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The Seizing Child
Recognize and React

273,940
US children hospitalized in 2005 with neurologic DX
~46% of these admitted patients died.
EMVERM® is indicated for the treatment of patients two years of age and older with gastrointestinal infections caused by *Ancylostoma duodenale* (hookworm), *Ascaris lumbricoides* (roundworm), *Enterobius vermicularis* (pinworm), *Necator americanus* (hookworm), and *Trichuris trichiura* (whipworm).

**INDICATION**

**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, steearic acid, sodium lauryl sulfate, sodium saccharin, and FD&C Yellow #6).

**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. Avoid concomitant use of mebendazole and metronidazole.

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

- anorexia, abdominal pain, diarrhea, flatulence, nausea, vomiting, rash.

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

- anorexia, abdominal pain, diarrhea, flatulence, nausea, vomiting, rash.

**Drug Interactions:**

Concomitant use of EMVERM and metronidazole should be avoided.

**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. There are risks to the mother and fetus associated with untreated helminthic infection during pregnancy. Untreated soil transmitted helminth infections in pregnancy are associated with adverse outcomes including maternal iron deficiency anemia, low birth weight, neonatal and maternal death.

**Lactation:** 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 tablet has not been established in pediatric patients less than two years of age. Convolusions have been reported with mebendazole use in children less than one year 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 of overdose:** In the event of accidental overdose, gastrointestinal signs/symptoms may occur.

**Treatment of overdose:** There is no specific antidote.

**Patient Counseling:** Healthcare professionals should advise the patient to read the FDA-approved patient labeling (Patient Information) before initiating therapy.

Advise 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 at www.EMVERMHCP.com and Brief Summary on following pages.

References:

EMVERM® (mebendazole) 100 mg Chewable Tablets

BRIEF SUMMARY: Complete information about EMVERM® can be found in the Full Prescribing Information.

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

DOSEAGE 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>
</tr>
</thead>
<tbody>
<tr>
<td>Pinworm (enterobiasis)</td>
<td>1 tablet, once</td>
</tr>
<tr>
<td>Whipworm (trichuriasis)</td>
<td>1 tablet morning and evening for 3 consecutive days</td>
</tr>
<tr>
<td>Roundworm (ascariasis)</td>
<td>1 tablet morning and evening for 3 consecutive days</td>
</tr>
<tr>
<td>Hookworm</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, stearic 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>Condition</th>
<th>Adverse Reaction(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Agranulocytosis, Neutropenia</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>Hypersensitivity including anaphylactic reactions</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Convolutions, Dizziness</td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td>Hepatitis, Abnormal liver tests</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>TEN, SJS, Exanthema, Angioedema, Urticaria, Alopecia</td>
</tr>
</tbody>
</table>

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

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

USE IN SPECIFIC POPULATIONS
Pregnancy

Risk Summary
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 in clinically recognized pregnancies is 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 (1.6 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.
Evolution of pediatric drug development

Pediatric drug development has made exceptional strides in the last 10 years. The outlook going forward is remarkably positive, but new pressures to expedite the process are emerging.

GILBERT J. BURCKART, PHARMD, FCP, FCCP

In 2019, we tend to take the inclusion of pediatric patients in a drug development program for granted. In fact, pediatric drug development is a new science that has just evolved in the last 20 years. The struggle to make pediatrics part of this multibillion-dollar industry is not only interesting, but it is also informative with regard to continuing pressures to expedite the pediatric component of the drug development process.

This pediatric drug development process affects every pharmacy and medical practitioner working with pediatric patients every day. Everything from the inclusion of a drug on the formulary, to drug shortages, to insurance coverage for a drug is affected by the information that was generated during the drug development process. This is very much in contrast to the situation before 1997, when drugs were routinely used for pediatric patients off label, and therefore the assumption always was that information about the use of a new drug in pediatric patients would not be available. Eventually there would be information in the literature or in the pediatric dosing handbooks about pediatric use, but the basis of that information was always either small numbers of pediatric patients or unknown.

The situation today is very different, when the numbers of off-label pediatric uses of medication are getting less and less, and the basis for the labeled pediatric dose and indication is available publicly. However, pediatric drug development continues to evolve, and pediatric practitioners should be aware of the basis on which pediatric doses and indications are given in US FDA labels.

Contemporary Pediatrics is meeting your need to stay current on pharmacologic best practices by bringing you this new recurring feature titled The Clinical Pharmacologist’s Notebook. Our goal is to provide pediatricians and pediatric healthcare providers with the most up-to-date information—and thinking—as provided by children’s clinical pharmacology experts.
History of pediatric drug development

The major flaw in the drug development system that excluded pediatric patients was brought into the light in 1963, when Dr. Harry C. Shirkey pointed out that, “By an odd and unfortunate twist of fate, infants and children are becoming therapeutic or pharmaceutical orphans.” This fact was particularly frustrating because the Kefauver-Harris Amendments (1962) to the Federal Food, Drug, and Cosmetic Act of 1938, establishing the need for efficacy in drug development, were in part the result of the thalidomide tragedy causing phocomelia in children. Shirkey, who was a pharmacist at a children’s hospital in Cincinnati, Ohio, went to medical school and took pediatric drug use as his career direction. He later became the chair of the American Academy of Pediatrics (AAP) Committee on Drugs.

The advancement of pediatric drug development actually required 2 separate but mutually supportive programs. One was the scientific understanding of drug disposition in pediatric patients, and the other was the regulatory preparation that was necessary for the eventual legislation that resulted in the laws that we have today.

The scientific endeavor was led by Sumner J. Yaffe, MD, who was a Harvard-trained physician. Yaffe was the program director of the Clinical Research Center for Premature Infants at Stanford University, Stanford, California, but was enticed to establish a clinical pharmacology center at Buffalo Children’s Hospital, Buffalo, New York, in the late 1960s. In Buffalo, Yaffe found the leaders in the scientific movement that was to become the science of clinical pharmacokinetics. Doctors Gerhard Levy, Milo Gibaldi, and William Jusko were leading an innovative movement to understand drug disposition using computational science, and Yaffe established close collaboration with this group. This collaboration is reflected in their early publications in the 1970s with Levy and Jusko. The use of pharmacokinetics in pediatric pharmacology was firmly established by Yaffe in his research through the 1980s and 1990s, and is the foundation of pediatric clinical pharmacology today. Yaffe has subsequently been known as the “Father of Pediatric Clinical Pharmacology.”

The regulatory preparation for the laws governing pediatric drug development first occurred in the 1970s. Initially, investigators had assumed that it was unethical to include children in drug development research. In 1974, the AAP published a report commissioned by the FDA titled “General Guidelines for the Evaluation of Drugs to be Approved for Use During Pregnancy and for Treatment of Infants and Children.” Based on this document, the FDA released a Guidance for Industry in September 1977 on the “General Considerations for the Clinical Evaluation of Drugs in Infants and Children.” The FDA also created a regulation in 1979 establishing a “Pediatric Use” subsection of the label, so the stage was set for the inclusion of pediatric patients in drug development. However, drug development studies were rarely conducted in spite of this regulatory preparation.

In 1997, Congress included an incentive section for conducting pediatric drug development studies in the FDA Modernization Act. The incentive provided an additional 6 months of patent exclusivity if the sponsor conducted the pediatric studies that the FDA requested. The incentive proved to be popular and was renewed at the end of the 5-year sunset as the Best Pharmaceuticals for Children Act (BPCA) of 2002. In that same period, a former “pediat-
ric rule” of the FDA was enacted in 2003 as the Pediatric Research Equity Act (PREA), stating that if the sponsor was developing the drug for an indication that also occurred in children, then the sponsor must also study pediatric patients. Therefore, BPCA and PREA could work together as the “carrot and the stick” to ensure that pediatric patients were included in most drug development programs.

Because BPCA and PREA had a 5-year sunset, they were both renewed in 2007 under the FDA Amendments Act, and finally made permanent in 2012 under the FDA Safety and Innovation Act.

Science behind pediatric drug development

As might be expected in any new science, multiple mistakes were made originally in designing pediatric drug development trials. For example, the FDA review division would ask for a pediatric study that, when conducted by the sponsor, was found to be insufficient for pediatric labeling. In other cases, the dose of the drug was incorrect. In all, 42% of the BPCA studies conducted in the 1998-2012 period failed to get any pediatric labeling.7 This was a remarkable statistic in that all these drugs had proven to be effective in adults, and there was an ethical concern because no benefit was being derived from these failed studies for the protected pediatric patient population.

Another analysis of the “failed” (failed to label) trials suggested that dosing, the placebo effect in pediatric patients, differences in the disease process between pediatric patients and adults, and study design were major problems in these studies.8 The dosing problem in pediatric drug development has been addressed in a number of ways. Using dose ranging during drug development in pediatric patients, an increased use of modeling and simulation techniques, and combined adolescent and adult trials all have improved pediatric dosing during drug development. For the placebo effect, one approach has been to use a double randomization that eliminates placebo responders, and this method has been effective in trials for migraine headache.

The trial design issues have been addressed through studies of the use of enrichment in pediatric trials and an examination of endpoints in pediatric drug development trials. Enrichment is the process of selecting a patient population that is most appropriate for the trial, and includes practical, prognostic, and predictive factors.8 An assessment of the use of enrichment in pediatric drug development trials demonstrated that the use of all 3 types of enrichment criteria led to labeling success in almost 90% of trials, whereas the use of no enrichment criteria was associated with only a 65% success rate.10

An examination of the endpoints used in pediatric drug development trials was similarly enlightening. The use of the same endpoint in the adult trial as in the pediatric trial was significantly more successful than when a different endpoint had to be used in the pediatric trial.11 Endpoints that were subjective or those that were objective have similar success rates. A separate evaluation was performed for surrogate endpoints.12

Where to find information

Most of the FDA-authored reviews of pediatric drug development programs are available publicly. For information on accessing these reviews, see “Public information available from the FDA,” page 7.

Summary

Pediatric drug development has made exceptional strides in the last 10 years. Failure rates in pediatric trials that exceeded 40% are now at about 20%. The outlook is remarkably positive,13 but new pressures are emerging. Questions about the appropriate use of the extrapolation of efficacy from adults to pediatric patients are still unanswered, as are questions regarding the use of modeling and simulation to decrease or eliminate pediatric clinical trials.

The failure rate for pediatric studies should be 10% or less, given our increased understanding of pediatric diseases and pediatric drug development. However, history has shown that pediatric practitioners are resilient and dedicated, and going forward these questions will be answered to the benefit of pediatric patients.

NOTE FROM DR. LEE  Significant advancements in Pediatric Drug Development science and policies have occurred over the past 2 decades. We hope that these efforts are sustained such that “therapeutic orphans” and “therapeutic miss-adventures” are no longer associated with Pediatric Pharmacology and Therapeutics.

—Carlton Lee, PharmD, MPH, FASHP, FPPAG

For references, go to ContemporaryPediatrics.com/pediatric-drug-development
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Maternal cotinine levels linked to ADHD in offspring

Children of women who smoke during pregnancy are more likely to have attention-deficit/hyperactivity disorder (ADHD) than children of nonsmoking mothers, according to the first study to investigate the association between smoking and ADHD based on nicotine serum biomarker levels rather than self-reported smoking. Further, the investigation found that as the amount of smoking increases, so does the likelihood of ADHD.

