrics (AAP) COVID-19 interim guidelines on returning to sports.18

These guidelines suggest that children who are asymptomatic or have mild symptoms should undergo a thorough evaluation by a physician. The evaluation should include a complete physical exam and a pre-participation screen with particular attention to cardiac symptoms. Patients with unremarkable findings can gradually return to sports 10 days after testing positive for SARS-CoV-2, with at least a 24-hour symptom-free period off fever-reducing medications. However, those with concerning findings will need further evaluation, such as an ECG and a pediatric cardiologist consultation.

Children who are positive for SARS-CoV-2, even those who are asymptomatic, are at risk for developing myocardial injury.

Children with moderate symptoms or those who have been admitted for nonintensive care to the hospital should receive an ECG and be evaluated by a pediatric cardiologist with additional testing. If the patient has a normal cardiac workup, they can gradually return to sports 10 days after testing positive for SARS-CoV-2, with at least 10 days of symptom resolution off fever-reducing medication. Those children who suffer from severe COVID-19 or MIS-C should refrain from exercise for 3 to 6 months, and they require extensive cardiac testing and cardiology clearance before resuming. The AAP further emphasizes that the return to play should be gradual and occur over 5 stages; patients should begin with 15 minutes or less of less intense activity in the first 2 days, gradually reaching full activity after 7 days.18

For symptomatic individuals, including those with chest pain, palpitations, breathlessness, exertional dizziness, or syncope, a normal ECG may not rule out myocardial injury and they will require close observation for worsening of symptoms. Consider referring these patients to a pediatric cardiologist for evaluation and further testing depending on ECG abnormalities and severity of symptoms, even in the absence of ECG changes. Physicians can often determine the significance and association of these symptoms regarding SARS-CoV-2 infection based on additional tests such as an echocardiogram or a Holter monitor. The patient’s gradual return to physical activity may be permitted after 10 days to 4 weeks, depending on symptoms and findings.

Conclusion

Patients who test positive for SARS-CoV-2 are at risk of developing myocardial injury, which varies greatly in its clinical presentation. Clinicians should be aware of the possibility of cardiac complications, including sudden death following vigorous exercise secondary to underlying myocardial injury. We recommend that patients are evaluated by a physician prior to returning to sport.

COMMENTS? Email them to levine@mh lifesciences.com

To read about the AAP updates on sports participations, scan this QR code

For references, go to ContemporaryPediatrics.com/return-to-sports-after-COVID

For Mental Health Guidance during COVID-19, go to bit.ly/3qQaXpf
Diagnosis and treatment of attention-deficit/hyperactivity disorder (ADHD) are associated with a variety of practical and clinical challenges. In a recent Viewpoints video series, available at Contemporary Pediatrics.com, Timothy Wilens, MD, a child and adolescent psychiatrist at Massachusetts General Hospital in Boston, Massachusetts, led a discussion regarding the multidisciplinary management of ADHD, the diagnostic and treatment obstacles during the coronavirus disease 19 (COVID-19) pandemic, and the effect of medication abuse. This article recaps the key clinical pearls and takeaways from the conversation.

**Diagnosis is key**

ADHD is the most common presenting neurobehavioral disorder that pediatricians and child psychiatrists will see in their course of practice and is second only to asthma when ranked among all chronic pediatric illnesses, Wilens explained as he opened the discussion. The prevalence of ADHD among children is between 6% to 9%, regardless of country of origin.

Diagnosis can be made as young as age 4, and stimulant medications are the first-line choice for pharmacotherapy, according to the 2019 American Academy of Pediatrics guidelines for the care of ADHD.

A key challenge associated with ADHD is making an accurate diagnosis, Robert L. Findling, MD, MBA said, noting that a countless number of things may make a child appear inattentive or fidgety. “[Diagnosis] can only be done by a careful assessment, both cross-sectionally and over time, and pediatricians are particularly well-equipped to do such a thing because they have the benefit of watching children grow up,” Findling explained.

He added that comorbidities, such as oppositional defiant disorder, anxiety, depression, and bipolarity, are the rule and not the exception in the setting of ADHD. These can complicate the clinical picture and, when left undiagnosed or untreated, can mask the benefits from ADHD medication. “You have to know the whole child,” he said. “There are many things that will not respond to ADHD treatment.”

Probably 70% to 75% of kids [with ADHD] have a comorbid or coexisting medical or psychiatric disorder, Harlan R. Gephart, MD added. “Autistic Spectrum Disorder, family issues, divorce, [a] parent’s separation, [the] death of a parent … can look like ADHD [and] would give you a positive Vanderbilt Rating Scale for ADHD,” he said. “[They can] make you inattentive and distractable. That all has to be sorted out.”

To help manage ADHD, pediatricians and child psychiatrists would benefit through collaboration, Findling said. “Sometimes it just takes a bunch of people working together, putting the kid right in the center,” he explained.
However, Mark Wolraich, MD explained that communication between all players remains an issue. Information asymmetry between parents, schools, pediatricians, child psychiatrists, and therapists is common in ADHD management. “Some [of these barriers] are there for protection of health information, but they [can] really decrease the communication,” he said.

ADHD management during the COVID-19 pandemic

Telemedicine
In addition to these challenges, the panelists discussed several downstream consequences of the COVID-19 pandemic and ADHD management; some of them have been positive, others have not.

