SELECT IMPORTANT SAFETY INFORMATION

Contraindication: EMVERM is contraindicated in persons with a known hypersensitivity to the drug or its excipients (mebendazole, microcrystalline cellulose, corn starch, anhydrous lactose, sodium starch glycolate, magnesium stearate, stearic acid, sodium lauryl sulfate, sodium saccharin, and FD&C Yellow #6).

Please see Brief Summary on pages 3-4. For Full Prescribing Information, visit EmvermHCP.com.
PRESCRIBE WITH CONFIDENCE

- The AAP Red Book recommends mebendazole as one of the drugs of choice for pinworm infection.²
- Mebendazole has been prescribed by physicians for more than 40 years.³

EMVERM DOSING FOR PINWORM

- Patients should be prescribed 2 tablets. EMVERM can often cure pinworm symptoms in a single dose. However, a second course of treatment may be necessary after 3 weeks to prevent reinfection and to kill any worms that hatched after the first treatment.¹
  - Dosing is the same for adults and children¹
    - One 100 mg tablet, for one day
  - Chewable, kid-friendly tablet can also be swallowed whole or crushed and mixed with food¹

AAP, American Academy of Pediatrics.

SELECT IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions:

- Risk of convulsions: Convulsions in infants below the age of 1 year have been reported
- Hematologic effects: Neutropenia and agranulocytosis have been reported in patients receiving mebendazole at higher doses and for prolonged duration. Monitor blood counts in these patients
- Metronidazole and serious skin reactions: Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) have been reported with the concomitant use of mebendazole and metronidazole

Please see Brief Summary on pages 3-4. For Full Prescribing Information, visit EmvermHCP.com.

EMVERM® (mebendazole) 100 mg Chewable Tablets

**INDICATIONS AND USAGE**

EMVERM® is indicated for the treatment of patients two years of age and older with gastrointestinal infections caused by *Ascaris lumbricoides* (roundworm), *Enterobius vermicularis* (pinworm), *Necator americanus* (hookworm), and *Trichuris trichiura* (whipworm).

**DOSAGE AND ADMINISTRATION**

The recommended dosage for EMVERM® is described in Table 1 below. The same dosage schedule applies to adults and pediatric patients two years of age and older. The tablet may be chewed, swallowed, or crushed and mixed with food.

Table 1: Dosage of EMVERM in Adult and Pediatric Patients (two years of age and older)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinworm</td>
<td>1 tablet, once</td>
<td>1 tablet morning and evening for 3 consecutive days</td>
</tr>
<tr>
<td>Whipworm</td>
<td>1 tablet, once</td>
<td>1 tablet morning and evening for 3 consecutive days</td>
</tr>
<tr>
<td>Roundworm</td>
<td>1 tablet, once</td>
<td>1 tablet morning and evening for 3 consecutive days</td>
</tr>
<tr>
<td>Hookworm</td>
<td>1 tablet, once</td>
<td>1 tablet morning and evening for 3 consecutive days</td>
</tr>
</tbody>
</table>

If the patient is not cured three weeks after treatment, a second course of treatment is advised. No special procedures, such as fasting or purging, are required.

**CONTRAINDICATIONS**

EMVERM® is contraindicated in persons with a known hypersensitivity to the drug or its excipients (mebendazole, microcrystalline cellulose, corn starch, anhydrous lactose, sodium starch glycolate, magnesium stearate, citric acid, sodium lauryl sulfate, sodium saccharin, and FD&C Yellow #6).

**WARNINGS AND PRECAUTIONS**

**Risk of Convulsions**

Although EMVERM® is approved for use in children two years of age and older, convulsions have been reported in infants below the age of 1 year during post-marketing experience with mebendazole, including EMVERM®.

**Hematologic Effects**

Agranulocytosis and neutropenia have been reported with mebendazole use at higher doses and for more prolonged durations than is recommended for the treatment of soil-transmitted helminth infections. Monitor blood counts if EMVERM® is used at higher doses or for prolonged duration.

**Metronidazole Drug Interaction and Serious Skin Reactions**

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) have been reported with the concomitant use of mebendazole and metronidazole. Avoid concomitant use of mebendazole, including EMVERM® and metronidazole.

**ADVERSE REACTIONS**

**Clinical Studies**

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

The safety of mebendazole was evaluated in 6276 subjects who participated in 39 clinical trials for treatment of single or mixed parasitic infections of the gastrointestinal tract. In these trials, the formulations, dosages and duration of mebendazole treatment varied. Adverse reactions reported in mebendazole-treated subjects from the 39 clinical trials are shown in Table 2.

Table 2: Adverse Reactions Reported in Mebendazole-treated Subjects from 39 Clinical Trials*

<table>
<thead>
<tr>
<th>Adverse Reaction(s)</th>
<th>Gastrointestinal Disorders</th>
<th>Skin and Subcutaneous Tissue Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Includes mebendazole formulations, dosages and treatment duration other than EMVERM® 100 mg tablet.

**Postmarketing Experience**

The following adverse reactions have been identified in adult and pediatric patients postmarketing with mebendazole formulations and dosages other than the EMVERM® 100 mg chewable tablet. 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 drug exposure.

Table 3: Adverse Reactions Identified During Postmarketing Experience with Mebendazole*

<table>
<thead>
<tr>
<th>Adverse Reaction(s)</th>
<th>Blood and Lymphatic System Disorders</th>
<th>Immune System Disorders</th>
<th>Nervous System Disorders</th>
<th>Hepatobiliary Disorders</th>
<th>Renal and Urinary Disorders</th>
<th>Skin and Subcutaneous Tissue Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Agranulocytosis, Neutropenia</td>
<td>Hypersensitivity</td>
<td>Convulsions</td>
<td>Hepatitis, Abnormal liver tests</td>
<td>Glomerulonephritis</td>
<td>TEN, SJS, Exanthema, Angioedema, Urticaria, Alopecia</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Includes mebendazole formulations, dosages and treatment duration other than EMVERM® 100 mg chewable tablets.

**DRUG INTERACTIONS**

Concomitant use of mebendazole, including EMVERM®, and metronidazole should be avoided.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

The available published literature on mebendazole use in pregnant women has not reported a clear association between mebendazole and a potential risk of major birth defects or miscarriages [see Data].

There are risks to the mother and fetus associated with untreated helminthic infection during pregnancy [see Clinical Considerations].

In animal reproduction studies, adverse developmental effects (i.e., skeletal malformations, soft tissue malformations, decreased pup weight, embryolethality) were observed when mebendazole was administered to pregnant rats during the period of organogenesis at single oral doses as low as 10 mg/kg (approximately 0.5-fold the total daily maximum recommended human dose [MRHD]). Maternal toxicity was present at the highest of these doses [see Data].
The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage is clinically recognized pregnancies in 2–4% and 15–20%, respectively.

**Clinical Considerations**

**Disease-Associated Maternal and/or Embryo-Fetal Risks**

Untreated soil transmitted helminth infections in pregnancy are associated with adverse outcomes including maternal iron deficiency anemia, low birth weight, neonatal and maternal death.

**Data**

**Human Data**

Several published studies, including prospective pregnancy registries, case-control, retrospective cohort, and randomized controlled studies, have reported no association between mebendazole use and a potential risk of major birth defects or miscarriage. Overall, these studies did not identify a specific pattern or frequency of major birth defects with mebendazole use. However, these studies cannot definitely establish the absence of any mebendazole-associated risk because of methodological limitations, including recall bias, confounding factors and, in some cases, small sample size or exclusion of first trimester mebendazole exposures.

**Animal Data**

Embryo-fetal developmental toxicity studies in rats revealed no adverse effects on dams or their progeny at doses up to 2.5 mg/kg/day on gestation days 6–15 (the period of organogenesis). Dosing at ≥10 mg/kg/day resulted in a lowered body weight gain and a decreased pregnancy rate. Maternal toxicity, including body weight loss in one animal and maternal death in 11 of 20 animals, was seen at 40 mg/kg/day. At 10 mg/kg/day, increased embryo-fetal resorption (100% were resorbed at 40 mg/kg/day), decreased pup weight and increased incidence of malformations (primarily skeletal) were observed. Mebendazole was also embryotoxic and teratogenic in pregnant rats at single oral doses during organogenesis as low as 10 mg/kg (approximately 0.5-fold the total daily MRHD, based on mg/m²).

In embryo-fetal developmental toxicity studies in mice dosed on gestation days 6–15, doses of 10 mg/kg/day and higher resulted in decreased body weight gain at 10 and 40 mg/kg/day and a higher mortality rate at 40 mg/kg/day. At doses of 10 mg/kg/day (approximately 0.2-fold the total daily MRHD, based on mg/m²) and higher, embryo-fetal resorption increased (100% at 40 mg/kg) and fetal malformations, including skeletal, cranial, and soft tissue anomalies, were present. Dosing of hamsters and rabbits did not result in embryotoxicity or teratogenicity at doses up to 40 mg/kg/day (1 to 3.9-fold the total daily MRHD, based on mg/m²).

In a peri- and post-natal toxicity study in rats, mebendazole did not adversely affect dams or their progeny at 20 mg/kg/day. At 40 mg/kg (1.9-fold the total daily MRHD, based on mg/m²), a reduction of the number of live pups was observed and there was no survival at weaning. No abnormalities were found on gross and radiographic examination of pups at birth.

**Lactation**

**Risk Summary**

Limited data from case reports demonstrate that a small amount of mebendazole is present in human milk following oral administration. There are no reports of effects on the breastfed infant, and the limited reports on the effects on milk production are inconsistent. The limited clinical data during lactation precludes a clear determination of the risk of EMVERM® to a breastfed infant; therefore, developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for EMVERM® and any potential adverse effects on the breastfed infant from EMVERM® or from the underlying maternal condition.

**Pediatric Use**

The safety and effectiveness of EMVERM® 100 mg chewable tablets has not been established in pediatric patients less than two years of age. Convulsions have been reported with mebendazole use in children less than one year of age.

**Geriatric Use**

Clinical studies of mebendazole did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

**OVERDOSAGE**

In patients treated at dosages substantially higher than recommended or for prolonged periods of time, the following adverse reactions have been reported: alopecia, reversible transaminase elevations, hepatitis, agranulocytosis, neutropenia, and glomerulonephritis.

**Symptoms and signs**

In the event of accidental overdose, gastrointestinal signs/symptoms may occur.

**Treatment**

There is no specific antidote.

**CLINICAL STUDIES**

Efficacy rates derived from various studies are shown in Table 4 below:

**Table 4: Mean Cure Rates and Egg Reductions from Clinical Studies**

<table>
<thead>
<tr>
<th></th>
<th>Pinworm (enterobiasis)</th>
<th>Whipworm (trichuriasis)</th>
<th>Roundworm (ascariasis)</th>
<th>Hookworm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cure rates mean</strong></td>
<td>95%</td>
<td>68%</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td><strong>Egg reduction mean</strong></td>
<td>---</td>
<td>93%</td>
<td>99%</td>
<td>99%</td>
</tr>
</tbody>
</table>

**PATIENT COUNSELING INFORMATION**

Advises the patient to read the FDA-approved patient labeling (Patient Information).

Advises patients that:

- Taking EMVERM® and metronidazole together may cause serious skin reactions and should be avoided.
- EMVERM® can be taken with or without food.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. To report SUSPECTED ADVERSE REACTIONS contact Impax Laboratories, Inc. at 1-877-994-6729.

Please see Full Prescribing Information including Patient Information at www.emvermhcp.com.

**Distributed By:** Impax Specialty Pharma

Hayward, CA 94544

07/2017 PP-XPI-MEB-US-0008
Navigating Autism
Primary care’s pathway to the medical home

Thyroid disorders
Manifestations, evaluation, management

Pharmacologist’s Notebook
Epinephrine autoinjectors

6 pitfalls in managing ADHD

Recognize and Refer
Dx clues from a pediatric allergist
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Epinephrine autoinjectors for anaphylaxis

Epinephrine is essential for treating anaphylaxis in children, and autoinjectors are the preferred method for administering epinephrine in an anaphylactic emergency. There is no one-size-fits-all approach to the optimal dose for all children, so here is expert advice about how to choose what’s best for your patient.

LISA M HUTCHINS, PHARMD, BCPPS; KEITH KLEINMAN, MD

Anaphylaxis is a severe systemic allergic reaction that may be life threatening if not quickly recognized and treated. Anaphylaxis most often results from immunoglobulin (Ig)E-mediated mast cell degranulation leading a combination of respiratory and circulatory compromise, coupled with dermatologic, gastrointestinal, and neurologic symptoms. Whereas the prevalence of anaphylaxis varies by location worldwide, it is estimated that 0.05% to 2% of people in the United States will experience anaphylaxis within their lifetime.

The most frequently identified out-of-hospital causes of anaphylaxis are insect stings and food allergies. In children, an allergic reaction to food is the most common reason for anaphylaxis. Incidence of anaphylaxis among children is increasing, which highlights the need for appropriate and affordable access to epinephrine. Prescribing intramuscular (IM) epinephrine for self-administration in the community setting is recommended for any patient who presents with an anaphylactic reaction.

Recently, it was found that when epinephrine was administered to pediatric patients in the prehospital setting prior to emergen-
from having to keep track of both the medication and the instructions separately. Some formulations also have a training device available so the patient and caregiver can practice and see what the product feels like in their hands before actual use. For details on administration and features of the available autoinjectors and other epinephrine products on the market, see the Figure below.

Dose selection of autoinjectors is another problem because the premeasured doses do not allow for manipulation. In children weighing less than 7.5 kg, the recommended dose is 0.01 mg/kg, which cannot be supplied by any of the currently available autoinjector products. The smallest available dose for the autoinjectors is 0.1 mg, which was added to the market in November 2017 for the treatment of anaphylaxis in children between 7.5 kg and 15 kg. In addition to the novel

---

**NOTE FROM DR LEE**  The diverse product line of epinephrine autoinjectors (EAIs) used for anaphylaxis requires patients, caretakers, and healthcare providers to be educated on the correct method for dose administration. With the prevalence of drug shortages and back orders, the need for reeducation to an alternative available dosage form is likely.

