PUZZLER: Girl presents with facial edema after surgery

Contemporary PEDIATRICS®

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MARCH 2020 VOL. 37 | NO. 03

Developmental & Mental Health

Nature play

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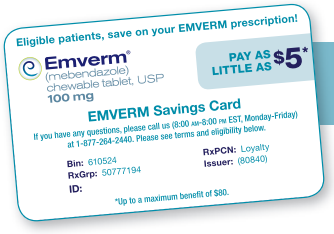
THE ONLY AVAILABLE FDA-APPROVED PRESCRIPTION TREATMENT INDICATED FOR PINWORM

95% CURE RATE AGAINST PINWORM[1]

- **EMVERM contains mebendazole,** the active ingredient that has been prescribed by physicians for more than **40 years**[2]
- The AAP *Red Book* recommends **mebendazole** as one of the **drugs of choice** for pinworm infections[3]
- The CDC recommends treating the **entire household** where more than one member is infected or where repeated, symptomatic infections occur[4]
- Patients should be **prescribed 2 tablets.** EMVERM can often cure pinworm infection with a **single tablet.** However, a *second* tablet may be necessary after 3 weeks to prevent reinfection and to kill any worms that hatched after the first treatment[1,4]
  - One 100 mg tablet is the **same dose for adults and children**[1]
  - Chewable, kid-friendly tablet can also be swallowed whole or crushed and mixed with food[1]



ELIGIBLE PATIENTS MAY PAY AS LITTLE AS $5.†
LEARN MORE AT EMVERMSAVINGS.COM/CP

†Subject to eligibility. Individual out-of-pocket costs may vary. Not valid for patients covered under Medicare, Medicaid, or other federal or state program. Please see full terms, conditions, and eligibility criteria at EmvermSavings.com.
AAP, American Academy of Pediatrics.

INDICATION

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).

IMPORTANT SAFETY INFORMATION

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

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

Adverse Reactions from Clinical Trials*: Anorexia, abdominal pain, diarrhea, flatulence, nausea, vomiting, rash.

Adverse Reactions from Postmarketing Experience with Mebendazole*: Agranulocytosis, neutropenia, hypersensitivity including anaphylactic reactions, convulsions, dizziness, hepatitis, abnormal liver tests, glomerulonephritis, Stevens-Johnson syndrome/toxic epidermal necrolysis, exanthema, angioedema, urticaria, alopecia.

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

Drug Interactions: Concomitant use of EMVERM and metronidazole should be avoided.

Use in Specific Populations:

- Pregnancy: Mebendazole use in pregnant women has not reported a clear association between mebendazole and a potential risk of major birth defects or miscarriages. However, there are risks to the mother and fetus associated with untreated helminthic infection during pregnancy.
- 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.
- 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.
- 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). 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.

To report SUSPECTED ADVERSE REACTIONS contact Amneal Specialty, a division of Amneal Pharmaceuticals LLC at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Full Prescribing Information at www.EMVERMHCP.com and Brief Summary on following pages.

References: 1. EMVERM [prescribing information]. **2.** Friedman AJ, Ali SM, Albonico M. [published online December 24, 2012.] *J Trop Med.* 2012;2012:590463. **3.** American Academy of Pediatrics. *Red Book: 2018-2021 Report of the Committee on Infectious Diseases.* 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:634-635, 994. **4.** Treatment. Centers for Disease Control and Prevention website. https://www.cdc.gov/parasites/pinworm/treatment.html. Updated August 30, 2016. Accessed June 20, 2019.

PRESCRIPTION POWER OVER PINWORM

Emverm®
(mebendazole)
chewable tablet, USP
100 mg

Printed in USA PP-ADP-MEB-US-0045 07/2019

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).

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

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

	Pinworm (enterobiasis)	Whipworm (trichuriasis)	Roundworm (ascariasis)	Hookworm
Dose	1 tablet, once	1 tablet morning and evening for 3 consecutive days	1 tablet morning and evening for 3 consecutive days	1 tablet morning and evening for 3 consecutive days

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*

Adverse Reaction(s)
Gastrointestinal Disorders
Anorexia, Abdominal Pain, Diarrhea, Flatulence, Nausea, and Vomiting
Skin and Subcutaneous Tissue Disorders
Rash

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

Postmarketing Experience
The following adverse reactions have been identified in adult and pediatric patients postmarketing with mebendazole formulations and dosages other than the EMVERM® 100 mg chewable tablet. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

	Adverse Reaction(s)
Blood and Lymphatic System Disorders	Agranulocytosis, Neutropenia
Immune System Disorders	Hypersensitivity including anaphylactic reactions
Nervous System Disorders	Convulsions, Dizziness
Hepatobiliary Disorders	Hepatitis, Abnormal liver tests
Renal and Urinary Disorders	Glomerulonephritis
Skin and Subcutaneous Tissue Disorders	TEN, SJS, Exanthema, Angioedema, Urticaria, Alopecia

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

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

USE IN SPECIFIC POPULATIONS
Pregnancy
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/m^2).

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/m^2) 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/m^2).

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/m^2), a reduction of the number of live pups was observed and there was no survival at weaning. No abnormalities were found on gross and radiographic examination of pups at birth.

Lactation

Risk Summary

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

Pediatric Use

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

Geriatric Use

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

OVERDOSAGE

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

Symptoms and signs

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

Treatment

There is no specific antidote.

CLINICAL STUDIES

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

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

	Pinworm (enterobiasis)	Whipworm (trichuriasis)	Roundworm (ascariasis)	Hookworm
Cure rates mean	95%	68%	98%	96%
Egg reduction mean	—	93%	99%	99%

PATIENT COUNSELING INFORMATION

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

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.

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

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Bridgewater, NJ 08807

07/2019 PP-XPI-MEB-US-0012

editorial advisory board

CHAIRMAN'S LETTER

What's great about the "great outdoors"?

It's just common sense. Outdoors. Fresh air. Grass, trees, and flowers. Water and rocks. Dirt and leaves. Sticks and stones. This is where children belong—not huddled around a flickering screen on a computer, iPad, or video game. This is where play happens—free and imaginative, challenging curious minds and nurturing growing bodies. This is the birthright of every child, and nature play is free for the taking. Read more from the experts about the importance of embracing the great outdoors as a prescription for overall health, beginning on page 12.

On a serious note, our panicked response to the coronavirus is objectively worse than the disease. Humans have been battling viruses since before our species evolved into its current form, and COVID-19 isn't the first coronavirus to affect us. Pediatricians caution that we be more concerned with the current influenza outbreak rather than the remote possibility of coronavirus infection and how we should protect ourselves and our children with flu shots and common sense infection prevention strategies. Turn to page 25 to read more, then remain calm, but it wouldn't hurt to stock up on disinfecting wipes and hand sanitizer. ■

Mike Hennessy, Sr.
Chairman and Founder
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Not actual patient.
Fictionalized for illustrative purposes.

Supernus® Pharmaceuticals

PUBLISHED IN *PEDIATRIC EMERGENCY CARE*

Is ordering a chest x-ray with a first episode of wheezing common practice?

"Yes" is the answer to this question, according to results of a survey targeting pediatric emergency medicine (EM) and general EM attending physicians. However, fewer pediatric residency-trained physicians (26%) routinely obtain a chest x-ray (CXR) than EM residency and other residency-trained physicians do (54% and 68%, respectively). The survey of 552 clinicians showed that fellowship training, resident supervision, years of independent practice, and practice location also influence the likelihood of routinely ordering a CXR in children who present with a first episode of wheezing.

The anonymous questionnaire included 14 closed-ended and free-text questions designed to elicit respondents' demographic characteristics and their belief and current practice of getting a CXR in children experiencing a first episode of wheezing. About half (54%) of respondents were from EM, 42% from Pediatrics, and 4% from other residency-training backgrounds. Most (58%) had practiced for fewer than 5 years and were board eligible or board certified in pediatric EM.

Of the about one-third of attending physicians who obtain a CXR in patients having a first episode of wheezing, 81% indicated that they believe it is the standard of care. Thirteen percent reported that they routinely obtain a CXR only for children younger than a certain age, which ranged from 2 weeks to 12 years (median age of 1 year). Physicians who do not supervise residents in their practice were most likely to obtain a CXR routinely as were those with 5 or fewer years of experience. In addition, practicing in suburban and rural areas and in parts of the country other than the Northeast was associated with higher use of routine CXR.

Of the about 1/3 of attending physicians who obtain a CXR in patients having a first episode of wheezing,

81%

indicated that they believe it is the standard of care.

—PATEL NH, ET AL. *PEDIATR EMERG CARE*; 2020.

The researchers noted that recent studies have concluded that a CXR is not routinely indicated in children presenting with a first episode of wheezing and pointed out that reducing unnecessary radiographs will lower care costs and increase emergency department efficiency as well as decrease these children's exposure to radiation (Patel NH, et al. *Pediatr Emerg Care*. 2020;36[1]:16-20).

THOUGHTS FROM DR. FARBER It has not been the standard of care to order a CXR for first episodes of wheezing for some years (Ralston SL, et al. *Pediatrics*. 2014;134[5]:e1474-e1502), but old habits die hard, particularly if access to an x-ray machine is easy, as in an emergency department. We also need to do a better job of getting the word out about not using albuterol for bronchiolitis, as indicated in the above clinical practice guideline.

Dr Farber, section editor for Journal Club, is a pediatrician in Woodbridge, Virginia. Ms Freedman is a freelance medical editor and writer in New Jersey. The editors have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of these articles.

PUBLISHED IN *THE JOURNAL OF PEDIATRICS*

Screening ultrasound after a first febrile UTI is not cost-effective

Although the American Academy of Pediatrics (AAP) recommends routine screening renal bladder ultrasound (RBUS) after a first febrile urinary tract infection (UTI), a comparison of this strategy with routine RBUS after a second UTI found that the AAP approach does not meet cost-effectiveness guidelines.

Investigators developed a decision analytic model to simulate a group of 2- to 24-month-old children who were followed for 5 years after a first febrile UTI. The model predicted incidence of recurrent UTIs in the context of vesicoureteral reflux and genitourinary anomalies and whether the child was treated. It compared estimated recurrent UTI rates and quality-of-life measures among children receiving routine RBUS after a first febrile UTI (intervention group) versus those receiving routine RBUS after the second UTI (control group).

The accuracy (true positives and true negatives) of RBUS for detecting an abnormality after a first febrile UTI was 64.5%. The sensitivity and specificity of detecting any abnormality were 29.2% and 84.0%, respectively. Among patients in the intervention group, the recurrent UTI rate was 19.9% compared with 21.0% in the control group, meaning that 91 patients would need to be screened, at a cost of $11,200, to prevent 1 recurrent UTI.