For years, telemedicine was not a reimbursable intervention for physicians, Wolraich pointed out. However, that changed during the pandemic when delivery of goods and services shifted to a more contactless approach. Telemedicine, Wolraich noted, is beneficial for ADHD management because it allows for better observation of the child in their more natural home environment and is more conducive to the shorter follow-up intervals required during rapid dose titration of ADHD medication.

“Patients can come to appointments much easier,” Wilens said. “[Parents] don’t have to drive far distances, [they] don’t have to take off a half day of work, kids don’t have to miss sports [or] school. Our no-show rates [have] dropped precipitously.”

In addition, as ADHD stimulant medications are scheduled drugs, Wilens also observed that the relaxing of regulatory oversight during the pandemic for prescribing controlled substances via telehealth visit has proven helpful.

The downside of increased telemedicine include access to adequate internet bandwidth, technical glitches, and a loss of in-person human connection, the panelists noted.

Virtual schooling
Another challenge associated with a more virtual world in the wake of the COVID-19 pandemic, is not all children are back to in-person learning at schools. This can be problematic for patients with ADHD, the panelists noted. “For many kids and families, it’s an absolute disaster,” Ann Childress, MD said. “[Kids with ADHD] can’t sit [still] in front of the camera … they are getting in trouble … they can’t figure out what link they’re supposed to [click on for] the next class … they’re running around the house.”

Parents fear their kids are falling behind and are considering quitting their jobs until in-person school resumes, she added.

But it’s not just concerns over learning, children with ADHD have strengths that can’t be observed virtually, Findling said. “[So] now they have lost the chance to succeed in domains that they might have
been successful at when [school] was in person and not via screen,” he explained.

**Medication access**

COVID-19 has also made for supply chain issues that have created access barriers for stimulant medications. “We’re dealing with distribution problems, [and] people are having more problems finding stimulants ... they may have to go to 3 or 4 different pharmacies,” Wilens said.

Because pharmacies will not always tell someone over the phone if they have a particular stimulant medication in stock over robbery concerns, a parent may drive there only to learn the medication isn’t available. “Then I have to ... go back and send [the e-script] to another pharmacy, [and] it takes up a lot of time just to try and get somebody their medicine,” Childress said.

Unfortunately, COVID-19 has forced many people out of work and that has also meant loss of health insurance for families, making it difficult to afford brand-name ADHD medications that they have already been taking. “I’m having to do things that I don’t like to do, and that’s switch people to immediate-release [agents] that they can afford,” Childress said.

**How to curb ADHD stimulant drug abuse**

The last big challenge in the management of ADHD that the panelists discussed is the misuse of prescription stimulant drugs.

Nonmedical use of prescription stimulants—using the drug differently than was prescribed or using the drug without a prescription—has now outpaced opioid [use] among teens and young adults, Wilens explained, with the highest rates of abuse aggregating at colleges and universities. “It turns out that about 40% of stimulant misuse is intranasal,” Wilens said. “This is a huge concern ... [because] if you use [it] intranasal[ly] or intravenous[ly], you have a 20-fold [higher] likelihood of serious medical morbidity or even death.”

The panelists offered several suggestions for curbing nonmedical use of prescription stimulants: prescribe extended-release formulations, monitor pill counts, and write [scripts] for the number of tablets the patient needs. Extended-release formulations have less intranasal abuse potential versus their immediate release counterparts, while pill counting and not writing for extra tablets helps prevent stockpiling.

Several stimulant drugs in development may also help control medication abuse because they are being made with manipulation-resistant technology, Childress explained. “There are about 40 drugs in the pipeline in various places,” she said. For instance, one product is a capsule containing crush-resistant pellets of an immediate-release amphetamine. The difficulty of grinding the pellets down into a powder for snorting prevents misuse intranasally. Other products in development use prodrugs which must undergo conversion in the gastrointestinal tract before becoming active. Nonstimulant drugs currently being investigated for use in ADHD have mechanisms similar to antidepressants.

“It’s really exciting to hear that we have new potential alternatives [for use in ADHD] ... [and that] they are trying to make them safer,” Wilens said.

---

**EXPERT PANEL**

**Timothy Wilens, MD**
Chief, Division of Child and Adolescent Psychiatry  
Co-Director, Center for Addiction Medicine  
Director, Substance Abuse Services in Pediatric Psychopharmacology  
Massachusetts General Hospital  
Boston, Massachusetts

**Ann Childress, MD**
Clinical Associate Professor  
University of Nevada School of Medicine  
Las Vegas, Nevada

**Robert L. Findling, MD, MBA**
Chair, Department of Psychiatry  
Virginia Commonwealth School of Medicine  
Richmond, Virginia

**Harlan R. Gephart, MD**
Author of ADHD Complex: Practicing Mental Health in Primary Care  
Bellevue, Washington

**Mark Wolraich, MD**
Professor  
University of Health Sciences  
Oklahoma City, Oklahoma
Sickle cell disease

Sickle cell disease is the most common inherited blood disorder in the United States, affecting approximately 100,000 people. The causative mutation results in valine replacing glutamic acid as the 6th amino acid of the β-globin chain, making these red blood cells prone to sickling due to polymerization of deoxygenated hemoglobin S. However, the pathophysiology of sickle cell disease is more complex than red blood cell sickling, and includes increased expression of adhesion molecules on the vascular endothelium, leading to leukocyte adhesion and vasculopathy. Life expectancy of patients with sickle cell disease has improved from 28 years to 43 years since 1979 but remains shorter than the life expectancy for the general population.