— CARLTON LEE, PHARM.D., MPH, FASHP, FPPAG

---

### EPINEPHRINE AUTOINJECTORS AND RELATIVE COSTS

<table>
<thead>
<tr>
<th>Patient at any weight range</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adyphren Amp II vial and syringe kit</strong>&lt;sup&gt;10&lt;/sup&gt;</td>
<td><strong>1 mg/mL</strong></td>
<td><strong>$</strong></td>
<td><strong>$</strong></td>
</tr>
<tr>
<td><strong>EpinephrineSNAP–V vial and syringe kit</strong>&lt;sup&gt;11&lt;/sup&gt;</td>
<td><strong>1 mg/mL</strong></td>
<td><strong>$$</strong></td>
<td><strong>$$</strong></td>
</tr>
<tr>
<td><strong>Patient weight 7.5 kg to &lt;15 kg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Auvi-Q autoinjector</strong>&lt;sup&gt;12&lt;/sup&gt;</td>
<td><strong>0.1 mg/0.1 mL</strong></td>
<td><strong>$$$$</strong></td>
<td><strong>$$$$</strong></td>
</tr>
</tbody>
</table>

---

**Table continued on page 8**
dose, this autoinjector also features a shorter needle length, which reduces the likelihood that the needle would unintentionally strike the bone when administered in the preferred location. The historical doses on the market are 0.15 mg and 0.3 mg, approved for patients 15 kg to 30 kg and greater than or equal to 30 kg, respectively. Prior to the introduction of the 0.1 mg dose, the American Academy of Pediatrics (AAP) recommended the use of the 0.15 mg autoinjector for infants as small as 7.5 kg, given the limitations to prescribing a 1 mg/mL vial and instructing the caregiver to draw up and administer an exact dose intramuscularly (IM). The 0.1 mg autoinjector also may not be readily available in many pharmacies, so the 0.15 mg autoinjector continues to be recommended as an alternative in patients between 7.5 kg and 30 kg if the caregiver is unable to obtain the 0.1 mg strength. In patients requiring a smaller dose than the autoinjectors provide, the available prescription option is a vial of epinephrine 1 mg/mL with education to the caregiver on drawing up the dose using a syringe and needle. This option requires significant education and, in a controlled scenario, caregivers were found to be significantly slower than trained healthcare professionals, in addition to drawing up an inaccurate dose, regardless of time required to prepare. Daycare providers and babysitters were not included in this study, and targeted education by a healthcare professional often does not include these caretakers. In these situations, a child would likely not be provided epinephrine in a timely manner or even before EMS arrival. **Summary** Anaphylaxis is a severe life-threatening condition with increasing incidence and lifetime prevalence. As **CONTINUED ON PAGE 10**
0 lbs., 14 oz., and made for EVERY INCH

RECOMMEND AQUAPHOR FOR BABY’S SKINCARE NEEDS

Beiersdorf
Data on file. Beiersdorf Inc. ©2017
such, the prescription of outpatient epinephrine, the only treatment known to be lifesaving in this condition, is more important now than ever before. Selection of an epinephrine product must take into account the product and patient-specific factors. There is not a one-size-fits-all approach to prescribing epinephrine. For children weighing less than 7.5 kg, risks of prescribing an inappropriately high dose of epinephrine when prescribing an autoinjector must be balanced with risks of delay in administration and potential errors in dosing in an emergency situation when prescribing a vial with a syringe and needle. In addition, the costs of EAI has recently been highlighted due to a large spike in patient out-of-pocket costs and increased charges by the drug manufacturers without a major change to the products.

CONTINUED ON PAGE 42
Applying sunscreen as often as manufacturers recommend results in plasma concentrations of sunscreen’s 4 active ingredients that exceed the threshold for safety concerns established by the US Food and Drug Administration (FDA), according to a recent study. The clinical significance of these findings has not been established, however.

Investigators enrolled in the trial 24 healthy volunteers aged from 18 to 60 years, 14 of whom were black or African American. Participants were divided into 4 groups of 6 individuals, with each group assigned to use 1 of 4 commercially available sunscreens—2 different sprays, a lotion, or a cream. They applied the products 4 times a day for 4 days, covering body areas generally left uncovered by swimsuits, but not exposed to direct sunlight. Investigators collected multiple blood samples on each of the 4 application days and 3 subsequent days (30 samples for each participant) and assessed them for each of the 4 active ingredients: avobenzone, oxybenzone, octocrylene, and ecamsule.

All 4 products were associated with concentrations greater than 0.5 ng/mL—the FDA’s safety cutoff—that were reached after 4 applications on the first day of the trial. For avobenzone, maximum plasma concentrations for the 2 different sprays, lotion, and cream were 4.0 ng/mL, 3.4 ng/mL, 4.3 ng/mL, and 1.8 ng/mL.
Using an asthma self-management tool improves outcomes

Children with asthma who use a web-and mobile–web-based self-management tool show high and sustained self-monitoring and improved asthma outcomes, a study in asthmatic children showed. The 2- to 17-year-old participants, whose persistent asthma was being managed at a pediatric ambulatory clinic, were matched with controls during the 1-year study period. Investigators compared outcomes in these weekly users of an electronic-AsthmaTracker (e-AT) with their own baselines as well as with outcomes in the controls—asthmatics who were receiving usual care at the study’s participating clinics.

The e-AT is based on the asthma control test, modified for weekly assessment, and coupled with decision support for proactive care. It features automated reminders to continue self-monitoring, graphing of real-time results, alerts for patients, parents, and the physician’s office (via e-mail or text) for early signs of asthma control deterioration, and real-time recommendations. The e-AT also records and promotes adherence by generating a congratulatory message and a $10 gift certificate every time 4 assessments are completed.

Of the 327 children and parents enrolled in the trial of e-AT, 65% had maintained adherence at 12 months. Compared with baseline, participants had significantly increased quality of life, asthma control, and had fewer reduced, interrupted, and missed school and workdays at all quarterly assessments. Compared with 1 year before the intervention, they had fewer emergency department (ED) and hospital admissions and less oral corticosteroid (OCS) use. Compared with controls, participants also had reduced ED and hospital admissions and OCS use. Participants who used the e-AT had significantly reduced ED, hospital, and OCS use.

In the 1-year study period, 92% of participants who used the e-AT were adherent to self-monitoring, compared with 82% of controls. The e-AT also generated a congratulatory message and a $10 gift certificate every time 4 assessments were completed. The e-AT helped improve quality of life, asthma control, and reduced ED, hospital, and OCS use.


The FDA published this highly publicized report as a preliminary study to determine if sunscreens should be tested for carcinogenicity and embryofetal toxicity. All the active ingredients generated blood levels higher than the threshold the FDA considers below consideration for systemic effect (0.5 ng/mL). However, the authors are quick to note that the clinical relevance of systemic absorption of these compounds is not yet known and suggest that these findings may induce the FDA to ask the manufacturers for further studies. In the meantime, they said, “These results do not indicate that individuals should refrain from the use of sunscreen.” So, as summer continues, recommend sun protection, including liberal use of sunscreen, but keep an eye out for revised recommendations or product changes based on further study.

**THOUGHTS FROM DR. BURKE**

The authors report that more than 8 million children in the United States have asthma and that 54% of them had an asthma exacerbation in 2016. Data from 2008 showed that asthma was responsible for 10 million missed school days and 14 million missed parent workdays that year. Imagine the impact if this program (with a 32% to 59% reduction in ED visits and hospitalizations and a 26% to 35% reduction in the need for oral steroid use) was implemented across the country. This innovative approach is worth a careful look. You can check out the e-AT at https://asthmatracker.utah.edu/public/index.php.

**IN MEMORIAM CONTINUED**

Those of us who knew and treasured Michael know there is no way to fully sum up what an incredible clinician, teacher, and human being he was.

—Tina L. Cheng, MD, MPH
*Johns Hopkins University School of Medicine*

What struck me [about Mike] was how kind and thoughtful he was.

—William T. Zempsky, MD, MPH
*Connecticut Children’s Medical Center*

Michael Burke’s humble and soft-spoken manner belied his tremendous impact on the field of Pediatrics and the world beyond. He inspired all of us who were fortunate to work with him by modeling kindness, compassion, service, and joy.

—Evelyn Cohen Reis, MD
*UPMC Children’s Hospital of Pittsburgh*

Dr. Burke was and remains a true hero to the innumerable people he touched during his life—as well as a leader and friend.

—Lesley S. Hanes, MD, MSc
*US Food and Drug Administration*

I hope the family and those who loved him find peace in their hearts as they know how many people he helped around the world with his knowledge and care for patients.

—Esteban Pérez, MD
*From online*

Few are those who stepped into my life to change it for the better. Dr Burke was one. [He] was a soft-spoken giant who embraced me with his genuine passion for teaching and mentorship. He led by example.

—Fatima Ismail, MBBS
*United Arab Emirates*

Dr. Burke was and remains a true hero to the innumerable people he touched during his life—as well as a leader and friend.

—Lesley S. Hanes, MD, MSc
*US Food and Drug Administration*

I hope the family and those who loved him find peace in their hearts as they know how many people he helped around the world with his knowledge and care for patients.

—Esteban Pérez, MD
*From online*

Dr. Burke was and remains a true hero to the innumerable people he touched during his life—as well as a leader and friend.

—Lesley S. Hanes, MD, MSc
*US Food and Drug Administration*

I hope the family and those who loved him find peace in their hearts as they know how many people he helped around the world with his knowledge and care for patients.

—Esteban Pérez, MD
*From online*
Sudden neutropenia and emesis in an SGA infant

A 24-year-old G2P1001 African American female at 38.2 weeks of gestation was induced for labor for a fetus with prenatally diagnosed intrauterine growth restriction (IUGR). She subsequently delivered via normal spontaneous delivery complicated by presence of heavily meconium-stained amniotic fluid with no signs of meconium aspiration. The infant cried immediately at birth with Apgar scores of 9/9, with deductions for color at 1 and 5 minutes.

On initial examination, the infant was notably small for gestational age (SGA) and below the 10th percentile (-3 SD) for weight (2047g), height (43.2 cm), and head circumference (30 cm). See Figure 1. No dysmorphic features were noted, and her newborn physical examination was otherwise normal. She was full term based on her Dubowitz assessment (Dubowitz score = 38).

Maternal and familial history
Maternal prenatal labs were all within normal limits with no tobacco, alcohol, or illicit substance use reported during the course of her pregnancy. The mother’s past medical history was significant for a learning disorder and a rare hemoglobinopathy called hemoglobin Willamette, a variant of the beta-globin gene that affects fewer than 20 individuals worldwide. She was not anemic, had no other chronic diseases such as hypertension, and was well nourished with adequate weight gain during pregnancy. The maternal blood type was A-positive; AB screen was negative; Group B strep (GBS) was negative; rubella immune. The remainder of prenatal labs were found to be negative/within normal limits.

The mother has another daughter (aged 5 years; gestational age at birth, 38.3 weeks) also found to have symmetric IUGR/SGA at birth with autism and developmental delay. The maternal grandmother of the infant died at age 31 years from kidney disease, and the siblings of the infant’s maternal great-grandmother also had passed away from kidney-related complications. The father of the infant is a 22-year-old African American male with a learning disability and is also the father of the mother’s first child. He has hemoglobin AA. Of note, this mother reported that she also was “very small” at birth.

Hospital course
Although rooming with the mother is the optimal environment for infants, those who are SGA need to be monitored closely to ensure adequate feeding, absence of hypoglycemia, and ability to maintain thermal stability. This infant initially latched well at the breast, was normoglycemic and normothermic, but shortly after birth had had a significant episode of blood-tinged emesis (not deemed to be swallowed maternal blood) and was transferred to the transitional nursery for further evaluation.

Due to persistence of emesis and subsequent hypothermia, a sepsis
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2. Ages 3 months to 4 years
Brushing Toddler’s Teeth

3. Ages 2 years and up
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screen was sent and the infant was started on empiric intravenous (IV) antibiotics of ampicillin and genta-
micin. After acute obstruction was ruled out, the infant was preferen-
tially fed with breast milk, and when that was not available was trialed with 3 different formulas for ongoing spitting and a concern for formula intolerance. The infant’s symptoms improved on ProSobee (soy formula) and she stools normally with benign abdominal examination.

After 48 hours, the blood culture on the infant was negative and the clinical symptoms had improved, so the antibiotics were discontinued. She also required thermal support in an incubator and weaning protocol was initiated based on monitoring of her ongoing weight gain and ability to

![FIGURE 1](image) Fetal growth chart obtained at time of birth. The infant met criteria for small for gestational age (SGA) in 3/3 parameters (weight, height, head circumference) and thus qualified as symmetric intrauterine growth restriction (IUGR).
maintain normothermia. Because of her mother’s history of a rare hemoglobin variant, close monitoring of her complete blood count (CBC) was initiated. The results revealed the beginnings of a sudden neutropenia on day of life 9—absolute neutrophil count (ANC) of 1472—for which she received another course of antibiotics and was placed on reverse isolation. Repeat culture results remained negative but despite initial improvement the neutropenia returned on day of life 16. Hematology consult revealed normal peripheral smears and no definitive diagnosis for the neutropenia. As part of the obstetric evaluation of the prenatally diagnosed growth restriction and complex family history, Genetics consultation with the mother had been ongoing. Results of the maternal genetic analysis were obtained during this infant’s hospitalization and this ultimately enabled the final diagnosis on this infant providing a probable cause for her constellation of clinical findings.

**Laboratory testing and imaging**

At the time of her initial presentation, blood was also sent for a CBC, comprehensive metabolic panel (CMP), and blood culture, and the infant was scheduled for an abdominal x-ray given her recurrent bouts of emesis. Her point-of-care glucose testing for 24 hours remained stable and was subsequently discontinued. Her abdominal radiograph (Figure 2) revealed a normal-sized heart with mildly distended segments of bowel in the abdomen and an overall gas pattern that did not appear to be obstructed. Her CMP levels were: sodium, 134-137; potassium, 4.5-5.9; chloride, 109; carbon dioxide (CO2), 17-20; creatinine, 0.22-0.32; and calcium, 9.9-11. Additional labs revealed a neutropenia that presented over the course of her hospital stay. A peripheral blood smear was examined and found to be within normal limits. Final blood cultures sent on 2 separate occasions showed no growth and urine cytomegalovirus (CMV) culture was negative. Pursuant to standard nursery protocol, a newborn metabolic screen was sent and came back positive for a hemoglobinopathy.

**Differential diagnosis**

Given the host of symptoms and complex history that the patient presented, there were multiple possible differentials (Table 1).

Exposure to drugs (prescribed or illicit) in utero can result in neonatal abstinence syndrome (NAS) due to withdrawal from illicit substances used prenatally or withdrawal due to discontinuation of prescription medications (typically narcotic therapy). Signs and symptoms of this withdrawal can include a high-pitched cry, emesis, tremors, fever and/or sweating, poor feeding, or diarrhea. This diagnosis was ruled out because of the combination of a negative urine toxicology screen (for both mother and baby) and noncontributory history; ie, the patient’s mother denied any tobacco, alcohol, illicit drugs, or prescription drug use during this pregnancy.