The population-based study was conducted in Finland among 1079 children born between 1998 and 1999 who were diagnosed with ADHD (at a mean age of 7.3 years) and an equal number of children without the diagnosis. Each child with ADHD was matched with a control who had the same birth date (within 30 days), sex, and place of birth. Investigators measured cotinine levels in the blood of maternal participants, using specimens collected during the first and second trimesters of pregnancy. The mean cotinine level among mothers who smoked was 27.4 ng/mL versus 11.3 ng/mL among control mothers.

Maternal cotinine levels were associated with offspring ADHD in analyses that accounted for confounding factors as well as those that did not. In the analyses adjusted for birth weight for gestational age, maternal and paternal psychopathology, and maternal and paternal age, the overall odds ratio (OR) for ADHD in children of mothers who smoked was 1.09. Children born to mothers with the highest cotinine levels (>50 ng/mL) were more than twice as likely to have ADHD (OR, 2.21) than the control children in these analyses. Moderate cotinine levels (20-50 ng/mL) were associated with an OR of 1.27. In the analyses that were not adjusted for confounding factors, heavy and moderate cotinine levels were associated with ORs of 2.95 and 1.92, respectively.

The strongest association between cotinine exposure and ADHD was in children of women whose cotinine levels were in the top 10% (90th to 100th percentile) with unadjusted and adjusted odds for offspring ADHD of 4.9 and 3.34, respectively. For the second highest cotinine levels (80th to 89th percentile), the unadjusted analysis showed an OR of 2.71 and the adjusted analysis of 1.91 (Sourander A, et al. Pediatrics. 2019;143[3]:e20183144).

In this study, researchers quantified prenatal smoke exposure by measuring cotinine, a metabolite of nicotine, in blood samples from a Finnish national blood bank of 2 million samples drawn from nearly 1 million expectant mothers beginning in 1983. It could be that the effect on childhood ADHD is due to some other product of cigarette smoking, but other studies the authors cite show nicotine crossing the placenta and changing maturation of central nervous system development. If nicotine is the guilty party, then prenatal nicotine exposure through electronic cigarettes will likely one day be associated with similar findings.
Provider recommendations increase HPV vaccinations

More providers have been recommending human papillomavirus (HPV) vaccination to their adolescent male patients in recent years, and the effort seems to be paying off: HPV vaccination coverage among boys aged 13 to 17 years increased from 8.3% in 2011 to 57.3% in 2016, while the proportion of providers who recommended the vaccination to this patient group increased from 14.2% to 65.5%.

In addition, vaccination coverage of male adolescents was significantly higher in 2016 in those with a provider recommendation than in those without it (68.8% vs 35.4%). These findings are based on an analysis of data from the National Immunization Survey–Teen, a national telephone survey, which included information for 9712 male adolescents.

The prevalence of provider recommendations for HPV vaccine among all adolescents aged 13 to 17 years ranged widely, from a low of 45.9% in Wyoming to a high of 82.4% in Maine. Also, HPV coverage in this age group among males varied, from 48.5% in Indiana to 90.6% in Rhode Island among those with a provider recommendation, and from 20.1% in South Dakota to 82.6% in Rhode Island among those without one.

Two-question teen screening tool predicts future alcohol use, drinking problems

Adolescents who initially screened as being at highest risk for alcohol problems on a 2-question screen were more likely than their peers to have more drinking days and be at higher risk for alcohol use disorders (AUDs) at 1, 2, and 3 years after the screen, a large study showed. Participants were 12- to 17-year-olds treated for a non–life-threatening injury, illness, or mental health condition in 1 of 16 pediatric emergency departments (EDs).

The questions on the screen, which was developed by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), address if and on how many days the participant had more than a few sips of alcohol and if and how much his or her friends drink. The questions differed slightly for middle school and high school students. Participants numbered 2209 for the initial screen, with somewhat fewer completing each of the successive 3 follow-ups.

Participants who were classified as nondrinkers at baseline had the fewest drinking days at all 3 follow-ups, whereas those who were considered at highest risk for drinking had the most. Further, the screen accurately predicted AUD diagnoses 1 and 2 years after the initial screening but did it somewhat less well for diagnoses 3 years ahead (Linakis JG, et al. Pediatrics. 2019;143[3]:e20182001).

Among all youngsters in the studied age group, characteristics independently associated with greater likelihood of HPV vaccination included, in addition to getting a provider recommendation, age 16 to 17 years; being black or Hispanic; Medicaid insurance; having 2 or more physician contacts in the previous 12 months; and living in an urban or suburban area (Lu PJ, et al. J Pediatr. 2019;206:33-41).
Fever, conjunctivitis, rash, and belly pain

MELINDA MURPHY, MD; JENNIFER TAKAGISHI, MD

A 3-year old male presents with 3 days of fever (maximal temperature, 105°F), diffuse abdominal pain, and several episodes of nonbilious, nonbloody emesis and loose nonbilious, nonmucousy stools. On day 3 of illness, he was seen at an urgent care clinic where he was diagnosed with acute otitis media and prescribed amoxicillin and ondansetron. He could not tolerate any oral intake and developed red eyes, abdominal pain, and redness of his hands and feet. Later that same night, he presented to the pediatric emergency department (ED) and was admitted to the pediatric ward for management of his fever, abdominal pain, and dehydration.

On examination, the child was notably unhappy and difficult to console. His eyes were crusted and injected bilaterally, and he had scleral icterus. His lips were erythematous and dry, and his tongue and tonsils were injected. He had no tonsillar enlargement or exudate.

His heart rate was increased, and he had a +1/6 systolic ejection murmur. His abdomen was diffusely tender to palpation, without rebound, guarding, organomegaly, or masses. His skin was covered with an erythematous macular papular rash on his entire body, and he showed moderate jaundice. He had no lymphadenopathy.

The boy’s labs were notable for a normal basic metabolic profile, but abnormal liver function testing included an alanine aminotransferase (ALT) of 249 and total bilirubin of 7.4 with a conjugated bilirubin level of 5.9. His total protein was increased at 6.3 but his albumin was low at 2.9. His C-reactive protein (CRP) was significantly elevated at 17.58. His clean-catch urinalysis showed small leukocytes and white blood cells of 50 to 100. His abdominal ultrasound was negative except for bladder wall thickening.

Blood, stool, and urine cultures were sent due to his high fever.

Hospital course 1
The patient was resuscitated with intravenous (IV) fluids and started on IV piperacillin and tazobactam empirically for systemic inflammatory response syndrome (SIRS) in the setting of bacteremia or viremia. Given his high fever and gastrointestinal (GI) symptoms of abdominal pain and diarrhea, his differential diagnosis included bacteria (such as Shigella, Salmonella, Yersinia, Escherichia coli, Campylobacter)
and viruses (adenovirus, enterovirus, and hepatitis A, B, and C). Syndromes that could explain his high fever, abdominal pain, rash, and ocular symptoms also included autoimmune and vasculitis diseases. The Table provides the working differential diagnosis. The Pediatric Infectious Disease service was consulted.

The boy continued to have fevers up to 104°F, abdominal pain, poor appetite, and multiple loose non-bloody stools. Repeat labs on day 2 of hospitalization revealed an increased CRP to 20.13 with slightly improved total bilirubin level of 6.9 and an even lower albumin level of 2.3. His initial stool testing was positive for enteropathogenic E coli (EPEC) by polymerase chain reaction (PCR), and he was continued on empiric piperacillin and tazobactam for presumed bacterial enteritis.

On day 5 of illness, (corresponding to hospital day 2), the patient’s CRP was decreased from admission but still elevated at 12.54. He met clinical criteria for the diagnosis of Kawasaki disease (KD) and was started on high-dose aspirin and IV immunoglobulin (IVIG). Given the concern for coronary artery dilatation with KD, an echocardiogram (ECHO) was performed but was negative for coronary artery changes.

After 1 dose of IVIG, he defervesced and had improvement in appetite and abdominal pain. His liver function tests showed steady improvement with a discharge total bilirubin level of 1.3. Urine and blood cultures remained sterile. Once he was afebrile for 48 hours, the antibiotics were discontinued, aspirin dose was decreased, and he was discharged home. A follow-up stool culture was negative, so the Pediatric Infectious Disease team determined that the E coli detected on the stool PCR study was a colonizing organism and not a true infection.

**Hospital course 2**

The day after discharge, the patient again began complaining of abdominal pain. He also developed a fever of 101°F and conjunctival injection, so his family returned to the ED. Laboratories at that time were remarkable for an elevated CRP (from 4.79 on his discharge day to 5.68) but stable liver function tests. He was given a second dose of IVIG and restarted on high-dose aspirin. A repeat ECHO showed a 3-mm dilatation of the left anterior descending artery (Figure).

The next day, his CRP trended down to 4.07. On the third day of this admission, his temperature increased to 100.3°F, so he was treated with a third dose of IVIG. He was observed in the hospital for an additional 72 hours.

**Kawasaki disease is an acute, self-limited, inflammatory vasculitis that occurs primarily in children aged younger than 5 years.**

**Patient outcome**

Following his third dose of IVIG, the patient did not have any further fever. His rash, conjunctival injection, abdominal pain, and loose stools fully resolved, but he did develop periungual peeling of his fingers. His transaminases normalized, and his hyperbilirubinemia resolved. He
was discharged home on low-dose aspirin and close follow-up with Cardiology. He continued on low-dose aspirin for 6 months as the ectasia of his coronary arteries was slow to resolve.

**Discussion**

Kawasaki disease was first described by Dr. Tomisaku Kawasaki in Japan in 1967. It is an acute, self-limited, inflammatory vasculitis that affects small and medium-sized arteries and occurs primarily in children aged younger than 5 years. The arteritis particularly affects the coronary arteries, which can lead to an increased risk of coronary artery disease as the child ages.

In the pre-IVIG era, 25% of patients with KD who received only aspirin had a coronary aneurysm. Those without abnormal findings at their first angiogram never developed any abnormal cardiac findings. Currently, 5% of children treated with IVIG and aspirin will still develop coronary artery lesions that lead to an increased mortality rate.

Diagnosis of KD is based on meeting 5 of 6 clinical criteria: fever for at least 5 days; bilateral nonexudative conjunctivitis; erythema of the lips/oral mucosa; extremity changes; rash; and cervical lymphadenopathy. Diagnosis of KD is based on meeting 5 of 6 clinical criteria: fever for at least 5 days; bilateral nonexudative conjunctivitis; erythema of the lips/oral mucosa; extremity changes; rash; and cervical lymphadenopathy. In this case, the patient initially met 4 of the 6 clinical findings (fever, conjunctivitis, mucosal redness, hand/foot redness and rash). His labs also showed sterile pyuria and an increased CRP—associated findings in KD but not diagnostic. Because the clinical symptoms typically develop over the course of a week or more, supportive laboratory findings are often used to make the diagnosis of typical or incomplete KD.

The treatment goal in the acute phase of KD involves decreasing inflammation in the coronary artery wall and preventing coronary thrombosis by giving IVIG and high-dose aspirin. Long-term therapy in patients with coronary aneurysms is aimed at preventing myocardial infarction or ischemia by long-term low-dose aspirin therapy and close surveillance by Pediatric Cardiology.

Gastrointestinal symptoms accompany the typical presentation in up to 20% of cases, the most frequently referenced being hydrops of the gall bladder. Such GI symptoms can confuse the initial presentation. Other illnesses or diseases that can fully explain the symptomatology must be ruled out before KD can be diagnosed. This child’s presentation was complicated by his jaundice, diarrhea, and abdominal pain. The initial positive stool PCR led to a high suspicion for bacterial enteritis but was ruled out once the repeat stool culture was negative.

