MISSION UNACCOMPONISHED

2-Decade Measles Setback

2000
US declares measles eliminated
CDC, 2018

2019
1095 cases of measles confirmed in 28 states*
CDC, 2019

*Jan. 1- June 27

PUZZLER Massive splenomegaly in a 6-year-old girl

Medical marijuana for children

Pharmacologist’s Notebook
Rifampin for biofilm infections
Quiz: Biofilms

Recognize & Refer
New guidelines for a high-risk dermatologic condition

Practice Improvement
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Office- and hospital-based pediatricians and nurse practitioners use Contemporary Pediatrics’ timely, trusted, and practical information to enhance their day-to-day care of children. We advance pediatric providers’ professional development through in-depth, peer-reviewed clinical and practice management articles, case studies, and news and trends coverage.

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Rifampin for biofilm-related infections

Specific therapies for biofilm-related infections are rare. However, studies have shown rifampin to be an effective treatment for these staphylococcal infections in children.

*S. aureus* is a major human pathogen causing various infections ranging from mild to life-threatening in both adults and children, and is a significant cause of morbidity in children requiring hospitalization. The bacterium colonizes both tissue and artificial surfaces in humans causing chronic persistent infections that are difficult to cure. These challenging infections include osteomyelitis, endocarditis, indwelling catheter-associated infections, lung infections (particularly in patients with chronic lung disease such as cystic fibrosis), and chronic wounds, which often necessitate surgical interventions and prolonged antibiotic treatment. Thus, there is an unmet clinical need to target *S. aureus* in biofilm-related infections.

Therapies for biofilm-related infection

New antibiotics aimed to overcome *S. aureus* antibiotic resistance are being developed with some already in clinical use in both adults and children. Specific therapies for biofilm-related infection, however, are scarce. Rifamycins are a class of antibiotics originally shown to be produced by a Gram-positive bacteria *Amycolatopsis rifamycinica* in 1957 (designated *Streptomyces mediterranei* at the time). It has excellent bactericidal activity against susceptible Gram-positive bacteria including *S. aureus* and inhibits bacterial DNA-dependent RNA polymerase independently of bacterial division, resulting in activity against slowly dividing “dormant” organisms. It is active within acidic environments as well as anaerobic conditions and accumulates within neutrophils and osteoblasts. These properties render rifamycins particularly attractive to be used as therapeutics for biofilm-related infections.

However, the high risk of emergence of rifamycin-resistant mutants requires the concomitant administration of another antibiotic. Preclinical data from animal models support the use of rifampin, the
certain antibiotics, such as vancomycin and linezolid. Early clinical attempts of combination therapy were promising; for example, 2 pediatric cases of endocarditis with failure to control bacteremia with vancomycin showed clearance of infection after addition of rifampin. A prospective double-blind, randomized controlled trial that examined the addition of rifampin to ciprofloxacin for Staphylococcus aureus orthopedic implant infection demonstrated cure without removal of the implant only when rifampin was added to the regimen.

However, other studies including 3 randomized controlled trials evaluating the utility of adjunctive rifampin together with cloxacillin, vancomycin, cotrimoxazole, or fusidic acid did not demonstrate any additional benefit. This may be due to interaction and, in some cases, even antagonism between rifampin and these antibiotics. Most recently, a large randomized controlled trial involving 758 adults with S. aureus bacteremia showed no benefit to adding rifampin over standard antibiotic therapy, although this was associated with a small reduction in bacteriologic failure or recurrence. A deep infection focus was present at baseline in only 301 (40%) participants and 139 (18%) had no established infection focus. The few patients with a deep infection focus or endocarditis included in the trial did substantially better with rifampin, although this trial cannot provide definite answers in these difficult-to-treat scenarios because very few patients were included (of 758 patients, 14 [2%] had prosthetic heart valves or joints and 36 [5%] had implanted vascular devices).

Finally, patients receiving rifampin with a second drug different from fluclouxacin (including other beta-lactams or vancomycin) had a worse outcome (primary endpoint, 29 [23%] of 127 patients), suggesting that the effect of rifampin could be associated with the companion antibiotic used. Currently, combination therapy with rifampin is recommended by the Infectious Diseases Society of America (IDSA) guidelines for the treatment of the following staphylococcal infections: prosthetic joint infections; infective endocarditis in the presence of prosthetic valves; and ventriculitis and meningitis with hardware. Some experts recommend the adjunctive use of rifampin for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) even without hardware, particularly for osteomyelitis and central nervous system infections.

Pharmacokinetics of rifampin
Rifampin is easily absorbed from the gastrointestinal tract and orally administered rifampin results in peak plasma concentrations (Cmax) in about 2 to 4 hours. Rifampin follows enterohepatic circulation and is metabolized by the liver. Once deacetylated, it can no longer be reabsorbed by the intestines and is eliminated from the body with 60% to 65% of the drug being excreted through feces. Urinary elimination accounts for only about 30% of drug excretion.

The activity of rifampin is concentration dependent, and either Cmax or the area under the concentration curve (AUC) divided by the minimal inhibitory concentration (MIC) best correlates with bacterial killing. Rifampin shows a nonlinear increase in exposure with dose-saturable biliary excretion. On the other hand, autoinduction by rifampin, caused by induction of liver enzymes and transporters, decreases rifampin exposure with time. Steady-state is achieved after at least a week of treatment, at which point Cmax and the AUC are both reduced to approximately half, compared with the levels following the first dose (for adults: Cmax 5.79 mg/L vs 8.98 mg/L; AUC, 38.73 mg/h/L vs 72.56 mg/h/L).

Despite the extensive clinical use of rifampin, the optimal daily dose and dosage frequency are not well defined. Adult dosage varies between 300 mg twice daily, 600 mg once daily, 450 mg twice daily, and 900 mg once daily. These are adequate in terms of achieving Cmax and AUC levels equal to or above the MIC. However, these were not compared with each other in terms of treatment efficacy as well as drug concentration at the site of infection.
Rifampin is easily absorbed from the gastrointestinal tract and orally administered rifampin results in peak plasma concentrations (C\text{max}) in about 2 to 4 hours.\textsuperscript{25,26}

Dosage recommended for children was extrapolated from the adult dosage based on the assumption that the same dose per kg is appropriate across all ages. The limited pharmacokinetic information in children suggests that young children receiving adult-derived dosages have drug exposures significantly lower than adults.\textsuperscript{31,32} In fact, children receiving recommended standard dosages of 10 mg/kg demonstrated very low serum rifampin concentrations with a mean AUC of 18.1 mg/h/L at steady-state, which is about half of adult levels.\textsuperscript{33} These recommendations also are at least partly based on historical concerns of toxicity with higher rifampin doses and what was then a high cost associated with the manufacturing of the drug.\textsuperscript{34}

Rifampin-related toxicity includes gastrointestinal symptoms, hepatotoxicity, hypersensitivity reactions, and, rarely, severe immunologic reactions including acute renal failure, thrombocytopenia, and “flu-like” syndrome. Severe toxicity with rifampin is infrequent and more recent studies demonstrate that higher doses up to 40 mg/kg are well tolerated in adults.\textsuperscript{35-38} Drug interaction is a major consideration as rifampin induces several cytochrome P450 enzymes, particularly CYP2C19 and CYP3A4, and thus increases the hepatic metabolism of numerous agents such as birth control pills, ketoconazole, quinidine, prednisone, oral hypoglycemics (sulfonylureas), digitalis, methadone, warfarin, clarithromycin, and protease inhibitors. One other adverse effect is orange discoloration of secretions, including urine, feces, saliva, sweat, and tears.