Role for prevention

Hydroxyurea has historically been the preventive strategy to decrease the occurrence of vaso-occlusive pain crises (VOC). VOC have been indicated to be responsible for more than 90% of hospital admissions in patients with sickle cell disease. Hematopoietic stem cell transplant is the curative treatment for sickle cell disease but major barriers prohibit its use, such as the limited availability of HLA-matched donors. This makes new strategies crucial to improving life expectancy and quality of life of patients with this disease.

Crizanlizumab

The US Food and Drug Administration (FDA) recently approved crizanlizumab to reduce the frequency of VOC in pediatric patients aged 16 and older with sickle cell disease. Crizanlizumab is a humanized monoclonal antibody that binds to P-selectin and blocks its interaction with P-selectin glycoprotein ligand 1 (PSGL-1). Binding P-selectin on the activated endothelium and platelets blocks interactions between endothelial cells, platelets, red blood cells, and leukocytes that would eventually lead to vascular obstruction, tissue ischemia, and vaso-occlusion.

The phase 2 SUSTAIN trial (NCT01895361) determined the efficacy of crizanlizumab in reducing the annual rate of sickle cell-related pain crises in 198 study participants. The study participants had experienced 2 to 10 sickle cell-related VOC in the 12 months prior to enrollment. They were assigned to receive low-dose crizanlizumab (2.5 mg/kg), high-dose crizanlizumab (5 mg/kg), or placebo over a study period of 52 weeks. The use of hydroxyurea was not an inclusion or exclusion criterion (participants receiving hydroxyurea were receiving it for at least 6 months, with no dose alterations).

According to the study results, the median rate of crises per year with high-dose crizanlizumab was 1.63 versus 2.98 with placebo, indicating a 45.3% lower rate of VOC with high-dose crizanlizumab (P = .01). The median time to the first crisis also was longer with high-dose crizanlizumab versus placebo, at 4.07 versus 1.38 months, respectively (P = .001). The primary outcomes in participants receiving the low-dose crizanlizumab were not found to be statistically significant. Adverse events from the study include arthralgia, diarrhea, pruritus, vomiting, and chest pain. The dose recommendation for crizanlizumab is 5 mg/kg intravenous (IV) on week 0, week 2, and every 4 weeks thereafter. Patients should be monitored for infusion-related reactions. No dose adjustments are required for hepatic or renal impairment. Further studies evaluating crizanlizumab in pediatric patients aged younger than 16 years are ongoing.

Voxelotor

The FDA also recently approved Voxelotor, which has a role in modifying the severity of disease through its unique mechanism as a hemoglobin modulator. Voxelotor acts as a polymerization inhibitor for hemoglobin S by
pharmacology

The international GBT_HOPE trial (NCT03036813), a phase 3, placebo-controlled study, evaluated the hemoglobin response to voxelotor. This study included 274 participants with sickle cell disease aged from 12 to 65 years; they had a hemoglobin level between 5.5 and 10.5 g/dL during screening and had experienced 1 to 10 VOC in the past 12 months. Participants were randomly assigned in a 1:1:1 ratio to daily oral dosing of 1500 mg, 900 mg, or placebo for a treatment period of up to 72 weeks. The majority were also receiving hydroxyurea that had been maintained at a stable dose for the past 3 months.

A hemoglobin response, defined as an increase from baseline of more

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**TABLE DRUGS IN ONCOLOGY RECENTLY APPROVED FOR PEDIATRICS (JUNE 2020 TO JANUARY 2021)**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>THERAPEUTIC CATEGORY (DOSEAGE FORM)</th>
<th>INDICATION</th>
<th>KEY POINTS</th>
</tr>
</thead>
</table>
| XALKORI (crizotinib)*  | Kinase inhibitor (oral capsule)     | ALK-positive, relapsed or refractory systemic anaplastic large cell lymphoma, age 1 and older        | ▶ Warnings and precautions: Visual loss – ophthalmologic exam at baseline and thereafter, monitor visual acuity and symptoms of ocular toxicity; monitor for QT interval prolongation  
 ▶ Drug interactions: Avoid co-administration with strong CYP3A inhibitors and inducers |
| GAVRETO (pralsetinib)* | Kinase inhibitor (oral capsule)     | Advanced or metastatic RET-mutant medullary thyroid cancer requiring systemic therapy and advanced or metastatic RET fusion–positive thyroid cancer requiring systemic therapy, radioactive iodine–refractory, age 12 and older | ▶ Continued approval contingent upon clinical benefit in confirmatory trials  
 ▶ Once-daily administration on an empty stomach (no food 2 hours before or 1 hour after)  
 ▶ Drug interactions: Avoid co-administration with strong CYP3A inhibitors and inducers |
| DANYELZA (naxitamab-gqgk)* | GD2-binding monoclonal antibody (intravenous [IV] infusion) | Relapsed or refractory high-risk neuroblastoma in the bone or bone marrow with partial response, minor response, or stable disease to prior therapy, age 1 and older (in combination with granulocyte-macrophage colony-stimulating factor) | ▶ Continued approval contingent upon clinical benefit in confirmatory trials  
 ▶ Black box warning: Serious infusion-related reactions and neurotoxicity; administer premedication prior to naxitamab infusion and monitor at least 2 hours post infusion |
| KEYTRUDA (pembrolizumab)* | Programmed death receptor-1 (PD-1) blocking antibody (IV infusion) | Refractory classical Hodgkin lymphoma (cHL) or cHL relapsed after 2 or more lines of therapy in pediatric patients | ▶ Warnings and precautions: Immune-mediated adverse reactions; infusion-related reactions |
| MYLOTARG (gemtuzumab ozogamicin)* | CD33-directed antibody and cytotoxic drug conjugate (IV infusion) | Newly diagnosed CD33-positive acute myeloid leukemia, age 1 month and older | ▶ Black box warning: Hepatotoxicity, including severe or fatal sinusoidal obstruction syndrome  
 ▶ Warnings and precautions: Infusion-related reactions; administer premedication with a corticosteroid, acetaminophen, and diphenhydramine and monitor at least 1 hour post infusion |