**Important takeaways**

The important learning point from this case is that children with KD and prominent GI or hepatobiliary involvement appear to be at a higher risk for IVIG failure such as occurred in this child. Patients with at least 1 abnormal liver panel test result (aspartate aminotransferase [AST], ALT, gamma-glutamyl transferase [GGT], or bilirubin in-
crease) presented earlier than children without abnormal liver panel tests and were 13% more likely (22% vs 9%, respectively) to be non-responsive to IVIG. The etiology of liver function test abnormalities is unclear, but hypotheses include generalized inflammation, vasculitis, congestive heart failure secondary to myocarditis, use of nonsteroidal anti-inflammatory medications (to decrease fever), toxin-mediated effects, or a combination of the above. Furthermore, ultrasound findings of gall bladder disease in the acute phase of KD, especially the presence of gall bladder distention, might be an important risk factor for coronary artery abnormalities as a complication.

Although this patient did not manifest gall bladder disease specifically, he did have hepatobiliary disease and developed coronary artery dilatation and impaired IVIG responsiveness. His long-term prognosis is worrisome for early coronary artery disease and he will require monitoring throughout his life.

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Pediatricians must be able to identify emergent neurologic problems when they present in the office or are suspected in children and proceed with appropriate workup and treatment.

PAT F BASS III, MD, MS, MPH; TIMOTHY LOTZE, MD; DONALD L GILBERT, MD, MS

Whereas neurologic problems are common in pediatric practice, pediatric neurologic emergencies are relatively uncommon. It is essential for the pediatrician to be able to identify these emergencies, and the pediatrician’s comfort level in addressing these problems is directly related to practice experience, often post residency. However, only about 20% of pediatricians report being “very comfortable” managing childhood neurologic problems, and many practicing pediatricians seek additional education post residency.\(^1\) Given workforce issues within pediatric neurology, the pediatrician may not have immediate access to pediatric neurology consultation.\(^2\)

This paper will review 3 conditions that can present in pediatric practice and identify an appropriate differential diagnosis and workup for each.

CONTINUED ON PAGE 18
Enhancing patient outcomes, managing costs, and optimizing delivery of care.

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Acute ataxia is a relatively uncommon presentation to the general pediatrician. Whereas most children have a benign, self-limited problem, the pediatrician must ensure that life-threatening conditions such as a brain tumor or central nervous system (CNS) infection are not present.

Acute ataxia may be defined as an unsteadiness of walking or other fine motor movement that is less than 72 hours old in a previously well child. Most children with acute ataxia present with a refusal to walk or development of a wide-based, drunk-like gait.

The differential diagnosis for acute ataxia is wide and includes acute infectious processes, postinfectious inflammatory conditions, drug ingestions, and other toxins, tumors, and trauma (Table 1).

However, a recent study looking at 11 years of referrals to a Division of Neurology at a large, urban pediatric medical center revealed cases of acute ataxia were primarily attributed to 3 diagnoses:
- Postinfectious cerebellar ataxia
- Drug intoxication
- Opsoclonus myoclonus (ataxia) syndrome (OMS/OMAS)

The characteristic eye movement problem of opsoclonus (ie, rapid, multidirectional saccades) may occur only intermittently, causing the diagnosis to be missed. This syndrome can be idiopathic or paraneoplastic, a presenting sign of neuroblastoma.

The pediatrician’s main focus is to exclude serious and life-threatening causes of ataxia. A thorough history and physical examination are essential in identifying possible cause of ataxia and in deciding a course of action. Signs and symptoms of recurring or frequent headaches (especially progressive early-morning or evening pattern), double vision, or vomiting suggest possible mass lesion or increased intracranial pressure. Recent head or neck trauma should prompt evaluation for vertebral artery dissection. Cranial nerve abnormalities such as papilledema and cranial nerve palsies suggest an intracranial lesion or hydrocephalus. Whereas nystagmus is seen in both benign and more serious conditions that impact the cerebellar region, pupillary abnormalities are more concerning and can be seen with mass lesions, elevated intracranial pres-

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>DIFFERENTIAL DIAGNOSIS OF ACUTE ATAXIA</th>
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<tbody>
<tr>
<td>Acute cerebellar ataxia/postinfectious encephalomyelitis</td>
<td>Posterior fossa tumor</td>
</tr>
<tr>
<td>Drug intoxication</td>
<td>Cerebellar hemorrhage or subdural hemorrhage</td>
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<tr>
<td>Opsoclonus myoclonus ataxia syndrome (paraneoplastic from neuroblastoma or idiopathic)</td>
<td>Head trauma</td>
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<td></td>
<td>Guillain-Barré syndrome (Miller-Fisher variant)</td>
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<td></td>
<td>Labyrinthitis</td>
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<td></td>
<td>Metabolic disease: Hartnup disease, maple syrup urine disease, pyruvate decarboxylase deficiency, familial periodic ataxia</td>
</tr>
<tr>
<td></td>
<td>Functional neurological symptom (conversion) disorder</td>
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In the child with active, generalized seizures, a brief physical exam should assess respiratory and circulatory status while supportive therapies are immediately initiated (eg, oxygen, frequent vitals, airway). Secure intravenous (IV) access should be achieved for blood sampling and administration of medication. Rapid neurologic exam and history from parent or caregiver should be obtained to ascertain possible causes or precipitants of the seizures.

A child is considered to be in status epilepticus (SE) if a single seizure lasts more than 5 minutes or if there are a series of seizures over a 30-minute period without a return to baseline mental status.

**ICD-10 Codes for Diagnosing Emergent Neurologic Symptoms**

The following are suggested ICD-10 codes for the diagnosis and treatment of emergent neurologic symptoms and associated comorbidities in children. Check with your contracted plan and individual state Medicaid program for coverage policy.

- **Ataxia**
  - R27.0 Ataxia, unspecified

- **Postinfectious cerebellar ataxia**
  - G32.81 Cerebellar ataxia in diseases classified elsewhere

- **Bell palsy**
  - G51.0 Bell palsy

**Drug Intoxication**

In ICD-10, codes for poisoning or adverse effects of drugs and chemicals are coded according to the symptoms/manifestations, causative agent, and whether it was a poisoning (intentional, accidental, or unknown), adverse reaction, or toxic effect.

- **Acute disseminated encephalomyelitis**
  - G04.01 Postinfectious acute disseminated encephalitis and acute disseminated encephalomyelitis (postinfectious ADEM)

- **Lethargy**
  - R53.83 Other fatigue

- **Slurred speech**
  - R47.81 Slurred speech

- **Confusion**
  - R41.0 Confusion, not otherwise specified.

- **Myoclonus**
  - G25.3 Myoclonus

- **Headaches**
  - R51 Headache

- **Double vision**
  - H53.2 Diplopia

- **Vomiting**
  - R11.10 Vomiting, unspecified
A child is considered to be in status epilepticus if a single seizure lasts more than 5 minutes or if there are a series of seizures over a 30-minute period without a return to baseline mental status.

The facial nerve supplies motor innervation to all parts of the face; parasympathetics to the submandibular, sublingual, salivary, and lacrimal glands; and taste fibers for the anterior two-thirds of the tongue. As a result, there are a number of infectious, cancerous, traumatic, idiopathic, or congenital etiologies in the differential (Table 2).

Bell palsy, characterized by rapid onset, unilateral weakness of the upper and lower face, presents with drooping eyelid, loss of nasolabial fold, and drooping of the corner of the mouth. It is the most common disorder impacting the facial nerve (ie, cranial nerve VII). It is responsible for approximately 80% of facial mononeuropathies.

In addition to the acute (usually over 1 to 2 days) unilateral facial weakness, patients may complain of:

- Decreased forehead movement
- Earache
- Hyperacusis
- Numbness of the face, tongue, and ear
- Taste disturbances
- Tinnitus
Facial movements are assessed by observing the child’s response to specific instructions such as:  
- Closing the eyes  
- Elevating the eyebrow  
- Smiling and frowning  
- Puckering the lips  
- Showing the teeth

In children not yet able to follow commands, observing while crying is generally adequate to observe the facial movements.

On examination, Bell phenomenon is a pathognomonic sign (upward movement of the eye on attempting to close the eyelid). The child’s ear also should be examined for vesicles or scabbing that would indicate zoster and possible Ramsay-Hunt syndrome.

One key concern is whether the cause is a central (brain or brainstem) versus peripheral (facial nerve) lesion. The strength of forehead muscles is a critical feature. Weakness of eyebrow raising and eye closure supports facial nerve localization. Lower face weakness with sparing of the forehead supports central localization. If accompanied by ipsilateral distal weakness in the arm and hand, a brain problem may be present. Similarly, concurrent inability to abduct the ipsilateral eye suggests a potential brainstem lesion.

Imaging may be necessary if physical signs are atypical but it is not required for all patients with Bell palsy. Similarly, neurodiagnostic testing and lumbar puncture are recommended if history or physical exam point to a disease process where these tests may be diagnostic. Lyme serologies, on the other hand, are recommended in any child with acute onset facial weakness for whom there is a possibility of exposure.

Treatment is guided by the underlying etiology, with most data coming from studies in adults. In the case of idiopathic facial or Bell palsy, treatment with oral steroids increases the likelihood of full recovery. Benefit from oral acyclovir is possible. Expert opinion seems to recommend antivirals for more severe disease. A 2012 evidence-based guideline from the American Academy of Neurology stated that it was “highly likely” antivirals would not produce a moderate (defined as a >7% difference between those treated and not) improvement in facial function, but that because of the nature of the studies a benefit could not be excluded.

**Conclusion**

Whereas pediatric neurologic emergencies are uncommon in pediatric practice, it is essential for the pediatrician to identify when they are present or suspected and proceed with appropriate workup and treatment.

---

**TABLE 2**

**DIFFERENTIAL DIAGNOSIS OF FACIAL PALSY**

- Bell palsy
- Guillain-Barré syndrome (Miller-Fisher variant)
- Mastoiditis
- Otitis media (Gradenigo syndrome)
- Herpes zoster (Ramsay-Hunt syndrome)
- Parotitis
- Other infections: Lyme disease, mononucleosis, diphtheria, West Nile virus
- Sarcoidosis
- Muscular disorders: myotonic dystrophy, facioscapulohumeral dystrophy
- Brainstem tumor
- Schwannoma
- Forceps delivery
- Asymmetric crying facies (sometimes associated with velocardiofacial syndrome, 22q11.2 microdeletion syndrome)
CBD oil’s effect may wane in managing seizures

A new study suggests that patients may develop a tolerance to cannabidiol (CBD) oil over time, resulting in a loss of efficacy for seizure control.

The US Food and Drug Administration (FDA) approved for the first time in June 2018 a CBD oral solution for children with 2 rare, severe forms of epilepsy—Lennox-Gastaut and Dravet syndromes. The approval, for children aged 2 years and older, revealed that the CBD solution was more effective in reducing seizures when used alongside other medications than a placebo.

The authors of the prospective study noted that, as with other antiepileptic medications, this research shows that CBD oil may also grow less effective over time when it comes to treating seizures. The study focused on individuals aged 1 to 37 years treated between 2014 and 2017 with CBD oil for treatment-resistant epilepsy of varying etiologies, including Lennox-Gastaut and Dravet syndromes.

Tolerance was defined by the research team as the need for a dose increase of 30% or more after efficacy declined, or a response reduction of 30% or more. Tolerance was noted in 30 patients, according to the abstract, with those patients using an average dose of 12.6 mg/kg/day. The mean time to achieve tolerance was 7.3 months.

The research team attempted to increase CBD dosing in patients who developed a tolerance, according to the abstract, and 12 of the 30 patients with tolerance were able to achieve their previous response level at an increased dose, but 15 did not. This led researchers to conclude that tolerance to CBD oil may limit its efficacy as an antiseizure treatment when considering it for long-term clinical management of epilepsy in both children and adults.