In the intervention group, 20.6% of children would receive unnecessary voiding cystourethrograms (VCUGs) compared with 12.2% in the control group. The simulation also showed that compared with RBUS after a second UTI, routine RBUS after a first UTI not only raises costs but results in a lower quality of life (Gaither TW, et al. *J Pediatr*. 2020;216:73-81).

THOUGHTS FROM DR. FARBER Years ago, the standard of care (without supportive evidence) for a first febrile UTI was RBUS and voiding cystourethrogram (VCUG). If the latter was positive, prophylactic antibiotics were started, and a VCUG was obtained on siblings aged younger than 10 years. As evidence accumulated, VCUG is now rarely performed and the value of antibiotics is in doubt. Studies like this may sound the death knell for routine RBUS, at least for children with antenatal ultrasounds.

PUBLISHED IN *THE LANCET*

Fenfluramine may be a new treatment option for Dravet syndrome

When added to existing antiepileptic treatment, fenfluramine hydrochloride significantly reduced the frequency of convulsive seizures in children and young adults with Dravet syndrome and had a dose-response effect, according to a randomized trial in patients in whom seizures had not been completely controlled by their current treatment regimen.

The 119 patients, who ranged in age from 2 to 18 years, were assigned to 1 of 3 groups: existing antiepileptic treatment and 0.2 mg/kg per day of fenfluramine; existing antiepileptic treatment and 0.7 mg/kg per day of fenfluramine; or placebo. Existing antiepileptic drugs most often were valproate, clobazam, topiramate, and levetiracetam.

During the 14-week treatment period, seizure frequency declined by a median 74.9% in the fenfluramine 0.7 mg/kg group, 42.3% in the fenfluramine 0.2 mg/kg group, and 19.2% in the placebo group. Fenfluramine was associated with decreased appetite, diarrhea, lethargy, and sleepiness but not with development of any cardiovascular adverse events (Lagae L, et al. *Lancet*. 2020;394[10216];2243-2254).

THOUGHTS FROM DR. FARBER It used to be that childhood epilepsy was believed to be due to obvious brain injury or was idiopathic. Now we are finding more genetic causes for seizures such as Dravet syndrome, and one can order genetic epilepsy panels to look for them. This in turn may lead to tailored treatment, as this article suggests.

Girl presents with facial edema after surgery

DANIELLE L SHORE, BS, MS4; PATRICIA BLANCO, MD, FAAP

THE CASE

A 9-year-old female presents to the clinic with facial edema that has progressively worsened over a period of a few weeks.

The patient's facial swelling had become more pronounced during the 3 days prior to the clinic visit, prompting the mother to bring her daughter to the pediatrician. The patient also was noted to be hypertensive with a blood pressure of 140/110 mm Hg. She denied fevers, headache, change in appetite or weight, chest pain, palpitations, shortness of breath, constipation, diarrhea, changes in urine, or swelling in the extremities.

History

The patient's past medical history was significant for Tetralogy of Fallot with pulmonary atresia. Her only medication is aspirin, 81 mg once a day. Her past surgical history was significant for left aortopulmonary shunt in June 2009; complete repair of Tetralogy of Fallot with pulmonary atresia in September 2009; reimplementation of right upper lobe aortopulmonary collateral in June 2011; and pulmonary valve replacement in January 2017.

Following that procedure, a 25-cm keloid developed over the median sternotomy wound. The patient subsequently had a scar revision surgery, five-and-a-half weeks prior to the current presentation, in order to remove this keloid. During this procedure, she received a single injection of Kenalog-40 (triamcinolone acetonide). A dose of 10 mL was dispensed by the pharmacy; however, the actual amount administered was not reported. Her family history was noncontributory.

Physical exam

On initial presentation to the clinic, the patient's vital signs were significant for a blood pressure of 130/94 mm Hg and a heart rate of 113 beats per minute. She was afebrile. On physical exam, her face demonstrated symmetric bilateral edema, characteristic of the Cushingoid moon facies (Figures 1 to 3). Cardiac exam was significant for a grade 3/6 holosystolic heart murmur. Her lungs were clear to auscultation bilaterally. The abdomen was soft, nontender, and nondistended with normoactive bowel sounds. There was no peripheral edema noted. Because of her cardiac history and physical exam findings, she was sent to the emergency department (ED) for further evaluation.

Laboratory testing

The patient's last echocardiogram performed 4 months prior to clin-

FIGURE 1
Photograph of the patient 8 days post scar revision surgery.

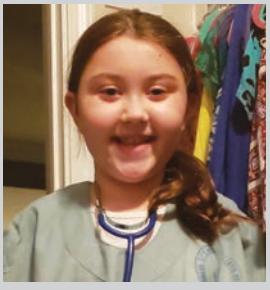

FIGURE 2
Photograph of the patient 2 days prior to her presentation in the clinic and 5 weeks post-operation. This was the first day her parents noticed her facial swelling.

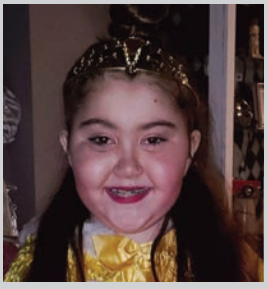

FIGURE 3
Photograph of the patient four-and-a-half months post-operation with pronounced facial swelling.

ALL PHOTOS USED WITH PERMISSION.

ic presentation demonstrated mild pulmonary valve stenosis; no pulmonary valve regurgitation; right ventricular dilation; normal right and left ventricular systolic function; and a right pleural effusion. In the ED, her chest x-ray showed a mildly enlarged cardiac silhouette, unchanged from previous imaging. Mild pulmonary edema also was noted. Her renal ultrasound was normal.

A complete blood count (CBC) showed a white blood cell (WBC) count of 12.4 µL/L (neutrophils, 69.9; lymphocytes, 20.7); hemoglobin of 14.6 g/dL; hematocrit of 43.8%; and platelets of 272 µL/L. Urinalysis was negative without hematuria or proteinuria. Electrolytes were within normal limits. Blood urea nitrogen was measured at 12 mg/dL and creatinine was 0.650 mg/dL. Glucose was 95 mg/dL. Brain natriuretic peptide (BNP) was normal at 4.7 pg/mL. Metanephrine and normetanephrine were within normal limits at 42 pg/mL and 48 pg/mL, respectively. The C-reactive protein (CRP) was normal. Antinuclear antibody (ANA) was negative. The C3 and C4 complement were 141 mg/dL (normal, 90-180 mg/dL) and 21.9 mg/dL (normal, 10-40 mg/dL), respectively. Nighttime cortisol level was <0.5 µg/dL. Adrenocorticotropic hormone (ACTH) was low at 6 pg/mL (normal, 9-57 pg/mL). Salivary cortisol was <0.010 mcg/dL. Allergy panel was negative.

Differential diagnosis

Initially, it was suspected that the patient's elevated blood pressure and tachycardia might be related to her history of Tetralogy of Fallot. Her chest x-ray was unchanged from previous films, thus ruling out a pulmonary cause. Her normal urinalysis and renal ultrasound contradicted a possible renal etiology, such as nephrotic syndrome. Whereas a pheochromocytoma would cause sudden onset hypertension and tachycardia, it would not explain the facial edema. The swelling of her face raised concern for an endocrinologic etiology (Table).

The patient was diagnosed with iatrogenic Cushing syndrome due to the low cortisol and ACTH levels, believed to be the result of the Kenalog-40 injection given during her scar revision surgery five-and-a-half weeks prior to clinic presentation.

Discussion

Cushing syndrome is attributed to an abnormally high level of cortisol in the body. Cortisol has many important effects on a wide range of organ systems. It plays a role in glucose metabolism, specifically by increasing gluconeogenesis in the liver. Cortisol exerts its effects on the cardiovascular system by increasing cardiac contractility, cardiac output, and blood pressure.[1] In addition, cortisol has activity on the immune, musculoskeletal, gastrointestinal, and neuropsychiatric systems.

Pediatric Cushing syndrome is a rare disease. The estimated incidence of Cushing syndrome overall is 2 to 5 cases per million persons per year, with approximately only 10% of new cases each year occurring in children.[2] The most common manifestations are weight gain, hirsutism, acne, and hypertension.[3] Children also can experience moon facies, early or delayed puberty, easy bruising, and purple striae. Normally, there is a stepwise process to diagnose Cushing syndrome. However, if there is a history of exogenous steroid use, then the diagnosis can be confirmed by suppressed cortisol and ACTH levels.[4]

Most case reports of pediatric Cushing syndrome have been attributed to either high-dose or prolonged use of steroids.[5-8] This patient, however, received only a single injection of Kenalog-40 leading to the development of systemic symptoms.

TABLE
DIFFERENTIAL DIAGNOSIS FOR FACIAL EDEMA

Cardiopulmonary	Congenital heart disease Coarctation of the aorta Primary hypertension Pulmonary hypertension
Renal	Polycystic kidney diease Wilm's tumor Hydronephrosis Renal artery stenosis Nephrotic syndrome
Endocrine	Cushing syndrome Hyperthyroidism Hyperaldosteronism Pheochromocytoma Pituitary adenoma
Other	Allergic reaction Autoimmune disorder

Author created.

Cushing syndrome can have long-lasting effects on the child and, therefore, it is important to diagnose and treat early. Some of these dreaded consequences are decreased adult height, hypertension, increased body mass index, impaired glucose metabolism, and osteoporosis.[9] Goals of treatment should focus on returning cortisol and ACTH to normal levels, return of physiologic adrenal function, as well as optimizing growth, pubertal development, and normal body composition. It is also imperative that physicians and parents are aware of the adverse effects of systemic steroids in order to recognize and treat the disease as soon as possible.

This patient was particularly unique because of her history of Tetralogy of Fallot. Steroids possess glucocorticoid properties, which act to increase peripheral vascular resis-

IMAGE CREDIT: AUTHOR SUPPLIED

tance causing blood pressure to rise. Unfortunately, the cardiovascular effects of high doses of steroids have not been largely studied in patients with Tetralogy of Fallot.

Intralesional injection of triamcinolone acetonide (TAC) has been recommended for the treatment of keloid scars.[10] However, the use of intralesional steroids and their accurate dosing have not been extensively studied in the pediatric population. For this reason, there are currently no guidelines on the subject, and children commonly receive dosages recommended for adults. Similar case reports detailing the administration of intra-articular and intradermal steroid injections in children have reported dosages ranging from 40 mg to 500 mg, all of which led to systemic toxicity.[11,12] Even low doses of TAC can lead to Cushing syndrome; therefore, this powerful medication should be used cautiously, especially in the pediatric population. In addition, families should be educated on the possible adverse effects and patients should be closely monitored.