Higher doses of rifampin for \textit{S. aureus} infections

Since its introduction in the 1960s, rifampin has been considered the cornerstone of tuberculosis (TB) treatments and was beneficial in shortening the treatment duration. With accumulating data demonstrating increased efficacy of high-dose rifampin for TB,\textsuperscript{28,35-38} higher doses of rifampin could be beneficial for \textit{S. aureus} infections as well, particularly when associated with biofilms with foreign materials.

Current recommendations of rifampin dosing in children with biofilm-associated \textit{S. aureus} infection is 10 mg/kg/d to 20 mg/kg/d, given in 1 to 3 doses, with a maximum of 600 mg per dose and 900 mg/d.\textsuperscript{20,21,23} Given the pharmacokinetic properties of rifampin in children and the probable lower risk of toxicity, we would favor a higher dose of at least 20 mg/kg/d. Further studies are needed to evaluate the potential of high-dose rifampin to better and even shorten the duration of treatment for biofilm-associated \textit{S. aureus} infections without added safety risks.

**For references**, go to ContemporaryPediatrics.com/rifampin

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**RIDDLE ME THIS**

**BIOFILMS**

In Drs. Gordon, Ordonez and Jain’s article “Rifampin for biofilm-related infections,” the authors discussed the efficacy of specific therapies for biofilm-related infections. But what about the role of biofilms in \textit{S. aureus} infections themselves? What enables them to challenge the immune system and facilitate antibiotic resistance?

**Welcome to The Matrix**

Accept this month’s 5-item quiz challenge and see how well you know the wiles of this cunning pathogen that deploys a matrix “force field” to evade detection and eradication. What children are especially at risk? What treatment course gives the best outcomes?

+ Your challenge awaits online at ContemporaryPediatrics.com/quiz-0719

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**ASK A CLINICAL PHARMACOLOGIST**

We’re on the cusp of the 1-year anniversary of our monthly feature “Dr. Lee’s Clinical Pharmacologist’s Notebook,” and its genesis was all about you—our readers.

Now, it’s your turn to Ask a Clinical Pharmacologist!

This month, we’re adding a new angle by asking you to pose questions for Dr. Lee and his experts to address in a future edition. Send your questions to cradwan@mmhgroup.com and watch these pages for this new interactive forum.
Parents who use a web-based educational tool to boost what they know about measuring and managing fever gain significantly more knowledge than parents who follow solely written and verbal instruction, according to a trial in caregivers of children with fever. Furthermore, parents prefer the web-based instruction.

Trial participants were 233 caregivers of children aged up to 17 years who visited a Canadian emergency department (ED) because of concern about a fever or whose child had a measured temperature higher than 100.4°F (38°C). Before beginning the trial, participants provided demographic information and completed an 18-item questionnaire that tested their knowledge of the etiology, measurement, therapy, and complications of fever in children. They then were divided into 3 groups, each of which was assigned to a different educational intervention: an interactive web-based module (WBM); read-only website (ROW); or written and verbal information (standard of care [SOC]).

All 3 interventions presented identical material, including the definition, measurement, and management of fever and when to seek medical attention. Participants in the WBM group used touchpads to activate interactive components, whereas ROW had no interactive components. The SOC was a paper document that detailed appropriate dosage and frequency of antipyretics. Participants in the WBM and ROW groups could access their interventions only in the ED but took the written SOC home. In addition, a nurse provided all participants with verbal instructions.

Immediately after the intervention, participants repeated the knowledge questionnaire and, compared with their pretest questionnaire scores, both the WBM and ROW groups had significantly higher scores, even after adjusting for caregiver education level, number of children, and other potentially confounding factors. The post-intervention scores of participants in the SOC, on the other hand, changed little from pre-intervention scores. Similarly, caregiver satisfaction scores were significantly higher in the WBM and ROW groups than in the SOC group (Hart L, et al. Pediatr Emerg Care. 2019;35[5]:353-358).

**THOUGHTS FROM DR. BURKE**

Using online, interactive education modules like this one may be an effective, efficient way to expand parents’ understanding on a broad array of topics. We should investigate what’s out there and direct parents to resources that are accurate and reflect good practice.

Michael G. Burke, MD is Chairman, Department of Pediatrics, Saint Agnes Hospital, Baltimore, Maryland.
Financial incentive program for providers reduces pediatric ED visits

A physician incentive program (PIP) that provides primary care providers (PCPs) with bonuses tied to specific goals to decrease pediatric emergency department (ED) use significantly decreases such visits, according to a retrospective analysis involving 1376 PCPs who participated in the PIP. The PCPs included pediatricians, other physicians, and various types of nurse practitioners from a single health maintenance organization; 86.1% of participants had a medical degree and 41.6% of participants specialized in pediatrics.

Investigators ranked participants in the PIP intervention according to their ED utilization rate and provided 3 potential incentives: PCPs in the quartile with the lowest rate of ED use received a $10,000 bonus each quarter for maintaining that low rate; PCPs who provided office hours a minimum of 4 hours a week during evenings or weekends received a $5,000 bonus for each quarter they maintained this availability; and any PCP who decreased his or her patients’ ED utilization rate by at least 5% compared with the same quarter of the previous year received a bonus that varied with the savings associated with the decreased number of ED visits.

During the 3-year study period, the PIP group was associated with a significantly lower average ED visit rate than the non-PIP group, even after adjustment for degree, specialty, education program, and board status. Further, compared with non-PIP practitioners, PIP providers who received any incentive payment had significantly fewer ED visits per 1000 member-months as did PIP providers who received at least 1 incentive payment for meeting after-hours criteria (Li J, et al. Pediatr Emerg Care. 2019;35[5]:363-368).

THOUGHTS FROM DR. BURKE
Here’s an example of aligning incentives to benefit providers, payors, and, potentially, patients. If these incentives decrease patient barriers to being seen in their medical home versus waiting in a busy ED, patients and their families may be happier and healthier.

WIC food-package changes align with decline in obesity risk

An evaluation of national and state-level trends in obesity prevalence among 2- to 4-year-old participants in the US Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) found that the changes in the 2009 WIC food packages to better align with dietary guidelines are associated with a decline in obesity prevalence among these children.

Investigators compared population trends in obesity prevalence in the selected age group from 2000 to 2014 using a study design that accounted for state-level differences, race or ethnicity, poverty trends, and trends in macrosomia and high maternal prepregnancy body mass index (BMI) among WIC participants.