Questions arise about tolerance

Although the authors of the abstract did not respond to media requests from *Contemporary Pediatrics* by press time, Emilio Perucca, MD, PHD, of the University of Pavia, Italy, and former president of the International League Against Epilepsy, who was not involved in the study, offered his take on the research.

"I am not impressed by this work—at best, it raises a signal but it does not really demonstrate tolerance. The data are based on uncontrolled observations, and it is unclear how seizure frequency was assessed, and what types of seizures were being treated," Perucca says.

"Patients typically improve after adding any treatment due to the so-called regression to the mean phenomenon—such as spontaneous fluctuation in seizure frequency, irrespective of any effect of treatment—and the loss of improvement could again be due to spontaneous fluctuation," he says.

Perucca also questions a note in the abstract that tolerance in 9 of the patients was observed concomitant with the drug’s tapering. Perucca says it is unclear from the abstract...
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whether this means that concomitant drugs were removed, which he says by itself could explain the worsening of seizure control in the study patients.

Perucca has previously reviewed a number of trials on the use of CBD oil for the treatment of seizures, concluding that CBD oil does work in reducing the frequency of seizures when used alongside other antiepileptic medications.

In the Journal of Epilepsy Research, Perucca wrote that interest in cannabis products for epilepsy treatment has skyrocketed in recent years. Recent evidence demonstrated in a high-quality, placebo-controlled trial of purified oil-based CBD preparation in patients with Lennox-Gastaut and Dravet syndromes showed that 10 to 20 mg/kg/day of CBD oil improved seizure control when used with other antiepileptic medications compared with when no CBD oil was used.2

"One of the reasons for the utilization of cannabis products to have become so popular among patients and their caregivers is that these products are generally regarded as causing fewer adverse effects compared with traditional antiepileptic drugs, partly out of the misperception that remedies derived from natural products are unlikely to be harmful," Perucca notes in his report.

Perucca’s report also reveals that unlike delta-9-tetrahydrocannabinol (THC), CBD is not associated with the development of tolerance after repeated administration in various seizure models, and there is no evidence of a withdrawal when CBD is discontinued.

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

For references, go to ContemporaryPediatrics.com/CBD-oil-for-epilepsy

Autism linked to mental, neurologic disorders in family members

Research suggests a family history of mental and neurologic disorders may increase risk factors for diagnosis of autism spectrum disorder in a child.

RACHAEL ZIMLICH, RN, BSN

Genes may play a greater role in the development of autism spectrum disorder (ASD) than previously thought, according to a new study, which found that children whose family histories include mental and neurologic disorders are at an increased risk for ASD.

The study, published in the JAMA Network Open, utilized the population-based Stockholm Youth Cohort—a cohort of more than 500,000 young persons aged up to 17 years in a single county in Sweden.

The registry tracked children in the cohort to a mean of 14 years and found overall prevalence of ASD to be 0.4% with intellectual disability, and 1.5% without.1 Researchers then delved into the family histories of those participants identified with ASD and found that 63.1% of the cohort that was identified to have ASD with an intellectual disability also had a parent with a history of mental and/or neurologic disorders, compared with 45.4% of participants without ASD.

Autism spectrum disorder affects 1% to 2% of the population worldwide, and children typically are diagnosed around age 8 years, according to the report, with about one-quarter of those with an ASD diagnosis also affected by some degree of intellectual disability. Family history of ASD is the strongest known risk factor, according to the researchers, based on twin studies, but this report indicates that other mental or neurologic disorders may be linked to ASD risk as well.

CONTINUED ON PAGE 26
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“Autism spectrum disorders with and without intellectual disability showed different patterns of familial association,” the report notes. “For the disorders that were associated with both, their associations with ASD with intellectual disability tended to be weaker, suggesting that family history of mental and neurological disorders was more relevant for higher-functioning ASD.”

Familial association
Researchers calculated odds ratios for having first-degree relatives with ASD with no intellectual disability, and those ratios were 4.1 for participants with ASD with intellectual disabilities, and 9 for participants with ASD and no intellectual disabilities. For those with first-degree relatives with an ASD diagnosis and intellectual disabilities, the odds ratio was 14.2 for children in the cohort with ASD plus intellectual disabilities, and 3.8 for participants with ASD and no intellectual disabilities, according to report data.

Specifically looking at other mental health disorders and their relation to ASD, the research team found high ratios for ASD in children whose relatives had attention-deficit/hyperactivity disorder, schizophrenia and nonaffective psychotic disorders, depression, bipolar disorder, and personality disorders. Neurologic disorders with a strong link to ASD in a family member included cerebral palsy and epilepsy, according to the report.

Researchers found links between ASD and family histories of mental or neurologic disorders as far as fourth-degree family members, but not that the more closely related an affected family member was, the higher the odds of an ASD diagnosis in the child. The study authors also note that overall, children with ASD without intellectual disabilities were more significantly associated with relatives with mental health disorders, whereas children in the cohort who had ASD with intellectual disabilities more often had neurologic diseases in their family histories.

Why family matters
Brian K. Lee, PhD, associate professor of Epidemiology and Biostatistics at the Drexel University Dornsife School of Public Health, Philadelphia, Pennsylvania, and co-author of the study, says this research shows that a family history of multiple common psychiatric and neurologic conditions—not just ASD or in first-degree family members, but not that the more closely related an affected family member was, the higher the odds of an ASD diagnosis in the child. The study authors also note that overall, children with ASD without intellectual disabilities were more significantly associated with relatives with mental health disorders, whereas children in the cohort who had ASD with intellectual disabilities more often had neurologic diseases in their family histories.

“ADHD in a first-degree relative was associated with 4.7 times higher odds of ASD without intellectual disability in a child, while intellectual disability in a first-degree relative associated with 7.6 times higher odds of ASD with intellectual disability in a child.”

—BRIAN K. LEE, PHD

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

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Risk of psychosis with stimulants used for ADHD

Ms Nierengarten, a medical writer in Minneapolis, Minnesota, has more than 25 years of medical writing experience, authoring articles for a number of online and print publications, including various *Lancet* supplements and Medscape. 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.

MARY BETH NIERENGARTEN, MA

The ability of physicians to talk to patients about their health concerns and how to manage them is fundamental to good clinical care. One important area of this conversation is the ability to help patients weigh the benefits and risks of medications based on the best evidence available.

This can be tricky. Patients need to know about common potential adverse effects, but how do physicians talk about the rare potential adverse effect? The inquisitive patient who reads the packing label on the medication may ask, as may the patient watching the evening news after hearing about new research on a rare risk linked to the medicine they are taking.

Pediatricians who prescribe stimulants for children and adolescents with attention-deficit/hyperactivity disorder (ADHD) may be asking themselves how best to talk with patients and their families about a rare potential adverse effect associated with stimulants—psychosis—given the recent media attention to a new study published in late March in the *New England of Medicine* that compared the incidence of psychosis between 2 major classes of stimulants used to treat ADHD.1

Specifically, the study compared the incidence of psychosis in children and adolescents with ADHD treated with either methylphenidate or amphetamines. Although the study found a low incidence of psychosis with any stimulant, it reinforces the need for pediatricians to talk to patients about the real risk of such a rare adverse effect by placing it in context with what the evidence actually shows as well as what it doesn’t show.

“[The study] provides relevant data on the prevalence of psychotic events during treatment with ADHD medications that clinicians should discuss with patients when they consider starting a pharmacologic treatment for ADHD.”

—SAMUELE CORTESE, MD, PHD

Talk to patients and their families about the benefits and risks of stimulants before initiating treatment in children with ADHD.

—SAMUELE CORTESE, MD, PHD
An important underlying issue of treatment for attention-deficit/hyperactivity disorder (ADHD) is recognition that ADHD is often misdiagnosed given symptoms that can mimic other disorders. Citing his experience of running an ADHD clinic in which he and his staff received 50 referrals a month for a second opinion because a child was not responding to a stimulant, Harlan Gephart, MD, emphasizes that about 20% of these patients did not have ADHD but a condition with similar symptoms, such as a learning disability; behavioral disorder; mental health issue such as anxiety or depression; family dysfunction issue caused by a death or separation; or an environmental issue such as bullying.

To make the correct diagnosis, he points out the need for a comprehensive assessment that includes the following:

- Take a thorough history (medical, family, educational, developmental, and behavioral).
- Do a thorough physical exam.
- Do a brief neurological exam (test fine and gross motor deficits).
- Talk to the child/adolescent 1:1 without parents present (assess mood, communication skills, unusual mannerisms).
- Use rating scales from 2 sources to document ADHD traits.
- Talk to teachers (can be invaluable in discerning whether a child has a problem with learning or attention).

Clinical Feature

Patients taking methylphenidate and 237 episodes (0.21%) in the patients taking amphetamines.

“The rate of psychosis after starting stimulant medication for ADHD is low—1 in 660 in adolescents and young adults,” says Michael S. Jellinek, MD, professor emeritus of Psychiatry and Pediatrics, Harvard Medical School, Boston, Massachusetts. “The rate is twice as high, but still low, when using amphetamines compared to methylphenidate.”

This last point underscores another key takeaway from the study—the higher incidence, yet still low occurrence, of psychosis in patients on amphetamines versus methylphenidate.

Methylphenidates as first-line treatment

“We’ve known for a long time that stimulants can lead to psychosis, but there hasn’t been any comparison between these two types of stimulants and this is the first study comparing the two,” says Moran.

For Moran, the finding of an increased incidence of psychosis in patients taking amphetamines compared with methylphenidate suggests that methylphenidates should be considered as first-line treatment for ADHD, particularly in children and young adolescents.

When looking at the prescribing practices by physician type, she says that family practitioners and psychiatrists were more likely to prescribe an amphetamine (ie, Adderall) and pediatricians more likely to be split, prescribing an amphetamine half the time and methylphenidate half the time.

Although current guidelines by the American Academy of Pediatrics (AAP) indicate equal efficacy between the 2 stimulant classes,3 Moran points out that many physicians perceive amphetamines as more potent.

Evidence from a recently published meta-analysis by Cortese and colleagues supports this.3 Pooled data from 133 double-blind, randomized controlled trials were assessed to compare the efficacy and tolerability of oral medications for ADHD in children, adolescents, and adults. The study underscored the efficacy of ADHD medications for all patients, showing that all the medications (except for modafinil in adults) were more efficacious for the short-term treatment (12 weeks) of ADHD for all age groups. When looking at head-to-head comparisons of the different medications, amphetamines were the most efficacious in all age groups.

However, the study highlighted the need to factor in the tolerability of these medications for prescribing practices. When looking at the tolerability, the investigators found that amphetamines were less well tolerated in children. Importantly, methylphenidate was the only medication with better acceptability compared with placebo for children and adolescents. As such, Cortese and colleagues say this most recent evidence supports methylphenidate as the first-choice medication for children and adolescents with ADHD for short-term treatment, whereas amphetamines could be considered the first choice for adults.3

Weighing in with a clinician’s perspective in managing ADHD in children and adolescents for many years, Harlan R. Gephart, MD, clinical professor of Pediatrics emeritus, University of Washington School of Medicine, Seattle, Washington, called methylphenidate more “gentle” than amphetamines and the preferred first choice for many children with ADHD because it lessens the most common adverse effects of stimulant medications—disturbances in sleep and appetite—and you can “fine-tune it.”