---

than 1 g/dL at week 24, was significantly greater in the 1500 mg voxelotor group (51% [46 of 90]; 95% CI, 41-61) compared with the placebo group (7% [6 of 92]; 95% CI, 1-12) in the intention-to-treat analysis (P < .001). The hemoglobin response was higher in the 1500 mg voxelotor group versus placebo regardless of concurrent hydroxyurea use or severity of anemia at baseline. Primary outcome in the 900 mg voxelotor group was not found to be statistically significant. The annualized adjusted incidence rate of VOC per person-year (95% CI) was 2.77 (2.15-3.57) in the 1500 mg group, 2.76 (2.15-3.53) in the 900 mg group, and 3.19 (2.5-4.07) in the placebo group, demonstrating a lower incidence of VOC in those receiving voxelotor.9

Adverse effects were similar for the 3 groups, with headache, diarrhea, and nausea common.9 The dose recommendation for voxelotor is 1500 mg daily in patients with sickle cell disease who are aged 12 years and older.9 Voxelotor is available as a 500-mg tablet. Dose adjustments are necessary with severe hepatic impairment and with concurrent use of interacting drugs (ie, CYP3A4 inducers and inhibitors).9 These 2 new therapies offer new pharmacotherapeutic options for sickle cell–related complications.9

ACP supports legislation increasing health care access, combatting COVID-19 pandemic

In letters to congressional committees, the organization extolls the benefits of provisions in upcoming COVID relief legislation. BY KEITH A. REYNOLDS

The American College of Physicians (ACP) has written to the House Committee on Ways and Means and the House Committee on Energy and Commerce to show their support for coronavirus disease 2019 (COVID-19) relief legislation.

According to a news release, the letters detail the benefits patients and physicians would see from provisions contained in the legislation. “The COVID-19 pandemic has thrown our health care system into crisis,” Jacqueline W. Fincher, MD, MACP, president of ACP, says in the release. “We believe that many of the actions outlined in these proposals will help physicians and our patients. We need to ensure that we bring the pandemic under better control as quickly as possible, and we need to ensure that no one is forced to go without health care during this time while everyone’s health is under threat.”

The letter to the Ways and Means Committee letter expressed the ACP’s support for recommendations to reduce health care premiums for low- to middle-income Americans through tax credit subsidies, subsidizing the Consolidated Omnibus Budget Reconciliation Act (COBRA) coverage, and providing premium subsidies for unemployed workers who are ineligible for COBRA.

In their letter to the Energy and Commerce Committee, ACP highlights its support for accelerating efforts to distribute vaccines and COVID-19 testing through higher levels of funding. The organization also indicates its support for provisions related to Medicaid that require the program to cover COVID-19 vaccines and treatments, according to the release.

“As we face the threat of more infectious variants, while at the same time grappling with the logistics issues of vaccine distribution, we need to ensure that our patients, our physicians, and our health care system have the resources they need to respond to these challenges,” Fincher says. “We urge both chambers to work in a bipartisan manner to ensure that these policies are enacted without further delay to meet the health care and economic challenges that we face.”
Pediatricians are often faced with questions about 

**Picky eating**

*But when is the time to act?*

Picky eating may very well be *the* battle of childhood. Whether it’s getting a child to eat a certain vegetable, eat something other than chicken nuggets, or eat at all, most parents go through feeding struggles at some point. The question for pediatricians is knowing when to offer reassurance and support, and when to offer intervention.

**RACHAEL ZIMLICH, RN, BSN**

The answer to this is very individu-alized, says Megan Pesch, MD, MS, who specializes in congenital dis-eases and childhood obesity at the University of Michigan Institute for Healthcare Policy and Innovation in Ann Arbor. Pesch coauthored a study in 2020 exploring picky eating habits in children of low-in-come families.

“Is the child limited [regard- ing] the variety or amount they eat, or willingness to try new foods?” Pesch asks. “What crosses that threshold?”

This question varies by socioeco-nomic group and household, she notes. A family who relies on public assistance to purchase food may be happy their child finishes their plate and meets their calorie needs. An-other family may want their child to try a new organic vegetable.

The 2020 study, published in *Pediatrics*, concluded that all children are picky eaters at some point during childhood. It’s a means of demonstrating independence. For the study, mothers answered questions about their child’s baseline behavior and eating patterns, and investigators reviewed the child’s growth. The team looked for patterns in children who were judged as being more picky than others.1

Children with higher emotional lability and lower self regulation were ranked among the pickiest eat- ers. Parents who were very strict or demanding in regard to their child’s eating habits also tended to have pickier eaters, the authors noted.