Treatment and follow-up

The patient was admitted to the Pediatrics floor and started on atenolol 12.5 mg every morning and atenolol 25 mg every night. Her blood pressure and heart rate normalized, and she was discharged 2 days later. She was referred to Endocrinology, who prescribed Solu-Cortef 50-100 mg for emergency injection to be used as needed for possible adrenal crisis.

The patient subsequently followed up in the clinic. One month later, she developed back and right ankle pain. She began having daily afternoon headaches but she denied blurry vision. The moon facies were still present. Two months after presenting, Ophthalmology was consulted for her headaches. She was told that her intraocular pressure was that of a normal adult. Her fasting glucose was noted to be 110 mg/dL. Morning cortisol was <0.2 µg/dL (normal, 10-20 µg/dL) and ACTH was 12 pg/mL (normal, 9-57 pg/mL) (Figure 4). After 3 months, she developed hirsutism and an elevated blood urea nitrogen (BUN)-to-creatinine ratio. Four months later, she still had excess hair growth on her back and forehead, as well as easy bruising.

Clinicians measured the patient's Kenalog levels monthly, which trended downward over time (Figure 5). A triamcinolone acetonide level in June, 3 weeks after her initial presentation, was 0.35 mcg/dL. It had decreased to 0.24 mcg/dL 1 month later in July. A third level was drawn in August and had decreased to 0.18 mcg/dL. A fourth level in September measured 0.13 mcg/dL. The final Kenalog level showed <0.10 mcg/dL in October. After five-and-a-half months, the steroid was finally metabolized and the levels were undetectable (Figure 5).

Six months post-presentation, the patient's ACTH was measured at 18 pg/mL and cortisol at 8.6 ug/dL (Figures 4 and 5). Her facial edema had improved significantly but had not resolved completely. ■

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Dr Blanco is a board-certified pediatrician at the Johns Hopkins All Children's Hospital Sarasota General Pediatric Ambulatory Clinic, Sarasota, Florida. The authors have nothing to disclose.

For references, go to **ContemporaryPediatrics.com/puzzler-0320**

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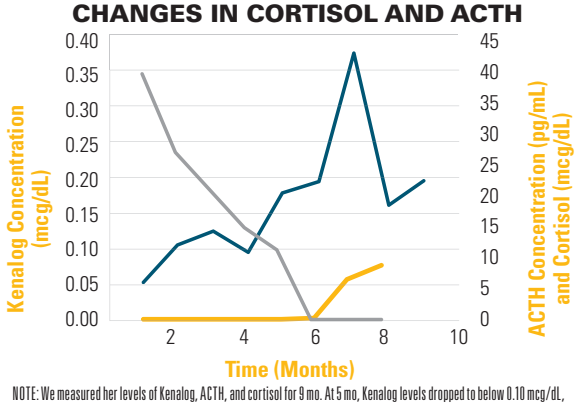
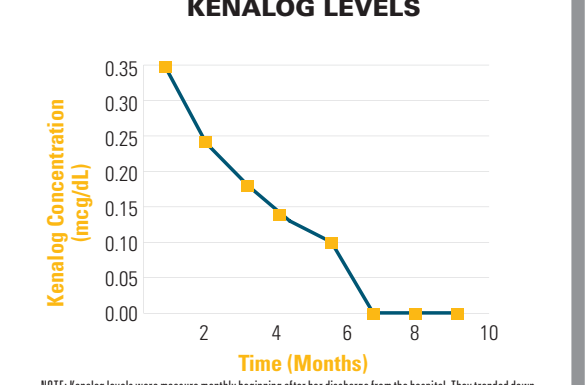
FIGURE 4



NOTE: We measured her levels of Kenalog, ACTH, and cortisol for 9 mo. At 5 mo, Kenalog levels dropped to below 0.10 mcg/dL, which was considered undetectable.

FIGURE 5



NOTE: Kenalog levels were measure monthly beginning after her discharge from the hospital. They trended downward over a 9-mo period. Her physical symptoms were still present after Kenalog was cleared from her body.

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PEER REVIEWED

Nature play

A prescription for healthier children

Dr Terrill Bravender is Rosen Professor of Adolescent Medicine, professor of Pediatrics and Psychiatry, Department of Pediatrics, University of Michigan, Ann Arbor, Michigan.

Ms Lee Smith Bravender is manager of the Gaffield Children's Garden, Matthaei Botanical Gardens and Nichols Arboretum, University of Michigan, Ann Arbor. The authors have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

It's no fantasy that children who play freely in the great outdoors are healthier in body and mind. New studies also suggest that active engagement with the natural environment reduces stress and relieves depression in all ages.

TERRILL BRAVENDER, MD, MPH
LEE SMITH BRAVENDER, MEd

The American Academy of Pediatrics (AAP) recently issued a position statement emphasizing the importance of play in promoting healthy development, particularly in children aged 0 to 6 years.[1] Whereas this play may be guided at first by parents, as children get older their free play becomes even more important. The benefits of such play are well documented, yet the benefits of exposure to the natural environment are less well studied in the medical literature. However, recent work in the fields of Psychology, Public Health, and Urban and Environmental Studies have shown a variety of physical and mental health benefits related to exposure to and interaction with outdoor green spaces.[2]

One way to combine the benefits of these areas is for pediatricians to recommend that parents promote *nature play* for their patients—that is, suggesting to parents that they should have their children go outside and encourage play in an engaging and ac-

◀ **The BUILDER'S GARDEN at the Gaffield Children's Garden, University of Michigan's Matthaei Botanical Gardens and Nichols Arboretum, Ann Arbor, invites children to create child-sized structures. This is boisterous, gross motor play.**

IMAGE CREDIT/LON HORWEDEL/MICHIGAN PHOTOGRAPHY. USED WITH PERMISSION.

TABLE 1
CREATING A CHILDREN'S GARDEN AT HOME

GAFFIELD CHILDREN'S GARDEN	AT HOME, INDOORS	AT HOME, OUTDOORS
Builder's Garden	Allow fort building using materials at hand.	■ Allow fort building play using found or collected natural materials. ■ Climb trees. ■ Build balance beams or seesaws.
Fairy and Troll Knolls	Forage small items on outdoor walks then use them inside when building tiny homes for imaginary creatures.	Use found natural objects to build tiny homes or villages for imaginary creatures.
Grower's Garden	Grow plants on window sill or in containers.	■ Cultivate a garden or a couple of food plants in containers on a balcony. ■ Consider joining a local community garden. ■ Let your child choose a food plant to grow.
Water and mud play	■ Listen to rain and make music with it. ■ Use bubble play, water-pouring play.	Make mud, mud pies, earthworks, and riverworks play.
Cutting Garden	Arrange flowers purchased at a market or bodega.	Grow flowers in backyard or on balcony; notice whether the flowers draw insects.
Nature observation play	■ Do a "window watch": Look out the window together in search of something living— birds, insects, trees, even stars. ■ Older kids might enjoy "citizen science" recordkeeping by creating written logs with lists.	■ Take walks in the neighborhood, schoolyards, parks, to the bus stop. Look for things that are living and let your child direct conversations and interactions. ■ Look for "signs of spring," etc. ■ Lead a worm rescue or test puddles on rainy days. ■ Organize a family nature play group.

Author created.

tive way. Such active engagement with the natural environment is likely to benefit children of all ages, not to mention their parents.

Overall health benefits of nature play

Play is critical to healthy child development. That children will spontaneously play and become engrossed in imaginary worlds is not news to any parent or pediatrician, but given the recent emphasis on preschool structured activities, it seems that policymakers have ignored the importance of play. Both the No Child Left Behind Act of 2001[3] and the Race to the Top Initiative from 2009[4] emphasized formal academic instruction and standardized testing of even elementary school-aged children.

Fortunately, the AAP strongly emphasizes the importance of play for children and provides a useful definition of something that seems intuitive but difficult to describe: "Play often creates an imaginative private reality, contains elements of make-believe, and is nonliteral."[1] Play is engaging and social, helping children learn new skills as well as how to get along with others and manage their own desires and emotions. Play can take place in any location, and outdoor play is a particularly important context. For example, promoting recess is one way to improve academic achievement,[5] and simply having preschoolers go outside to freely play increases levels of moderately vigorous physical activity.[6]

One fascinating study from Los Angeles compared 2 elementary schools that were matched for proximity, playground square footage, and playground design. Both locations had outdoor space for basketball, kickball, dodgeball, volleyball, 4-square, tetherball, and handball, as well as an open field and other nondesignated space near the school buildings. The control school did not change its playground environment but the intervention school replaced about 21,000 square feet of asphalt with green space. This green space included the introduction of trees,

mulch, and boulders; the replacement of an asphalt field with grass and trees; and the replacement of another asphalt field with an "outdoor classroom." This outdoor classroom was made of decomposed granite flooring, mulch, and log seating with plant borders.

In addition to the hoped-for decreases in sedentary activities for the children with the "greened" playground, there also was a significant decrease in physical and verbal conflicts among these children.[7] There are a variety of reasons why increased exposure to natural areas may have helped decrease conflicts. Most notably, children shifted away from prescriptive games with rules (such as kickball or basketball) and more toward imaginative and unstructured play, which may have decreased the opportunity for conflicts and helped develop improved socialization.