“Methylphenidate is somewhat less likely to affect sleep and appetite than the amphetamines, particularly in the younger population,” Gephart says. However, he underscores that only about 70% of children will respond to methylphenidate, as is true of amphetamines. “Together if we try one stimulant and then another, we can usually get 90% or better response,” he says.

Gephart points out, however, that his choice of stimulant is not based on the potential risk of psychosis given its rarity as well as the lack of evidence showing a causal relationship between stimulants and psychosis.

“I don’t want people to think that the medications are the cause of psychosis because there are so many confounding factors,” he says, adding that the medications may act as a trigger to children who are vulnerable to experiencing a psychotic episode.

CONTINUED ON PAGE 32
FLARES AREN’T GOING TO PREVENT THEMSELVES

BABY ECZEMA RELIEF BODY CREME helps prevent the incidence of flare over time with daily use¹

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The lack of proven causality between stimulants and psychosis and the need to tease out confounding factors when assessing the risk of psychosis with stimulant use are important issues for pediatricians both in their assessment of patients and their vulnerability to psychosis as well as when talking to patients and families about the risk of psychosis when taking a stimulant.

Predicting psychosis

In a commentary accompanying the study by Moran, Cortese highlighted the limitations of retrospective studies such as the study by Moran and colleagues that permit observations about common adverse events in clinical practice but cannot control for confounding factors to establish causality.4

For example, Moran and investigators cite a number of potential confounding factors that may influence the incidence of psychosis observed in their patient population. These factors also may be considered risk factors for the development of psychosis, including ongoing substance abuse or using cannabis, or family history of psychosis.

“I think it is important to mention that all medications that work on the nervous system have the capability of causing strange but intolerable effects on the personality, such as causing aggressive behavior and hallucinations.”

—HARLAN R. GEPHART, MD

“Because [psychosis] is such a rare side effect, you should consider other risk factors for psychosis if you’re going to start someone on a stimulant, particularly an amphetamine,” Cortese says, adding that if a patient presents with a risk factor for psychosis, “you may want to shy away from an amphetamine or try methylphenidate first.”

Jellinek also stresses the importance of comprehensive care when assessing a child/adolescent with ADHD, which, he says, includes taking a family history of mental illness that covers ADHD, substance use, depression, and psychosis.

“I would look for any signs of prodrome for psychosis, such as social isolation, mania that looks like ADHD, or severe depression,” Jellinek says. “If I was concerned about any aspects of the history, I would proceed with caution, closer monitoring, and likely a psychiatric consultation.”

Cortese, however, stresses the impossibility of predicting which patients may develop a psychosis while on a stimulant. Citing data suggesting that persons may have a low or high vulnerability risk to developing psychosis while on stimulants, Cortese wrote in his commentary that “whether psychosis is due to stimulant use, to inherent vulnerability to psychosis, or to the interaction of these 2 factors remains unclear.”

Jellinek echoes these concerns. “We do not know family histories of these patients that may have added to their vulnerability and we do not know the role of any substance abuse. Maybe college-aged patients were less adherent in taking their medication or diverted it to peers,” he says. “So, despite the high quality of this study, we cannot predict which patients taking stimulants will develop psychosis.”

CONTEMPORARY PEDIATRICS CLINICAL VIDEO EXCLUSIVE

For Contemporary Pediatrics, Dr Bobby Lazzara discusses a study in Pediatrics that looked at what occurred in the wake of California’s Senate Bill 277, which removed nonmedical, personal belief exemptions for vaccines.

ContemporaryPediatrics.com/vaccine-exemptions-video
**Benefits vs risks of stimulants**

What is important for pediatricians to glean from this study and how to talk to patients about the risk of psychosis?

The study raises again the importance for pediatricians to educate their patients about ADHD; the overall treatment approach that includes school accommodations; behavioral therapy; as well as stimulants and how to weigh the benefits and risks of stimulants.

"Because [psychosis] is such a rare side effect, you should consider other risk factors for psychosis if you’re going to start someone on a stimulant, particularly an amphetamine,"

—SAMUELE CORTESE, MD, PHD

Gephart underscores that stimulant medication with careful monitoring of adverse effects and regular follow-up is the standard of care for most adolescents correctly diagnosed with ADHD (see “Correct diagnosis of ADHD,” page 29), and that discussion of developing a very rare adverse effect like psychosis is not a major factor in the decision to treat or not. He also emphasizes the need to talk about the risks of not treating ADHD, particularly in adolescents, given the clear evidence in untreated adolescents on the increased incidence of driving accidents/fatalities, school drop-outs, and substance abuse. "Basically, all the risk factors of adolescence are 2 to 3 times greater in the nonmedicated ADHD adolescent compared to the medicated ADHD adolescent," he says.

When talking about the adverse effects of stimulants, Gephart focuses first on the common adverse effects such as appetite suppression and sleep disturbances and how to work around these. For example, because stimulants suppress the appetite, he recommends that children/adolescents eat a good breakfast because they may not be hungry at noon when they take their medication. He next talks about potential significant adverse effects, such as aggressiveness and acting like a "zombie," that are intolerable and unacceptable and that usually indicate the need to adjust dose, and then explains the very rare potential adverse effects of delusions or hallucinations.

To help parents and patients understand better how stimulants work and the potential adverse effects, Gephart talks about their mechanisms of action on enhancing dopamine in the frontal lobes where behaviors including attention, distractibility, and organizational skills are moderated. "I think it is important to mention that all medications that work on the nervous system, including allergy medications, cardiac and blood pressure medications, antidepressants, and anxiety medications, have the capability of causing strange but intolerable effects on the personality, such as causing aggressive behavior and hallucinations," he says. "Fortunately, with ADHD medications, these adverse effects are very rare, occur only 1 per several hundreds of patients, and remit when the medication is discontinued."

Finally, Gephart emphasizes the importance of frequent monitoring of patients, both during the first 4 to 6 weeks of treatment initiation (weekly calls) to establish the appropriate therapeutic dose and look for adverse effects as well as throughout treatment (3 to 4 appointments each year) to ensure lack of significant adverse effects, medication compliance, adequate growth, appropriate academic progress, and no new mental health issues.

For references, go to ContemporaryPediatrics.com/stimulants-for-ADHD

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Pediatric cardiothoracic surgery centers
How to compare outcomes for kids with congenital heart defects

A yearly research report highlights mortality risk data for cardiothoracic surgery centers across 5 categories of surgical outcomes for congenital heart defects (CHD) in children.

Mortality risk for children with congenital heart conditions varies greatly among US cardiothoracic surgery centers, and these programs differ when it comes to patient volume and case complexity.

It’s a complicated and still imperfect process of comparing apples to apples when reporting on US cardiothoracic surgery program data, according to John E. Mayer Jr., MD, who chairs the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database Task Force.

However, there are some resources that can help pediatricians and patients’ families find the best center for each patient’s needs.
Mortality risk data

The STS publishes an annual report on hospitals’ voluntary reporting of mortality risk associated with congenital heart surgery procedures. The Society’s 2018 Congenital Heart Surgery Database mortality risk model is based on reporting by over 95% of the US centers. Now, nearly 74% of US centers that perform these procedures are publicly reporting, an increase from only 23% publicly reporting the data in January 2015, according to Mayer.

In the latest report, 12 of 119 participating centers received the highest 3-star designation, 85 got 2 stars, and 13 received 1 star, or the lowest rating. Nine had no stars because of incomplete data.

The report offers aggregate data over a 4-year period for each participating hospital, including a list of the surgeons whose cases make up that hospital’s data. Cases are broken down into 5 risk categories, with category 1 including lower mortality risk procedures, such as atrial septal defect repair, to category 5, which includes first-stage palliative procedures for a particular type of single ventricle known as hypoplastic left heart.

Reading between the lines

The STS report is a good place to start for researching centers for CHD patients, but it should not be a pediatrician’s or family’s only reference for a center’s outcomes, according to Mayer. It’s important to clarify the meaning of the star rating system because that’s largely misunderstood, he says.

“What the stars are intended to depict is how an institution is doing relative to its case mix. That’s an important detail because it is an incorrect conclusion that an institution that has a 3-star ranking is better than an institution with a 2-star ranking. That’s where the star system has created potential confusion,” Mayer says.

“If one institution has a higher percentage of the more complicated cases, then even if it does just as well, if not better, than another institution that has a lower percentage, it turns out that the institution that is doing the more complex case mix actually can appear to be performing as well,” Mayer explains. “It’s one of the real limitations in the star system and the STS website makes it clear that the star rating should not be used to compare 2 institutions.”

The STS is making a substantial financial commitment to develop a system that more accurately risk adjusts the mortality rates by institution, according to Mayer. There isn’t yet a reporting system that perfectly risks adjusts for the specialty due to the range and complexity of the operations, particularly when one has to consider hundreds of different types of diagnoses and operations, he says.

“One fundamental problem is we are still defining patient cohorts by the operations that they received. It turns out that you can have 2 different patient populations who receive the same operation and, because of other coexisting factors, they actually...
behavior quite differently,” Mayer says. “For example, there is a defect called an atrioventricular canal [AV canal] defect, which occurs in about 20% of patients with Down syndrome. If you have an AV canal defect repair and Down syndrome, you actually have a lower [mortality] risk than if you don’t. And yet if you go to a different patient population—patients undergoing operations for single ventricle and a patient with Down syndrome—the relative risk is several times higher than the rest of the population with single ventricle having the same operation. You have to have a risk-adjustment system that includes not only the presence or absence of Down syndrome but also in the context of the underlying heart disease. There are many such syndromes and non-heart anomalies that must be considered.”

The stars are, however, an indication of how an institution is performing for its case mix, he says. Mayer says he and colleagues are also concerned about only using the current STS reporting as a patient/family awareness tool for centers that got only 1 star. Rather, it might signal that a pediatrician considering referring to that center do a little more digging about why the center got this rating. It shouldn’t be a knockout factor, he says.

For example, some institutions’ observed-to-expected mortality rates might fall on the border between star ratings, which can create a perception that there is a difference when one doesn’t actually exist, according to Christopher A. Caldaron, MD, chief of Congenital Heart Surgery at Texas Children’s Hospital, Houston, a 3-star program according to the STS report.

“Another problem is some institutions may be quite superior in their ability to take care of one problem in congenital heart surgery but markedly less so in another type of problem. If that institution happens to be a 3-star program, [it] may look like [it’s] superior when in fact, for that particular problem, a 2-star or even a 1-star program might be superior,” Caldaron says.

The STS report is a good starting place when researching cardiothoracic centers, according to Riley Children’s Health cardiothoracic surgeon Mark W. Turrentine, MD. Riley Hospital for Children at Indiana University Health in Indianapolis, Indiana, is among the 3-star centers in the most recent STS report. “But not all highly respected programs are going to be 3-star,” he says.

Turrentine says that when he looked at the 10 cardiothoracic surgery centers he would consider sending someone to, half were 3-star and half were 2-star.

“I think the 3-star is a place to start because you know that it’s data that has been validated and it’s comparing a program’s outcomes to what their expected outcomes should be,” Turrentine says. “To be 3-star you have to have less than a 1 O/E [observed/expected outcomes] ratio. That allows you to see what centers are performing better than expected. It doesn’t mean that they’re the only programs to think about.”

**A comprehensive picture**

Pediatricians and families should look at a cardiothoracic heart program’s case volume, according to Mayer. High-volume programs tend to be exposed to not only many patients but also to more cases on the complex end of the spectrum, according to Turrentine. “I think having a program that has been established and has a stable surgical workforce is also important,” he says. “If people that have performed well are no longer with that institution, that institution might still carry the designation for several more cycles.”