The package change was associated with a reversal of the increasing trend in obesity prevalence among WIC participants observed from 2000 until the package change in 2009. After 2009, childhood obesity prevalence among 2- to 4-year-old WIC participants shifted from a 0.23 percentage point annual increase to a 0.34 percentage point annual decrease. Furthermore, changes in sociodemographic and other obesity risk factors did not account for this change in the trend in obesity prevalence (Daepp MIG, et al. Pediatrics. 2019;143[5]:e20182841).

THOUGHTS FROM DR. BURKE
The 2009 changes to the WIC package included additional allowances for fruits and vegetables; reductions in how much juice and cheese were covered; requiring low-fat or skim milk after the first 2 years of life; and requiring whole-grain instead of refined-grain products. I am convinced that progress in preventing and treating obesity requires large community-wide public health measures like this one. Similar efforts include taxing sugar-sweetened beverages and addressing the availability of healthy food in food deserts.
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

44% reduction in risk of flare in pediatric subjects

4 out of 5 children remained flare-free for six months

Steroid-free | Fragrance-free

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Massive splenomegaly in a 6-year-old girl

A 6-year-old female with history of previously resolved iron-deficiency anemia presents to the emergency department (ED) for numerous episodes of nonbloody, nonbilious vomiting and diffuse abdominal pain that began on the day of presentation. She had initially presented to her pediatrician who felt a large left-upper-quadrant abdominal mass and referred her to the ED for further evaluation. She has no associated diarrhea or urinary symptoms.

The patient’s mother noticed that her daughter’s abdomen had gradually been looking larger and fuller over the past several days, and today the child began vomiting whenever she ate or drank. Her mother also described a flat, nonpruritic rash that appeared diffusely on her daughter’s body over the preceding days. When asked about other bruises or abnormal bleeding, the mother shared that the child had been having epistaxis bilaterally more frequently and severely than ever before, now occurring most days and without excessive nose-blowing, picking, or recent respiratory illness. The remainder of the patient’s review of systems was negative including fever, household sick contacts, and abdominal trauma.

The patient was found to have massive splenomegaly measuring approximately 6 cm below the left costal margin without hepatomegaly. The spleen extended toward the pelvis and medially toward midline, palpable just lateral to the umbilicus. The remainder of her physical exam was otherwise unremarkable.

At this time, an abdominal ultrasound was performed to confirm that what was initially described as a right upper-quadrant mass was her enlarged spleen. Abdominal and pelvic computed tomography (CT) was also obtained at this time in the ED to better assess for mass effect of her organomegaly, further characterize the spleen, assess for abdominal lymphadenopathy, and confirm a normal-sized liver (Figure 1). At this time, clinicians presumed that her severe splenomegaly was causing a pseudo-obstructive effect resulting in emesis with oral intake.

Initial bloodwork was obtained including a complete blood count (CBC) and coagulation studies given her diffuse petechiae on exam and history of recurrent epistaxis. Her CBC showed significant pancytopenia with leukopenia to 3.9 K/uL with absolute neutrophil count (ANC) of 1300 K/uL; normocytic anemia...
with hemoglobin (Hgb) of 10.2 g/dL; hematocrit (Hct) of 29%; however, platelets clumped so were unable to be calculated on this first sample. Her prothrombin time (PT) was elevated to 16.5 sec with an international normalized ratio (INR) of 1.4 sec.

Given her vomiting, electrolytes were obtained using a comprehensive metabolic panel that revealed normal electrolytes, renal function markers, and unremarkable liver function tests. Due to her pancytopenia with neutropenia, there was now concern for a malignancy as cause for her symptoms, so uric acid and lactate dehydrogenase (LDH) were added to her bloodwork, often elevated in leukemia and other malignancies and helpful to trend if concerned for tumor lysis syndrome. At this time, both tests were normal.

The patient was admitted to the hospital with plans to observe overnight. Labs were repeated the next day and showed interval worsening of her pancytopenia: WBCs were 2.0 K/µL; ANC, 800 K/µL; Hgb, 7.8 g/dL; Hct, 23%; and platelets were now calculated at 26 K/µL. At this time, it was decided to include various subspecialists in the patient’s care and assessment of her condition given the broad differential diagnosis. With their guidance, additional tests were performed to ultimately diagnose the patient’s condition.

### Differential diagnosis

The etiology of pancytopenia in the pediatric population is diverse, ranging from transient bone marrow suppression secondary to acute infection and nutritional deficiencies to hematologic malignancies and bone marrow failure syndromes (Table).

A review study in 2010 estimated that 64% of pediatric pancytopenia is caused by infectious origins, 28% is attributed to primary hematologic/oncologic causes, and the remaining 8% is due to miscellaneous etiologies including metabolic disease. For this reason, common infectious causes were considered, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), parvovirus, and human immunodeficiency virus (HIV). Testing was performed for these etiologies and ultimately all were negative. Bacterial causes such as *Bartonella* and tuberculosis were considered less likely at this time given the patient’s low risk of exposure when asked related questions in her history.

Rheumatology was consulted as several conditions including systemic lupus erythematosus (SLE), systemic juvenile idiopathic arthritis (JIA), and Sjögren syndrome can cause splenomegaly, and an antinuclear antibody (ANA) sent at the time of admission showed moderate elevation to 1:320. Additional rheumatologic workup including complement levels and double-stranded DNA (dsDNA) were obtained but anticipated to be unrevealing as the patient lacked other systemic symptoms of these illnesses such as arthritis and skin findings.

Hematology/Oncology was consulted for further assessment of malignancy with primary concern for leukemia over lymphoma or a solid mass given CT findings and the lack of abnormal lymph nodes on this study and by physical exam. Other hematologic conditions such as myelodysplasia or aplastic anemia, which could be secondary to infection, could cause this degree of marrow suppression.

### TABLE

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<th>Differential Diagnosis: Pancytopenia and Splenomegaly</th>
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<td><strong>Hematologic/Oncologic</strong></td>
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<td>Systemic lupus erythematosus (SLE)</td>
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<td>Sjögren disease</td>
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Author created.
and given the persistence and worsening of her pancytopenia, there was a question about the utility of a bone marrow aspirate to further assess the appearance of her marrow cells.

Although reassuring for this patient’s overall clinical status to not have laboratory evidence of overt tumor lysis, the findings did little to reassure against a diagnosis of malignancy. With a low white blood cell count, tumor lysis could be absent despite the presence of acute malignancy, as tumor lysis is more likely to occur in a patient with a high tumor burden. Furthermore, normal LDH, uric acid, and electrolytes have very little significance in the evaluation of a plausible, nonmalignant underlying diagnosis such as aplastic anemia or myelodysplastic syndrome.