The second most likely differential was a possible TORCH infection: infection from toxoplasmosis, other (syphilis, parvovirus, varicella zoster virus [VZV], human immunodeficiency virus [HIV], Zika virus), rubella, cytomegalovirus (CMV), or herpes simplex virus (HSV). Of these, infection with CMV, rubella, or VZV can result in IUGR. However, the patient’s mother was rubella immune, so congenital rubella was not suspected. Fewer than 2% of women who contract VZV during their first 20 weeks of pregnancy give birth to an infant with congenital varicella syndrome. It is also probable, given the mother’s age, that she obtained the VZV vaccination as a child or contracted it prior to becoming pregnant. Furthermore, cutaneous scars in a dermatomal pattern can be seen at birth or as a rash within the first

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Differential Diagnosis for IUGR and Emesis in the Neonate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonatal abstinence syndrome</strong></td>
</tr>
<tr>
<td><strong>TORCH infections</strong></td>
</tr>
<tr>
<td><strong>Sepsis</strong></td>
</tr>
<tr>
<td><strong>Hemoglobinopathy (chromosomal)</strong></td>
</tr>
<tr>
<td><strong>Other chromosomal abnormality</strong></td>
</tr>
</tbody>
</table>

Abbreviations: IUGR, intrauterine growth restriction; TORCH, toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex virus.

---

**FIGURE 2** The patient’s heart is normal size. There are mildly distended segments of bowel in the abdomen. Overall bowel gas pattern does not appear obstructed at this time.
Abbreviation: IUGR, intrauterine growth restriction.

10 days of life (not observed on this patient). Thus, VZV was not high on the list of suspected TORCH infections. If the IUGR was caused by a TORCH infection, the most likely one would have been CMV, but the viral culture came back negative.

Lower on the differentials were sepsis and a possible inherited hemoglobinopathy. There are a host of hematologic disorders associated with diminished fetal growth. Given that this patient’s mother has hemoglobin Willamette (β51Pro→Arg)—an extremely rare hereditary hemoglobinopathy caused by structural defects as a result of a mutation that substitutes proline with arginine at the 51st position in the β chain—clinicians suspected it as a possible cause for the host of symptoms the patient displayed. A review of the research showed that it does not produce clinical evidences of significant hematologic or chemical abnormalities, except for the presence of target red blood cells (RBCs). Most patients are asymptomatic, but some can present with hemolytic anemia due to its high reticulocyte index and RBCs. The mother was not diagnosed with anemia during pregnancy, and the patient’s peripheral blood smear displayed normochromic and normocytic RBCs with no evidence of hemolysis or abnormal cells, particularly target RBCs, leaving a possible other chromosomal abnormality as the most likely cause of the patient’s symptoms.

The infant had symmetrical IUGR, recurrent episodes of emesis, and unexplained neutropenia in the context of an extremely complex family genetic history. Intrauterine growth restriction is defined as a fetus with an estimated weight below the 10th percentile for gestational age. Overall, IUGR affects about 5% of the general obstetric population. However, the incidence varies depending on survey demographics (eg, geographic location, standard of growth curve used). It is most often idiopathic, but it can be grouped based on etiology: symmetric versus asymmetric.1,3

Symmetric growth restriction (Table 2) implies a fetus who is undernourished and is directing most of its energy to maintaining growth of vital organs at the expense of fat deposition. These infants will have preservation of limb length and head circumference but be of low birth weight. This type of growth restriction is usually the result of placental insufficiency.2

Symmetric IUGR (Table 3), also called early-onset IUGR, implies a fetus whose entire body is proportionally small. The period of insult for symmetrical IUGR is generally earlier in gestation (first trimester) when compared with asymmetrical IUGR (third trimester), and the prognosis is poorer.4 Symmetric IUGR encompasses a minority of cases (30%) and is due to intrinsic factors such as chromosomal anomalies and aneuploidy, congenital infections in early pregnancy, congenital malformations, and multiple gestations.5

Common chromosomal abnormalities of IUGR are considered fetal risk factors, including Trisomy 13, Trisomy 18, Trisomy 21, and Turner syndrome.1,3 Other fetal risk factors for symmetric IUGR include congenital malformations such as gastroschisis, congenital heart disease, and renal abnormalities. Russell-Silver syndrome manifests as IUGR with postnatal growth deficiency, limb and facial asymmetry, clinodactyly, and episodes of hypoglycemia.5

Maternal risk factors for symmetric IUGR include prior IUGR, as is the case in this infant. Certain medications such as the anticonvulsants phenytoin and valproic acid, antico-

### TABLE 2
#### ASYMMETRIC IUGR
- Placental insufficiency
- Maternal hypertension
- Both chronic and gestational
- Preeclampsia
- Maternal vascular disease
- Chronic severe diabetes
- Chronic pulmonary disease

Abbreviation: IUGR, intrauterine growth restriction.

### TABLE 3
#### SYMMETRIC IUGR

<table>
<thead>
<tr>
<th>CHROMOSOMAL ABNORMALITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 13</td>
</tr>
<tr>
<td>Trisomy 18</td>
</tr>
<tr>
<td>Trisomy 21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CONGENITAL MALFORMATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroschisis</td>
</tr>
<tr>
<td>Congenital heart disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MATERNAL DRUG USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Cocaine use</td>
</tr>
<tr>
<td>Other substance abuse</td>
</tr>
<tr>
<td>Anticonvulsants (phenytoin and valproate)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CONGENITAL INFECTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Syphilis</td>
</tr>
<tr>
<td>Varicella</td>
</tr>
<tr>
<td>Malaria</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; IUGR, intrauterine growth restriction.
Should antibiotics be prescribed for pink eye?

Viral conjunctivitis is the most common cause of infectious conjunctivitis, also known as pink eye.¹ With significant overlap between viral and bacterial infections in clinical signs and symptoms, a misdiagnosis of type could lead to serious complications, spread of infection, unnecessary antibiotic prescriptions, ocular allergies and toxicities associated with antibiotic use and antibiotic resistance.

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agulants warfarin and heparin, and antineoplastic agents such as methotrexate and cyclophosphamide are known to cause growth restriction.6,7 Maternal infection with toxoplasmosis, syphilis, varicella, malaria, tuberculosis, HIV, rubella, CMV, and Zika virus can be transmitted across the placenta and lead to symmetric IUGR depending on when the mother acquires the infection.

There are also other risk factors that have been associated with IUGR.2,4 These are listed in Table 4.

Other than symmetric IUGR, this infant did not present with any other features typical of intrauterine infections or known genetic syndromes. However, a genetic etiology was highest on the list of differential diagnosis due to the complex history. The mother consented to genetic testing of this infant, and the patient was subsequently found to have the chromosomal deletion Xp11.4p11.23—the same Xp deletion shared by the infant’s mother and sister. A detailed review of open-source genetic databases (Online Mendelian Inheritance in Man: OMIM, www.ncbi.nlm.nih.gov/omim; and Decipher, https://decipher.sanger.ac.uk/) found several syndromes linked to Xp deletion within or adjacent to the Xp deletion found in the infant, including ornithine transcarbamylase (OTC) deficiency, Kabuki syndrome, Norrie disease, and Wiskott-Aldrich syndrome.6-10

The database also identified one infant in whom the clinical presentation of the Xp deletion also included neutropenia (via de novo mutation [DNM]).8 The clinicians were unable to identify a link between persistent neutropenia and this patient’s Xp11.4p11.23 deletion in the literature. Of additional interest were the results of her newborn metabolic screen that were positive for an unspecified hemoglobinopathy, indicating that she may be a carrier of hemoglobin Willamette, which typically does not produce significant chemical and hematological abnormalities or anemia.

**Patient outcome**

The infant needed a final hemoglobin electrophoresis, so she was referred to the outpatient Genetics and Hematology specialists at the local children’s hospital. Unfortunately, she was lost to follow-up.

**Summary**

Pediatricians working in the newborn setting are often the first to detect potential genetic insults. Because of the increased morbidity and mortality of infants with symmetrical IUGR, a thorough physical examination and a detailed genetic family history should be obtained. Of particular note, potential cardiac, renal, and other life-threatening complications need to be ruled out early. In this case, despite both the parents having learning disabilities, they were able to provide a comprehensive history that prompted clinicians to communicate with their prenatal genetic counselor and lead to the final and unique diagnosis.

In settings where access to genetic specialists is limited, the National Institutes of Health’s OMIM database can be an extremely helpful tool from both clinical and diagnostic standpoints.8 Although difficult, communicating genetic diagnoses with families of newborns can be done compassionately and lead to early intervention and coordination of much-needed outpatient services for these infants as they grow.
Building a medical home for children with autism

For a child with a developmental disorder, the pathway from screening for autism spectrum disorder (ASD) to diagnosis of ASD to lifelong care takes place in the child’s medical home.

MARY BETH NIERENGARTEN, MA

In 2007, the American Academy of Pediatrics (AAP) published a clinical report on autism spectrum disorder (ASD) providing pediatricians with information on the identification/evaluation and management of children with this disorder based on the available evidence.1,2 The report highlighted the important role pediatricians play in identifying and caring for these children.

Since that report, the reported prevalence of ASD has grown substantially.3-5 In 2007, the Centers for Disease Control and Prevention (CDC) estimated that 1 in 150 children aged 8 years had an ASD diagnosis based on 2000-study-year data.3 In 2018, the prevalence was reported as 1 in 59 children aged 8 years based on 2014-study-year data.5 This shows an estimated prevalence increase to 1.71% in 2018, up from 1.47% in 2007.

As more evidence has accrued since the 2007 report, a deeper understanding of the needs of these children and how to better help them has evolved. One tangible sign of this deeper understanding is action taken to promote improved diagnosis and treatment as shown by the autism legislation that exists in most states supporting payment for diagnosis and treatment where no such legislation existed in 2007.6 As such, the AAP, the Council on Children with Disabilities, Subcommittee on Autism, and Section on Developmental and Behavioral Pediatrics are updating the clinical report to keep pediatricians current on the evolving understanding of ASD and its management.

Susan L. Hyman, MD, Golisano Children’s Hospital, Rochester, New York, and Susan E. Levy, MD, MPH, the Children’s Hospital of Philadelphia, Pennsylvania, members of the Autism Subcommittee of the Council on Children with Disabilities, provided a brief primer of current information about ASD in a session during the 2018 AAP National Conference and Exhibition (NCE) titled “Autism spectrum disorder and the medical home: Identifica-
As indicated by the title of the session, a key focus of their presentation was to emphasize the need to establish and maintain a medical home for these children once screening has confirmed a diagnosis of ASD to support children and families through the challenges of different stages of their lives.

“We know so much more about autism spectrum disorder than we did 10 years ago, so we hoped that this talk along with other supportive tools would help primary care pediatricians feel more comfortable taking care of kids with autism and more able to serve as a medical home for them,” says Levy.

She stresses, however, that pediatricians are not expected to be experts in all the specialty areas that may be required to help a child with ASD, but that they should be able to provide a medical home for the child and his/her family to turn to when they are not sure about where to get help.

“Even if pediatricians are not sure what to do, they can provide the big picture and help support families,” Levy says, and, importantly, “enter into shared decision-making with families to help arrive at a consensus about the best treatment and the one the family wants to pursue.”

This article summarizes key issues highlighted in the AAP NCE presentation, with a particular focus on management and the important role of pediatricians to provide a medical home to these children and their families to help them navigate the lifelong challenges of this disorder. Emphasized is the importance of identifying and managing co-occurring conditions that often accompany ASD and contribute to the complexity of ASD, which supports the need for a medical home for these children and their families.

### Screening and diagnosis

In their presentation, Hyman and Levy first spoke on key issues in screening and diagnosis that ensure ASD is correctly identified. One clear change since the AAP clinical report in 2007 is the change in how autism is categorized in the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5).* With the changes in the *DSM-5* published in 2013, ASD now is a single category that covers and replaces the subtypes of autistic disorder, Asperger syndrome, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) in the *DSM-IV-TR.*

Identification through screening remains key in identifying ASD early and ensuring the child receives the best care possible. Data show that intervention provided in children aged younger than 3 years has a greater

### TABLE 1 SCREENING TOOLS: AUTISM SPECIFIC

<table>
<thead>
<tr>
<th>CURRENT SCREENING TOOLS</th>
<th>SCREENING TOOLS IN DEVELOPMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-CHAT (Modified Checklist for Autism in Toddlers)</td>
<td>ESAC (Early Screening for Autism and Communication Disorders)</td>
</tr>
<tr>
<td>SCQ (Social Communication Questionnaire; &gt;4 y)</td>
<td>Infant Toddler Checklist</td>
</tr>
<tr>
<td>STAT (Screening Tool for Autism in Toddlers and Young Children)</td>
<td>SWYC/POSI (Survey of Well-being of Young Children/Parent’s Observations of Social Interaction)</td>
</tr>
</tbody>
</table>

Adapted from Hyman SL, et al.7

### TABLE 2 MEDICAL WORKUP

<table>
<thead>
<tr>
<th>History</th>
<th>Physical examination</th>
<th>Neurologic examination</th>
<th>Etiologic evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of observable behaviors (historical and observational pattern of development) and social affective symptoms and restricted and repetitive behaviors meeting <em>DSM-5</em> criteria for ASD.</td>
<td>Growth parameters, including height, weight, body mass index, and head.</td>
<td>MRI and EEG only if indicated by history and physical.</td>
<td>Includes risk factors.</td>
</tr>
<tr>
<td>Family history of ASD.</td>
<td></td>
<td></td>
<td>Genetic testing.</td>
</tr>
</tbody>
</table>

*2013 recommendation for genetic testing is for chromosomal microarray.20

Abbreviations: ASD, autism spectrum disorder; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; EEG, electroencephalogram; MRI, magnetic resonance imaging. Adapted from Hyman SL, et al.7
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impact than intervention provided in children aged older than 5 years.9 In recognition of the importance of early detection, the AAP published guidance for early screening that recommends general developmental screening at ages 9, 12, and 30 months and autism-specific screening at 18 to 24 months with ongoing developmental surveillance through school age.10 Although other groups, notably the US Preventive Services Task Force (USPSTF), could not recommend for or against early screening based on the current literature, the USPSTF does urge clinicians to use clinical judgement and to use validated tools to assess if symptoms and signs in a child warrant further diagnosis or services.11 Table 1 lists standardized screening tools along with several promising tools under study.7 One key change in screening since 2014, according to Levy, is that most pediatricians across the United States responding to practice surveys now screen for autism whereas only a few practices did so in 2004.12 Screening results suggestive of a diagnosis of ASD require further diagnostic workup to confirm a diagnosis of ASD, determine the severity (ie, overall level of functioning), and assess its etiology (Table 2).1 Hyman and Levy emphasize that a child who is evaluated for ASD, regardless of age, should undergo an assessment of psychoeducational, adaptive, and language abilities (including pragmatic or social language) by a multidisciplinary team comprised of, for example, a psychologist and speech/language therapist and occupational therapist and/or other disciplines as indicated. Further assessment may also be needed to identify co-occurring medical, psychiatric, and behavioral conditions that may affect the child’s function and quality of life. These assessments may include magnetic resonance imaging and electroencephalogram as indicated by history and physical, and referral to a developmental/behavioral pediatrician, neurologist, or psychologist/psychiatrist. Distinguishing autism from conditions that may present with similar symptoms is critical to ensure a correct diagnosis, as well as to identify co-occurring conditions for which treatment may be needed. An etiologic evaluation, including assessment of risk factors and genetic testing, should be offered to all families. Table 3 provides updated knowledge regarding known and putative risk factors.