Rankings in the *US News and World Report* also may help to distinguish the better centers, according to Mayer, although the *US News and World Report* system has its own limitations.

“Then, I suggest contacting the institution directly and asking what the results are for a given diagnosis,” Mayer says. “My recommendation would be to try to understand what the results are for the diagnosis your patient actually has. Or the pediatrician, if he knows what the diagnosis is, can

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“A small center can perform as well as a large center. Nevertheless, having high volume helps us to do well because there’s a lot of practice within the team.”

—CHRISTOPHER A. CALDARONE, MD
TEXAS CHILDREN’S HOSPITAL, HOUSTON

“All the surgeons that have been here have made careers of being here in the Division of Cardiothoracic Surgery. We’ve had no turnover of surgeons.”

—MARK W. TURRENTINE, MD
RILEY HOSPITAL FOR CHILDREN, INDIANAPOLIS, INDIANA
go to that institution’s website. Almost all the institutions now have a website that provides outcomes by diagnosis.”

Beyond the stars
Contemporary Pediatrics talked with surgeons from 4 of the 3-star centers and asked what they think makes their institutions stand out as quality cardiothoracic surgery centers.

Mark W. Turrentine, MD, Riley Hospital for Children at Indiana University Health: Riley is a long-standing program that has been training residents and fellows for about 60 years, according to Turrentine.

“Up until about 15 years ago, it was the only program in the state, so it has enjoyed a high volume of work, as well as a very balanced exposure to all aspects of congenital heart surgery,” he says. “All the surgeons that have been here have made careers of being here in the Division of Cardiothoracic Surgery. We’ve had no turnover of surgeons. Our cardiologists have an exceedingly stable workforce as well. When you have good people that get along, the focus is entirely on outcomes.”

Riley has an integrated care model, with a floor dedicated to cardiovascular care. That includes a dedicated surgical/cardiology/cardiovascular intensive care unit (ICU), cardiovascular nursing, and cardiovascular anesthesia staff members. Riley is one of the few places in the country to have an embedded cardiac newborn ICU pod built into the heart center, according to Turrentine.

“The floor is designed in an integrated way so that care delivery is standarized and is modeled in a way that we can adopt best practices,” he says.

“When you do 500-plus operations a year, it’s hard not to have the high-level complex patients. That’s how we have been able to show that we’re at the top of our game.”

—DANIEL VELEZ, MD
PHOENIX CHILDREN’S HOSPITAL, PHOENIX, ARIZONA

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—MARK S. BLEIWEIS, MD
UF HEALTH SHANDS CHILDREN’S HOSPITAL, GAINESVILLE, FLORIDA

Christopher A. Caldarone, MD, chief of Congenital Heart Surgery at Texas Children’s Hospital, Houston: Texas Children’s Hospital has one of the highest volume centers for congenital heart surgery in North America, according to Caldarone.

“A small center can perform as well as a large center. Nevertheless, having high volume helps us to do well because there’s a lot of practice within the team. Rare lesions are encountered more frequently and therefore the group is more familiar with dealing with them than might be possible at a smaller institution,” he says.

Texas Children’s also has a well-orchestrated, team-based system for surgical decision-making in which a large group of clinicians in multidisciplinary conferences review every surgical decision for every patient. On elective patients, it’s typically done twice to make sure the patients obtain the maximum benefit of the group’s collective expertise.

“I think we have a lot of very experienced clinicians and rigorous processes for making high quality surgical decisions,” Caldarone says. “I’m not talking about just the surgeons. We depend upon highly experienced cardiologists, intensivists, cardiac anesthesiologists, and nurses. A well-organized team will outperform a group of individual practitioners practicing in isolation, and that’s an important part of delivering high-quality care.”

Daniel Velez, MD, division chief of Cardiothoracic Surgery at Phoenix Children’s Hospital and co-director of the Phoenix Children’s Heart Center, Arizona: This is the sixth consecutive year that Phoenix Children’s Heart Center has received 3 stars. It’s a high-volume institution. Surgeons there performed more than 600 cardiac surgeries in 2018, according to Velez.

“We perform all levels of complexity—stat categories 1 through 5. We have a very robust heart transplant program and a strong mechanical-assist device program,” Velez says. “When you do 500-plus operations a year, it’s hard not to have the high-level complex patients. That’s how we have been able to show that we’re at the top of our game by performing when operating on those patients who are not expected to make it.”

In the mix of complex surgeries at the Phoenix Children’s Heart Center: neonatal repairs; the use of surgically implanted transcatheter valves; tricuspid valve repairs using the Cone procedure; heart transplantation; and medical-assist devices. “Last year, we implanted the youngest patient in the world (10 years old) with the new 50-cc total artificial heart,” Velez says.

Mark S. Bleiweis, MD, director, University of Florida (UF) Health Congenital Heart Center, UF Health Shands Children’s Hospital, Gainesville: “We’re a program that uses a multidisciplinary approach, with experts in cardiac surgery, cardiology, anesthesia, and critical care,” Bleiweis says. “It’s a very specialized team that can take care of the entire array of and spectrum of CHD, including premature neonates to adults with CHD, as well as transplant patients. We exceed the expectations in outcomes even though we have a very complex practice. We have a very high survival rate for all comers with CHD.”

Bleiweis says UF Health Shands has one of the largest pediatric transplant programs in the country and one of the largest ventricular-assist device programs for pediatrics in the United States. He and his cardiothoracic surgeon colleagues operate on a high proportion of neonates and infants with hypoplastic left heart syndrome. “We’ve achieved outstanding outcomes with that disease, which is a very complicated and difficult disease to manage,” he says.

The center’s dedication to having a seamless multidisciplinary approach is key to achieving better-than-expected mortality and other outcomes, according to Bleiweis. “You can imagine when you have a smooth system where the cardiologists, surgeons, ICU doctors, and anesthesiologists are all on the same page. We’re not in separate departments, which leads to the best outcomes and care for our patients,” he says.
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**Syndromic Testing: The Right Test, The First Time.**
Peanut allergies are a growing concern in pediatrics, but recent research indicates that few primary care practices are following existing peanut-allergy–related guidelines. It’s not that they don’t want to, but with so much to do in so little time, clinicians reveal they have a hard time figuring out how to incorporate the guidelines into practice and how to sell parents on the process.

Three separate abstracts recently presented at the American Academy of Allergy, Asthma, and Immunology (AAAAI) Annual Meeting in San Francisco, California, showed that pediatricians are not using the screening tools available to them—either for lack of time and understanding about the guidelines, or because of hesitation from parents.

Peanut allergies increased from 0.4% of children in 1999 to 2% by 2010, according to the 2017 National Institute of Allergy and Infectious Diseases (NIAID) addendum guidelines for the prevention of peanut allergy.1 Peanut allergies are the leading cause of death related to food-induced anaphylaxis. Whereas mortality is low in these reactions, there is high level of fear among parents and patients that contributes to the cost and burden of disease in these cases, according to the guidelines.

Unfamiliarity with new peanut-use guidelines

The 2017 addendum guidelines recommend that clinicians perform an assessment of peanut allergy risk for infants at age 4 to 6 months before early introduction of peanut-containing foods.2 However, in the first abstract (no. 258; Gupta RS, et al) addressed at the AAAAI meeting, Ruchi S. Gupta, MD, MPH, Northwestern University Feinberg School of Medicine and Anne and Robert H. Lurie Children’s Hospital, Chicago, Illinois, and colleagues revealed that 11% of the 369 pediatricians who participated in e-mailed surveys about the use of the guidelines actually did not use them at all.3

Gupta’s abstract also noted that although 92% of pediatricians were aware of existing guidelines, 62% were using only portions of the guidelines. Forty-one percent of those who used all or parts of the guidelines stated that parental concerns about allergic reactions were one barrier; 35% revealed that they didn’t fully understand the guidelines; and 30% cited a lack of clinic time as a barrier to using the guidelines. Of those clinicians who did not use the guidelines, 67% cited a lack of understanding about the guidance.

Although the abstract’s findings seem to focus on the fact that pediatricians are not using the guidelines to their full potential, Gupta says the bigger takeaway is the identification of the barriers pediatricians are facing in implementing the guidelines and what they need to be more successful. Gupta, a general practice pediatrician herself and co-author of the guidelines, has been working to implement the guidelines in her own practice, and admits that it can be difficult. There is already so much to accomplish at the 4- and 6-month well visits, and the guidelines are such a departure from previous recommendations, that it can be a difficult transition to make for both pediatricians and parents, she says.

“I’m hoping by understanding the barriers that pediatricians are facing that we can address them,” Gupta says. “I really want the message not to be what pediatricians aren’t doing, but how do we help facilitate [implementing the guidelines] for pediatricians who are so busy.”

—RUCHI S. GUPTA, MD, MPH
Allergy screenings miss at-risk infants

In a second abstract (no. 809; Volerttas S, et al) presented at the AAAAI meeting, another team of researchers reviewed the results of the NIAID’s addendum guidelines for early peanut introduction with screening for specific at-risk populations. The review was conducted using retrospective records of children aged younger than 11 months between January 2017 and February 2018.

Researchers found that 100 infants had testing performed for peanut allergies—81 as a screening and 19 after reaction concerns. Of the 81 infants screened, 67 were referred by pediatricians, but just 40% met NIAID screening guidelines. Of those referrals that did not meet criteria, 52% were made as a result of family histories of food allergies, and 100% were made as a result of mild-to-moderate cases of eczema. The study concluded that most infants screened in allergy clinics did not meet NIAID screening guidelines and, in fact, there were infants who met screening criteria that were missed.

Unmet need to educate about peanut allergy

A third abstract (no. 830; Tapke DE, et al) presented at the AAAAI meeting found that in implementation of the NIAID guidelines, there were few instances of discussion about early peanut introduction in at-risk infants in the primary care setting. The study involved a retrospective review of infants who had suspected allergies based on the presence of eczema.

Discussion of early peanut introduction occurred in just 3.3% of 4-month visits, 3.3% of 6-month visits, and 3% of 9-month visits. Additionally, the research team noted that early peanut introduction was discussed only 21 times in 17 unique patient visits, and always ended with a referral to an allergist. Eczema care was discussed in roughly half the visits reviewed in the study, but researchers highlight the missed opportunities for education about peanut-allergy screenings and early peanut introduction.

Paradigm shift in guidance has come

Missed opportunities and confusion about the guidelines is expected given the complete shift from traditional guidance, says David R. Stukus, MD, associate professor of Pediatrics in the Section of Allergy/Immunology at Nationwide Children’s Hospital, Columbus, Ohio. and co-author of the 2017 NIAID guidelines. Stukus says there has been a huge paradigm shift in recommendations for feeding allergenic foods.

“What we are really trying to do is change the recommendation pediatricians give to all children with food allergies,” Stukus says. “This is very different than what we’ve recommended for decades.”

Traditionally, the recommendation has been to wait until at least 2 to 3 years of age to introduce highly allergenic foods, Stukus says, but new research shows that by introducing these foods at younger ages—4 to 6 months—and offering them regularly in the child’s diet, food allergies might be avoided altogether.

“We now have good evidence that shows if we actively feed babies allergenic foods around 4 to 6 months of age, we can dramatically reduce the development of food allergies,” Stukus says. The biggest hurdle, he notes, is getting both parents and pediatricians on board with the new recommendations.

The challenge for pediatricians is in having the time and education to understand the new guidelines to the point where they are comfortable using them, and to be able to educate parents when there is so much else to cover in a well visit. Gupta says her research made it clear that pediatricians need more education and resources for themselves, clear algorithms to use in practice, and better education and handouts to help parents.