Other studies have identified additional benefits of nature exposure that also could play a role. For example, adults who intentionally sought "nature exposure" for at least 10 minutes 3 times weekly for 8 weeks saw a significant decrease in salivary cortisol and alpha-amylase, important biomarkers for general stress.[8] Other studies have observed a decrease in internalized mental health symptoms in adolescent girls who spend more than one-half hour per week outdoors[9]; a decrease in depression symptoms in adults who spend more time outdoors[10]; and even improved long-term outcomes in adults with severe depression who participated in a rehabilitation gardening program.[11]

There are 3 key messages from these research studies to communicate to parents. Most importantly is the incredible value of simply encouraging their children to play outside. Although this might be easier in some climates than others, we are fond of recalling the old saying that there is no bad weather, only bad clothing choices. In addition to simply going outside, children should be exposed to the natural environment. This means not only outdoors on a playground but also outdoors in the woods or an open field with parental supervision, and the more exposure to green space, the better. This is healthy for all ages—infants carried by their parents, toddlers directly supervised, school-aged children more

TABLE 2

NATURE PLAY ANTICIPATORY GUIDANCE BY AGE

AGES	SUGGESTIONS FROM BRIGHT FUTURES[14]
Infants	■ Consider asking parents: "*Do you spend time outside with your baby?*"
Toddlers/ Preschoolers	At this age, preschool-aged children can learn things such as language, early literacy, and early math skills from well-designed educational TV and apps. Content is very important, and many educational shows have good messages about positive behaviors and friendship. However, children need other experiences, too, such as unstructured play alone and with peers, time outdoors, and hands-on learning to develop all parts of their brain, including more complicated skills such as executive functioning and social skills. ■ Consider asking parents: "*Does your child play with other children? Does he/she play outdoors as well as indoors? Is your community safe for your child to play outdoors?*" Families with older children may find it challenging to limit media exposures for their younger child. Offer alternatives such as reading, singing, and physical or outdoor activities. ■ Consider asking the child: "*Where do you go when you play outdoors?*"
School-aged	Children this age can learn reading, science, and math skills from computers and may be using computers and other Internet-connected media in school. However, they need other experiences such as unstructured play alone and with peers, time outdoors, physical activity, and hands-on learning. These kinds of activities help them develop all parts of their brain, including more complicated skills such as executive functioning and social skills. ■ Consider asking the child: "*What do you like to do outdoors?*"
Adolescents	Motivate and promote your child's physical activity by encouraging and offering indoor and outdoor choices for physical activity and by providing games and equipment that encourage physical activity. Identify community resources such as recreation centers and schools that offer programs. ■ Consider talking with the teenager about the benefits of outdoor activities and engagement with nature: *"Do you enjoy outdoor activities? Do you know where the parks are in your neighborhood? Does your family enjoy being in nature?"*

From Hagan JF, et al.[14]

distantly supervised, and adolescents progressively granted more independence. Finally, when children are outside in the natural environment, they should be encouraged to participate in imaginative free play that they themselves (not a parent, not a teacher) direct.

University of Michigan's Gaffield Children's Garden

Like similar gardens throughout the country, **Gaffield Children's Garden** at the University of Michigan's Matthaei Botanical Gardens and Nichols Arboretum has applied these guiding principles in creating a natural, engaging environment that promotes creative and independent play for the children who visit the garden. A grounding principle of Gaffield Children's Garden is the modeling of easily replicable nature play for all visitors.

Loose nature parts play is accessible and can be easily incorporated in home spaces, neighborhoods, backyards, apartment balconies, parks, and schoolyard settings. Loose parts play invites imagination and divergent thinking opportunities, and supports curiosity about the natural world. What makes loose parts play so compelling is that there is no single way to play, and, for the most part, loose parts are also found parts: twigs, branches, stones, seed heads, water, and so on. These parts can be combined, moved, manipulated, redistributed, and reassigned many times over, taking different roles in different settings and play times. Whereas Gaffield Children's Garden is designed for nature play, the various areas also provide models for parents and children to continue their engagement with the natural world even when not visiting the Garden.

▶ In the GROWER'S GARDEN, children play by watering, mulching, raking, composting, and tasting the foods directly from the garden plots.

◀ Children explore the wonders of the GAFFIELD CHILDREN'S GARDEN, University of Michigan's Matthaei Botanical Gardens and Nichols Arboretum, Ann Arbor.

Suggestions for using these models, both indoors and outdoors, are summarized in Table 1.

Loose parts play is a type of self-directed play that can feature both small parts and large parts, each offering different elements of play and discovery. Stocked with tree branches, fence planks, stumps, and boulders, the **Builder's Garden** invites children to create child-sized structures, practice communication and negotiation, and experiment with physics, engineering, and, of course, imagination. Forts are built and rebuilt, simple lever-based machines are constructed, and play features such as balance beams and tree stump obstacle courses are constructed by children according to their play needs. This is boisterous, gross motor play.

Conversely, **Fairy and Troll Knolls** are stocked with the tiny, subtle bits of nature—stones, tree cookies, bits of bark, flower heads, and found ephemera—that invite children to create tiny worlds for imaginary creatures. This tends to be independent and quiet play. Children employ small motor skills, imagining single dwellings or entire ecosystems. Both these ideas can be replicated to varying degrees in backyards, schoolyards, parks, and on apartment grounds or balconies.

In the **Grower's Garden**, children play by watering, mulching, raking, and composting, and, more importantly, they taste foods as they grow directly from the garden plots, again with parental supervision. At home, plants can be grown in cups or pots on window sills, community plots, or backyards.

Water and mud play is a magnet to young children, offering simple opportunities to experiment with early earth science and chemistry

▲ The **FAIRY AND TROLL KNOLLS** invite children to create tiny worlds for imaginary creatures through independent and quiet play.

▲ Exploring the **CHILDREN'S GARDEN NATURE TRAIL** can offer opportunities to observe nature in many kinds of settings.

concepts, to create rivers, streams, lakes, and bridges, and to concoct elaborate "mud meals." Animal models indicate that interactions with certain bacteria present in clean soils may strengthen immune responses and support mental well-being.[12] Families can enjoy mud play simply by setting up a couple of pots or tubs, one with water, one with soil or sand, and a spoon and cup. Waterworks play can be added by offering hollow tubes, such as bamboo or plastic tubing, and a funnel.

The **Cutting Garden** invites children to observe plant-pollinator relationships, participate in social practices of creating bouquets, and to delight in the sheer beauty of angiosperms—flowering plants. At markets or in fields, children can help choose objects of seasonal beauty, arranging and rearranging them for aesthetic and celebratory displays. Families can take walks past neighborhood or public gardens to observe the insect and wildlife visitors foraging from the flowering displays. And, of course, families may wish to grow their own flowering plants in containers, backyards, or community plots. For children, seeing the enormous plant that grows quickly from a single sunflower is a delight and a wonder.

Nature observation play is a flexible type of play that may include quiet observation such as butterfly or bird watching, or lively, active play such as trying to catch insects, fish, frogs, and tadpoles. Across the spectrum, this type of play invites children to surreptitiously develop attention and classification skills. Walks in local parks, nature trails, or simply the walk to school or bus stops, can offer opportunities to observe nature in many kinds of settings. A look at the night sky—available to all of us no matter where we are—offers the opportunity to observe discreetly and over time.

TABLE 3
MORE RESOURCES FOR PARENTS

- **TinkerGarten** offers outdoor play-based classes and activities for children aged 6 months through 8 years. There is also an online database of nature play activities for families at home. https://tinkergarten.com/
- Children and Nature Network is an advocacy group dedicated to reconnecting children with nature. www.childrenandnature.org/
- North Carolina State University (Raleigh, North Carolina) Natural Learning Initiative publishes online 1-page tip sheets for parents with suggested activities to promote healthy child development involving the natural environment. https://naturalearning.org/ResourceType/infosheet/
- Kids Gardening provides grants, education, and advocacy work promoting opportunities for children to play and learn through gardening activities. https://kidsgardening.org/
- Nature Play QLD's mission is to increase the time children spend in unstructured play outdoors and in nature. Although based in Australia, the group offers downloadable content providing information for parents about creating family nature clubs that may be used anywhere. www.natureplayqld.org.au/

How to promote nature play

Given the demands of a busy pediatric practice and the growing list of anticipatory guidance items in routine pediatric visits, adding anoth-

CONTINUED ON *PAGE 22*

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BFR0000-507-2-01

Common virus wreaks havoc on VLBW infants

Cytomegalovirus is common throughout childhood, but the virus can cause a host of complications for very low-birth-weight (VLBW) infants.

RACHAEL ZIMLICH, RN, BSN

Many problems can arise in very low-birth-weight (VLBW) infants, but one common virus has been shown in a new study to increase hearing and respiratory problems, as well as extend hospital stays after birth.

"Preterm, VLBW infants who are infected with cytomegalovirus (CMV) after birth are at higher risk for significant morbidity at discharge from the neonatal intensive care unit (NICU)," says Rachel G. Greenberg, MD, MB, MHS, assistant professor of Neonatology at Duke University Medical Center, Durham, North Carolina, and co-author of the study.

The study, published in *JAMA Pediatrics*, reveals that CMV is associated with a number of lasting effects.[1]

"Historically, CMV acquired postnatally was thought to have no long-term sequelae for preterm infants," Greenberg says. "Our study resulted in new findings—that postnatal CMV in preterm, VLBW infants was associated with increased risk of failed hearing screen, longer length of stay in the NICU, and decreased weight-for-age at discharge. We also confirmed our previous study showing an association between postnatal CMV infection and bronchopulmonary dysplasia."

CMV packs a punch for preemies

Exposure to CMV is common enough, infecting as many as 60% to 80% of children by adulthood in developed nations such as the United States. Most children are infected by age 3 years by the virus—a member of the herpesvirus family. Although the virus does not typically cause many symptoms in healthy individuals, it can hit young infants and individuals with weakened immune systems the hardest. It is the leading infectious cause of developmental impairment and hearing loss in the developed world, according to the study.

"Our study resulted in new findings—that postnatal CMV in preterm, VLBW infants was associated with increased risk of failed hearing screen, longer length of stay in the NICU, and decreased weight-for-age at discharge."

—RACHEL G. GREENBERG, MD, MB, MHS

Historically, CMV was transmitted to hospitalized infants through blood transfusions, but modern health care practices have reduced this risk. Today, the most common exposure comes from the breast milk of CMV-infected mothers, as the virus remains in the body for life once an individual is infected. Whereas CMV is known to cause severe illness in VLBW infants, it was not previously believed to have any lasting effects. This study indicates otherwise.

Researchers investigated the effects of the virus in 273 VLBW infants with postnatal CMV compared with the same number of VLBW infants who were not infected with the virus across 302 NICUs between 2002 and 2016.

The research team found that 16.5% of VLBW infants with the virus failed their initial hearing screen compared with 9.2% of healthy

VLBW infants. The virus was also associated with VLBW infants having their postnatal age at discharge increased by nearly 12 days, and decreased weights at discharge. The research team also associated the presence of the virus with bronchopulmonary dysplasia, according to the report. Overall, the VLBW infants in the study that were infected with the virus had an 80% relative increase in failing a hearing screen over VLBW infants without the virus.

The study found no increased association, however, between CMV and necrotizing enterocolitis, which Greenberg says is surprising.

"We were somewhat surprised that we did not find an association between postnatal CMV infection and necrotizing enterocolitis in preterm infants. Postnatal CMV infection is known to cause enteritis, and small previous studies have linked postnatal CMV infection to the development of necrotizing enterocolitis," Greenberg says. "However, we think our finding can be explained by the fact that the incidence of necrotizing enterocolitis was very low in our study because we only considered postnatal infections occurring after the first 21 postnatal days."