### Medical home: intervention and management

Once a child is screened and diagnosed with ASD, lifelong care in a medical home is essential to ensure that ongoing care is comprehensive, coordinated, family-centered, and can anticipate and address specific issues related to ASD. Hyman and Levy emphasize the importance of pediatricians feeling comfortable in helping patients and their families plan and coordinate care across health and life transitions. To do this, pediatricians should be ready to manage multiple needs of their patients and families.

---

**TABLE 3**

<table>
<thead>
<tr>
<th><strong>RISK FACTORS FOR ASD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parental age</strong></td>
</tr>
<tr>
<td>Advanced paternal and maternal age.</td>
</tr>
<tr>
<td><strong>Sibling</strong></td>
</tr>
<tr>
<td>Increased risk of ASD and language delays if a sibling has ASD.</td>
</tr>
<tr>
<td><strong>Drugs taken by the mother during pregnancy</strong></td>
</tr>
<tr>
<td>▪ Valproic acid increases risk of ASD.</td>
</tr>
<tr>
<td>▪ Folic acid supplementation decreases risk of ASD.</td>
</tr>
<tr>
<td>▪ SSRIs reported to increase risk of ASD.</td>
</tr>
<tr>
<td><strong>Health factors of the mother during pregnancy</strong></td>
</tr>
<tr>
<td>▪ Obesity.</td>
</tr>
<tr>
<td>▪ Interpregnancy interval.</td>
</tr>
<tr>
<td>▪ Fever/infection.</td>
</tr>
</tbody>
</table>

*May be related to maternal diagnosis related to SSRI prescription. Abbreviations: ASD, autism spectrum disorder; SSRI, selective serotonin reuptake inhibitor. From Hyman SL, et al.7*
that the most effective intervention is early and intense and involves family.15 Table 4 lists specific interventions pediatricians might discuss with patients and families.

Other interventions that are being used by children and their families and that pediatricians may be asked about include diet (eg, gluten-free casein-free) or dietary supplements (eg, multivitamins, omega-3 fatty acids, and vitamin D) and different types of therapy (eg, music, equine-assisted, hyperbaric oxygen, and stem-cell).16-18

“The use of unproven therapies is common and the pediatrician should be comfortable entering into a dialogue with families about the importance of examining the claims made by practitioners providing nonstandard therapies and the risk for adverse effects,” says Levy, who adds that some interventions, such as chelation and bleach enemas, have such serious adverse effects that families must be counseled regarding their danger, whereas others, as the gluten-free casein-free diet, may be tried safely with appropriate nutritional guidance. “Data collection regarding target symptoms may help a family track the impact of unproven therapies in an individual child,” she says.

Pediatricians play an important role in helping guide patients and their families through these many intervention strategies, Hyman and Levy emphasize. This role, they say, has taken on even greater importance over the past decade given the amount of and accessibility to information on the Internet and social media that has outpaced changes in practice.

**TABLE 4 INTERVENTIONS FOR CHILDREN WITH ASD**

<table>
<thead>
<tr>
<th>EDUCATION</th>
<th></th>
</tr>
</thead>
</table>
| Preschool | Refer for services even before confirmation of an ASD diagnosis.  
Therapy in natural settings (this is home for youngest children.)  
Evidence-based interventions include: applied behavioral analysis, developmental skill building, parent management training. |
| Public education (age 3-21 y) | Least restrictive environment (integrated and co-taught classrooms).  
Hierarchy of services.  
Co-occurring learning needs that are characteristic of ASD (eg, challenges with reading for meaning) and those not unique to ASD (eg, executive functioning and organizational skills). |

<table>
<thead>
<tr>
<th>COMMUNICATION</th>
<th></th>
</tr>
</thead>
</table>
| Speech and language therapy | Need to reinforce communicative acts throughout the day.  
About 30% of children with ASD do not speak.  
Alternative to oral language may include: signing; use of picture exchange communication systems (PECS); use of voice output devices.  
Practice language skills in integrated settings. |
| Social communication and skills | Important to address in school plan and outside of school.  
Adult-guided approaches include Social Stories.  
Evidence-supported peer-mediated strategies, including: children with ASD in play with peers during recess; using group-based approaches to learning social language. |
| Sensory processing | Calming techniques, such as the use of a weighted vest or use of earphones to minimize hyperacusis.  
Learning to tolerate stressors to improve state regulation. |

Abbreviation: ASD, autism spectrum disorder.
Adapted from Hyman SL, et al.7

Distinguishing autism from conditions that may present with similar symptoms is critical to ensure a correct diagnosis.

One primary way to help patients and families decide on which therapies may be appropriate for them is to engage in shared decision-making with caregivers and the patient to understand whether or not an interven-
Along with helping patients and families choose which interventions may best address core symptoms of ASD, pediatricians are also well suited to help manage conditions that may co-occur with ASD, such as other developmental or psychiatric conditions (eg, attention-deficit/hyperactivity disorder [ADHD], affective disorders, cognitive abnormalities), behavioral issues (eg, sleep difficulties, feeding disorders, aggression/irritability/self-injury, wandering, pica), and medical conditions (eg, allergy, gastrointestinal [GI] symptoms/disorders, immune abnormalities, seizures, and tic disorders). Hyman and Levy highlighted several of these in their talk (Table 5).

Finally, an important component of establishing and providing a medical home for children with ASD is to help them and their families transition through the various phases of their life—from childhood to adulthood—to help them deal with the many issues in each phase including education, employment, and issues of sexuality.

**Take-home message**

“What we intended to do in this talk was to remind primary care providers of the pathway of ASD from screening to diagnosis to lifelong care that takes place in the medical home,” says Hyman.

The need for a medical home to manage this lifelong care of a child with ASD underscores the complexity and chronic nature of this condition. As such, Hyman and Levy suggest several changes that pediatricians may want to make in their practices to better meet the needs of these patients (Table 6).

---

**TABLE 5**

**EXAMPLES OF COMORBIDITIES WITH ASD**

<table>
<thead>
<tr>
<th>PSYCHIATRIC</th>
<th></th>
<th>BEHAVIORAL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADHD</strong></td>
<td>Children with ADHD are diagnosed with coexisting ASD on average 3 years after the ADHD diagnosis.</td>
<td>Half of families report their child with ASD wanders.</td>
<td>Intervention includes prevention, physical barriers, supervision, and home alarm systems (or dead bolts).</td>
</tr>
<tr>
<td>25%-60% of children with ASD will have coexisting ADHD (diagnosed or symptomatic).</td>
<td>Risk factors include decreased awareness of social convention, impulsivity, perseverative interests, co-occurring intellectual disability.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BEHAVIORAL**

<table>
<thead>
<tr>
<th>Wandering</th>
<th>Half of families report their child with ASD wanders.</th>
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<td>Risk factors include decreased awareness of social convention, impulsivity, perseverative interests, co-occurring intellectual disability.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Sleep disorders**

| Common and reported in 30%-90%. | Management includes sleep hygiene, delayed sleep onset, and medication (eg, melatonin). |
| Includes insomnia, bedtime resistance, night wakings, and parasomnias. | |

**MEDICAL**

| GI difficulties are reported in >50% of children with ASD. | Management of symptoms. |
| Selective eating in up to 75%. | |

**Abbreviations:** ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; GI, gastrointestinal.

Adapted from Hyman SL, et al.7

**TABLE 6**

**CHANGES TO MEDICAL PRACTICE**

| Schedule more frequent follow-ups with patients you refer for further evaluation or services to encourage adherence and assess for co-occurring challenges. |
| Have a handout or templated letter with local resources and support information. |
| Know your local autism support group for referral of newly diagnosed families. |
| Include anticipatory guidance specific for ASD. |
| Educate the patient’s siblings about ASD. |
| Make certain your patients with ASD know how to work with you for provision of a medical home. |

**Abbreviation:** ASD, autism spectrum disorder. From Hyman SL, et al.7

For references, go to ContemporaryPediatrics.com/medical-home-for-autism
Elopement and wandering with ASD

Practical tips for PCPs

Over one-quarter of parents of children with autism spectrum disorder (ASD) report that their children have wandered or eloped from them in the previous year.1 Currently, the prevalence of ASD is estimated at 1 in 59 children, and it is 4 times higher in boys than girls.2 Within this population, safety concerns are prominent and are fundamental priorities for care. These behaviors impact children and families who experience other neurodevelopmental differences, including developmental delays, intellectual disabilities, genetic syndromes, emotional disorders, and behavioral disorders. Primary care providers (PCPs) are on the front lines to address these concerns, yet resources are limited and difficult to access.

Defining elopement and wandering

Elopement has been more clearly defined as leaving a designated supervised area without permission.2 The concept of wandering, however, has not been clearly delineated from elopement. In clinical practice, elopement is a term used to describe behaviors that occur impulsively and quickly, such as running or bolting from caregivers or contained supervised areas. In contrast, wandering is a more unfocused behavior. For example, it may consist of straying from a designated supervised area away from the sight of a caregiver.

Although elopement and wandering are common and serious problems for families of children who have ASD, there is limited research on this subject and few treatments have been shown to successfully prevent or reduce these behaviors.

Of all the interventions studied, many have small sample sizes (1 to 3 participants) and, therefore, cannot be generalized to the larger population.4 The dearth of research is an important opportunity to prioritize the research agenda to align with family priorities and clinical practice guidelines. Primary care clinicians...
are often asked how to respond to these behaviors. It is an issue that leaves families, educators, and clinicians feeling helpless, but this does not need to be the case. In fact, there are practical ways clinicians and families can work together to decrease elopement and wandering.

In children with ASD, elopement risk increases with severity of symptoms.\textsuperscript{1} Studies have shown that approximately 50% of caregivers of children with ASD eloped at least once after age 4 years. Approximately 25% of individuals with developmental disabilities and 35% of individuals with co-occurring intellectual disabilities have eloped within the last year.\textsuperscript{1,3}

In some circumstances, elopement and wandering behaviors do not cause imminent harm, such as when a curious child wanders to the next aisle in the grocery store or is attracted to an enticing activity or event nearby. However, current research has highlighted the overwhelming amount of children placed in situations where elopement and wandering result in imminent harm or accidental death. These situations may include when a child exits the family home and wanders to the next aisle in the grocery store, walks into traffic, or strays in public spaces with potentially predatory strangers. As such, these behaviors do increase the likelihood of childhood trauma, injury, and death, as well as subsequent familial distress.

**Scope of the problem**

According to the National Autism Association (NAA),\textsuperscript{5} 58% of parents ranked wandering among the most stressful behaviors associated with ASD. Nearly half of children with ASD attempt to elope from safe environments, and this is quadruple the rate of their typically developing siblings. More than one-third of children with ASD who wander or elope are never or are rarely able to communicate information to community members who can help identify or reunite them with their caregivers (ie, indicating their name, address, and phone number).

Moreover, 66% of parents report a “close call” with a traffic injury and 33% describe a “close call” with drowning.\textsuperscript{2} Furthermore, due to fears that their children may run away from them in public places, 62% of families do not attend activities outside the home. Forty percent of parents indicate that these fears impact their abilities to sleep. Alarmingly, half of families of children who have eloped report never having received guidance from a professional. In fact, only 14% of affected families report receiving guidance from their pediatrician.

An updated 2017 study from the NAA reported even higher occurrences of elopement and wandering.\textsuperscript{6} Of 808 missing person cases of wandering and elopement in individuals with ASD reported between 2011 and 2016, 17% resulted in death, 13% required medical attention, and 38% were at increased risk of bodily harm. Accidental death remains the highest lethal outcome at 71% of individuals with ASD followed by traf-
fic injuries in 18% of reported deaths.

According to the NAA study, children aged younger than 5 years experienced the highest incidence of lethal outcomes.6 Sixty percent of children in this age group died as a result of elopement/wandering. As for sex differences, females experienced the highest number of fatalities but fewer instances of wandering/elopement compared with males.

Deaths were highest in the spring to summer months, with over half of deaths occurring between May and August, according to the study data.6 Other times of increased risk included the following: times of transition; playing outdoors; family and social gatherings; overnight hours; and stressful or emotionally salient times. Individuals were often found near water, traffic, wooded areas, or a stranger’s residence. Additionally, with the onset of summer break from school creating greater availability for family vacations or local adventures, more opportunities for elopement and wandering may exist due to an increase in less familiar or nonroutine experiences. A list of high-risk situations for elopement and wandering is provided in Table 1.

These sobering statistics manifest the need to ask about injury prevention and safety skill building, particularly as families are interested in and are likely motivated to take preventable action that may save the life of their child.

**Therapy priorities**

Accessing effective interventions to prevent elopement and wandering can be challenging, as this behavior can be difficult to predict and serves several functions (eg, gaining attention from others; getting access to a tangible item or preferred activity; escape or avoidance; and/or sensory). In addition, families of children with ASD are already participating in various types of interventions across a multidisciplinary team of providers in outpatient and school settings. These providers often include speech therapists, occupational therapists, physical therapists, physicians, psychologists, and behavioral therapists.

It is critical to consider injury prevention and safety skill building as clinical priorities by primary care teams. As such, appropriate screening during patient care visits to examine risk and/or severity in occurrence of elopement and wandering...
behavior is strongly recommended. Furthermore, intervention aimed at prevention is key.

More recent literature has examined parents’ priorities for therapies for their children with ASD. These are behaviors and skills that they identify as high-need areas for educational training, treatment, or intervention. In particular, parents prioritize treatment concerns according to what they view as key areas of deficit.

What PCPs can do
In addition to screening for elopement and wandering during well child visits, providing parent education about the likelihood of elopement and wandering can be a key prevention tool. The questions listed in Table 2 can help PCPs advise families with ways to assess a child’s risk for wandering and elopement.