Stukus agrees. “We know that it takes years before clinical guidelines are put into practice. We need people to understand the science and buy into it,” he says. “We need to help people understand and continue to educate. This is a huge development in our specialty.”

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

For references, go to ContemporaryPediatrics.com/shift-in-peanut-allergy-guidance
Vision screening update

New device detects amblyopia and strabismus

Neural performance scanning (NPS) technology outperforms photoscreeners for analyzing binocularity in a child’s eyes in mere seconds, and with higher sensitivity and specificity.

ANDREW J SCHUMAN, MD, FAAP

The American Academy of Pediatrics (AAP), the American Association for Pediatric Ophthalmology and Strabismus (AAPOS), the American Association of Certified Orthoptists, and the American Academy of Ophthalmology (AAO) last updated their guidelines on pediatric vision screening in 2016, after endorsing instrument-based vision screening 4 years earlier in 2012.1,2 Despite these recommendations, less than 40% of children have had their vision tested even once by age 5 years.3

I last reviewed instrument-based vision screening for *Contemporary Pediatrics* in February 2014. This update will review the importance of vision screening preschool children as well as introduce pediatricians to a new technology that will significantly improve the detection of amblyopia and strabismus in our patients.

**Why screen for vision problems in children?**

Approximately 2.5% of all children have amblyopia.4,5 Amblyopia is poor vision, typically in one eye, that occurs when the brain does not recognize the sight from that eye, even if the eye itself is structurally normal. Amblyopia responds best when detected and treated in the preschool years. If treatment does not start by age 7 years, amblyopia may never improve. Delayed detection of amblyopia leaves a child with permanent uncorrectable monocular vision loss that was potentially preventable. Children with amblyopia lack binocular vision and as a consequence are likely to suffer from poor school performance, reduced fine motor skills, and impaired self-esteem. Children with amblyopia are asymptomatic and remain undiagnosed and untreated unless they undergo vision screening.

**Whom (and how) to vision screen**

In theory, children can be screened for vision problems with traditional eye charts by the age of 3 to 5 years. Screening is possible with Snellen eye charts, Tumbling E vision charts, or picture tests such as Allen Visual Acuity Cards, but this is time consuming and can lead to inconsistent or erroneous results. In reality, however, visual acuity testing in children aged younger than 5 years in a medical office can be challenging, and few chil-
The US Preventive Services Task Force recommends that children undergo instrument-based vision screening at least once between the ages of 3 to 5 years.7

**TABLE 1** RISK FACTORS FOR AMBLYOPIA

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>DESCRIPTION</th>
<th>INCIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strabismus (strabismic amblyopia)</td>
<td>Ocular misalignment; most common cause of amblyopia</td>
<td>2.0%</td>
</tr>
<tr>
<td>Anisometropia (anisometropic amblyopia)</td>
<td>Asymmetric refractive error between the 2 eyes, which causes image suppression in the eye with the larger error</td>
<td>1.2%</td>
</tr>
<tr>
<td>Astigmatism</td>
<td>Blurred vision at any distance because of abnormal curvature of the cornea or lens</td>
<td>15%</td>
</tr>
<tr>
<td>Hyperopia</td>
<td>Farsightedness; visual images come to focus behind the retina</td>
<td>6%</td>
</tr>
<tr>
<td>Myopia</td>
<td>Nearsightedness; visual images come to focus in front of the retina</td>
<td>0.6%</td>
</tr>
<tr>
<td>Media opacity (deprivation amblyopia)</td>
<td>Opacities of the clear refractive media of the eye such as the cornea, anterior chamber, lens, and vitreous humor may cause vision loss as manifested by blurry vision or reduced visual acuity.</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Arnold RW.8

**Amblyopia risk factor screening limitations**

According to Robert Arnold, a pediatric ophthalmologist and co-author of the current AAPOS automated vision screening guidelines, ARFs are very common, with a mean combined prevalence of 21% compared with a prevalence of amblyopia (20/40 and worse) of 2.5%. By his estimates, the approximate prevalence of astigmatism is 15%, strabismus is 2.0%, hyperopia is 6%, myopia is 0.6%, and anisometropia is 1.2% (Table 1).

Although photoscreening in pediatric practice has improved the number of children diagnosed with and treated for amblyopia, this technology has limitations and has not evolved since its introduction over a decade ago. Because the incidence of ARFs is 1 in 5 children, and the incidence of amblyopia is 1 in 40 children, only about 1 in the 8 children with risk factors who undergo a thorough examination by an ophthalmologist will be diagnosed with amblyopia.

In 2013, the AAPOS Vision Screening Committee revised its criteria for instrument-based vision screening because “many children, especially those having mild amblyopia, often have marked improvement (and sometimes even resolution) of their amblyopia with spectacle treatment alone; this phenomenon is seen in children with anisometric amblyopia as well as those with strabismic amblyopia.” The committee noted that the referral criteria for photoscreening instruments should have high specificity for ARFs in young children this age can be screened with any type of vision chart.

Over the past 10 years, many pediatric practices have adopted instrument-based vision screeners, called photoscreeners, to identify children with amblyopia risk factors (ARFs) that predispose toward the development of amblyopia. These devices use an infrared camera that captures and analyzes images of the red reflex of undilated pupils to screen for refractive error (hyperopia or myopia), astigmatism (warped lens), anisometropia (significant refractive difference between eyes), strabismus (eye misalignment) and lens opacity. (Please see my 2014 article for a detailed description of several photoscreeners—all the devices in that article are still on the market.) The advantage of photoscreeners is that little cooperation, and no verbal response, is required for testing, and the screening can be completed in less than a minute.

According to AAP guidelines, a visual acuity screen is recommended at ages 4 and 5 years, as well as in cooperative 3-year-olds. Additionally, instrument-based screening may be used for children aged 12 and 24 months, as well as for children aged 3 through 5 years. Visual acuity screening also should be performed by pediatricians at ages 6, 8, 10, 12, and 15 years and any time vision problems are suspected. The US Preventive Services Task Force (USPSTF) recommends that children undergo instrument-based vision screening at least once between the ages of 3 to 5 years.7
practice improvement

TABLE 2  AAPOS-RECOMMENDED AMBLYOPIA RISK FACTOR TARGETS

<table>
<thead>
<tr>
<th>Age, months</th>
<th>Astigmatism</th>
<th>Hyperopia</th>
<th>Anisometropia</th>
<th>Myopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-30</td>
<td>&gt;2.0 diopters</td>
<td>&gt;4.5 diopters</td>
<td>&gt;2.5 diopters</td>
<td>&gt;-3.5 diopters</td>
</tr>
<tr>
<td>31-48</td>
<td>&gt;2.0 diopters</td>
<td>&gt;4.0 diopters</td>
<td>&gt;2.0 diopters</td>
<td>&gt;-3.0 diopters</td>
</tr>
<tr>
<td>&gt;48</td>
<td>&gt;1.5 diopters</td>
<td>&gt;3.0 diopters</td>
<td>&gt;1.5 diopters</td>
<td>&gt;-1.5 diopters</td>
</tr>
</tbody>
</table>

NONREFRACTIVE RISK FACTOR TARGETS

<table>
<thead>
<tr>
<th>All ages</th>
<th>Media opacity &gt;1 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Manifest strabismus &gt;8 prism diopters in primary position</td>
</tr>
</tbody>
</table>

Abbreviation: AAPOS, American Association for Pediatric Ophthalmology and Strabismus.

Donahue SP, et al.9

children (to minimize false-positive referrals) and high sensitivity for the detection of amblyopia risk factors in older children (when children are approaching an age when treatment becomes less effective).9 See Table 2 for the current age-related thresholds recommended by the AAPOS.

Additionally, many pediatricians and ophthalmologists report that only 38% to 48% of patients who are referred following photoscreening actually make appointments for follow up.10-12

So, to summarize, the current referral rate from photoscreening is too high (poor specificity for amblyopia detection) and compliance with referrals is so poor that many young children with amblyopia continue to go undiagnosed.

Amblyopia diagnosis and treatment

The most common cause of amblyopia in children aged 3 years and younger is strabismus, occurring in 82% of cases, whereas combined strabismus and anisometropia is the cause in approximately 13% of cases, with 5% resulting from anisometropia alone.13 In older children aged 3 to 6.9 years, strabismus or anisometropia each occur in 40% of cases, with about 20% of cases resulting from combined strabismus and anisometropia.14 Thus, many children with amblyopia may not have ARFs other than strabismus.

To confirm a diagnosis of amblyopia, an ophthalmologic exam is needed to perform the following: measure visual acuity; perform a cover test for strabismus; test depth perception (stereopsis); dilate the pupils (cycloplegia); perform a refraction; and examine the inside of the eye to confirm there is no structural eye disease (Figure 1). Although ophthalmologists and pediatricians both measure visual acuity, testing is more accurate when performed by ophthalmologists given the nature of their training and child-specific testing methods available to them.

The relationship between refractive error and the likelihood of amblyopia depends on the child’s age, severity of blurred vision, and other factors such as their ability to accommodate and their propensity for developing strabismus.9 For children aged 3 years and younger, the prevalence of amblyopia correlates with the severity of anisometropia.15 Many children with mild amblyopia from anisometric amblyopia or strabismic amblyopia improve with eyeglass treatment alone.16 Treatment options for children in whom eyeglasses are not appropriate or are ineffective include patching the
better-seeing eye or using atropine drops to blur vision in the better-seeing eye.

Early detection and treatment of strabismus (of any degree) is important even in children who don’t have amblyopia, because timely correction of strabismus with glasses or surgery can preserve or recover binocular vision (depth perception). Also, strabismus may lead to the development of amblyopia! This is particularly true of children with esotropic strabismus, less so with children with exotropic strabismus.

**A new technology for amblyopia detection**

David Hunter, MD, PHD, is the Ophthalmologist-in-Chief at Boston Children’s Hospital, Massachusetts. He has spent more than 15 years developing a new technology for detecting amblyopia and strabismus in young children. This technology is called retinal polarization scanning (RPS), and the prototype device using the technology was originally called the Pediatric Vision Scanner. He formed Rebion (formerly REBIScan) in 2009 to commercialize the device, and the final version, recently released, has been appropriately named “blinq.” (Figure 2). Hunter named the propriety technology behind the blinq “neural performance scanning (NPS)” to remind users that the screening device was developed to help detect amblyopia “which is a brain disease, not an eye disease.”

The technology is based on the fact that when one eye has diminished vision, the brain cannot align both eyes to achieve stable binocular fixation. When polarized light is projected on the nerve fibers surrounding the fovea (the area of the retina responsible for central vision), these fibers change the polarization of light projected onto this area. The blinq device projects a beam of polarized light onto the retina while the child focuses on a light target 14 inches away, and the changes from the light reflected by the fovea of each eye are analyzed by the device (Figure 3). Five scans are completed in a 2.5-second interval and the device calculates a binocularity score. A score above 60 indicates perfect eye alignment. A score below this measurement indicates amblyopia, strabismus, or microstrabismus.

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The device can detect as little as 1 degree of strabismus. (In contrast, at least 8 degrees of strabismus must be present before it can be detected visually by a non-ophthalmologist.)