The study is the first to show the association between many of these problems and postnatal CMV, the study notes, and indicates that CMV is an important consideration in neurodevelopmental outcomes for preterm infants.

The study group had a lower overall incidence rate for CMV of 0.4% compared with other estimates of 6.5% across other NICUs, with 1.4% experiencing sepsis-like illness as a result of the virus. Screening for CMV rarely occurs, but rather is done after symptoms develop, the study notes.

Screenings and treatments are needed

Greenberg says the study was not designed to investigate treatments but illustrates the need for more research.

"Our study was not designed to study treatment, but our findings underscore the need for prospective studies, ideally with long-term neurodevelopmental follow-up, to fully define the effects of postnatal CMV and evaluate whether antiviral treatment can improve outcomes," Greenberg says. "The findings highlight the importance of screening for this infection in at-risk preterm infants when there is clinical suspicion. Given that this population of infants is already at high risk for neurodevelopmental impairment, we hope that our study will increase clinicians' awareness of the long-term sequelae associated with postnatal CMV infection." ■

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

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

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https://www.contemporarypediatrics.com/pediatric-asthma/there-link-between-rsv-and-asthma-development

Influenza and RSV: How to suspect, diagnose, treat
https://www.contemporarypediatrics.com/infectious-disease/influenza-and-rsv-how-suspect-diagnose-treat

Are children with Down syndrome at increased risk of severe RSV infection?
https://www.contemporarypediatrics.com/infectious-disease/are-children-down-syndrome-increased-risk-severe-rsv-infection

WIC program cuts infants' risk for early death and preterm birth

Low-income pregnant women who receive Women, Infants, and Children (WIC) federal nutrition assistance reduce their offspring's risk for infant mortality and premature birth.

CATHERINE RADWAN, MANAGING EDITOR

With government focus on reducing federal safety net benefits for low-income populations comes news that the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) reduces infant mortality by one-third during the first year of life and lowers the risk of preterm birth for expectant mothers who participate.

The study, published online in the *JAMA Network Open*, analyzed the live birth certificates of babies born to more than 11 million women between January 1, 2011, and December 31, 2017, from the National Center for Health Statistics, which had recorded insurance coverage and receipt of WIC benefits on the birth certificates, for outcomes of gestational age at birth and death within the first year of life.[1] Of these mothers, about 8 million (73%) had received WIC benefits during pregnancy.

Infant mortality

The odds of infant mortality in the first year after birth were lower for babies of mothers who had received WIC benefits during pregnancy (adjusted odds ratio [OR], 0.84; 95% confidence interval [CI], 0.83-0.86). The infant mortality rate was 5.2 deaths per 1000 live births among those who had received WIC benefits during pregnancy and 8.2 deaths per 1000 live births among those who did not (a 36.6% relative risk reduction).

Currently, about 40% of expectant mothers in the United States participate in the WIC program.

Premature birth

The odds of preterm birth compared with normal term birth were lower among expectant mothers covered by Medicaid who had received WIC benefits than for mothers who did not receive WIC benefits (adjusted proportional odds ratio [OR], 0.87; 95% CI, 0.86-0.87). For extremely premature birth, the prevalence was 0.7% among women who received WIC benefits during pregnancy and 1.2% among those who did not receive WIC benefits ($P<.001$); for very premature birth, 1.3% among those who received WIC benefits during pregnancy versus 1.7% for those who did not receive WIC benefits ($P<.001$); for moderate-to-late premature birth, 10.5% among those who received WIC benefits during pregnancy and 11.2% among those who did not ($P<.001$).

The study also found that the odds of preterm birth compared with normal gestational age birth were lower for non-Hispanic white, non-Hispanic black, and Hispanic expectant mothers covered by Medicaid who had received WIC benefits during their pregnancies compared with expectant mothers in these groups who had not received WIC benefits. Likewise, the researchers found that odds of infant mortality were lower for these groups of expectant mothers when they had received WIC benefits during their pregnancies than for those mothers who had not participated in the WIC program.

Benefits of WIC nutrition

The researchers note that participation in WIC enables higher overall and protein-specific caloric intake in pregnant women that improve fetal growth and increase infant birth weight. In addition, WIC increases vitamin D intake that may lower the risk of pregnancy-induced hypertension and preeclampsia, major risk factors for fetal mortality, as well as greater maternal iron intake that may increase birth weight for gesta-

tional age. Finally, WIC encourages breastfeeding by providing new mothers with guidance and breast pumps. Breastfeeding can reduce the risk of postnatal death between 28 days and 1 year after birth.

The researchers note that one drawback of their study was that it focused on live births and not pregnancies resulting in miscarriage or stillbirth. They say that participation in the WIC program may reduce the incidence of these outcomes among high-risk pregnancies through better nutrition and prenatal visits.

Also, they call for public health campaigns and increased federal funding so that all expectant mothers who are low income or at risk for poor nutrition can receive WIC benefits during their pregnancies. Currently, about 40% of expectant mothers in the United States participate in the WIC program. ■

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

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Food additives can be endocrine disruptors

Pediatricians often focus on nutrition, but guidance for food additives should be included.

RACHAEL ZIMLICH, RN, BSN

We are what we eat, but unfortunately, we don't always know everything about *what* we eat.

Pediatricians are often asked by parents about foods to avoid, or food safety concerns, but they might not understand all the nuances about food safety issues.

"Most pediatricians probably think in the framework of is it healthy or not healthy, and they may not be thinking about the chemical exposures that could be occurring," says Sheela Sathyanarayana, MD, MPH, FAAP, associate professor of Pediatrics and adjunct professor of Environmental and Occupational Health Sciences at the University of Washington, medical director of the newborn nursery, and director of the pediatric Continuity Clinic program at the University of Washington Medical Center in Seattle.

Sathyanarayana led a session titled "Food additive safety: How to advise families about flavors, colors, chemicals" at the 2019 American Academy of Pediatrics (AAP) National Conference and Exhibition in New Orleans, Louisiana.

The session covered food additive categories, data on the health effects of food additives, concern about exposure in children, and regulation of food additives. Sathyanarayana offered advice for pediatricians on guiding parents on ways to limit exposure to food additive and endocrine-disrupting chemicals.

Oftentimes, pediatricians are focused on nutrition and feeding practices because obesity has become such an epidemic problem, she says.

"I think that a lot of pediatricians understand that processed foods likely contain components that are not good for our health," Sathyanarayana points out. "Processed foods are based on convenience, and it's hard when marketing is focused on this. It's important to reinforce healthy, fresh foods."

> **"Processed foods are based on convenience, and it's hard when marketing is focused on this."**
>
> —SHEELA SATHYANARAYANA, MD, MPH, FAAP

Although pediatricians aren't expected to move regulatory mountains, Sathyanarayana says they should be aware of our government's policies on food safety, particularly the risks posed by some foods in the "generally recognized as safe" category—a loophole that allows for shortcuts and that has been recommended to be changed. There is a push at the regulatory level to take a deeper look at the health impact of chemicals that have been allowed into our food supply and to be more transparent, she adds.

Sathyanarayana co-authored

guidance for AAP on food additives in 2018 and says the goal is to promote regulation revisions that create a safer food supply. As for the role of pediatricians, she says her goal is simply to raise awareness and provide education similar to what she gives her patients.

"People tend to think, 'It might be bad for me, but I don't know why,'" Sathyanarayana says. "It's about filling that gap."

The main takeaway, she says, is that there are a number of direct and indirect food additives that are not well regulated and could have harmful health effects in children. Some ways to minimize these effects include reinforcing key messages, such as promoting the consumption of fresh fruits and vegetables, avoiding microwaving food in plastics, avoiding heating and eating food in packaging, and avoiding processed meats. As for more proactive efforts, Sathyanarayana says some pediatricians have found a lot of success in organizing clinics for families on preparing healthy meals. For more suggestions, see the 2018 policy statement "Food additives and child health" from the AAP.[1] ■

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

Ms Zimlich is a freelance writer in Cleveland, Ohio, who writes regularly for *Contemporary Pediatrics*. She has nothing to disclose.

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Nature Play

CONTINUED FROM PAGE 16

er task to the checklist may seem daunting. However, questions about nature play can be easily integrated with the questions that we all ask regarding safety, play, and physical activity. For infants, guidance about safe clothing and sun protection can be provided along with messages about the importance of being outside. Developmental screening questions about types of play in toddlers and preschoolers can be asked along with the location of such play—time indoors versus outdoors, and free versus directed play. School-aged children and adolescents should be encouraged to get 60 minutes of physical activity daily,[13] and pediatricians should emphasize the added benefits that being outdoors may confer. Specific examples of anticipatory guidance from Bright Futures[14] are listed in Table 2.

In addition to discussing nature play with parents and patients, pediatricians should consider promoting nature within their offices. One simple practice to promote nature is to decorate offices with photos and other artwork depicting the natural environment. Providing such natural scenes also may have some direct benefit for patients. One study in adults found that participants who viewed photographs of nature scenes had quicker autonomic function recovery following an acute psychologic stressor when compared with those who viewed scenes of the man-made built environment.[15] Thus, decorating with such scenes may help children manage the stress of a doctor's appointment as well as demonstrating that the pediatrician's office values the natural environment.

Finally, pediatricians should be advocates for local nature areas and parks. In addition to the developmental and other health information handouts that usually are available for parents to browse in the examination and waiting rooms, offices should include lists of local parks and other opportunities for families to get outside. Such information could include maps of local hiking areas; information about local outdoor play groups; local, state, and national park educational activities; and summer camps for children.

Examples of national and international advocacy groups are listed in Table 3. Many of these organizations offer free downloadable handouts for parents promoting nature play. The possibilities are numerous, and having such information readily available in the office may also spark conversations about the importance of families and children being outdoors together. ■

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

For references, go to **ContemporaryPediatrics.com/nature-play-RX**

FLARES

AREN'T GOING TO

PREVENT THEMSELVES

DAILY USE OF **ECZEMA RELIEF BODY CREAM** REDUCES THE INCIDENCE OF FLARE AND INCREASES THE TIME-TO-FLARE RECURRENCE[1]

44% reduction in risk of flare in pediatric subjects

4 out of 5 children remained **flare-free for six months**[1]

Steroid-free | **Fragrance-free**

Eucerin®

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1. J Drugs Dermatol (2015) 14:478-479.

What to consider before running a diagnostic test

Is ordering a diagnostic test for a suspected infection always the best decision? Maybe not.

MIRANDA HESTER, EDITOR

After assessing a child who is presenting with some type of infectious disease, the next step is to run a diagnostic test, such as a rapid strep test or measles. Perhaps you should wait.