Providing families with starter kits (Table 3) such as the NAA’s Big Red Safety Box® and the Be REDy Booklet for Caregivers® can provide information and tools to get started. Similar to the NAA initiatives, in partnership with Safe Kids Chicago, the Pediatric Developmental Center and Injury Prevention team at Advocate Children’s Hospital at Advocate Illinois Masonic Medical Center, Chicago, offers Safety Backpacks with tools that a family can start using immediately to help create physical barriers for elopement and wandering, as well as to prevent injuries. Additionally, connecting families to web resources such as Autism Speaks® can help them gain access to personalized social stories that teach their children about the dangers of elopement and wandering and how to stay safe. Encourage patients to register with their local first responders with Smart911® that provides key information to help keep their child safe or gain access to assistance in emergency situations.

What families can do
Families should be encouraged to utilize individualized identification methods with the names and phone numbers of caregivers when venturing out into the community. For example, parents may purchase identification bracelets, available in cloth, plastic, or metal, to cater to a given child’s potential tactile sensitivities. Consider encouraging families to explore the possibility of a child-wearable GPS device. For children unable to tolerate bracelets, many families have used personalized labels tied into shoe laces or affixed to clothing that are difficult for a child to remove but hold necessary information to contact a parent or guardian if the child should become lost. Temporary tattoos are another option for children who do not tolerate bracelets.

Additionally, parents can take measures such as installing physical barriers that would prevent a child from exiting the family home. This may include tamperproof locks on exterior doors installed at heights that cannot be reached; bells or

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**TABLE 2**

**ASSESSING SAFETY IN THE PRIMARY CARE OFFICE**

- Does your child respond to his/her name?
- How often does your child respond to his/her name?
- What is the likelihood that your child will come when called in a fun and/or crowded space? What level of language/communication ability does your child currently have?
- Is your child able to ask for help?
- Can your child recite or provide his/her phone number or address upon adult request?
- Can your child identify a stranger (ie, potential predator) from a safer stranger (eg, store clerk, police officer) if help is needed?
- When out in the community, does your child hold your hand?
- Will your child run away from you if you’re not holding his/her hand?
- Are you worried about using public transportation with your child due to your child’s behavior?
- Does your child hold your hand while crossing the street?
- Is your child vigilant around traffic or crowded spaces?
- Does your child ever play with locks on doors, tamper with seatbelts when riding in the car, or attempt to open closures/latches on indoor or outdoor gates?
- Has your child ever bolted away from you in an open space, such as a store or parking lot? Does your child get distracted by preferred things and gradually increase his/her distance from you in public spaces?
alarms to signal opened windows or doors; and weights, bolts, and straps to stabilize furniture that may be easily knocked over if children climb on them.

### Tips for traveling

Families also express concern about safe travel with their children. In particular, children escape from car seats while driving or do not stay with parents while riding the bus or train. Initial questions to consider with families are depicted in Table 4.

For families of children with developmental differences, traveling may pose its own challenges. This may include traveling for a family vacation but also traveling short distances to school, daycare, or the grocery store in a car or school bus. As previously mentioned, family vacations occur at higher rates during the summer months while children are typically out of school. Greater likelihood of elopement and wandering may occur in novel situations, such as when traveling on an airplane, staying in a hotel, and exploring resorts or amusement parks with water sources and large crowds. Referring families to the Transportation Security Administration (TSA) website for further information on Disabilities and Medical Conditions allows families to select specific travel recommendations for individuals with ASDs and/or intellectual disabilities to facilitate success when navigating security checkpoints. Additionally, many airports or airlines offer walkthroughs or mock flights. Consider helping your families to better prepare themselves by encouraging them to inquire about this opportunity at your local airport.

Vehicle travel, whether via car or school bus, can be a distressing situation if a child tends to wander or attempts to escape a vehicle while in motion. It is important for PCPs to inquire about traveling in a vehicle and how the family believes their child tolerates this. Situations may include daily car rides with family or riding the school bus.

Vehicle safety includes maintaining appropriate behaviors in the car (ie, not grabbing or throwing things at the driver or passengers) but should also place emphasis on the child’s ability to tolerate safety restraints, such as car seats and seat belts. Angell and Solomon in their 2018 study discuss the necessity of evaluating “transportation situations” for children with ASD.

For children who display wandering behaviors, exiting a school bus at the appropriate bus stop can be a challenging situation. For children who are minimally verbal, responding to appropriate verbal cues may be an issue. For children riding the school bus, it is recommended that

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**TABLE 3**

**RESOURCES FOR PEDIATRICIANS AND FAMILIES**


- **Autism Speaks** offers a variety of resources for families on wandering and elopement, including social stories and ways to protect children and prevent injuries. [www.autismspeaks.org/wandering-prevention-resources](http://www.autismspeaks.org/wandering-prevention-resources)


- **Smart911** is a program to help first responders know how to respond to children's individual needs in case of an emergency. [www.smart911.com](http://www.smart911.com)

- **The Transportation Security Administration** (TSA) offers information to families about airport travel in special circumstances, including if an individual has autism or other developmental differences. [www.tsa.gov/travel/special-procedures?field_disability_type_value=0%20](http://www.tsa.gov/travel/special-procedures?field_disability_type_value=0%20)
PCPs encourage a family’s collaboration with school staff and administration, as well as the school bus company, to help put procedures in place to help prevent serious safety situations that may endanger a given child and fellow passengers. Families may be advised to talk to their educational teams regarding safety as a goal within their child’s Individualized Education Plans.

As car seat laws continue to change to ensure children are riding in the appropriate safety restraint up to a higher age and weight limit, it is crucial for PCPs to address safe travel options for children who have a tendency to elope or try to “escape” their car seats. Some children with ASD will attempt to open car doors while the car is in motion, or unbuckle their car seat harness or seat belt, placing them at further risk for greater injury or accidental death. Seat belts and car seats are essential for families to help control for situations in which a child may sustain further injury due to inability to perceive danger, or to respond to a caregiver’s verbal directives due to limitations based on the child’s age, language, or cognitive level.

With motor vehicle accidents being the leading cause of death in children across the United States, it may also be necessary for families to consult a certified child passenger safety technician to discuss the options for “car seat escape artists.” The Injury Prevention Program at Advocate Children’s Hospital offers Free Car Seat Checks with certified car seat technicians who can evaluate and give instruction on proper car seat installation at no cost to families. Appointments for a Free Car Seat Check are available across many Advocate Chicagoland locations. Many major hospitals and community organizations are beginning to offer a similar service and may do so in your community.

### Some strategies to ensure safe travels include the following:

1. Teach children what to expect while traveling in the car.
2. Praise and reward children for positive car seat behaviors.
3. Be consistent with rules while traveling in the car.
4. Children may require an adult to sit in the back with them for supervision.
5. Consider consultation with a car seat technician with special-needs training.

### Treatment goals

In clinic, treatment goals in pediatric populations often include working on decreasing problematic behaviors, skill building, and socialization. Behavioral interventions can be helpful in both preventing and reducing occurrence of elopement and wandering. Clinically, these behaviors can be difficult to treat, as the function of elopement and wandering behavior can vary from child to child. In general, functions of behavior include gaining attention; escape or avoidance; obtaining access to preferred tangibles or activity; autonomic action; and meeting sensory needs.

### Summary

Rates of elopement and wandering have increased, indicating more affected families and more children at risk of serious injury or death. These behaviors leave families frightened and in a constant state of stress. Given that few families report receiving consultation from their PCPs, first steps include asking families if they are concerned about their children’s safety and ability to ask for help.

Primary care providers are on the front lines of helping families feel supported, hopeful, and connected with resources to address these behaviors. These behaviors must be addressed prior to moving forward with other developmental, educational, social, and adaptive goals for children with developmental differences. In addition to asking about safety, specific resources are available to prevent these behaviors and to decrease them when they occur. Educators and therapists are also critical resources for families as they may support children’s individual learning styles.

### Acknowledgement

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### For references

For references, go to ContemporaryPediatrics.com/wandering-with-ASD
Thyroid disorders

Manifestations, evaluation, and management in children and adolescents

Thyroid hormones play an essential role in growth, development, and physiology. Abnormal thyroid function can have profound detrimental effects in the pediatric population. Thyroid disorders can present with or without thyromegaly (goiter), with overt symptoms, or insidiously with few symptoms or signs of thyroid disease. Whereas the evaluation and management of pediatric thyroid disorders typically involves a pediatric endocrinologist, the primary care provider plays a critical role in identifying children with thyroid disease or those who need referral. This article provides an overview on the manifestations, evaluation, and management of the most common thyroid disorders seen in the pediatric population.

Evaluation of the thyroid

ASSESSMENT OF THYROID STRUCTURE/ANATOMY

Examination of the thyroid gland for symmetry, consistency, and size should be part of the complete physical examination performed in children. The examination consists of both visual inspection and palpation (see Figure; also go to https://www.youtube.com/watch?v=Z9norsLPKU). The visual inspection portion is as important as palpation.

Until the end of puberty, the thyroid gland size (in grams) is approximately equal to the patient’s age in years multiplied by 0.5 to 0.7. For example, normal total gland weight in a 10-year-old child would be 5 g to 7 g, and the size of each lobe would be approximately equivalent to a one-half teaspoon.

If thyroid asymmetry is noted or if the gland is believed to be enlarged, further evaluation is needed. This evaluation may include assessment of thyroid hormone concentrations, a thyroid ultrasound (see “Thyroid ultrasound,” page 40), and/or referral to a pediatric endocrinologist.

THYROID PHYSIOLOGY AND BIOCHEMICAL ASSESSMENT

Laboratory findings for select thyroid disorders are outlined in the Table. Tetraiodothyronine (T4; also known as thyroxine) and triiodothyronine (T3) are the
Examination of the thyroid gland is an important and readily accomplished aspect of a complete pediatric physical examination. The examination follows the important steps of any examination; look (A) and feel and listen (B and C). An enlarged thyroid (goiter) is defined by the ability to visualize the shape of the thyroid gland during physical examination (A and Table 3). Auscultation may be restricted to patients with suspected hyperthyroidism, in which a bruit, a continuous “murmur-like” sound from increased blood flow in the gland, may be appreciated using the bell of the stethoscope. A complete examination of the lateral neck lymph nodes (C) is an important addition to the examination of patients with thyroid nodules because differentiated thyroid cancer frequently metastasizes to lymph nodes in the neck. Palpable symmetric level IIA and IIB lymph nodes are a common finding in pediatric patients but thyroid cancer should be in the differential diagnosis for patients found to have persistent, large, firm lymph nodes in levels III, IV, and V.
major thyroid hormones, and their production is regulated by the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH; also known as thyrotropin-releasing factor) produced by the hypothalamus stimulates anterior pituitary production of thyroxine stimulating hormone (TSH; also known as thyrotropin). Thyrotropin then binds to TSH receptors on thyroid follicular cells, causing the production and release of T3 and T4. T4 represents the majority of thyroid hormone released by the thyroid gland, but it is T3 that principally binds to thyroid hormone receptors. Most T3 in the circulation is derived from peripheral deiodination of T4. In the circulation, both T4 and T3 are mostly bound to proteins (thyroxine-binding globulin [TBG], prealbumin, and albumin). Concentrations of the thyroid-binding proteins are affected by genetic conditions, decreased by androgens, and increased by estrogens (eg, with use of oral contraceptives). Only free (unbound) T3 and T4 are biologically active.

The euthyroid state is maintained by a feedback loop in which TRH production is suppressed by increasing circulating T3/T4 concentrations and increased when T3/T4 concentrations decline. Thyroid hormone production also can be affected by antibodies that stimulate or block TSH action. For example, in Graves’ disease (GD), which is the most common form of hyperthyroidism in children, thyroid-stimulating immunoglobulins [TSI; also known as thyroid receptor antibodies [TRAb]] bind to and activate TSH receptors in the thyroid. TSH receptor-blocking immunoglobulins (TBI) that antagonize TSH action are a rare cause of hypothyroidism.

Laboratory testing of thyroid function includes assessments of total T4 and total T3; T3 resin uptake, which is an index reflecting thyroid hormone-binding proteins; free T4 (FT4), representing the unbound hormone; and TSH. Assays for T3 are usually not necessary for diagnosing hypothyroidism. Because TBI is elevated in infants, estimated FT4 values may not be accurate; equilibrium dialysis assay or measurement by tandem mass spectrometry (MS) will provide a more accurate measurement of FT4.

Thyroid stimulating hormone (TSH) is the most sensitive marker for evaluating thyroid gland function, and assessment of TSH with ultrasensitive assays has greatly improved the evaluation of thyroid status. Critical in the interpretation of TSH values in children is recognition that the normative range differs from that of adults—the upper normal limit of TSH is 5.6 μIU/mL in healthy children and adolescents without thyroid disease versus 4 μIU/mL in adults.2,3 However, one should always compare the measured value with the reference range for each specific assay used. Application of the adult reference range to children risks erroneous diagnosis of subclinical hypothyroidism and unnecessary referral for subspecialty care. It is also important to obtain a repeat determination before referral if the TSH is only slightly elevated, as concentrations will normalize in the vast majority of children.2 In addition, overweight and obese children also often have a mildly elevated TSH without this being caused by thyroid disease.4

**Hypothyroidism**

Among the 2 functional disorders, hypothyroidism is more common in children than hyperthyroidism. Hypothyroidism can occur as a congenital or acquired condition and is also categorized based on whether it is due to disease of the thyroid gland itself (primary) or a defect at the level
of the pituitary gland (secondary) or hypothalamus (tertiary). Hypothyroidism related to a pituitary or hypothalamic disorder is also referred to as central hypothyroidism and is much less common than primary hypothyroidism.

**CONGENITAL HYPOTHYROIDISM**

Congenital hypothyroidism (CH) is the most common preventable form of mental retardation. It occurs in about 1 in 3000 to 4000 newborns and is more common in Asian, Native American, and Hispanic infants than in Caucasians and African Americans. Among infants born in developed countries, CH is most often due to thyroid dysgenesis (about 90%) in which there is complete or partial failure of gland development or failure of normal migration to a eutopic position. Approximately two-thirds of all thyroid dysgenesis is due to ectopic glands. Thyroid dyshormonogenesis, defined by defects in thyroid hormone biosynthesis or secretion, accounts for most of the remaining cases (about 10%), and central hypothyroidism is even less common. Congenital hypothyroidism also can occur as a transient condition secondary to maternal transfer of TSH receptor-blocking antibodies or medications that interfere with fetal thyroid function.

The majority of cases of CH occur sporadically, so it is not possible to predict which infants are likely to be affected. Rare familial as well as sporadic cases of thyroid dysgenesis are due to mutations in certain transcription factors (PAX-8, TTF-1, and TTF-2) involved in thyroid morphogenesis and differentiation. Thyroid dyshormonogenesis, on the other hand, is typically transmitted in an autosomal recessive pattern.