Although photoscreeners provide a readout indicating that strabismus is present, they also require at least 8 degrees of strabismus, the same as what can be detected visually by parents or pediatricians. Independent comparative studies have shown excellent sensitivity (97%) and specificity (87%) of the blinq prototype for detection of amblyopia or strabismus.17-19 In short, the blinq detected all the conditions listed in Figure 1 with 97% sensitivity, in contrast with photoscreeners, which detect only refractive error and had only 74% sensitivity. Photoscreeners also resulted in a lower specificity, with a false referral rate of 38%.17

The blinq device is a grey orb with
rubber handles on either side. It is roughly the size of a soccer ball and slightly heavier than the PlusoptiX 12C photoscreener that we use in our clinic. A touchscreen walks the user through the test sequence. One can enter patient information via the screen or via an online patient portal. One can also initiate a “quick” screen without inputting any information simply by pushing one of the buttons on either handle (my preferred method as this expedites screening). Testing is performed in an exam room with ambient lighting, or slightly dimmed lighting—bright lights are to be avoided.

To begin a blinq screening, a tap of the scanning button will conduct a 1/10-second calibration. The child is then instructed to look at the lighted face image at the center of the orb and the examiner positions the 2 red targeting lights emitting from the device on the bridge of the nose, guiding blinq to/from the child to horizontally align the targeting lights. The device automatically performs 5 scans in a 2.5-second period, calculates a binocularity score, and displays a pass or refer result (Figure 4). If a patient is uncooperative, the testing sequence will time out in a preset time period that can be adjusted by the user—usually it is set at 10 seconds. As with all screening devices, only 1 successful screening result is necessary. If a time-out result occurs twice, then referral is recommended.

As of this writing, I have used the blinq device in my clinic for about a week and found it quite easy to hold and operate. As with any screening device, there is a “learning curve” until users achieve proficiency with testing. This was much the same when my clinic deployed routine photoscreening several years ago.

The blinq device weighs 4 lbs and has been approved by the US Food and Drug Administration (FDA) for use in patients aged from 2 to 8 years. The device operates on a rechargeable lithium battery, making it portable throughout the practice (clinic, exam room to exam room), but it also can be used with the charging cable attached. It has no direct printing capability but can connect via your practice’s wireless network to a cloud-based portal for storing information and printing results to a network-connected printer.

Rebion is working on integration for electronic health records (EHR) systems and this will be available in the near future with a software update. If you want to stay low tech regarding result documentation, Rebion provides a sample pack of prescription-sized result reporting pads to which you can affix patient labels, check the “pass” or “refer” box, and hand to your patient or scan into your EHR.

The device sells for $8995 and comes with a 1-year warranty. Rebion suggests users bill insurance companies using the CPT code 07X6T: “retinal polarization scan, ocular screening with on-site automated results bilateral.” By my estimates, if insurance companies reimburse $25 per test, the device will pay for itself after 360 screens, which for many prac-
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tices can be easily achieved in 6 to 12 months’ time. It is possible that the test may be reimbursed at a higher rate.

We can do better
I said earlier that compliance of parents keeping appointments with pediatric ophthalmologists following referrals is below 50%. I have 2 suggestions to improve screening and follow-up rates. First, consider screening children overdue for screening exams whenever the opportunity arises (ie, screen at ill visits and not just at well-child exams). Secondly, I suggest that following a “refer” on a blinq screen, given its high accuracy, your practice makes an appointment with a pediatric ophthalmologist to ensure follow-up. Rebion is working on a “motivational” handout to educate parents regarding the importance of seeking a follow-up evaluation for diagnosis and treatment when indicated.

Also, be aware that the AAP has a Practice Improvement Module, called “Improve Preschool Vision Screening Performance Improvement Module,” that requires 3 cycles of 20 patient screens to complete. Upon completion, you can get 20 valuable Maintenance of Certification (MOC) part-4 credits for participation!

Lastly, in my opinion, practices would benefit from having both the blinq device and a traditional photoscreener. The blinq should be used in younger children to rule out amblyopia and strabismus, while photoscreeners can be used in older children at routine checkups, for those who have repeatedly passed a blinq screen every year through age 5. Photoscreeners used to screen patients at age 6 years and older can identify children with refractive errors and astigmatism that warrant referral to an eye professional. Photoscreeners used in this way will expedite vision testing in your office while improving workflow for well-child exams.

Retinal polarization scanning is an exciting new technology that has the potential for improving detection and treatment of the preschool child with amblyopia and strabismus. If you’d like to learn more, I’ve posted a review and discussion of the blinq device and technology on my Medgizmos.com website along with a webinar and an interview with the CEO of Rebion, Justin Shaka, and the inventor, David Hunter, as well.

Dr Schuman, section editor for Practice Improvement and Editorial Advisory Board member of Contemporary Pediatrics, is clinical assistant professor of Pediatrics, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire. He is CEO of Medgizmos.com, a medical technology review site for primary care physicians.

For references, go to ContemporaryPediatrics.com/vision-screening-update-0519

<40% OF CHILDREN HAVE HAD THEIR VISION TESTED EVEN ONCE BY AGE 5 YEARS.3

Study recommends vigilant eye screening in JIA
ContemporaryPediatrics.com/JIA-eye-screening

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Instrument-based vision screening: Update and review
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Atopic dermatitis manifests as an erythematous eruption with intense pruritus. The lesions in young children tend to be moist and crusted, becoming less exudative with increasing age. This picture can be easily confused with SD, and AD may develop concurrently. Both AD and SD can be associated with hypopigmentation and/or hyperpigmentation, but lichenification, excoriations, and sparing of protected areas (eg, intertriginous and diaper areas) are typical of AD in infancy.\(^3\)

The integrity of the epidermal barrier is compromised in AD, increasing risk of infection. Be aware that the motor coordination facilitating scratch does not mature until age 2 to 3 months.\(^3\) Thus, for infants aged younger than 2 to 3 months, pruritus may be more difficult to identify. Infants will manifest with irritability often writhing against clothing and stationary objects. Additionally, infants aged 2 to 3 months may also involve the forehead, cheeks, and scalp, such as SD adding to misdiagnosis, but will later spread to cover the trunk and extremities.

At this age, sparing of the intertriginous regions of the diaper may be used with caution as a distinguishing factor. The converse may also hold, that involvement of the diaper region may raise concern to consider alternative diagnoses (ie, infection or concomitant SD).

Management

Seborrheic dermatitis is a benign and self-limiting condition. The fundamental basis of treatment is emollients in order to loosen scales so they may be easily removed. In children, scalp involvement is most common and is treated with shampoos—typically twice per week—preferentially containing selenium sulfide or zinc pyrithione.\(^4\) After bathing, a fine comb may be used to remove any scales. For SD involving other areas such as the face and body, topical antifungal agents are considered first-line treatment due to the association with Malassezia yeast.

Infant SD is not associated with significant morbidity, as symptoms are often mild and self-limiting, resolving by age 12 months.\(^2\)

Options include ciclopirox and ketoconazole creams applied twice daily for up to 4 weeks, or the anti-seborrheic shampoos containing these agents may be gently lathered on the face, ears, and neck. Alternatively, topical corticosteroids (1%-2.5% hydrocortisone) applied sparingly, not more than twice daily, and tapered as soon as possible, may clear the rash. Topical calcineurin inhibitors also may be helpful but are not approved for children aged
younger than 2 years despite data demonstrating safe use in AD in children aged as young as 3 months. Although many children with AD go into remission by elementary school, AD can be chronic with intermittent exacerbations if not controlled. Key principals in the management of AD include avoiding known triggers and treatment aimed at reducing pruritus and inflammation and maintaining barrier function. Skin hydration is paramount as the disrupted barrier leads to transepidermal water loss and xerosis. Daily soaking in lukewarm water, without use of any detergents or skin products, is recommended with immediate occlusive seal thereafter. This is referred to as the “soak-and-seal” method and involves application of a thick emollient after light drying to create a protective barrier.

For “hot” areas, topical corticosteroids are most effective. Hot areas are active areas during times of exacerbation. The goal is to use the lowest potency for the shortest interval in order to minimize potential adverse effects. If patients require long-term treatment, topical calcineurin inhibitors such as tacrolimus (Protopic) and the topical phosphodiesterase 4 inhibitor crisaborole may be used, particularly in sensitive areas such as the face and intertriginous areas. These are steroid-sparing agents that lack the adverse effects seen by long-term corticosteroid use.

The most distressing symptoms for children are the pruritus and scratching that only perpetuates these symptoms. Since the inflammatory process is primarily T-cell driven, antihistamines have not shown efficacy in controlling such symptoms. However, as skin hydration and inflammation improve with emollients and corticosteroids, the pruritus will usually decrease.

### Patient outcome

The patient’s SD was treated with antiseborrheic shampoo for the scalp and a low-potency topical steroid for his face and trunk. The SD cleared but recurrent patches of AD were treated with occlusive clothing, emollients, and low-potency topical steroids. 

### Table: Comparison of Atopic Dermatitis vs Seborrheic Dermatitis

<table>
<thead>
<tr>
<th></th>
<th>Atopic Dermatitis</th>
<th>Seborrheic Dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>2 mo but sometimes earlier; majority before age 1 y</td>
<td>&lt;6 mo</td>
</tr>
<tr>
<td><strong>Involvement</strong></td>
<td>Infant’s face, upper chest, extensor surfaces of arms and legs. Children/adolescents: flexural surfaces</td>
<td>Face, scalp, posterior auricular, nuchal +/- intertriginous regions; may disseminate in infancy</td>
</tr>
<tr>
<td><strong>Excoriations</strong></td>
<td>Pruritus, excoriations</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Functioning</strong></td>
<td>Sleep impairment, reduced ability at school</td>
<td>No sleep impairment</td>
</tr>
<tr>
<td><strong>Lesions</strong></td>
<td>Salmon-pink patches, with white scales; +/- postinflammatory pigmentary changes</td>
<td>Erythematous base with greasy yellow exudate; postinflammatory pigmentary changes.</td>
</tr>
<tr>
<td><strong>Resolution</strong></td>
<td>Chronic, persistent with intermittent flares</td>
<td>Before age 1-2 y, often by 6 mo</td>
</tr>
<tr>
<td><strong>Triggers</strong></td>
<td>Heat, sweat, stress, dry environment</td>
<td>None</td>
</tr>
<tr>
<td><strong>Xerosis</strong></td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

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Diffuse rash spreads from infant’s scalp to extremities

MARK MAHON, MS5

A 3-month-old boy presents for evaluation of a diffuse asymptomatic rash that began on his scalp (Figure 1) and skin creases 6 weeks ago and has spread over his trunk and extremities (Figure 2). This week he has begun to scratch at his neck and abdomen.

**FIGURE 1** Asymptomatic, erythematosus greasy scales are distributed throughout the patient’s scalp.

SEBORRHEIC DERMATITIS

**Discussion**

The pattern, morphology, and symptoms associated with rashes in young infants help to establish the diagnosis and treatment regimen. Atopic dermatitis (AD) and seborrheic dermatitis (SD) present commonly in early infancy and clinical features can overlap, leading to a delay in diagnosis and effective management (Table).

Seborrheic dermatitis has a prevalence of 4% in infants aged younger than 5 years.1 Within the first 3 months, SD often manifests as “cradle cap” with erythematosus scaly plaques beneath a thick yellow greasy exudate. Other common sites have been coined the “seborrheic areas,” notably the face, neck, and groin. Such areas have a high density of sebaceous glands. Infant SD is not associated with significant morbidity as symptoms are often mild and self-limiting, resolving by age 12 months.2

Almost one-quarter of pediatric patients referred to pediatric dermatologists have AD.3 A majority (90%) of patients are aged younger than 5 years at presentation. Many develop symptoms within the first 3 months of life; and onset may overlap with SD. Unlike SD, AD is a chronic condition with intermittent flares that has a significant impact on a developing child’s quality of life.
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