Gary S. Marshall, MD, FAAP, professor of Pediatrics and division chief of Pediatric Infectious Diseases at the University of Louisville School of Medicine in Kentucky, presented "To order or not? Appropriate use of infectious disease labs" at the 2019 American Academy of Pediatrics National Conference and Exhibition in New Orleans.

Marshall discussed the way that common diagnostic tests can provide false positives, false negatives, and true positives that are not relevant to the child's current clinical presentation. For example, cultures can give false positives because of lab contamination, false negatives because of recent antibiotics use, and true positives resulting from bacteria introduced during the culture process such as clean capture.

His main message to the clinician was to utilize Bayesian thinking when determining whether to order a test. He illustrated this process by looking at a patient who presents with a sore throat and fever and who may have strep throat. The question becomes, "If my rapid strep test is positive, do I have strep throat and if my rapid strep test is negative, do I not have strep throat?" The clinician should use the likelihood ratio of a positive (probability of a positive result in disease over a positive result in no disease) and the likelihood of a negative (probability of a negative result in disease over a negative result in no disease) to determine how necessary running a test really is.

Cultures can give false positives because of lab contamination, false negatives because of recent antibiotics use, and true positives resulting from bacteria introduced during the culture process.

—GARY S. MARSHALL, MD, FAAP

During the winter months when strep throat is rife and the probability of strep throat is approximately 50%, running a test and getting a positive result means that the child is 95.6% likely to have strep throat, and getting a negative result means that the child is 11.9% likely to have strep throat. However, during the summer when strep is unlikely, a positive test means that the child is only 53.4% likely to have strep throat. With this test result, Marshall said that a coin toss could be just as effective as running a test. He also stressed paying attention to the current environment. If a child is presenting with rash and fever, it's not necessary to run a measles test. However, if that child has rash, fever, coryza, Koplik spots, conjunctivitis, travel to an area where measles has become common, and no vaccine against the disease, the child should be tested for measles.

He also covered panel tests and the potential pitfalls because of pretest probabilities, focusing on the gastrointestinal (GI) panel test. A child with a pet turtle who has GI symptoms is more likely to have salmonella than a teenager who is on the swim team. Marshall highlighted his frustration with the tick-borne disease panel at his hospital that includes Lyme disease, despite the fact that the species of tick responsible for the disease is not endemic to his geographic area.

Concluding his presentation, Marshall implored clinicians to remember the negative consequences of inappropriate infectious disease testing, including delays in diagnosis, inappropriate use of antimicrobial therapy, and higher costs that have no association with outcomes. ■

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

What to tell parents about coronavirus and influenza

Parents might be worried about coronavirus, but flu is a much greater threat for their children.

MIRANDA HESTER, EDITOR

Coronavirus is dominating the health news in mainstream media, but parents should be more concerned about the current influenza epidemic here at home and the vulnerability of children to influenza and pneumonia.

Coronavirus

Coronavirus is giving the manufacturers of face masks a boost. It may even bring parents to your office convinced that their child's fever and cough are the sure signs of infection. It's been named COVID-19, and it's responsible for 28,276 infections and more than 564 deaths, according to the World Health Organization on February 6, 2020.

Fortunately, a recent study in the *New England Journal of Medicine* has some comforting information for pediatricians: No case has been found in children aged younger than 15 years.[1] The researchers also found that earlier onset of symptoms was linked with being younger. They did say that children could be underrepresented in the case count because they could have milder symptoms, and that further research should look specifically for cases in children as well as health care workers.

Influenza

"In my pediatric practice, this is the worst influenza season in recent memory. While coronavirus may or may not be a concern in the United States, parents should be much more concerned about influenza," says Andrew J. Schuman, MD, whose pediatric practice is in New Hampshire. "We are seeing lots of children with influenza B and influenza A, with an inordinate number of children requiring hospitalization."

As of this writing, influenza has claimed the lives of 125 US children aged younger than 18 years in the 2019-2020 flu season so far—87 deaths from influenza B viruses and 38 from influenza A—according to Centers for Disease Control and Prevention (CDC) surveillance for the week ending February 22, 2020.[2]

Schuman stresses that immunization is the parent's best tool for protecting their children from the flu, and it's still not too late to get the flu shot. "We are telling parents to be sure to get the flu vaccine," he says, "and if they suspect their child may have symptoms of influenza (fever, sore throat, chills, myalgias, or severe/worsening cough) to be evaluated by their pediatrician within 2 days of illness onset."

CDC recommendations

For parents wondering what they should be doing to prevent coronavirus infection, the CDC has advice.[3]

Parent and children *should not*:

- Travel to China.
- Use face masks.
- Assume that someone who is either Asian or of Asian descent is more likely to get COVID-19.

Parent and children *should*:

- Stay informed by visiting www.cdc.gov/coronavirus/2019-ncov
- Seek medical care if they have fever, coughing, and shortness of breath, or exposure to someone with a diagnosis of COVID-19 or who has traveled to China in the past 14 days.

Parents and children should also avoid contact with sick people; stay home when sick; cover the nose and mouth when coughing or sneezing; disinfect surfaces and objects; and wash hands often with soap and water or use an alcohol-based hand sanitizer with at least 60% alcohol.

The CDC has interim guidance and provides a flowchart for assessing potential COVID-19 infections.[4] ■

For references, go to ContemporaryPediatrics.com/coronavirus-and-influenza

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PHARMACOLOGIST'S NOTEBOOK

Gene therapies show promise for pediatric treatment

Gene therapies have ushered in an exciting new era of treatment for some of the most challenging pediatric conditions, and the results are most encouraging.

JESSICA OGAWA, MD, MS
JOANN BODURTHA, MD, MPH, FAAP, FACMG

Approximately 20 years ago, the tragic death of a young man with ornithine transcarbamylase deficiency marked the first death related to gene therapy and sent shock waves throughout the medical community. Since then, the National Institutes of Health (NIH) and the US Food and Drug Administration (FDA) have taken steps to ensure patient safety by modifying their guidelines and oversight with organizations such as the Recombinant DNA Advisory Committee and the Genetic Modification Clinical Research Information System (GeMCRIS).[1]

The vehicles used to carry genetic material also have changed, resulting in a reduction in adverse effects. For example, adeno-associated virus vectors have replaced the previously used adenovirus vectors and invoke a weaker immune response. Additionally, the development of self-inactivating (SIN) viral vectors has decreased the risk of unintentional insertions of the vector-activating proto-oncogenes. This was linked to the development of leukemia in some patients with X-linked severe combined immunodeficiency (SCID) who received earlier forms of gene therapy.[2] A handful of relatively newly approved gene therapies are currently available with encouraging results. Long-term outcomes of these treatments are still unknown.

FDA-approved pediatric gene therapies

Currently, there are 3 FDA-approved gene therapies for pediatric patients (Table 1 and below), but more are in various stages of research and development (Table 2).

TISAGENLECLEUCEL (KYMRIAH)

Acute lymphocytic leukemia (ALL) is the most common pediatric malignancy. Fifteen percent to 20% of those with B-cell ALL are not responsive to initial treatment or will have a relapse. Kymriah was the first FDA-approved gene therapy to treat patients aged to 25 years who have refractory B-cell precursor ALL or at least 2 relapses. Kymriah is a chimeric antigen receptor (CAR) T-cell therapy wherein a patient's own

NOTE FROM DR. LEE Refinements to gene therapy technology have produced viable life-saving therapies for devastating genetic diseases such as SMA. The price of these agents may seem overwhelming at first, but their single dose regimen may actually be more cost effective than the traditional life-long chronic therapies with potentially better efficacy. We look forward to the long-term effect of these therapies with the development of additional therapies in the future.
—CARLTON LEE, PHARMD, MPH, FASHP, FPPAG

TABLE 1

CURRENTLY APPROVED FDA GENE THERAPIES FOR PEDIATRIC PATIENTS

INDICATION	CURRENT RECOMMENDED DOSAGE	COMMON OR SERIOUS ADVERSE EFFECTS	ADMINISTERED WITH	COST
Tisagenlecleucel (Kymriah) [4,6] NOTES: Can have false-positive HIV test. Administration is delayed if the patient has active uncontrolled infection, active graft vs host disease, worsening of leukemia burden after lymphodepleting chemotherapy, or unresolved adverse reaction to prior chemotherapies such as hypotension.				
Refractory or in second or more relapsed B-cell ALL in patients aged ≤25 y.	In patients ≤50 kg, a single dose of 0.2-5.0 x 10^6 CAR-positive viable T cells per kg are administered by IV. In patients >50 kg, a single dose of 0.1-2.5 x 10^8 CAR-positive viable T cells are administered by IV.	Cytokine release syndrome, neurotoxicity.	Fludarabine IV daily and cyclophosphamide IV daily x 2; acetaminophen and antihistamine prior to infusion.	$475,000
Voretigene neparvovec-rzyl (Luxturna) [7-9] NOTES: Must wait at least 6 d between subretinal administrations of each eye. Although *RPE65* pathogenic variants are associated with Leber congenital amaurosis, not all cases of Leber congenital amaurosis are due to *RPE65* pathogenic variants.				
Biallelic *RPE65* pathogenic variant-associated retinal dystrophy with viable retinal cells in patients aged 1-64 y.	Single dose of 1.5 x 10^{11} vector genomes (total volume 0.3 mL) per eye administered by subretinal injection on separate days.	Endophthalmitis, permanent decline in visual acuity, cataract development/ progression, increased intraocular pressure, conjunctival hyperemia.	Systemic corticosteroids x 7 d followed by 10 d taper for each eye.	$425,000 per eye
Onasemnogene abeparvovec-xioi (Zolgensma) [10] NOTES: Not recommended for premature neonates before reaching full-term gestational age.				
SMA due to biallelic *SMN1* pathogenic variants and aged ≤2 y.	A single dose of 1.1 x 10^{14} vector genomes per kg are administered by IV.	Emesis, aminotransferase elevations, thrombocytopenia, acute liver injury, increased levels of troponin I.	Systemic corticosteroids x 30 d.	$2,125,000

Note: Therapies shown are current as of 12/10/19. Abbreviations: ALL, acute lymphocytic leukemia; CAR, chimeric antigen receptor; FDA, US Food and Drug Administration; HIV, human immunodeficiency virus; IV, intravenous; SMA, spinal muscular atrophy. Author created.

cells are genetically modified ex-vivo to contain genes that code for CARs. These modified T cells are then infused back into the patient. These receptors direct the T cells to target CD19 on the B-precursor lymphoblasts.