**DETECTION** When the mother has normal thyroid status, the fetus is at least partially protected from effects of hypothyroidism in utero. Children with CH are typically asymptomatic at birth. Newborn screening tests using blood from a heel stick have therefore been instrumental for allowing timely diagnosis and initiation of thyroid replacement treatment critical for normal neurocognitive development. A low T4 and/or high TSH represents a positive result and indicates a need for confirmatory testing with blood obtained by venipuncture to measure TSH and free T4. However, practitioners need to be aware that the screening test will not detect all cases of CH. A low TSH will not be detected by some screening tests, thus CH due to pituitary or hypothalamic defects may be missed. In addition, newborn screening within the first 24 hours after birth can result in false-positive results because of the surge in TSH immediately after birth.

**Newborn screening (for congenital hypothyroidism) within the first 24 hours after birth can result in false-positive results because of the surge in TSH immediately after birth.**
may be done before stopping the LT4 to check for normal thyroid gland development and position. Thyroid scintigraphy (technetium scan) is the best radiologic study to detect ectopic thyroid gland position.

**ACQUIRED HYPOTHYROIDISM**

Delayed treatment of hypothyroidism in children aged up to 3 years can result in permanent decrements in neurocognitive function. Children who develop hypothyroidism after age 3 years may develop reversible behavior changes and growth issues but are not at risk for having permanent neurocognitive development deficits.

The most common clinical features of acquired hypothyroidism are tiredness and fatigue, cold intolerance, constipation, dry skin, and menstrual irregularities. Because these signs and symptoms are nonspecific and can overlap with common complaints of daily life, diagnosis based on symptoms alone may result in overdiagnosis. Thyroid gland enlargement is also a common feature of hypothyroidism but is also a sign of hyperthyroidism. Hypothyroidism does not cause obesity, but TSH may be slightly increased in obese patients, which can lead to a misdiagnosis of hypothyroidism.

Autoimmune thyroiditis, or Hashimoto thyroiditis, is the most common cause of acquired hypothyroidism among children and adolescents. It occurs more often in females than males, and affected children often have a family history of autoimmune thyroid disease.

Autoimmune thyroiditis is associated with antibodies against thyroglobulin (Tg) and/or thyroperoxidase (TPO). Lymphocytic infiltration of the thyroid gland results in thyromegaly, and thyroid damage occurs by both antibody- and cell-mediated pathways. The thyroid gland has a pebbly surface (“cobblestone effect”) on palpation.

**Laboratory Findings for Select Thyroid Disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>TSH</th>
<th>T4</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital primary hypothyroidism</td>
<td>↑</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Autoimmune hypothyroidism (Hashimoto thyroiditis)</td>
<td>Usually ↑, but could be N</td>
<td>Usually ↓, but could be N</td>
<td>↑ anti-Tg and/or anti-TPO</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>↑</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Prematurity</td>
<td>↓ or N</td>
<td>↓</td>
<td>N FT4</td>
</tr>
<tr>
<td>Central hypothyroidism</td>
<td>↓, N, or slightly ↑</td>
<td>↓ or N</td>
<td>FT4 usually ↓; evaluate for other pituitary hormone deficiencies and consider CNS imaging</td>
</tr>
<tr>
<td>Autoimmune hyperthyroidism (Graves’ disease and Hashitoxicosis)</td>
<td>↓</td>
<td>↑</td>
<td>↑T3, ↑TSI and TRAb in Graves’ disease</td>
</tr>
<tr>
<td>Differentiated thyroid cancer</td>
<td>N</td>
<td>N</td>
<td>Abnormal thyroid ultrasound</td>
</tr>
<tr>
<td>Medullary thyroid carcinoma</td>
<td>N</td>
<td>N</td>
<td>Elevated calcitonin</td>
</tr>
</tbody>
</table>

Note: ↑, elevated; ↓, decreased

Abbreviations: CNS, central nervous system; FT4, free tetraiodothyronine; N, normal; T3, triiodothyronine; T4, tetraiodothyronine; Tg, thyroglobulin; TPO, thyroperoxidase; TRAb, thyroid receptor antibodies; TSH, thyroid stimulating hormone; TSI, thyroid-stimulating immunoglobulin.

Children with lower antithyroid antibody values can be followed up with thyroid indices every 6 to 12 months and started on therapy only if TSH rises above the upper limit of normal using the pediatric reference standard. When T4 concentrations are modestly depressed (<5 ug/dL) or normal, LT4 can be initiated with a dose of 1 to 2 μg/kg/day to prevent frank hypothyroidism and progressive gland enlargement. Laboratory testing should be repeated every 6 months with a goal of maintaining a TSH concentration of 0.5-5 μIU/mL.
**SUBCLINICAL HYPOTHYROIDISM**

Subclinical hypothyroidism refers to a condition in which circulating T4 and T3 concentrations are normal, but TSH is elevated.

Only a minority of children with mild TSH elevations (5-10 μIU/mL) progress to develop TSH elevations greater than 10 μIU/mL, and available evidence indicates that children with TSH just slightly above 5 μIU/mL do not exhibit somatic or other benefits when treated with levothyroxine.6,7

**CENTRAL HYPOTHYROIDISM**

Central hypothyroidism should be considered in children with a history of head trauma, brain tumors, meningitis, central nervous system irradiation, or congenital nervous system malformations. In contrast to primary hypothyroidism, the diagnosis of hypothyroidism related to hypothalamic or pituitary dysfunction may be difficult to establish. Often, circulating T4 is in the low-normal range, and TSH may be low, normal, or elevated. FT4 values, however, are usually low.

When central hypothyroidism is suspected, central nervous system imaging should also be performed to look for congenital malformations or hypothalamic-pituitary lesions. Care should be taken to search for other pituitary hormone deficiencies, especially abnormalities of the hypothalamic-pituitary adrenal and growth hormone axes.

**Hyperthyroidism**

Hyperthyroidism has profound influences on the fetus, neonate, growing child, and adolescent, including physical and behavioral effects. It is often present for extended periods before recognition, contributing to significant health problems. Hyperthyroidism typically presents with specific symptoms that include decreased attention and school performance, anxiety, increased heart rate, weight loss, fatigue, tremor, and thyroid enlargement (goiter), although onset may also be indolent. Hyperthyroidism is unlikely in the association with severe and even fatal liver injury. In contrast, the risk of liver injury in children treated with MMI is rare, but MMI is not free from serious adverse effects. Agranulocytosis can occur, and MMI should be stopped immediately and a complete blood cell count obtained if a patient feels ill, becomes febrile, or develops pharyngitis (this could lead to the development of a retropharyngeal abscess). The risk of agranulocytosis is greatest in the first 100 days of therapy and is dose related. Thus, it is best to begin with relatively low doses. Time to resolution of hyperthyroidism is comparable using low- or high-dose MMI.

Dosing of MMI may be determined by patient age that generally corresponds to 0.1–0.3 mg/kg/day: infants, 1.25 mg/day; age 1 to 5 years, 2.5 to 5.0 mg/day; age 5 to 10 years, 5 to 10 mg/day; and age 10 to 18 years, 10 to 20 mg/day. The MMI dose may also be weight-based (0.2 to 1 mg/kg/day). The MMI tablets (5 mg and 10 mg) are small and difficult to cut, thus one-quarter or one-half fraction of tablets can be used, avoiding the need for compounding. Because it takes 1 or 2 months for biochemical hyperthyroidism to resolve, treatment with a beta-blocker (propranolol, atenolol, or metoprolol) can be used in the interim to control hyperthyroidism symptoms.9

Even after several years of ATD therapy, however, the majority of pediatric patients with GD will not achieve remission after MMI is discontinued. Thus, most pediatric patients will require definitive therapy with either radioactive iodine (131I) or surgery.

The goal for 131I therapy for GD is to induce permanent hypothy-
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Thyroidism. Antithyroid drug therapy should be stopped 3 to 5 days prior to treatment with 131I, and children should be placed on a beta-blocker until T4 and/or FT4 levels normalize post 131I therapy. There are rare reports of children with severe hyperthyroidism developing thyroid storm after receiving 131I. Thus, children should be treated with MMI until T4 and/or FT4 levels normalize (T4 ≤20 μg/dL; FT4 <5 ng/dL) before proceeding with 131I therapy. Because of concern about total-body radiation exposure, it is prudent to avoid 131I therapy in children aged younger than 5 years and, if possible, to avoid >10 mCi in children aged younger than 10 years.

Surgery is an effective form of therapy for GD and is preferred over 131I in children aged younger than 5 years when definitive therapy is needed, and the procedure can be performed by a skilled pediatric thyroid surgeon. Surgery is also recommended for patients who have a large thyroid gland (>80 g) because they have a poor response to 131I. When surgery is performed, near-total or total-thyroidectomy is indicated, as subtotal thyroidectomy is associated with a higher relapse rate. Hypothyroidism is nearly universal after total thyroidectomy.

**Thyroid nodules and thyroid cancer**

Thyroid nodules and masses occur in children much less often than functional thyroid disorders but can portend the presence of thyroid cancer. In children, about 20% of thyroid nodules larger than 1 cm in diameter are malignant. Differentiated thyroid cancer (DTC), which includes papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC), is the most common form of thyroid cancer in children. With rare exception, medullary thyroid cancer (MTC) in children and adolescents is associated with multiple endocrine neoplasia type 2 (MEN2).

**THYROID NODULES**

The workup for a child with a thyroid nodule should include serum TSH, T4 or FT4, ultrasound (US) of the thyroid and neck, and serum calcitonin if MTC is suspected. If the TSH is low and T3 and/or T4 levels are high-normal or elevated, a radionuclide scan may be performed to identify a hyperfunctioning nodule, which carries a lower risk for malignancy. A thyroid US should be considered in all patients with persistent, cervical lymphadenopathy prior to excisional biopsy to determine if the adenopathy is secondary to thyroid cancer metastasis. Ultrasound of the thyroid is the most efficient and accurate method for determining if a thyroid nodule may be surveilled or should undergo further evaluation with fine needle aspiration (FNA). Although certain features on US indicate a higher likelihood of malignancy, for many nodules the US appearance cannot reliably distinguish whether the lesion is benign or malignant; thus, FNA is the most accurate method to determine if a thyroid nodule is malignant. Ultrasound assessment of the lateral neck should be performed on all patients with an indeterminate or suspicious thyroid nodule to determine if there is lymphadenopathy, which raises concern for thyroid cancer metastasis. Recently detailed guidelines have been published to aid in the evaluation and management of thyroid nodules in children and adolescents.

**THYROID ULTRASOUND**

Ultrasound (US) of the thyroid is the most accurate method of visually assessing health of the thyroid tissue. The US provides information about gland location, shape, and size, tissue uniformity, and blood flow that can supplement findings from the physical exam and help with interpretation of the laboratory assessment of thyroid function.

Thyroid US should be considered in babies with congenital hypothyroidism and in patients with an abnormal physical exam (ie, gland asymmetry, suspected thyroid nodule, or persistent cervical adenopathy). Thyroid US is also considered an important tool to surveil patients at increased risk of developing thyroid nodules and thyroid cancer based on a history of exposure to radiation therapy for a nonthyroid malignancy or familial or personal history of a thyroid cancer predisposition syndrome.
are the only known risk factors for developing DTC. However, in most patients there will be no identifiable explanation for why the cancer developed.

Compared with adults, children with DTC present with more extensive disease at the time of diagnosis. Fortunately, even in the presence of metastatic disease, long-term follow-up data show 30-year survival rates of 90% to 99% for children with DTC.\textsuperscript{18-20} Even with distant metastases, mortality rates are more favorable in children than adults, and pulmonary metastases can remain stable over years to decades of time.\textsuperscript{21,22}

Total thyroidectomy with prophylactic central compartment lymph node dissection is usually recommended as treatment for DTC because of the increased incidence of bilateral/multifocal disease and regional lymph node metastasis in pediatric patients.\textsuperscript{23} Adjunctive treatment with radioactive iodine is recommended for patients categorized as being at intermediate or high risk of persistent postoperative disease. Referral to a center with expertise in thyroid cancer is critical to optimize the outcome and reduce complications of therapy.

Because TSH suppression reduces the DTC recurrence rate, patients are placed on supraphysiologic doses of LT4 after surgery.\textsuperscript{24,25} The TSH goals proposed in the American Thyroid Association pediatric guidelines recommend maintaining TSH levels in the low normal range (0.5-1.0 μIU/mL) for low-risk patients, between 0.1-0.5 μIU/mL for intermediate-risk patients, and <0.1 μIU/mL for high-risk patients.\textsuperscript{16} Once a patient enters remission, TSH suppression may be relaxed into the low-risk range (0.5-1.0 μIU/mL). Follow-up care of the child with DTC involves regular assessment of circulating thyroid hormone levels, measurement of Tg and anti-Tg, and radiologic imaging. The Tg concentrations must be interpreted in relation to simultaneous TSH, and every effort must be made to use the same lab and assay method in order to accurately determine the trend in the Tg level.\textsuperscript{26}

**Conclusion**

Thyroid disorders are among the most common endocrine conditions that pediatricians will encounter in their patient population. Examination of the thyroid gland should be incorporated into all regular physical examinations and trigger further evaluation if thyroid asymmetry, enlargement, or nodularity is found.

Functional problems, which include hypothyroidism and hyperthyroidism, can present with few symptoms. Thus, thyroid function tests should be obtained in children with nonspecific symptoms of not feeling well or poor growth without other detectable causes.

The care of children with CH and GD should involve the expertise of pediatric endocrinologists. Pediatricians have the necessary expertise to manage care for their patients with Hashimoto thyroiditis or subclinical hypothyroidism.

Fortunately, irrespective of the diagnosis, the majority of pediatric patients with thyroid disease can be effectively treated with minimal disruption to daily activities, go on to achieve their goals, and experience a healthy and productive life.

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**Ultrasound of the thyroid is the most efficient and accurate method for determining if a thyroid nodule may be surveilled or undergo further evaluation.**

Ultrasound of the thyroid is the most efficient and accurate method for determining if a thyroid nodule may be surveilled or undergo further evaluation. Ultrasound is the most efficient and accurate method for determining if a thyroid nodule may be surveilled or undergo further evaluation.