Given the concern for malignancy, bloodwork was sent for flow cytometry and cytogenetics and found to be negative. Her bone marrow suppression persisted despite several days of hospitalization without any meaningful cell recovery. In a patient with persistent pancytopenia in the absence of a clear diagnosis, and particularly in this patient who also presented with splenomegaly, bone marrow evaluation is the gold standard for diagnosis or exclusion of malignancy, regardless of peripheral blood lab results. Additionally, the aim of the bone marrow evaluation is not only to properly assess for evidence of malignant cells, but also to evaluate for other nonmalignant etiologies. In the case of a patient with persistent pancytopenia, peripheral blood flow cytometry that does not identify any malignant cells would not obviate the need for bone marrow studies, as the clinical picture still suggested some pathology of the bone marrow and therefore further workup was warranted.

The etiology of pancytopenia in the pediatric population is diverse, ranging from transient bone marrow suppression secondary to acute infection and nutritional deficiencies to hematologic malignancies and bone marrow failure syndromes.

At this time, the decision was made to proceed with bone marrow biopsy to assess for both primary marrow production states and infiltrative processes. This led to further discussion of infiltrative processes that also may cause splenomegaly. Abnormal deposition of substances such as proteins or lipids can cause a similar presentation. Thus, genetic metabolic conditions including glycogen and lysosomal storage disorders are included in the differential diagnosis. An angiotensin converting enzyme (ACE) level was obtained to access for this and found to be elevated to 211 u/L.

The bone marrow biopsy revealed Gaucher cells, macrophages filled with lipid material that accumulate in Gaucher disease (GD) and that are a primary feature. These cells have a characteristic histologic appearance (Figure 2). However, there are several conditions including hematologic malignancies in which Gaucher-like cells, or “pseudo-Gaucher,” cells have been noted, particularly in circumstances with high cell turnover. Glucosylceramide is a
The diagnosis of Gaucher disease should be made by measuring glucocerebrosidase activity in peripheral leukocytes and confirmed via gene mutation analysis of the GBA gene.9

Discussion

The diagnosis of GD should be made by measuring glucocerebrosidase activity in peripheral leukocytes and confirmed via gene mutation analysis of the GBA gene.9 Ideally, it would not be made by finding Gaucher cells on bone marrow biopsy because this study is not necessary to make the diagnosis and is more invasive than enzymatic analysis. In addition to confirming the diagnosis, gene mutation analysis can be of clinical utility, as there is a genotype-phenotype correlation with some mutations. For example, patients homozygous or compound heterozygous for the c.1226A>G allele, as with this patient, have type 1 GD, rather than a neuronopathic type of GD. Type 1 is the most common form and is the non-neuronopathic form of GD.9 It is also the one for which the best therapies are available.

Patient follow-up

Goals of therapy include eliminating or minimizing symptoms, prevention of comorbidities associated with the disease, and improvement in growth and overall quality of life.10 This patient had a port-a-cath placed and was started on enzyme replacement therapy (ERT) with recombinant glucocerebrosidase, given both the severity of her laboratory markers and physical exam findings causing symptomatic disease. This would require every-other-week intravenous (IV) infusions for the foreseeable future, with regular monitoring of labs and imaging.

The patient and her family were counseled not only on the basics of her disease, as it was not known to cause any symptomatic disease in known family members, but also the long-term sequelae and comorbidities of GD; the genetic tests that would be performed; the frequency of additional future testing; and the burden of management with ERT. Her family was counseled further on the autosomal recessive genetic component of her disease and the impact this might have on future family planning.

As both parents were carriers for a pathogenic allele, their future offspring had a 1 in 4 chance of having the disease.9 Additionally, as patients with type 1 GD can have very different phenotypes even with the same genotype, clinicians discussed with the parents the utility of performing genetic testing for the mutations for the patient’s 3 sisters.

Conclusion

Gaucher disease presents similarly to malignancy in many cases, as seen with the patient in this case. Common presenting symptoms include hepatomegaly and/or splenomegaly, bone marrow suppression, bleeding, and bone pain.5,10 It should be included in the differential diagnosis for a patient presenting with symptoms such that clinicians might be considering leukemia as a potential diagnosis. ■

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For references, go to ContemporaryPediatrics.com/puzzler-0719
Measles makes a comeback

What to know, what to do

Measles is once again a significant public health problem in the United States. Many pediatricians and most parents have never seen actual measles in a child, hence the urgent need to reeducate clinicians and caregivers about clinical manifestations and prevention of the disease.

PAT F BASS III, MD, MS, MPH

In 2000, the United States achieved a monumental public health goal—elimination of sustained transmission of measles for more than 12 months. Unfortunately, this achievement was relatively short-lived, and the United States has been experiencing significant measles outbreaks in the last several years. It is essential for the pediatrician to understand the measles virus including the clinical manifestations, diagnosis, complications, management, and postexposure prophylaxis (PEP) so that by identifying the disease in its earliest stage its spread among the vulnerable pediatric population can be contained.

Epidemiology

Measles is a highly contagious disease with 90% of susceptible individuals developing measles following exposure.1 Transmission may occur person-to-person or via respiratory droplets/small particle aerosols. Respiratory droplets may remain airborne for up to 2 hours, increasing the risk of transmission in public and crowded places.2 Transmission via fomites is possible but less common.3 Underimmunization is the primary source of immunity gaps, and the unvaccinated or unknown vaccination status represents 85% of infected individuals.4

Clinical manifestations

Classic measles proceeds through 4 clinical stages from incubation to recovery:

INCUBATION—The incubation period for measles varies from 7 to 21 days (median, 13 days) after the virus enters via the respiratory tract or conjunctiva.5 Infected individuals are generally asymptomatic during the incubation period. Infected children are contagious from 5 days before the appearance of the rash until 5 days after.6

THE CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC) ESTIMATES THAT

VACCINES PREVENTED more than 21 million hospitalizations and 732,000 deaths among children born during 1994 to 2013.

—CDC. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6316a4.htm; 2014.

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PRODROME—The prodromal phase lasts 2 to 4 days and is characterized by coryza, cough, and conjunctivitis (the “3 Cs”); fever; anorexia; and malaise. Photophobia, lacrimation, periorbital edema, and myalgia can sometimes be present. The fever pattern is variable. Prodromal symptoms often worsen several days before the exanthem appears. In the 48 hours before the appearance of the exanthem, Koplik spots may appear. These 1-mm to 3-mm, whitish-blue/gray papules on an erythematous base appear on the buccal mucosa opposite the molars. Koplik spots may coalesce and will begin to fade as the exanthem appears. They are pathognomonic for measles and can prompt the pediatrician to begin appropriate management and control measures. However, not all patients will present with Koplik spots.

EXANTHEM—The exanthem of measles, referred to as morbilliform, is a macular-papular, erythematous, blanching rash. Beginning on the face around the hairline, sides of the neck, and ears, it spreads downward to the trunk and extremities becoming more confluent. The palms and soles are generally spared. In children, the extent of the rash and degree of confluence generally correlate with the severity of the illness. In more severe cases, the rash may be petechial or hemorrhagic. High fevers are often seen 2 to 3 days following the appearance of the rash and are associated with lymphadenopathy and respiratory symptoms. Patients usually begin to improve 48 hours after onset of the rash.