A common and serious adverse effect is cytokine release syndrome (CRS), which can lead to hypotension, pulmonary edema, and coagulopathy.[3,4] In a recent pediatric and young adult clinical study, Kymriah was shown to have an 81% remission rate at 3 months with a 90% survival rate at 6 months and 76% survival rate at 12 months. Seventy-seven percent of patients had CRS and 40% had neurologic events.[5] In order to minimize reactions, administration of Kymriah is held if the patient has an active infection or inflammatory disorder. Additionally, because of these risks, only certified places are allowed to administer Kymriah. Currently there are 54 centers in the United States.[6]

VORETIGENE NEPARVOVEC-RZYL (LUXTURNA)

Biallelic *RPE65* pathogenic variant-associated retinal dystrophy is thought to affect between 1000 to 2000 persons in the United States. This is associated with 2 conditions that cause alterations in vision, with a large portion of these patients having Leber congenital amaurosis and a smaller portion having retinitis pigmentosa. With Luxturna, a viral vector administered via subretinal injection delivers a normal copy of the *RPE65* gene.[7,8] Long-term follow-up of participants who received Luxturna varies with some studies showing initial improvement in visual sensitivities with a peak between 6 months and 3 years, but this effect declined or disappeared between 3 to 6 years after treatment. Ongoing efforts aim to

determine the optimal dosing schedule and timing to improve outcomes.[9]

ONASEMNOGENE ABEPARVOVEC-XIOI (ZOLGENSMA)

Occurring in 1 in 10,000 live births, spinal muscular atrophy (SMA) is an autosomal recessive condition attributed to pathogenic mutations or deletions of the *SMN1* gene. Patients with SMA have degeneration of the motor neurons and subsequent muscle weakness. Some die in early childhood secondary to respiratory failure. Zolgensma is indicated for patients with SMA aged younger than 2 years who have biallelic pathogenic mutations in *SMN1*. Zolgensma is a viral vector that delivers a copy of *SMN1*.

Clinical studies have shown that patients who received Zolgensma have prolonged survival, improved motor skills, and less dependency on permanent ventilation compared with the natural history cohort. One ongoing trial that enrolled 21 patients with the average age of 3.9 months showed survival without permanent assisted ventilation in 19 of them at 7.9 to 15.4 months after treatment. Based on natural history reports, approximately 5 patients would have survived past 14 months without permanent assisted ventilation.[10] Of note, nusinersen (Spinraza) is another therapeutic option for children with SMA. It increases the production of protein required to maintain the motor neurons, but it is not a gene therapy. No clinical trials comparing Spinraza to Zolgensma have been completed.[11] ■

The authors and section editor have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

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For references, go to **ContemporaryPediatrics.com/gene-therapies-2020**

HELPFUL RESOURCES

Newborn screening (NBS) can help with early identification of certain genetic conditions. It is important to remember that not every disease is covered by NBS, and the conditions that NBS examines vary from state to state. Spinal muscular atrophy (SMA) was added to the Recommended Uniform Screening Panel in 2018. At this time, only 12 states are screening for SMA as part of their NBS protocol.[12]

With the gene therapy field rapidly progressing, there is an ever-growing number of trials for gene therapy. **ClinicalTrials.gov** is an excellent resource for both providers and patients. More than 200 studies are actively recruiting for various gene therapy clinical trials as of January 2020.[13]

Specialists in areas of known Mendelian conditions are another resource and can help assist families and patients in determining if gene therapy is right for them.

TABLE 2 PEDIATRIC GENE THERAPIES IN DEVELOPMENT

INDICATION	IMPORTANT PATIENT CRITERIA	STATUS	CURRENT RECOMMENDATION OF ADMINISTRATION	PRODUCT	COST
Zynteglo[14] NOTES: Cells are transduced ex vivo. Requires myeloablative preconditioning.					
Beta thalassemia	■ Aged at least 12 y. ■ Require regular blood transfusions. ■ Do not have the β^0/β^0 genotype. ■ Are eligible for stem cell transplant but without an HLA match.	EMA approved.	Single dose of 5-20 x 10^6 cells/kg administered by IV.	Autologous β-A(T87Q)-globin gene-transduced CD34+ cells.	$1,800,000
LentiGlobin[15] NOTES: Cells are transduced ex vivo. Requires myeloablative preconditioning.					
Sickle cell	■ Aged 12-50 y. ■ βS/βS or βS/β0 or βS/β+ genotype. ■ Had 4 vaso-oclusive events in past 2 y.	Clinical trials ongoing.	IV	Autologous β-A(T87Q)-globin gene-transduced CD34+ cells.	—

Abbreviations: EMA, European Medicines Agency; HLA, human leukocyte antigen; IV, intravenous. Author created.

Banish burnout with *passion!*

Pediatricians can turn away from the path to physician burnout by finding their inner fire. Here are suggestions for finding that passion—and to keep smiling.

CHARLES T CAPPETTA, MD
ANDREW J SCHUMAN, MD

The Physicians Foundation 2018 Survey of America's Physicians is the organization's most recent survey of physician's opinions regarding medical practice. This survey of 8774 physicians indicates that US physicians handle over 1 *billion* patient encounters each year. Eighty percent of physicians surveyed describe themselves at full capacity or overextended, and report that 23% of their time is spent on nonclinical paperwork.[1]

Perhaps most revealing is that 78% of surveyed physicians report they *sometimes*, *often*, or *always* experience feelings of burnout, and over the past few years many physicians feel their morale is worsening (Table 1 and Table 2).

It is no wonder that we pediatricians are at times overwhelmed by the reality of generating relative value units (RVUs) and aggravated by our schedules and regulations that are often frustrating and exhausting. Previous articles in *Contemporary Pediatrics* have discussed physician burnout and have detailed ways to prevent burnout from occurring, and also described methods that can be used to treat burnout once the symptoms have appeared. (See "Watercooler wisdom 2: Preventing [and treating] physician burnout," November 2016; "Burnout: Pediatrician, heal thyself," June 2018; and "How coaching could reduce burnout," August 2019).

The authors of this article believe that finding a "passion" within the context of one's pediatric practice or in the community is one of the best methods of preventing or treating burnout and straightening one's moral compass.

This can take a variety of forms, and there are several ways to become a compassionate pediatrician with a "passion."

Acquire more skills!

Even though general pediatricians are nonspecialists, one can consider acquiring additional training or certifications to expand one's scope of practice, or just seek supervised learning from consultants to improve diagnostic or therapeutic capabilities. For example, Dr. Cappetta has received additional training in the care of patients with concussions through his active involvement as a member of the American Academy of Pediatrics (AAP) Executive Committee of the Council on Sports Medicine and Fitness (COSMF) and has shared his knowledge with colleagues. Dr. Schuman is interested in patients with attention-deficit/hyperactivity disorder (ADHD) as well as patients with depression and anxiety disorders, and he has developed a telehealth practice to facilitate care for these patients.

TABLE 1
To what extent do you have feelings of professional burnout in your medical career?

	AGE ≤45 Y	AGE ≥45 Y	ALL RESPONDENTS
No such feelings	5.0%	6.0%	5.7%
Rarely have these feelings	16.2%	16.8%	16.6%
Sometimes have these feelings	37.7%	37.7%	37.7%
Often have these feelings	31.5%	30.7%	31.0%
Always have these feelings (significant burnout)	9.6%	8.8%	9.1%

Adapted from Physicians Foundation.[1]

GRANITE STATE FITKIDS

Granite State FitKids (GSFK) is a nonprofit New Hampshire Charitable Trust educating 4th-graders about their bodies and how to take care of them. Through a series of 7, 1-hour weekly "Body Shop" lessons, we talk about the various systems of the body including the heart, lungs, guts, brains, bones, and muscles along with 3 sessions on the importance of exercise and physical activity, the ill effects of smoking/vaping/chewing tobacco, and the long-term benefits of a healthy diet and good nutrition.

Named one of the top 150 programs in the country in the battle against childhood obesity in 2005 by the Cooper Institute, Dallas, Texas, GSFK has taught more than 44,300 children all around New Hampshire and northern Massachusetts, and can be found in more than 25 elementary schools every year.

For me, my passion for kids comes alive in the local schools.

Being in the school environment is where every child needs to be "treated" as different, unique, and special, and must be afforded the best opportunity to maximize his/her individual learning potential.

The sounds of laughter in the hallway, the thrill of being in the classroom, teaching future leaders on how to become healthy adults are all paramount and essential to being in their world.

I need to walk in their shoes. I need to understand their past and sit in their chairs, and see their "job as a student" through their eyes—as I need to be a small part of their "today" to better understand the unlimited capacity and potential for their "tomorrow."

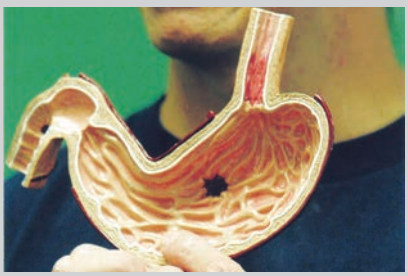
Granite State FitKids was created in 1997 to achieve just this goal. Its mission is to capture the energy of youth with all its splendor and vitality and channel such energy into a lifelong understanding and appreciation of one's own body systems.

The GSFK vision is to promote the 5 E's—Excitement, Enthusiasm, Energy, Exercise, and Education—at home, at school, and in the community while engaging children and their families in regular physical activity and encouraging them to embrace a lifelong healthy respect for mind, body, and spirit with the long-term goal of prevention of older life risks such as heart disease, lung disease, cancer, and excessive use of alcohol and illicit drugs.

The GSFK program remains free to the school and is financially supported by local hospitals, clinics, and grants to meet the growing request for the curriculum.

We work with the physical education, art, and music teachers in a combined collaboration of lesson plans that bring home the message of "this is your body, which is like a car and the only one you are getting." By providing small "tools" of knowledge on how to better care for their bodies, their "car" will hopefully run better for a long time to come. *—Charles T. Cappetta, MD*

For more information on the GSFK program, check out the website at granitestatefitkids.org.



▲ FIGURE 1 **The stomach model in week 5 shows ulcer formation in the stomach wall from unhealthy diet, the ill effects of nicotine, and lack of exercise.**

▲ FIGURE 2 **In the "Guts Game," participants learn about the different actions of the gastrointestinal (GI) tract turning food into energy.**

▲ FIGURE 3 **On Parents' Night, Dr. Cappetta and FitKids present a night of fun celebrating the culmination of the 7-week program.**

IMAGE CREDIT/PHOTOS COURTESY OF GRANITE STATE FITKIDS.

Teach!