“Feeding is cultural,” Pesch explains. “There’s no right way to do things. Where picky eating is con-cerned, I think there is something inherent—maybe even evolution- ary—in parents, especially mothers, that feels like an instinct to feed your child well.”

That very definition though, has evolved over time. Whereas at one point, feeding your child well simply meant providing them with food, to-day it means so much more.

“These days, there’s even more pressure on parents to make the Instagram-perfect meal for their child to eat,” she says. “The pressures on parents to feed their children to this high standard is real.”

When the research team investigated the eating and feeding behaviors of chil-dren aged 4 to 9 years in low-income groups, Pesch says the overall finding was that kids were “stably picky.” There were really only 5 chil-dren in the study group of 300 that ever “grew out” of their picky eating,1 and the team couldn’t find any reason. “There was no real reason. They just stopped,” Pesch says.

This may not be good news for parents looking to find an answer on how to change their child’s picky eat-

**A family on public assistance may be happy their child finishes their plate; another family may want their child to try a new organic vegetable.**
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Nutrition behaviors. However, Pesch notes that parents have to realize their own role in these behaviors, too. "The mother's approach to feeding was also stable, but mothers of picky eaters tended to be more demanding." Demanding behavior by parents is really just a way to get their kids to eat, but these demands and rewards for eating come at a price, Pesch cautions. The children in the study who were less picky and gave in to parents' demands had a higher risk of obesity than the children who were more picky, she says. She also noted that none of the children in the picky eating group were underweight.

"Maybe picky eating in kids is what we're trying to achieve when we try to be mindful eaters as adults," she suggests. "Maybe we should not stress so much about fixing picky eating. Maybe we need to just focus more on positive experiences with food that families deem to be healthy and that they usually eat."

Parents will always worry whether their children are eating well enough, and sometimes there is cause for concern. There may be physical or mental problems that complicate feeding and impair growth and development. In most cases, however, children are not being harmed by their picky eating and it's more of a frustration for both them and their parents.

"Parents can have permission to just not fight that battle if that's not a priority for them," Pesch says. The main concern is that children are growing and developing. Most picky eaters don't have macronutrient deficiencies, she adds.

"You don't want to feed them nuggets for dinner every night, but there is a happy medium to work toward," Pesch says. "The needle on picky eating moves so slowly. Things that backfire are forcing kids to eat and making it a power struggle."

An exception to this is when picky eating turns into a more serious medical issue. Avoidant/restrictive food intake disorder is the term now used to describe "extreme picky eating." This eating disorder affects thousands of people, mostly children, and involves a true fear of food, unlike other eating disorders. The person is scared knowing they must eat while also worrying about choking or becoming sick, or just having no interest at all in eating. These children may get full quickly.

Parent perceptions may be the issue in some cases, and pediatricians may wish to provide parents with information about how much food their child actually requires to meet nutritional goals. The 2014 paper includes a reference table with protein and calorie recommendations for infants through children 8 years of age. Pediatricians can also share feeding tips with parents:

- Allow autonomy. Offer the right amount and mix of food, but allow the child to decide how much to eat.
- Serve small meals and snacks at consistent times, with 2 to 3 hours between. Allow the child to get hungry between snacks and meals.
- Provide the child with a distraction-free area to eat.
- Eat together as a family to promote interaction and bonding. This can also help to demonstrate healthy eating habits to the child.
- Encourage independent eating.
- Limit mealtimes to no more than 30 minutes.
- Offer age-appropriate food that is targeted to the child's size and stage of development.
- Remain neutral during mealtimes—avoid games to promote eating, as well as punishments, bribes, or threats. These actions do not promote healthy eating.
- Offer a variety of foods early, ideally before age 2 years.
- Don't cook a separate meal for children. They should eat what the family eats with the exception of highly allergic foods or choking hazards.
- Involve your child in meal planning and food preparation.

CONTINUED FROM PAGE 36
or have physical problems eating or even sensory avoidance, Pesch says.

For problems of this nature, pediatricians should involve someone in child psychology who specializes in treating eating or feeding disorders. Dieticians and nutritionists may also be helpful, she adds. Close follow-up of these children is necessary to make sure they keep gaining weight or at least are not losing any.

“You have to treat it like an eating disorder,” Pesch says. “A child’s No. 1 job is to grow.”

According to a 2014 paper in the *Singapore Medical Journal* on behaviors of picky eaters, 20% to 50% of parents perceived their children as picky, yet the majority of these children were not deficient in terms of either growth or nutrition. However, telling parents there is nothing to be concerned about when discussing picky eating isn’t usually helpful.

Pediatricians need to look for feeding problems or other serious issues that could be causing picky eating or failure to absorb nutrients. Advice on helpful feeding practices and nutritional requirements based on age and size are helpful in terms of tempering parental anxieties and frustrations. “Picky eaters” can be tricky to define, but the issues that lead parents to this complaint usually involve low food consumption, a tendency to only eat certain foods’ refuse food, or be unwilling to eat certain foods or try new foods. Others have strong food and drink preferences. These behaviors are most common in children up to age 10, according to the 2014 paper. The biggest worry among parents is whether their children are getting the nutrition they need to meet their development needs.