The rash lasts from 5 to 7 days and will fade in the same pattern as it appeared. Desquamation may be seen in areas that were more severely affected.

RECOVERY—If fevers persist beyond day 4 following rash onset, the pediatrician should consider a possible measles-associated complication. Cough may persist for several weeks. Immunity following infection is generally considered lifelong.

Complications
Complications of measles are common and occur in 10% to 40% of affected individuals. Complications are more common in the very young, very old, women who are pregnant, or in any patient with an immunocompromised state. Pneumonia, due to measles itself (the so-called Hecht giant-cell pneumonia) or a secondary bacterial infection, is the most common complication. Otitis media, croup, laryngotracheobronchitis, and diarrhea are also common. Pregnant women are at risk for spontaneous abortion, in utero fetal death, and low-birth-weight infants.

Keratoconjunctivitis may lead to blindness when there is a concomitant vitamin A deficiency.
Although not common, central nervous system complications carry significant morbidity. Complications include encephalitis, acute disseminated encephalomyelitis (ADEM), measles inclusion body encephalitis (MIBE), and subacute sclerosing panencephalitis (SSPE).

**ENCEPHALITIS**

One of every 1000 measles cases develops acute encephalitis.12 Symptoms generally begin 5 days after the rash onset and can include:
- Fever
- Altered mental status
- Headache
- Vomiting
- Stiff neck
- Meningeal irritation
- Seizures

Workup will reveal a cerebrospinal fluid (CSF) with lymphocytic pleocytosis, elevated protein, and a normal glucose level. One in 4 children will develop neurologic sequela and the encephalitis is fatal in 15% of cases.14

**ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)**

A demyelinating complication that also occurs in 1 of every 1000 measles cases,12 ADEM is a postinfectious autoimmune response that occurs within 2 weeks of the exanthem.13 Symptoms are similar to that of encephalitis but may also include ataxia, myoclonus, and choreoathetosis. Patients with ADEM also may have signs of myelitis (back pain, para/quadruplegia, sensory loss, and loss of bowel/bladder control). The CSF will demonstrate lymphocytic pleocytosis and an elevated protein concentration.

Additionally, ADEM is associated with a 10% mortality rate and neurologic comorbidities are common, including epilepsy and behavior disorders.13

**MEASLES INCLUSION BODY ENCEPHALITIS (MIBE)**

This complication of measles primarily occurs in patients with an impaired cellular immunity within several months of the primary infection. With MIBE, patients will present with seizures, mental status changes, and myoclonus. Some patients may have a concomitant giant cell pneumonia.

**SUBACUTE SCLEROSING PANENCEPHALITIS (SSPE)**

This progressive degenerative central nervous system disease presents 5 to 10 years following measles infection and is fatal, occurring in 1 in 10,000 measles infections.10 It is most common in children who develop measles before age 2 years. Prior to 1975, the rate of SSPE was 8.5 cases per million cases of measles and declined to 0.06 cases per million with vaccination.17 In the late 1980s and early 1990s as measles cases surged, the incidence of SSPE was thought to be 200 to 400 cases per million.18 In California, SSPE has appeared at much higher rates in unvaccinated children: 730 per million in infected children aged younger than 5 years, and 1640 per million in infected children aged younger than 1 year.19

**Diagnosis**

In areas where measles is not common, diagnosis can be difficult. The pediatrician should consider measles in any pediatric patient with the following findings:
- One of the 3 C’s: coryza, cough, and conjunctivitis.
- Fevers ≥101°F (38.3°C).
- Erythematous maculopapular rash spreading cephalocaudally from the face downward.
- Koplik spots (when present are pathognomonic).

If the pediatrician is considering the diagnosis of measles, patients should be placed in respiratory isolation within healthcare facilities. Suspicion is particularly important in patients with:
- Unknown or questionable immunity to measles.
- Travel to endemic measles areas.
- Potential exposure in a measles outbreak.

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**NUMBER OF MEASLES CASES REPORTED BY YEAR**

*2010-2019* (as of June 27, 2019)

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*Cases as of December 29, 2018. Case count is preliminary and subject to change.*

**Cases as of June 27, 2019. Case count is preliminary and subject to change. Data are updated every Monday.*

Laboratory confirmation of suspected measles cases is essential in febrile pediatric patients with other measles symptoms or other risk factors.12,20 There is a positive serologic test for measles-specific immunoglobulin M (IgM) antibody or detection of measles virus RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) from blood, throat, nasal, nasopharyngeal, or urine samples. The Centers for Disease Control and Prevention (CDC) recommends obtaining 3 samples when possible:12
- Serum sample for measles IgM.
- Throat or nasopharyngeal swab for viral culture.
- Urine sample for viral culture.

Diagnosis with RT-PCR is most likely in the 3 days following rash onset.1,12,20 The IgM may not be detectable on the day of rash appearance and will be present for approximately 3 days.20

Additional diagnostic options include a 4-fold or greater rise between acute and convalescent sera of measles-specific IgG titers or isolation of measles virus from cultures from specific sites such as blood mononuclear cells, urine, conjunctival swabs, or nasopharyngeal secretions. The IgG titers may not be detectable until 7 days after rash onset and will peak at approximately 14 days. Additionally, there are some false-positive results attributed to cross-reactivity due to IgM caused by parvovirus B19.20

The pediatrician should report any suspected case of measles to his/her local health department within 24 hours.

Management
In general, treatment for measles is symptomatic and includes:
- Control of fever with antipyretics.
- Prevention and control of dehydration.
- Infection-control measures.
- Treatment of bacterial infections such as pneumonia or otitis media.
- Treatment of other complications such as seizures or respiratory problems.

Vitamin A supplementation reduces complications of measles, decreases measles deaths, and prevents delayed recovery because of vitamin A deficiency. It is recommended that vitamin A be administered immediately at diagnosis and again the following day.13 Additionally, a third dose should be administered to any child with clinical evidence of vitamin A deficiency (xerophthalmia, xerosis, Bitot spots) 4 to 6 weeks later.21-23

Vitamin A dosing is age dependent:13
- Infants aged 6 months: 50,000 international units (IU)/day.
- Infants aged 6 to 11 months: 100,000 IU/day.
- Children aged 12 months and older: 200,000 IU/day.