Pediatricians have acquired lots of knowledge over the years and it is very rewarding to teach—be it cardiopulmonary resuscitation classes, Pediatric Advanced Life Support (PALS), or neonatal resuscitation—wherever your skill set leads you. It is also fun to teach medical students, physician assistants, or nurse practitioner students should the opportunities be available. One also can teach parenting skills to young parents or hold classes for daycare providers. Not only is this rewarding, but it helps build your practice.

Dr. Cappetta ran a Newborn Father's Group every 2 weeks for 10 years (1994-2004) for new dads and their infants as a way to help fathers appreciate the important role

TABLE 2
Which best describes your professional morale and your feelings about the current state of the medical professional?

	SOMEWHAT OR VERY POSITIVE	SOMEWHAT OR VERY NEGATIVE
2018	44.7%	55.3%
2016	46.1%	53.9%
2014	44.4%	55.6%
2012	31.8%	68.2%

Adapted from Physicians Foundation.[1]

they play in raising their children. He also has developed a unique education program for children in the Nashua, New Hampshire, school system to stay fit and healthy and has been doing so for more than 23 years (see "Granite State FitKids," page 30). Dr. Schuman recently started a program in his clinic where motivated premedical students can "shadow" him during clinic hours while the student is on summer break.

Rage against the status quo!

We all know that our healthcare system is breaking, so why not stop complaining and take measures to fix problems? In the wise words of the late Jerry Garcia of the Grateful Dead, "Somebody needs to do something. It's just incredibly pathetic that it has to be us."

Become a member of your state's AAP chapter and work toward accomplishing achievable goals. One can work with the state AAP chapter and, if necessary, your state legislature to right wrongs and facilitate better care for children. Several years ago, the authors of this article worked with the New Hampshire state legislature to "motivate" insurance companies to reimburse pediatricians for performing instrument-based vision screening. More recently, Dr. Schuman provided testimony to the New Hampshire state legislature supporting passage of SB258, a bill mandating that clinic-based providers can provide telehealth services to patients in their residences who have either commercial or Medicaid-funded insurance. The bill was signed into law in August 2019.

Volunteer!

There are many opportunities for pediatricians to help others in the community. One can become a camp doctor or a sports team physician. One can offer to be a resource for school nurses when questions arise (Dr. Cappetta has been the official physician for multiple schools in the Greater Nashua, New Hampshire, area for the past 26 years) or serve as an adviser for daycares in a similar capacity. At your local hospital there are plenty of opportunities to serve on various committees that work toward improving patient care.

Think inside the box!

If you'd prefer to direct your passion into your practice, there are plenty of ways to reshape your practice to make it more patient- and parent-friendly, or to improve office capabilities. You can build a lending library to encourage your patients to read, or even consider having a regular story hour to entertain nervous patients. A pediatrician in your practice can volunteer to obtain the training necessary to become an ultrasound technician so that you can purchase a handheld scanner to facilitate diagnosis of bone fractures, pneumonias, or joint injuries. You can integrate telehealth into your practice if you have not already done so, or improve the practice's mental health services by hiring a psychologist.

Cheers!

The above are just a few of the many ways pediatricians can rise above the distracting noise and confusion that leads us down the path of burnout and keep us cheerful and smiling while others frown. ■

COMMENTS? Please contact the authors if you have other thoughts and ideas regarding burnout prevention or easy-to-acquire passions that pediatricians should consider. Dr. Cappetta can be reached at Charles.T.Cappetta@hitchcock.org. E-mail Dr. Schuman at andrew.schuman@ymail.com

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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 reference, go to **ContemporaryPediatrics.com/banish-burnout**

Diaper banks underutilized for families in need

For families living in poverty, diaper banks can help keep their children clean and dry. Pediatricians can step up referrals to these resources.

RACHAEL ZIMLICH, RN, BSN

A ready supply of clean diapers for an infant may seem like a basic need, but for some families, it's an undreamed of luxury.

According to a new report, nearly half of families with infants and toddlers in the United States live within 200% of the federal poverty level and struggle to afford basic necessities such as diapers. The study,[1] published in the *American Journal of Public Health*, investigates this unmet need and reveals that just 4% of children in these low-income households find relief through community diaper banks.

Diaper banks are available across the country to help families in need keep their infants clean and dry—in turn preventing problems including diaper rash and urinary tract infections. Although there are a host of diaper banks opened by clinicians, health systems, and community organizations, the new study reveals that there are many areas where families in need don't have access to these resources. Kelley Massengale, PHD, MPH, of the National Diaper Bank Network in New Haven, Connecticut, led the study, and says the problem isn't how much existing diaper banks are utilized but rather the amount of resources available.

NEARLY HALF of families with infants and toddlers in the US live within 200% of the federal poverty level and struggle to afford basic necessities such as diapers.

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Too much need, not enough support

"Existing diaper banks are not necessarily underutilized. Rather, the challenge is that not all communities have diaper banks," Massengale says."Within communities served by diaper banks, the percentage of met diaper need is much higher than when looking at a larger geographic area such as a state or the entire country. The diaper bank community has built an effective infrastructure across the country but at this time does not serve every community."

Not only do diaper banks meet a basic need, Massengale says, but they also help engage families in other needed social support services. The problem with trying to do more comes down to funding, she says.

"Diaper banks are nonprofit organizations that rely on philanthropy and public charity. When we consider other unmet basic needs that low-income

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families may have—housing, food insecurity, trouble paying for utilities, transportation needs, health care, and other challenges—our country has federal policy programs that can address at least a portion of these needs," she says. "There are no federal policy programs that address diaper need for all low-income families. Our society relies on a network of nonprofit organizations to address the public health concern of diaper need."

For the study, Massengale and her research team polled 262 diaper banks supported by 3500 community organizations across the country. More than 52 million disposable diapers were distributed in 2016 and 74% of those diapers were donated. The remainder, she says, had to be purchased by community organizations. In addition to disposable diapers, diaper banks also distributed 4395 reusable diaper kits. It's still not enough, however, according to the study, which revealed that just 300,000 of the 7 million children in need received diapers from these resources.

The study investigated only diaper banks and did not include other ways families might get the roughly 6 diapers their children need each day, but the fact remains that less than 16% of the families that need diapers can be served through existing diaper banks.

A call to action

Pediatricians can help, Massengale adds, by assessing for diaper needs and referring families in need to community resources where available. Each visit offers a pediatrician the opportunity to assess for unmet diaper needs and make referrals, she says.

"Research I have previously published documents that families receiving free products from a diaper bank report that their children are healthier and happier, and parents are less stressed," Massengale says, adding that clinician awareness of local resources is key. "Before implementing diaper need screening in clinical practice, it is important to first know what resources exist in the community to address diaper need and what local procedures are for accessing them. Practitioners, especially those in communities without a diaper bank, are encouraged to increase awareness that diapers are a basic need for young children and that families' needs for diapers are unmet."

Lastly, pediatricians can help advocate for increased public health and philanthropic support for these programs.

"Diaper need is a public health concern that impacts infant health, parental stress, and families' abilities to fully participate in society," Massengale says. "We need federal, state, and local policies that address diaper need. It can take time to implement such policies. In the meantime, diaper banks need increased support so that they can continue serving their communities and grow to serve others." ■

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

Ms Zimlich is a freelance writer in Cleveland, Ohio, who writes regularly for *Contemporary Pediatrics*. She has nothing to disclose.

For reference, go to **ContemporaryPediatrics.com/diaper-banks**

DERMCASE

Kiss of the spider or something more?

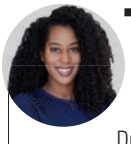
CONTINUED FROM PAGE 37

Patient outcome

The spider angioma was not symptomatic, so the family opted to monitor their daughter's benign lesion clinically. ■

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

For references, go to **ContemporaryPediatrics.com/dermcase-0320**



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SECTION EDITOR

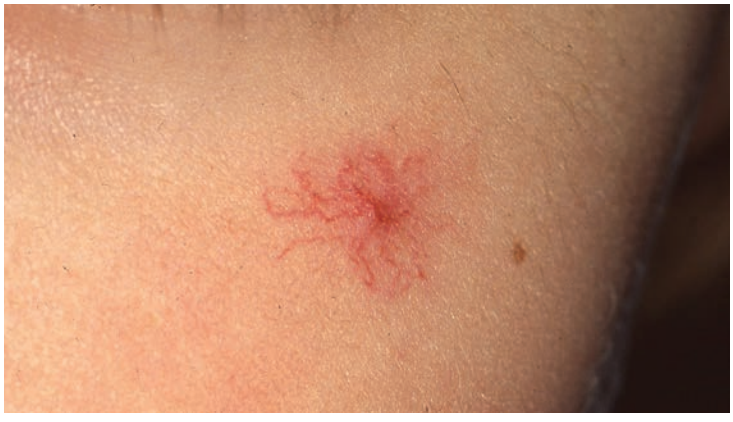
DERMCASE

Kiss of the spider or something more?

CHELSEA HANDFIELD, BA, MS4

THE CASE

The parents of a healthy 8-year-old girl are worried about an asymptomatic red spot on their daughter's left cheek that has been enlarging for more than a year.



▲ **Spider angioma is a benign vascular malformation often found on the face, forearms, or hands.**

IMAGE CREDIT/AUTHOR SUPPLIED

SPIDER ANGIOMA

Spider angiomas are a benign vascular malformation commonly found in infants and children.

Also known as spider nevus, spider telangiectasia, vascular spiders, and nevus aranei, a spider angioma is an arterial vascular malformation attributed to idiopathic dilation of central arterioles just beneath the skin surface.[1] These lesions occur in children often on the face, forearms, and hands. On exam, a spider angioma appears as a central pink to red macule with symmetrically radiating branches that blanche with pressure.[2] These lesions are underreported and likely represent an exceedingly common benign finding.

An observational study in Dublin, Ireland, found that 38% of children aged 1 to 15 years without any signs of liver disease had at least 1 spider angioma, and often 1 to 4 spider angiomas were found.[3] Another study in Bristol, England, found that 47.5% of healthy children aged 3 to 17 years had at least 1 spider angioma.[4] In contrast, the sudden appearance of multiple spider angiomas in adults may be associated with underlying liver disease, pregnancy, or estrogen therapy. The lesions may regress on their own or remain throughout life.[2] Bleeding from the lesions is uncommon unless the spots are picked or traumatized.

Management

No intervention is necessary. However, electrocoagulation, pulsed dye laser, and neodymium-doped yttrium aluminum garnet (Nd:YAG) are possible treatments.[5] When lesions have been traumatized or become elevated and pose a risk of bleeding, laser treatment is effective and associated with a very low risk of scarring.

FOR MORE ON THIS CASE, TURN TO PAGE 34. ▶

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