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**Thyroid testing: When to worry (not often) and when to reassure**

Thyroid problems can be worrisome, but relatively few children referred for an abnormal thyroid test have clinically significant disease. For references, go to ContemporaryPediatrics.com/thyroid-testing

**Why quantity and quality matter for thyroid surgery**

Volume and experience, especially with the right surgeon, go hand-in-hand when it comes to optimal outcomes at high-volume, pediatric thyroid surgery centers. For references, go to ContemporaryPediatrics.com/thyroid-surgery

**First guidance for kids with thyroid nodules**

The American Thyroid Association has issued guidelines specifically for evaluating and managing benign thyroid nodules and differentiated thyroid cancer in children and adolescents. For references, go to ContemporaryPediatrics.com/thyroid-cancer
Table continued: Epinephrine autoinjectors and relative costs

<table>
<thead>
<tr>
<th>EPINEPHRINE PRODUCT</th>
<th>DIRECTIONS FOR USE</th>
<th>HIGHLIGHTS</th>
<th>LIMITATIONS</th>
</tr>
</thead>
</table>
| **EpiPen autoinjector**<sup>14</sup> 0.3 mg/0.3 mL $$$ | - Remove autoinjector from carrier tube.  
- Grasp autoinjector in your fist with the orange tip (needle end) pointing downward.  
- Pull blue safety release by pulling straight up.  
- Swing and push the autoinjector into the middle of the outer thigh until it clicks.  
- Hold in place for 3 sec.  
- Massage injection area for 10 sec. | - Training device available.  
- Orange tip extends to cover needle for safety after use.  
- Instructions written on autoinjector. | - Cost  
- Intermittent shortage issues |
| **Generic autoinjector** 0.3 mg/0.3 mL $$ | - Varied | - Training devices may be available. | - Not all products equivalent to brand autoinjectors, so substitutions are not automatically allowed at the pharmacy level. |
| **Symjepi autoinjector**<sup>15</sup> 0.3 mg/0.3 mL $$ | - Pull cap off to expose needle without touching plunger.  
- Slowly insert needle into middle of outer thigh.  
- After needle is in thigh, push plunger all the way down until it clicks.  
- Hold for 2 sec.  
- Remove syringe and massage area for 10 sec.  
- Slide the safety guard up until it clicks to cover the needle. | - Instructions written on syringe. | - No training device available.  
- Manual dexterity required to push plunger.  
- Exposed needle may cause anxiety prior to injection.  
- Safety concerns with exposed needle before and after injection. |

*Average wholesale price, scale: $=0-$100; $$=101-$300; $$$=301-$1000; $$$$=1001-$2000; $$$$$>2000.*  
Abbreviations: AAP, American Academy of Pediatrics; FDA, Food and Drug Administration.  
Author created from: US National Library of Medicine<sup>10</sup>; US National Library of Medicine<sup>11</sup>; US Food and Drug Administration, et al<sup>12</sup>; Amedra Pharmaceuticals LLC<sup>13</sup>; US Food and Drug Administration, et al<sup>14</sup>; US National Library of Medicine.<sup>15</sup>

This is a major limitation to access for many patients. For children who meet the weight criteria for the available autoinjectors, factors such as ease of product use and accessibility, including insurance coverage and out-of-pocket costs, must be evaluated to determine appropriate product selection.

For more information on pediatric anaphylaxis, see these articles:

- **Anaphylaxis essentials for infants**  
The American Academy of Pediatrics (AAP) has updated its Allergy and Anaphylaxis Emergency Action Plan for the treatment of infants at risk for an allergic emergency.  
ContemporaryPediatrics.com/infant-anaphylaxis

- **AAP’s first-ever action plan for epinephrine and anaphylaxis**  
The American Academy of Pediatrics (AAP) has published 2 clinical reports that discuss guidance on appropriate epinephrine use for anaphylaxis and developing an emergency action plan for patients at risk.  
ContemporaryPediatrics.com/AAP-anaphylaxis-action-plan
Attention-deficit/hyperactivity disorder (ADHD) may affect a significant number of children in a pediatric practice. This article reviews diagnostic criteria, comorbidities, and complications of ADHD as well as pitfalls that confront the treating pediatrician.

PAT F BASS III, MD, MS, MPH; DAVID O CHILDERS JR, MD

Attention-deficit/hyperactivity disorder (ADHD) and its comorbid conditions represent a significant problem to the children in a pediatric practice. Pediatricians need to be not only cognizant of the diagnostic criteria, clinical mimics, comorbidities, and complications of ADHD, but also be comfortable with managing a whole host of complications and other issues, such as stimulant abuse and diversion, that can be very subtle. This article will review the diagnostic criteria for ADHD and discuss 6 pitfalls that may face the treating pediatrician.

Criteria of ADHD

As the pediatrician commonly experiences in practice, ADHD has 2 main types: inattentive and hyperactive.

The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) requires 6 or more symptoms of hyperactivity or inattention in children aged younger than 17 years and 5 or more in adolescents aged older than 17 years.

Whereas most pediatricians understand the diagnostic criteria, the DSM-5 expanded the age of symptom onset from prior to age 6 years to prior to age 12 years, in recognition of the later presentation of inattentive symptoms. Additionally, the DSM-5 also recognizes the presence of ADHD in adults, and requires 5 symptoms of the inattentive subtype or the hyperactive-impulsive subtype for diagnosis.

What many clinicians are not explicitly taught, however, is that the DSM-5 (and earlier editions) requires the critical diagnostic requirement that ADHD symptoms must be assessed at the “appropriate developmental age” and NOT the chronologic age.

Assessing a 7-year-old with a language age of a 4½-to-5-year-old (the lower end of the typical range) likely results in a diagnosis of ADHD because the child’s behaviors, attention, and activity level are inappropriate for a 7-year-old child. However, if these same symptoms are assessed at a 4½-to-5-year-old level, they may be much more appropriate.
Starting medication too soon.
The American Academy of Pediatrics (AAP) guidelines for the diagnosis of ADHD were expanded to include children aged 4 to 5 years in 2011. However, 388,000 children aged 2 to 5 years have been diagnosed with ADHD despite there being no guidelines for a diagnosis before age 4 years.

Although the pediatrician is well aware of the “terrible 2s,” not every child aged younger than 4 years with impulsivity, decreased attention span, tantrums, and high levels of activity goes on to develop ADHD. It is important for the pediatrician to remember the link between language age and behavior. A 5-year-old child with a language delay who speaks at a 3-year-old level will generally have the attention span of a 3-year-old. It is the internal monologue that keeps our attention directed appropriately. This child may be challenged when trying to communicate his or her needs and resultantly acts out or has a tantrum in a similar fashion as a child with ADHD. However, this tantrum may be age appropriate for a 3-year-old. It is not chronological age but language age that is most important. Children are likely to function at the age of their language.

Diagnosing preschool-aged children with ADHD can be incredibly difficult. If the pediatrician decides a preschool-aged child has ADHD, behavior therapy is recommended as an initial therapy. However, the Centers for Disease Control and Prevention (CDC) estimates that fewer than half of children diagnosed with ADHD receive appropriate behavioral treatments.

In children who do not meet diagnostic criteria for ADHD, it is reasonable to provide behavioral interventions.

Not everything that is hyper is ADHD.
There is a saying in Pediatrics that all that wheezes is not asthma. Similarly, not all hyperactivity, impulsivity, or inattention is ADHD.

Several disorders have behavioral phenotypes with findings similar to ADHD:
- Extreme prematurity
- Fetal alcohol syndrome
- Spina bifida
- Genetic syndromes
- 22Q11 deletions (velocardiofacial (VCF) syndrome, DiGeorge syndrome)

Other conditions need to be considered when children present with symptoms of ADHD. Other medical conditions can cause similar symptoms, including:
Dosing problems.
The pediatrician is faced with a number of issues in following patients with ADHD once they have been placed on medication. One common response from parents is “my child’s body got adjusted to it.”

The Multimodal Treatment of Attention-Deficit/Hyperactivity Disorder (MTA) study may provide some insight into this challenge.

The study included nearly 600 7-year-old to 9-year old children randomized to 1 of 4 treatment modes over a 14-month period:6
- Intensive medication management alone.
- Intensive behavioral treatment alone.
- Combination therapy.
- Routine community care (the control group).

The combined treatment and medication management groups showed significantly greater symptom improvement compared with the intensive behavioral treatment and community care. Compared with the community care arm, participants in the intervention groups receiving medication generally received higher doses of medication. The first effective dose was not always the most effective dose. Dosing in the intervention groups was as much as 50% higher than community-treated participants.6

Because children in community treatment only saw providers 2 to 3 times per year compared with monthly in the intervention groups, they may have been at risk for a “honeymoon effect” in which they initially responded to a low dose of medication, but then required a higher dose after a few weeks or months. Because of the nature of the intervention, this was more likely to be addressed.

Parents may also describe their child as “spacey” or “zombie-like” after starting ADHD treatment. This can be thought of as hyperfocus from a dose that is too high. In most instances, this is due to too high a dose and treatment should be reduced. If ADHD symptoms return, the pediatrician can consider a different stimulant or nonstimulant therapy.

The purpose of stimulants is to increase ability to focus on 1 item, not decrease hyperkinesis. Decreased hyperactivity is a frequent benefit but targeting hyperkinesis as a treatment goal is not appropriate and can lead to overdosing.

Unfortunately, it is often the teacher report that drives medication dosing, and the teacher-targeted behavior goal may not be attention but may be hyperactivity. The stimulant medication should never alter the child’s personality.

Stimulants come from either methylphenidate or amphetamine categories. If a stimulant trial is not effective at an appropriate dose, then a medication from the other category is indicated. A failure to manage targeted attention issues in ADHD after trials at an appropriate dose of both a methylphenidate and an amphetamine product should raise a diagnostic concern. If the pediatrician finds the patient on multiple stimulants or treatments for ADHD, it is important to step back and rethink the diagnosis. Could the patient have a different diagnosis?

Masked or coexistent mental health issues.
In children, the presentation of ADHD symptoms may also be the presenting symptoms of a mood disorder or a learning disability (LD) (after 3rd grade).

After beginning ADHD treatment in a patient, the pediatrician may be occasionally faced with a call from a parent stating that “my child has been crying every day since starting the stimulant medication!”

Whereas the prevalence of ADHD is estimated to be nearly 10%, childhood mood disorders are estimated to occur in 5% of the pediatric population. More than 7% of children have been diagnosed with anxiety and more than 3% have been diagnosed with depression.7 Among children with ADHD, 33% may have coexistent anxiety and 17% may have coexistent depression.3 While comorbid, if the mood issue is the primary diagnosis, a stimulant trial may exacerbate the presenting symptoms, resulting in the parent phone call.

The inability to understand/comprehend academic material can result in the child not paying attention or acting out behavior (unconsciously, getting into trouble may be better than feeling academically inadequate as the classroom work demands are generally removed when the consequences for poor behavioral actions in the classroom are instituted).

All 3 conditions (ADHD, mood disorders, and LD) present with similar symptoms and can be comorbid.
clinical feature

A high index of suspicion for a primary mood disorder should be maintained if there is a paradoxical response early in stimulant treatment. The pediatrician must consider if the patient has another condition that needs treatment in addition to his/her ADHD. It is important to realize that even if the pediatrician feels there is a comorbid diagnosis, symptoms will often resolve with stimulant treatment. The addition of a second agent such as a selective serotonin reuptake inhibitor (SSRI) may be considered if monotherapy does not produce adequate symptom relief.

Although stimulants are effective in treating ADHD, they can sometimes exacerbate a patient’s symptoms. It is important for the pediatrician to identify the timing of when emotional lability occurs. Stimulant-induced emotional lability may need to be treated by discontinuing or switching medicines. The pediatrician would expect this to occur as blood levels of the stimulant are peaking.

Conversely, some patients may be actually experiencing “rebound irritability” as the stimulant blood levels begin to decline. This is an important distinction to make as this can be treated with adding a short-acting dose of medication as the morning dose begins to wane.

Finally, inattentive ADHD is much more common in females and may present as depression in early/mid-adolescence when the ADHD results in academic struggles relative to peers. Until the DSM-5 age expansion of ADHD symptom presentation, these young women often were diagnosed with only a mood disorder, and the ADHD was never even considered.

Misuse, abuse, and diversion.

The pediatrician may also occasionally encounter patients or parents asking to be switched from long-acting to short-acting formulations or frequently running out of medication. The pediatrician needs to begin by asking why.

Reports of the misuse of stimulants have been increasing for some time. Estimates of misuse (use of ADHD medication not prescribed to an individual or taking differently than prescribed) among grade and high school students range from 5% to 9%, and from 5% to 35% for college students. Estimates of diversion (selling, trading, or giving medication to a person without a prescription) occurred in 16% of grade school and high school students and 23% of college students. High school students reported giving ADHD medications away (15%), selling (7%), or having their medications stolen (4%). Among college students with a prescription for ADHD medication, 30% reported selling their medication and more than 50% said they were approached by another student to give or sell their medication.
as improving cognitive performance is the main factor for college-aged students. Among all children misusing stimulants, the most common source is friends and family members followed by physicians.14,15

Parents also have been noted to divert ADHD for themselves or another family member. In 1 study, 16% of parents admitted to self-administering their child’s medication and 13% had considered it.16 This is not commonly diagnosed, but parents may see a benefit to self-administering their child’s medication for their own use as there can be a high rate of undiagnosed ADHD in parents of children with ADHD.

If there is a suspicion that a parent is also manifesting adult ADHD, a recommendation to discuss the symptoms with the parent’s primary care provider is not only appropriate, but good medical care. If the parent’s ADHD is managed, the child’s outcome can be improved.

Pediatricians need to emphasize to their patients that it is inappropriate and illegal to share, sell, or distribute their stimulant medication. The pediatric office should have clear procedures and policies about refills and what to do if medication is lost or stolen. Parents and patients need to be educated about the importance of safe storage and what to do if they are pressured into sharing their medication with someone else.

Likewise, the pediatrician should consider use of long-acting formulations as these have less potential for abuse compared with the short-acting formulations. Finally, the pediatrician needs to be aware that some parents and patients may seek a diagnosis of ADHD in order to obtain a stimulant prescription. In fact, adults are highly successful in obtaining stimulant medication when coached about ADHD symptoms.17

Conclusion
Attention-deficit/hyperactivity disorder and its comorbid conditions represent a significant problem to the children in a pediatric practice. Pediatricians need to be not only cognizant of the diagnostic criteria, comorbidities, and complications of ADHD, but also comfortable with addressing other issues such as stimulant abuse and diversion.

For references, go to ContemporaryPediatrics.com/managing-ADHD

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used to seeing it in an older child. So, hives and vomiting are the most commonly described thing that people will see with anaphylaxis in infants and toddlers. We do know that, so that’s something they need to be aware of. Anaphylaxis is not always going to present with hives, but when there are hives and there’s vomiting or any kind of gastrointestinal (GI) complaint, that fits the criteria for anaphylaxis because it’s usually 2 symptoms within basically a system—2 different symptoms from that standpoint.