Although data are limited, in vitro studies demonstrate possible efficacy of ribavirin against the measles virus. As a result of measles-associated mortality that can approach 35% in some high-risk groups, some experts recommend its use. High-risk patients include those aged younger than 1 year diagnosed with pneumonia and children aged older than 1 year with pneumonia requiring mechanical ventilation. Small series of case reports have demonstrated beneficial effects.24,25 One randomized trial of ribavirin along with supportive management compared with only supportive management demonstrated decreased duration and severity of fever as well as decreased complications.26

Postexposure prophylaxis
Children exposed to measles who cannot demonstrate immunity should receive postexposure prophylaxis (PEP) or be excluded from...
certain settings (schools, hospitals, childcare facilities).12

Providing PEP may protect patients from or modify the clinical course of the disease. The 2 options include administration of either: 1) measles/mumps/rubella (MMR) vaccine within 72 hours of initial measles exposure; or 2) immunoglobulin (IG) within 6 days of exposure.12

High-risk patients (infants aged younger than 12 months, pregnant women without evidence of measles immunity, and people with severely compromised immune systems), should receive IG. Intramuscular IG (IMIG) should be given to all infants aged younger than 12 months, but MMR vaccine may be substituted if given within 72 hours of initial measles exposure for children aged 6 to 11 months.12

The pediatrician cannot administer both the MMR vaccine and IG as this will invalidate the vaccine. If not able to administer MMR vaccine within 72 hours as PEP, the vaccine should still be offered to offer protection from future exposures.12

Conclusions
Measles is a significant public health problem. Pediatricians need to vaccinate patients in their offices, promote vaccination in their communities, and, especially, be able to identify and manage measles cases in their practice.

Pediatricians are wrestling with how they should deal with a growing antivaccination movement—one that’s taking a heavy toll on population health.1

Take measles, for example. “The resurgence in measles cases is all the more frustrating since the disease is entirely preventable through vaccination,” according to the perspective “Measles in 2019—Going backward” by Catherine I. Paules, MD, and colleagues, published April 17, 2019, at NEJM.org.1 “The growing antivaccination movement, based heavily on philosophical objections to vaccinations, poses a threat to public health,” Paules writes. “Vaccine hesitancy has been identified by the World Health Organization (WHO) as one of the top 10 threats to global health and is a serious hurdle to the global elimination and eradication of measles.”

So, how does a pediatrician charged with doing no harm help, care for, and come to terms with families who are firmly against vaccinating their children or hesitant to do so? We asked several pediatric infectious disease control experts for their advice.

Ms Hilton is a medical writer who has covered health and medicine for 25 years. She resides in Boca Raton, Florida. 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.
Change this equation: The risk of vaccines is greater than the risk of disease
One can’t underestimate the challenge that pediatricians are facing when it comes to the antivaccination movement.

“The amount of information and disinformation that’s circulating has created a climate where this is a big problem and one that’s not easily solved,” says Mark H. Sawyer, MD, professor of Pediatrics at the University of California San Diego (UCSD) School of Medicine and a pediatric infectious diseases specialist at Rady Children’s Hospital-San Diego. “I think that one of the most important ingredients for pediatricians to keep in mind is to enter these discussions with both respect and empathy for the family.”

The families that question or refuse vaccines are, by and large, not on the fringes of society. Rather, they’ve gotten hold of information that makes them anxious about vaccines in particular and, based on the information, they’ve reached the conclusion that the risk of the vaccine is greater than the risk of disease, according to Sawyer.

“First of all, you need to find out what information families are reacting to that’s making them hesitant—whether it’s specific issues they’re concerned about or it’s a more generic feeling that vaccines are just bad,” he says.

That’s where the hard work starts, according to Sawyer. “You can’t simply say that. You can’t quote a bunch of statistics that would illustrate that because these people are pretty invested in their decision-making up to the point that you’re seeing them, and it’s not something that you’re going to turn around necessarily quickly or with any particular set of facts,” he says. “So, you sort of have to feel your way with each patient interaction for the kind of information that will at least cause these parents to rethink their decision, eventually.”

Role of the pediatrician
It is important to emphasize that as a pediatrician you’re recommending vaccines because you have the same goal as parents do: to maximize the health of their children and protect them as much as possible.

“That sometimes can be done by sharing personal stories about vaccine-preventable disease that you have seen as a pediatrician, which makes it more real to families. It’s not something that is rare or unusual,” Sawyer says. “Sometimes it’s effective to share that your own children or your extended family’s children are all vaccinated as an illustration that you are putting your money where your mouth is and have come to the conclusion that the risk of the disease is much greater than the risk of the vaccine.”

Another option that can be effective: connect parents to other parents who have had children suffer from vaccine-preventable diseases. This can be done virtually, as there are such videos on the Internet, or with parents in the practice who might want to share their stories.

For some people, the science will work. For others, a more personal approach might help parents rethink the equation between vaccine safety and disease risk.

“Those are guidelines or road maps, but the trouble is there’s not one solution for all families. It depends on what their concern is, what their experiences are, what your relationship with them is, and how powerful the network they’re circulating in is to immunize or not to immunize,” Sawyer says.

Still, not every family will agree to vaccinating their children. That can be difficult for pediatricians who have put in the time and effort.

“I’m well aware of the evolution of the American Academy of Pediatrics’ recommendations about whether to continue working with these families or consider not working with these families and refer them to some other provider,” Sawyer says. “I am in the camp of saying that we really should try and continue to work with these families. The only hope of them eventually immunizing their children is to have a long-standing and supportive relationship with a provider who can keep discussing the issues with them. I don’t think it really serves either the child or the community in general to get frustrated and say I’m not going to deal with these families anymore.”

Sawyer says he appreciates physicians’ concerns about having unimmunized children in their offices. Solutions to that dilemma include having unimmunized patients wait in a separate place in the waiting room; having
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Craft the message: Vaccines are routine, safe, preventive medicine

Pediatricians play a powerful role in educating parents about vaccines’ importance and proven safety. The way they present the information can impact whether a vaccine-hesitant or opposed parent listens and ultimately approves or disapproves of childhood vaccines, according to Patricia Whitley-Williams, MD, president-elect of the National Foundation for Infectious Diseases and chief of the Division of Allergy, Immunology, and Infectious Diseases at Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey.

In the United States, pediatricians have done a remarkable job in immunizing children and largely have been responsible for the marked decrease in vaccine-preventable diseases in the last century, Whitley-Williams says. To help ensure that as many parents as possible vaccinate their children, according to Patricia Whitley-Williams, MD, president-elect of the National Foundation for Infectious Diseases and chief of the Division of Allergy, Immunology, and Infectious Diseases at Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey.

In the United States, pediatricians have done a remarkable job in immunizing children and largely have been responsible for the marked decrease in vaccine-preventable diseases in the last century, Whitley-Williams says. To help ensure that as many parents as possible vaccinate their children, the pediatrician’s communication strategy should include these important steps, she notes.

Steps to guide the conversation
First, pediatricians should present vaccines as part of normal, routine preventive care for children—not a question. The conversation might start like this at a visit at which a child is due for vaccines: “As part of your child’s one-year visit he [or she] will be receiving the [x, y, and z] vaccines. Here is information you can read about the vaccines. It’s part of a packet we give to all parents.” That’s as opposed to: “Your child is supposed to receive these vaccines today. How do you feel about that?”

If the parent objects or expresses hesitation, the pediatrician can then engage in a conversation asking about the parent’s specific concerns and addressing those.