A starting point for education from the pediatrician might focus on a discussion about normal growth benchmarks and nutrition requirements:

- For infants, a tripling of birth weight by 50% from birth weight in the first year of life.
- In the second year, a growth in height of about 12 cm and an increase in weight of 2 to 3 kg is expected.
- Beyond age 2 through puberty, average increases between 6 to 8 cm in height and 2 kg in weight are expected.

Pediatricians should also advise parents not to take these benchmarks too literally, and inform them that genetics play a big role in how a child’s height and weight develop. Parents should also keep in mind that children often refuse new foods at first, but increase acceptance with repeated exposure. The authors of the 2014 study note that it’s not a question of the food being offered, but rather the avoidance of new foods in general. The child’s personality, temperament, culture, and family dynamics also play a big role in feeding practices.

Additionally, the amount a child consumes at each meal can vary, sparking parents’ concern. Parents should be reminded to consider the entire day’s consumption when measuring their child’s intake.

**COMMENTS?** Email them to llevine@mjhiflsciences.com

**For references, go to** [ContemporaryPediatrics.com/picky-eaters](ContemporaryPediatrics.com/picky-eaters)

Rachael Zimlich, RN, BSW, is a freelance writer in Cleveland, Ohio. She has nothing to disclose.
Disseminated erythema migrans as a result of Lyme disease

You are asked to evaluate a healthy 17-year-old boy who developed a fever, sore throat, and malaise several days after removing a tick from his right arm after a hike in the woods. He noted a solitary, red expanding lesion on his right arm at the site of the tick bite. Three days later, multiple lesions developed on his trunk, face, and extremities (Figure). He takes no medications and has no personal or family history of skin disorders.

Diagnosis
Disseminated, expanding, annular, red plaques with central clearings following a single lesion at the site of a tick bite are strongly indicative of Lyme disease. A singular targetoid lesion is the presenting symptom in 89% of pediatric patients (23% of whom develop multiple lesions). These skin manifestations are often associated with systemic symptoms including fever, malaise, and arthralgia; if left untreated, they can progress to include cranial...
al nerve palsy, arthritis, meningitis, or carditis. In early localized disease, as seen in this patient, serological studies of immunoglobulin G for *Borrelia burgdorferi* are often negative, as the body has not had sufficient time to build an adaptive immunological response (ie, less than 3 weeks since infection). There are also tests available to detect immunoglobin M antibodies against *B burgdorferi*, which can be indicative of active infection; however, only 20% to 40% of patients with active Lyme disease will be seropositive. It can be more clinically useful to observe the rapid clearing of the “bull’s eye” rash and associated symptoms (within 1-2 days of starting antibiotic therapy) to confirm the diagnosis of Lyme disease in an endemic area, especially if the patient has a history of tick exposure.

**Treatment**

Although several antibiotics have been shown to be effective in treating early Lyme disease, doxycycline is usually recommended due to its efficacy in treating possible coinfections. Other antibiotic options, which are usually preferred for pregnant women and children aged younger than 8 years, include amoxicillin and cefuroxime axetil.

**Our patient**

This patient started on oral doxycycline, and 36 to 48 hours after starting the antibiotic, he reported feeling much better; his skin rash had almost completely resolved. He completed 3 weeks of oral antibiotic therapy and experienced complete resolution of symptoms without lasting pigmentation changes or scarring. Most patients with acute Lyme disease recover completely within 20 days of onset.

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

**For references, go to ContemporaryPediatrics.com/dermcase-0321**

Bernard Cohen, MD, is a professor of Pediatrics and Dermatology, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Sarah Miller is an MS2 at Johns Hopkins University School of Medicine, Baltimore, Maryland.

The authors have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.
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  You save $100.83!

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Antibiotics are frequently prescribed to treat a variety of conditions in patients who benefit from their use. Although beneficial, antibiotic use can lead to common adverse effects that include rashes and diarrhea in addition to less common events, such as severe allergic reactions and *Clostridium difficile* infection. Unnecessary antibiotic prescribing is a risk factor for antibiotic resistance, which can result in increased healthcare costs, morbidity, and mortality. In 2016, to combat the growing threat of antibiotic resistance, the president’s National Action Plan called for a goal of reducing antibiotics prescribed for acute respiratory conditions by 50% in 2020. Efforts to measure antibiotic prescribing patterns help encourage antibiotic prescribing only for infections that warrant their use, ensure correct dosing and duration, and minimize the occurrence of misdiagnoses. All of these steps are fundamental to reducing inappropriate antibiotic prescribing.

**Antibiotic Prescribing Patterns for Acute Respiratory Infections**

Bronchitis, otitis media, pharyngitis, sinusitis, tonsillitis, pneumonia, and the common cold are among some of the most frequently diagnosed acute respiratory infections for which antibiotics are prescribed. Among ambulatory care visits in the United States, only 50% of antibiotic prescriptions for acute respiratory infections (ARIs) were estimated to be appropriate. Using ICD-9-CM diagnosis codes to identify children (<18 years) who had 5 specific ARIs (ie, acute otitis media, sinusitis, bronchitis, upper respiratory infection, and pharyngitis), a retrospective analysis was conducted using data collected from the National Ambulatory Medical Care Survey from 2000 to 2010 to determine rates of outpatient visits and antimicrobial prescribing. Additionally, bacterial prevalence rates for the 5 ARIs were estimated from a meta-analysis of studies published from 2000 to 2011. A mean of 56.9% (95% CI, 50.8%–63.1%) of ARI visits led to overall antibiotic prescribing while the overall expected prescribing rate of the 5 ARIs was 27.4% (95% CI, 26.5%–28.3%), based upon the estimated prevalence rates. This difference in prescribing compared with the expected prescribing rate represents approximately 11.4 million unnecessary antibiotic prescriptions to pediatric patients annually.