**Q.** What are the best treatment options for anaphylaxis in children?

**A.** What has also changed a little bit is that treatment is still epinephrine. We need it to be epinephrine—epinephrine is the first choice and the one that we should always be using. Epinephrine is now available in an infant dose for children, one that’s available at 0.1 mg and that actually is available. Pediatricians should have epinephrine stocked in their office, too, to make sure that they have it available.

**Q.** If pediatricians identify a patient that has anaphylaxis or with these diagnostic clues that you’ve given, at what point should they refer to a specialist?

**A.** That’s another great question. So, you’ve treated that anaphylaxis in your office. You then send the child to the ED, which would be the proper thing to do. The ED may give Benadryl or some other things after you’ve given the epinephrine. Then it’s really finding out what caused this anaphylaxis, what’s the trigger of the anaphylaxis. That basically means sending the patient to an allergist to help figure that all out; do the proper training for the self-injectable epinephrine at home; go over with parents what they need to be looking for and how they can avoid that trigger in the future. If it’s a food, what to look for, for cross-contamination and so on. So almost any child who has had anaphylaxis really should be sent to a pediatric allergist or an allergist.

**Q.** Is there anything else that you would like to add as a final thought for our community of pediatricians?

**A.** Well, I think it’s not to be afraid of using epinephrine. If that child is presenting to you, there are some people who feel you can’t use epinephrine until that child is shocky. You can’t give it until they’ve dropped their blood pressure or they’re really having trouble breathing, and you’re going to give them nebulizer first or you’re going to give Benadryl first. Epinephrine is the one drug that will actually treat the anaphylaxis and most of the symptoms to the greatest degree, so don’t be afraid of it and to feel really comfortable with its use in your office.

**Disclaimer:** Dr. Mahr reports receiving honoraria from Kaléo, ALK-Abelló, GlaxoSmithKline, AstraZeneca, Sanofi/Regeneron, and Optinose, and consulting fees from Kaléo and ALK-Abelló.

Dr. Johanek is a staff pharmacist at Southwest General Health Center, Middleburg Heights, Ohio. She has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

For references, go to ContemporaryPediatrics.com/recognizing-anaphylaxis

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**READ MORE ABOUT ANAPHYLAXIS**

in these articles by Todd A. Mahr, MD:

- **Anaphylaxis essentials for infants**

- **AAP’s first-ever action plan for epinephrine and anaphylaxis**

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**PLUS** For advice on choosing epinephrine autoinjectors for your patients, see page 6.
Montelukast treatment for asthma raises risk of a neuropsychiatric event

Children who are prescribed montelukast for managing their asthma are nearly twice as likely to experience a neuropsychiatric event as asthmatic children who are taking other asthma maintenance medications. Canadian investigators based this finding, which controlled for sociodemographic factors and measures of asthma severity and treatment, on analysis of data from 2004 to 2015 related to a group of asthmatic children aged from 5 to 18 years old.

Each of the 898 study children with asthma who experienced a neuropsychiatric event was matched to a maximum of 4 controls who had no neuropsychiatric events. The most common events were anxiety (48.6%) and sleep disturbance (26.1%), almost half of which arose within 90 days of the most recently dispensed asthma maintenance prescription.

In addition to being more likely to have been exposed to montelukast in the previous year, children who experienced an event also had significantly more ED visits and hospitalizations for asthma during this period and were more likely to have a dispensed prescription for systemic corticosteroids and other asthma maintenance medications (Glockler-Lauf SD, et al. J Pediatr. 2019;209;176-182).

THOUGHTS FROM DR. BURKE

These findings won’t stop me from using this medication in a child who needs it, but if a child with asthma who is on montelukast develops anxiety or another neuropsychiatric conditions, I’ll consider stopping it.

Michael’s death leaves a huge hole in the lives of so many. I was one of the many privileged to have been touched by his wisdom, grace, and generosity.

—Jane A. Oski, MD, MPH
Former EAB, Contemporary Pediatrics

Read the full collection of tributes for Dr. Michael Burke online at ContemporaryPediatrics.com/Dr-Burke-remembered
The diagnosis of MC is usually made by examination of the skin, although scraping or performing a biopsy, which is usually unnecessary, can help confirm the diagnosis. Examination with a dermatoscope or magnifier can easily help to confirm the diagnosis quickly, and siblings or other close friends often have a recent history of MC.

**Differential diagnosis**

The diagnosis of MC is usually made by examination of the skin, although scraping or performing a biopsy, which is usually unnecessary, can help confirm the diagnosis. Examination with a dermatoscope or magnifier can easily help to confirm the diagnosis quickly, and siblings or other close friends often have a recent history of MC.

**Treatment and management**

Molluscum contagiosum usually resolves on its own within a few months to years. Therefore, if an individual is asymptomatic, the progression of the infection should be observed. Emollients may be used and topical antibiotics as well if the lesions become infected. However, if an individual is symptomatic, then treatment for the symptoms may be beneficial. For instance, in cases of severe pruritis, a short course of topical corticosteroids may be used but long-term use should be discouraged as it may delay resolution of the viral infection.

There is little evidence that aggressive destructive measures are effective, and these may result in scarring. Furthermore, when comparing resolution of MC in treated versus untreated patients, a study found that treatment did not shorten the course of infection.

**Patient outcome**

Because this patient complained only of mild pruritus, clinicians recommended emollients and a low-potency topical steroid when symptoms flared. He also was given topical mupirocin ointment for use only for signs of secondary infection. The family was reassured that the “id” reaction was a harbinger of MC resolution, and MC and the dermatitis cleared over the next 2 months.

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

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**CONTEMPORARY PEDIATRICS**

**CLINICAL VIDEO EXCLUSIVE**

For Contemporary Pediatrics, Dr. Bobby Lazzara discusses the findings of a recent retrospective study that looked at injuries from cosmetic products related to nail care, hair care, skin care, and fragrance in a national sample of children aged 5 years and younger as reported by US emergency departments from 2002 to 2016. There is an important take-home message here for parents, so check it out.
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Emergent itchy rash in a 5-year-old boy

PRACHI AGGARWAL, BA, MS2

A healthy 5-year-old boy with a 6-month history of asymptomatic 2-mm to 3-mm papules on his legs presents for evaluation of a red, slightly itchy rash that just developed on the back of his right knee.

FIGURE A red itchy rash developed on the patient's right leg.

Clinical findings
Molluscum contagiosum (MC) is a self-limited pox-virus infection of the skin usually spread through direct skin-to-skin contact of the involved area or autoinoculation.1 The lesions usually present as 1-mm to 3-mm pale or skin-colored papules with central umbilication and commonly arise in the face, extremities, and trunk regions.1,2 In many cases, the MC lesions can become inflamed and surrounded by eczematous dermatitis known as molluscum dermatitis or “id” reaction (Figure).

Epidemiology/Etiology
Whereas the manifestation of molluscum dermatitis is well recognized, the prevalence has not been well characterized. Across 6 studies examining molluscum dermatitis in MC patients, the prevalence ranged from 9% to 39%.3 It may actually be higher because it is often a harbinger of regression, and there may be a bias of ascertainment as many cases may go undocumented.

Currently, the exact cause of an id reaction in molluscum contagiosum is unknown.4 However, it has been suggested that it may be a T-cell-mediated, delayed-hypersensitivity reaction that represents an immunologic response to the virus, leading to inflammation of the MC lesion and an eczematous rash.1 This hypothesis is supported by biop-
Focus on anaphylaxis

This month’s spotlight is Pediatric Allergies as *Contemporary Pediatrics* sits down exclusively with Todd A. Mahr, MD, FAAP, FAAAAI, FACAAI, president of the American College of Allergy, Asthma, and Immunology (ACAAI), director, Pediatric Allergy, Asthma, and Immunology at Gundersen Health System in La Crosse, Wisconsin, and adjunct clinical professor of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, to discuss the one key condition for which he believes community pediatricians should be especially aware—anaphylaxis.

ERIN JOHANEK, PHARMD

Q. Dr. Mahr, why do you think anaphylaxis is of particular concern for pediatricians?

A. As a pediatric allergist, I see this in the community quite a bit. Anaphylaxis is a serious allergic or hypersensitivity reaction that’s rapid in onset and can lead to death. So, I can’t imagine a key condition that isn’t more practical for a pediatrician to know about. The issue with anaphylaxis is that the diagnosis is really based on clinical symptoms and signs for which pediatricians need to be aware. Also, there’s obviously the history—what activities lead up to it, and so on.

Q. What do you think are the underlying reasons for the increased severity or frequency of anaphylaxis in children?

A. Well, we know that for children anaphylaxis is becoming more prominent because we’re seeing more food allergies. Food allergies have increased by 18% from 2007 to 2012, and another study found a 50% increase in episodes of food-induced anaphylaxis that presented to the emergency department (ED). What we’re seeing is also more common in 0- to 5-year-olds, and that’s something that maybe a lot of pediatricians aren’t as familiar with. They’re thinking bee sting anaphylaxis or food allergy in an older child and not really thinking about anaphylaxis in that 0- to 5-year-old child and what we need to know about what to do for that child.

Q. What advice can you offer as far as those diagnostic clues that the pediatrician should be on the lookout for to properly diagnose anaphylaxis?

A. That’s a great question because basically it’s a little bit different. I mean, we all know what we think about. We think about anaphylaxis, we think about trouble breathing, hives, tightness in the throat, hoarse voice, feeling impending doom. In infants, that might be a bit different because the symptoms of anaphylaxis—vomiting, throat itching, and throat tightness—in an infant or toddler may be regurgitation or irritability and fussiness, drooling, inconsolable crying. and obviously they might have a rash, but they also might be lethargic and sleepy. So pediatricians need to be aware of that.

Anaphylaxis may not present in a younger child like pediatricians are.

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Parents of infants are bombarded with information from all angles. Their families have advice on how to survive those first few weeks. Their friends stop by to commiserate about hourly feedings. Their pediatrician provides a long list of infant “do’s and don’ts.”

In that environment, it shouldn’t be surprising that oral care often gets overlooked during a child’s first few months. While many pediatricians will perform a basic oral exam once a baby’s first tooth erupts, putting an oral care routine in place and establishing an oral care routine from birth (or before it) can help prevent downstream issues.

The Dangers of Early Plaque Buildup

In a simplistic sense, tooth decay requires 3 factors — the presence of a tooth, a bacteria living on the surface of a tooth, and a fermentable carbohydrate. When an infant’s mouth is colonized with harmful bacteria, that bacteria will find its way to an erupting tooth as soon as it appears. The bacteria will then digest excessive fermentable carbohydrates such as lactose, fructose, and glucose to create an acid that slowly eats away at the surface of the tooth enamel. If there is no intervention for a significant amount of time, a cavity will form. CAVITIES, of course, create a slew of potential problems, including the need for unexpected dental visits and/or dental procedures, problems with chewing and nutrition, tooth alignment issues, and pain. Children with untreated tooth decay have a 3-to-4-fold greater risk of poor performance in school compared to children without these issues. In serious instances, infections in the tooth can proceed through the gum line to the bony ridge or face and cause cellulitis or infection of the skin or, in rare cases, the brain.

When to Start the Conversation

Having discussions with parents about the oral health of their infant should take place as soon as possible, typically at either the 1- or 3-month well visit. At these visits, the focus should be on anticipatory guidance that addresses use of appropriate liquids for infants, cleaning of gums, preventative oral health, and establishing an oral care routine. Early intervention is thought to be key to preventing future oral health issues and acquainting the child with an oral exam and the oral health team.

In a 2016 survey of 203 office-based pediatricians, only 19% of respondents said that they begin discussions with parents about oral health care prior to an infant’s third month. The majority (68%) said that they wait until months 3–8 to have that initial conversation (Table 1). Table 2 shows the age in which respondents typically recommend the introduction of specific oral care activities, with many not recommending anything specific until the infant reaches at least 5 months of age. This data reflects a missed opportunity to set up an effective dental routine during early infancy.
Tips to Help Parents Establish Healthy Routines

A few simple actions can make a big difference in the healthy development of teeth and gums. Tooth and gum cleansers are appropriate to use in infants after 3 months of age to not only help prevent the development of bacteria in the mouth but also to establish an effective oral care routine. Orajel™ offers fluoride-free cleansers to avoid the risk of excess fluoride ingestion. These tooth and gum cleansers can be applied by the parent with a finger brush or small toothbrush after the infant finishes his/her bottle. A wet rag or washcloth may be alternatively suggested. The use of these products should help get an infant accustomed to having cleansing products in their mouth early in life, making the eventual transition to toothpaste simpler.

Other oral care suggestions for parents of an infant include the following:4

1. Avoid sharing spit with your infant, pre-chewing food, and sharing utensils, cups, spoons, or toothbrushes
2. Discourage the use of whole milk, sugary drinks, and fruit juice from a bottle, especially at night
3. Avoid dipping pacifiers in any sweetened liquid, sugars, or syrups

Relief from Teething Issues

Irritability due to teething issues is common among babies starting as early as 3 months of age. While parents will sometimes discuss possible remedies with their pediatricians, many will turn to over-the-counter pain relievers to soothe a fussy baby. It may therefore be wise to provide proactive guidance regarding potential teething remedies prior to eruption of the first tooth.

For milder teething issues, rubbing the gums with a clean finger or a small rubber finger massager can temporarily ease an infant’s pain. Letting an infant chew on a frozen or wet washcloth can also be effective.

For more serious or chronic teething discomfort, benzocaine-free teething gels are now available from Orajel™ as an option. These cooling gels can be applied up to 4 times a day in infants aged 4 months and older to soothe sore gums. Daytime and nighttime formulas are both available from Orajel™. In addition to being benzocaine free, these gels are also free of artificial colors, menthol, sugar, parabens, belladonna, sodium lauryl sulfate, gluten, and dairy. The nighttime formula has chamomile for use at bedtime.

Conclusion

For many years, pediatricians have treated early oral hygiene as a lower priority on the list of issues to discuss with parents of infants. In many ways, this is understandable. There is a lot to cover during these appointments. However, taking a moment to have conversations about oral health and the establishment of an oral care routine during initial baby well visits may prevent future tooth and gum issues.

There remains a pervasive myth in the general public that cavities in baby teeth are “no big deal” and that we all get a second chance with our adult teeth, yet data is clear that the most significant predictor of cavities in adult teeth is cavities in baby teeth.5 Developing good oral hygiene practices from birth does not require a complicated regimen, and Orajel™ offers a variety of products that can help with the introduction of oral products in infants and toddlers. There are simple, easy-to-understand recommendations to offer patients that can help establish and maintain a healthy oral care routine and allow their children to enjoy a lifetime of smiles.

REFERENCES

3. Internal survey data

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