“Some parents will be hesitant about giving measles/mumps/rubella (MMR) on time, at 12 months of age, because they’re afraid of autism. Or they just may not believe in vaccinations. Or they don’t want to be mandated to have their children vaccinated and see vaccination as an order from the government,” Whitley-Williams says. “Let’s say the parent is afraid of the adverse events or risks or thinks that vaccines are not safe. That gives the pediatrician an opportunity to speak with the parent and to make sure they are basing this on factual material and not on what they are reading off websites on the Internet.”

Among her talking points for the pediatrician: Present the facts and then point out that millions of doses of vaccines are given safely every year. Assure the parent that there is surveillance—there are several different sources or methods of how public health organizations monitor vaccine safety—even vaccines that have been around for years.

Offer resources other than from the government if parents are antigovernment. The Centers for Disease Control and Prevention (CDC) has a comprehensive website for the public and healthcare professionals (www.cdc.gov/vaccines/vpd/index.html) but there are also nongovernmental organizations such as the National Foundation for Infectious Diseases (www.nfid.org) that offer public education about vaccines. Others include the Immunization Action Coalition (immunize.org) and the website for Families Fighting Flu (www.familiesfightingflu.org).

For parents concerned about the MMR and autism, the Institute of Medicine has extensively reviewed studies and confirmed there is no causal relationship between the MMR vaccine and autism.
Speak from the heart as both physician and parent

Most humans are not moved by data. “You can read a statistic, and it’s just a statistic,” says John V. Williams, MD, professor of Pediatrics, chief, Division of Pediatric Infectious Diseases, and Henry L. Hillman Endowed Chair in Pediatric Immunology at the University of Pittsburgh Medical Center (UPMC) Children’s Hospital of Pittsburgh, Pennsylvania.

So, when Williams talks with vaccine-hesitant or opposed parents, he’ll often talk about what he has seen as a pediatrician and done as a parent. He’ll share stories such as this one of suffering and preventable mortality.

Williams saw a child a few years ago. The parents had 3 children. The older boys were both vaccinated, but when the “pro-life” family heard that vaccines were made of aborted fetuses, they questioned whether they should vaccinate their youngest daughter.

The mother asked her pediatrician at the time about what she had heard. Instead of explaining to the mother that it wasn’t true and educating her about vaccines, the pediatrician responded with a simple “I don’t know,” according to Williams. As a result, the mother decided to put off the vaccinations until the child turned a year old.

“One week shy of her first birthday, that little girl got bacterial meningitis, a vaccine-preventable form,” Williams says. “Fortunately, she did really well. She lost hearing in one ear but otherwise it was a good outcome. The mother became a very passionate advocate for vaccines.”

The story represents a missed opportunity to move parents who were misinformed to vaccinate their children, but it also is an opportunity to educate others who might be on the fence about vaccines.

Williams doesn’t shy away from making the issue of vaccines a personal one as well.

“I explain that I have 4 kids, and they’ve all gotten their vaccines. They’ve even taken part in vaccine trials. That’s how strongly I feel,” he says. “Families often say, ‘Hmmm. If you do it for your kids, maybe it’s not so bad.’”

He’ll also share the triumphs, solely from vaccines. “We see a lot less bacterial meningitis than we did when I was a young doctor 25 years ago. The vaccine is the only reason for the dramatic decline in bacterial meningitis. Thirty years ago, I knew people who had bacterial meningitis as children—it was that common. It’s not now. Most people under age 40 don’t know anybody—they don’t have a neighbor or a family member—who had bacterial meningitis as a child,” he says.

People forget these diseases exist. So, pediatricians need to remind people that lots of these germs are still around.

“The germs that cause bacterial meningitis still live in a half to two-thirds of kids’ noses. The reason there is no meningitis is not because the bacteria are gone. They’re not. And they still cause ear infections and sinus infections. Rather, what’s keeping kids safe is the vaccine. It’s preventing the germs from invading,” Williams says. “Maybe vaccine-hesitant people are aware of tetanus and that it remains a risk, but I think they believe a lot of the other germs are gone. Some are gone: Smallpox is gone from the
world. Polio is gone from the Western Hemisphere. But many of these germs are still around right here in our country—right here in our kids’ noses.”

**How to address hesitancy**

For parents who argue vaccines aren’t natural, Williams stresses that death from infection in childhood is natural. Until 150 years ago, childhood mortality was 20% before age 5 years, according to Williams. Parents, in this case, might choose vaccines to combat what’s natural and deadly.

The conversations can be long and arduous—especially for pediatricians trying to see a patient every 15 minutes. “I’ve personally cared for many children who suffered and even died from vaccine-preventable infections and yet I feel sometimes like I just don’t want to go there and have that conversation,” he says. “But we need to go there.”

Williams says he often schedules time just for the conversation, as a separate visit. He says it helps to stay focused on the topic and this is more efficient than trying to tackle the talk during a regular pediatric appointment.

“This is true for almost any health behavior—smoking cessation, quitting alcohol, exercising more. Everybody knows they should be doing these things, but if the doctor thinks it’s important enough to talk about, that does move people. It is important for physicians to realize that they may not change that family’s mind today, but if they discuss it they are helping move that family toward acceptance,” Williams says.

**Vaccine-hesitant vs vaccine-refusing**

The frank refusers are a different story. Pediatricians struggle with what to do with parents who are dead-set against vaccinating their children. “Do we retain those families in our practice, and by retaining those families in our practice, do we put our other patients at risk because these children come in for sick visits and potentially expose our vulnerable patients?” he asks. “I’ve gone back and forth on that question in recent years.”

Schleiss says he shares his concerns with parents about continuing to care for their unvaccinated children and says that although he cannot endorse their antivaccine stance, he worries about who might care for the children should they get life-threatening, vaccine-preventable infections. So, he’ll often continue to

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**Mark R. Schleiss, MD, professor of Pediatrics and holder of the American Legion and Auxiliary Heart Research Foundation Endowed Chair of Pediatric Infectious Diseases, University of Minnesota Medical School, Minneapolis.**
clinical feature

“I think there is an evolving and constantly changing distrust of people in authority positions, and the lack of trust in scientists is at the top of that list.”
—MARK R. SCHLEISS, MD

establish rapport and to try to be available for questions.”

For those parents whose children remain under Schleiss’s care and whose children get vaccine-preventable illnesses because of the family’s antivaccine stance, Schleiss says it does not do any good to say, “I told you so.”

Parents know that their refusal to vaccinate their children led to their illness, he says. He’ll care for the

REPORT FROM GROUND ZERO: PUBLIC HEALTH CRISIS IN NEW YORK

Contemporary Pediatrics spoke with Mary Koslap-Petraco, DNP, PNP-BC, CPNP, FAANP, a nationally known expert in immunization practice, about why measles infection rates have skyrocketed in her home state of New York, what’s in store for the rest of the United States during the current measles outbreak, and how physicians can engage with parents to boost immunization rates.