**Factors Contributing to Inappropriate Antibiotic Prescribing Patterns**

Most antibiotic healthcare expenditures in the United States result from prescribing in the outpatient setting, although antibiotic use is not always necessary. The decision-making process used by physicians to prescribe antibiotics is complex and can be influenced by both clinical and nonclinical factors. These factors include:

- **Pressure from parents.** Clinicians feel pressured by parents to prescribe antibiotics to pediatric patients; pediatricians express that they have prescribed antibiotics, even when they are not clinically indicated as a result of the “culture of expectations” held by parents.

- **Time constraints.** Busy appointment schedules, especially during peak seasons of respiratory illness, leave little time for clinicians to spend with each patient. Pediatricians report that it is quicker to prescribe an antibiotic than to explain to parents why it is not necessary.

- **Diagnostic uncertainty regarding the type of infection (eg, bacterial or viral).** Clinicians indicate that despite treatment guidelines, they are not always confident of whether the infection is bacterial; they sometimes prescribe antibiotics to avoid undertreating the infection.
Diagnostic Testing
Diagnostic testing is useful to clinicians in determining if an infection is bacterial or viral, which contributes to prescribing decisions. Although molecular-based respiratory panels are often used in hospitals and emergency department settings, the cost and extensive turn-around time associated with these diagnostics result in infrequent use in outpatient practices. Cost-effective, accurate, and sensitive diagnostic testing that can provide rapid results through an on-demand platform would be beneficial in the ambulatory setting to minimize inappropriate antibiotic prescribing, further improving the quality of patient care.

Onsite Respiratory Testing
Traditionally, clinical care of respiratory tract infections is designed around syndromic disease management and centralized laboratory testing. Now, laboratory testing is shifting to decentralized, near-patient settings, creating a simplified process with faster results. With the shift toward value-based care, syndromic testing from BioFire Diagnostics, LLC contributes to doing what is best for the patient while reducing untimely and expensive sending-out tests. The BioFire® FilmArray® Respiratory EZ (RP EZ) Panel, which is cleared for use with the BioFire® FilmArray® 2.0 EZ System, tests for a comprehensive set of 14 respiratory targets, facilitating rapid near-patient molecular diagnostic testing. Attributes of the BioFire® FilmArray® 2.0 EZ System Configuration include:
- Designed for use with the BioFire RP EZ Panel in CLIA-waived testing sites, including clinics and physician offices
- Enables decentralized molecular testing throughout a provider network
- Features a simplified and intuitive interface and results report

Exploring the Real-world Use of the BioFire RP EZ Panel
The real-world use of the BioFire RP EZ Panel was investigated and results were published in The Pediatric Infectious Disease Journal (March 2020, 39 (3): 188-191 doi: 10.1097/INF.0000000000002544). The following is a summary of the key findings from that study.

Performance and Impact of a CLIA-waived, Point-of-care Respiratory PCR Panel in a Pediatric Clinic

Study Description
This is a prospective study to evaluate the impact of using the BioFire RP EZ Panel in a pediatric outpatient clinic. At clinic A, patients for whom respiratory pathogen testing was deemed appropriate by the clinician were tested on-site using the BioFire RP EZ Panel and/or rapid antigen tests. Use of the BioFire RP EZ Panel was encouraged, and prescriptions for antimicrobials were delayed until test results were available. At clinic B, on-site testing was limited to rapid antigen tests, however, residual respiratory samples were frozen and later tested for definitive pathogen identification. The primary study aim was to determine the proportion of patients that received appropriate antimicrobial therapy based on pathogen detection. Patients with positive rapid antigen results for strep throat were excluded because antibiotic use would be unrelated to the results of the BioFire RP EZ Panel. The study also evaluated the impact to clinic workflow.

Summary of Results and Discussion
During the 1-year study period, a total of 430 samples (298 at clinic A and 132 at clinic B) were tested with the BioFire RP EZ Panel. As shown in the Figure 1, the overall positivity rate and co-detection rates were similar.

Figure 1. Pathogen Detection Rates by Clinic

Patients tested at Clinic A were significantly younger (3.19 vs 5.89, \( P < .0001 \)), had lower detection rates for influenza A and B, and a higher detection rate for respiratory syncytial virus (RSV) and human rhinovirus/enterovirus. Continued use of rapid antigen tests at clinic A (350 additional samples) likely contributed to the differences in pathogen detection rates as samples with positive rapid antigen results may have been excluded from testing with the BioFire RP EZ Panel at clinic A. The high positivity rate at both sites indicates appropriate use of diagnostic testing at both locations. Importantly, 51% (153/298) and 36% (48/132) of samples tested at clinic A and clinic B had pathogens detected by the BioFire RP EZ Panel that cannot be detected by rapid antigen tests.

Appropriate use of antimicrobials was determined by comparing antimicrobial prescriptions to detected pathogens (Table 1). Both clinics had high rates of appropriate use of antibiotics indicating strong antimicrobial stewardship. However, use of the BioFire RP EZ Panel demonstrated a significant improvement in the appropriate use of antimicrobials. Specifically, antimicrobials were avoided more often for patients with no pathogen detection (97.6% vs 90.5%) or with viral detections other than influenza or RSV (98.1% vs 94.1%). Clinic B had a higher use of oseltamivir for influenza positive patients, however, a post-hoc analysis of patients with influenza determined that all 55 patients at both clinics were managed appropriately when including factors such as age and duration of symptoms.

An evaluation of clinic workflow at clinic A found that the average duration of appointment times was shorter (mean 48.0 vs 53.7, \( P = .0009 \)) for patients tested with the BioFire RP EZ Panel compared to those that were not tested. Results for the BioFire RP EZ Panel were called to the patients after the test results were available.

**Key Points**
- Approximately 50% of respiratory pathogens detected by the BioFire RP EZ Panel are not detectable by rapid antigen testing due to the limited number of rapid antigen tests available for detecting pathogens.
- Use of the BioFire RP EZ Panel significantly increased appropriate use of antimicrobials even in a setting with strong antimicrobial stewardship.
- Use of the BioFire RP EZ Panel reduced appointments times and subjective feedback from the clinical staff was positive.

**Clinical and Practical Considerations for BioFire RP EZ Panel Implementation in the Outpatient Setting**

Clinics can provide more timely and accurate diagnosis with on-site testing using the BioFire RP EZ Panel. Each test takes just 2 minutes of hands-on time and 1 small sample, helping to streamline workflow and provide results to patients in about an hour.

 Rapid and comprehensive test results from the BioFire Panels may help in discussing the efficacy of antibiotics with patients. Accurate and timely diagnosis may increase patient satisfaction while potentially reducing unnecessary antibiotic prescriptions.

Furthermore, when patients have clear answers about what’s probably causing their respiratory infection, they may be less likely to seek additional care in the emergency department.

**Table 1. Key Findings of Appropriate Use of Antimicrobials with BioFire® RP EZ Panel Detection**

<table>
<thead>
<tr>
<th>BioFire RP EZ Panel Detection</th>
<th>Study Defined Appropriate Treatment</th>
<th>Clinic A</th>
<th>Clinic B</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>No antibiotics or antiviral</td>
<td>83/85 (97.6%)</td>
<td>38/42 (90.5%)</td>
<td>.0923</td>
</tr>
<tr>
<td>Influenza</td>
<td>Oseltamivir</td>
<td>6/19 (31.6%)</td>
<td>27/36 (75%)</td>
<td>.0018</td>
</tr>
<tr>
<td>RSV</td>
<td>No antibiotics or antivirals</td>
<td>37/38 (97.4%)</td>
<td>3/3 (100%)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Virus other than influenza/RSV</td>
<td>No antibiotics or antivirals</td>
<td>152/155 (98.1%)</td>
<td>48/51 (94.1%)</td>
<td>.16727</td>
</tr>
<tr>
<td>Atypical bacteria</td>
<td>Appropriate antibiotic</td>
<td>1/1 (100%)</td>
<td>0/0</td>
<td>--</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>279/298 (93.6%)</td>
<td>116/132 (87.9%)</td>
<td>.0445</td>
</tr>
</tbody>
</table>

EV, enterovirus; hMPV, human metapneumovirus; HRV, human rhinovirus; RP EZ, BioFire RP EZ Panel; RSV, respiratory syncytial virus.

Key Takeaways: How the BioFire® RP EZ Panel Can Benefit a Practice and Patients

- **Improve Operational Efficiency**
  The BioFire RP EZ Panel has been shown to reduce appointment duration.9

- **Reduce Unnecessary Testing**
  The BioFire RP EZ Panel offers results in about an hour, potentially enabling faster diagnosis and decreased follow-up care.

- **Put Confidence in Treatment Plans**
  Choosing a syndromic panel means choosing greater accuracy and a higher standard of care. A panel that identifies a broad range of pathogens can better detect co-infections and help to put a name on the pathogen. This can increase confidence in the treatment plan for the patient.

- **Prescribe the Right Treatment**
  The BioFire RP EZ Panel has demonstrated an increase in the occurrence of appropriate treatment.9

**The BioFire® Respiratory 2.1-EZ Panel (EUA)† With SARS-CoV-2**

Because a large number of pathogens cause respiratory infections, tests that only identify SARS-CoV-2 or influenza run the risk of missing the real culprit. In fact, SARS-CoV-2 has been detected in respiratory samples less than 10% of the time in the United States,13 and many rapid influenza diagnostic tests sacrifice accuracy for speed, with sensitivities ranging from 50% to 70%.14 That’s why the BioFire Respiratory 2.1- EZ Panel (EUA) uses a syndromic approach to accurately detect and identify a wide range of pathogens. The panel identifies a menu of 19 respiratory targets, including SARS-CoV-2, in one multiplex PCR test, with results in about 45 minutes. The BioFire Respiratory 2.1-EZ Panel (EUA) is designed to run on the CLIA-waived BioFire® 2.0 EZ Configuration System. This sample-to-answer respiratory pathogen panel is a frontline solution for clinics of every size.

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**REFERENCES**


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1 This test has not been FDA cleared or approved; this test has been authorized by FDA under an EUA for use by authorized laboratories; this test has been authorized only for the detection and differentiation of nucleic acid of SARS-CoV-2 from multiple respiratory viral and bacterial organisms; and this test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostics tests for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

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