Dr Koslap-Petraco, pediatric nurse practitioner and community health specialist, is a nurse consultant on the staff of the Immunization Action Coalition (IAC) and CEO and primary care provider in her own private practice. She serves on the board and executive board of Vaccinate Your Family (VYF): The Next Generation of Every Child by Two, a national nonprofit organization founded in 1991 that is committed to reducing the burden of vaccine-preventable diseases in families and individuals. She is a nationally known expert in immunization practice and has been an advisor for the Centers for Disease Control and Prevention (CDC), serving on the CDC’s Advisory Board of the IAC and National Vaccine Advisory Committee. She is an adjunct clinical assistant professor at Stony Brook University School of Nursing, Stony Brook, New York, where she teaches in the Pediatric Nurse Practitioner Program.

“Experts almost equate how measles damages the immune system to the way that [human immunodeficiency virus] damages the immune system. It’s the same type of mechanism. It literally turns the immune system off—for measles it’s about 3 years—but in that period of time, there’s also the opportunity for children and adults to get sick with a lot of other things and they won’t have that robust immune system to protect them.”
—MARY KOSLAP-PETRACO, DNP, PNP-BC, CPNP, FAANP

To listen to the entire podcast interview with Dr. Mary Koslap-Petraco, go to ContemporaryPediatrics.com/podcast-0719

care for the child.

“I like to believe that even the frank vaccine-refusing parents will, with the establishment of rapport over time, begin to at least open up to potentially some vaccines, but they’re much tougher,” he says. “The overarching message I offer from my experience is that you really aren’t going to change these parents with facts. At the end of the day, these refusals are not really related to science or factual information. There is some other deeper element. I think it’s complex. I think there is an evolving and constantly changing distrust of people in authority positions, and the lack of trust in scientists is at the top of that list.”

What pediatricians can do

Pediatricians and others have to be part of an anti–antivaccination movement, aimed at reversing propaganda—much of which has been disproved but continues to live online.

“You don’t have time in the office to engage in a polemic on all these issues, and if the process evolves toward that of an argument or debate, you’re always going to lose. That drives patients away,” Schleiss says. “I do like to point out some simple truths that are uncontroversial, such as the fact that Andrew Wakefield (a leader in the antivaccine movement) attempted to publish fraudulent, fabricated information that was eventually retracted from the medical journal Lancet where it originally appeared.1 We have all the research that we’re ever going to need about vaccines in practice. They save lives. My bigger strategy is to try to es-
A frustrating but necessary investment in time

Pediatricians spend precious time talking with parents whether they’re vaccine hesitant or vaccine opposed. Yet the time pediatricians spend trying to understand and educate families who are hesitant or against vaccinating their children is important and can be effective, according to Tina Q. Tan, MD, professor of Pediatrics at Northwestern University Feinberg School of Medicine and a Pediatric Infectious Diseases attending at Ann and Robert H. Lurie Children’s Hospital of Chicago, Illinois.

“For the vaccine-hesitant people, the major reason they’re hesitant is either a friend has basically told them vaccines are dangerous, or parents have been reading information on the Internet and they’re just not quite sure what to think,” Tan says.

Even parents who are favorable to vaccination can be confused by the ongoing debate, leading them to question their choices, researchers write in an article published last year in *Cureus.*

“Many parents lack basic knowledge of how vaccines work, as well as access to accurate information explaining the importance of the process,” according to the article.

Often pediatricians can turn around the vaccine-hesitant by educating—not lecturing—parents about their concerns, Tan points out.

Challenges to vaccination

Parents who refuse vaccines or refuse the recommended vaccine regimen are far more challenging for pediatricians because these parents are unlikely to budge even after pediatricians talk with them at length about vaccine safety and benefits. Many pediatricians end up dismissing these families from their practices, with good reason, Tan says.

“These children pose a public health risk to other kids that are in the waiting room that are either too young to be immunized or who have medical conditions that prevent them from being immunized,” she says. “I understand it really is a quandary.”

With time, patience, and good communication techniques, however, there is a chance that pediatricians might convince even the most adamant parents that they should have their children vaccinated.

“Listen to [parents]. Be empathetic about their fears and then provide them with accurate information.” —TINA Q. TAN, MD

Importance of trust

Empathy and respect can lead to trust, and studies show that maintaining trust is important for physicians trying to sway families who might be opposed to vaccinating their children. Whereas the chances of converting adamantly opposed parents are slim, those individuals make up a small proportion of all parents who are concerned enough about vaccinations to question their value, according to Tan.

Most of the process involves pediatricians’ verbally discussing vaccines with parents, Tan says, but there are free, credible materials that help to back up those talks. CDC.gov offers detailed information about the importance of vaccines for patients. The American Academy of Pediatrics also has handouts for patients and information on its website about the value and safety of vaccines.

Dr. Tan discloses no conflicts of interest.

“Dr. Schleiss discloses no conflicts of interest.”

For references, go to ContemporaryPediatrics.com/antivax-advice-schleiss

For reference, go to ContemporaryPediatrics.com/antivax-advice-tan
0 lbs., 14 oz., and made for EVERY INCH

RECOMMEND AQUAPHOR FOR BABY’S SKINCARE NEEDS

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CLINICAL FEATURE  Medical marijuana

In 2015, the American Academy of Pediatrics (AAP) published an updated policy statement on marijuana in youth in which it reaffirmed its opposition to the use of medical marijuana outside the regulatory process of the US Food and Drug Administration (FDA). The AAP cited the lack of evidence on the efficacy of marijuana as medicine for children, as well as the potential long-term harms based on data on recreational marijuana use.

The updated policy, however, did provide an exception: It recognized that medical marijuana may be a viable option for children with life-limiting or life-threatening conditions for whom there are no other alternative treatments available.

Given some evidence for the potential benefits of medical marijuana, the AAP said it "strongly supports research and development of pharmaceutical cannabinoids and supports a review of policies promoting research on the medical use of these compounds."  

The case for medical marijuana in children is therefore far from closed. It could be argued that it is just getting started. As such, pediatricians may be increasingly required to address this with their patients and families and to understand the complex landscape of varying state laws and regulations, the wide range of products comprised of different cannabis compounds and doses, as well as the ongoing research on the benefits and safety of these products in children.

To help pediatricians traverse this landscape—for many, foreign terrain—Elissa Miller, MD, clinical associate professor of Pediatrics, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania, and Nemours/Alfred I. duPont Hospital for Children, Wilmington, Delaware, and G. Sam Wang, MD, FAAP, assistant professor of Pediatrics, University of Colorado Anschutz Medical Campus, Children’s Hospital Colorado, Aurora, co-presented a session during the 2018 AAP National Conference and Exhibition in Orlando, Florida, titled “Marijuana as medicine.”

MARY BETH NIERENGARTEN, MA

The case for medical marijuana in children is just getting started. Here’s how pediatricians can navigate the complexities and discomfort of this issue and address the risks and benefits of pharmaceutical cannabinoids for their patients.
As reflected in the title of Wang's portion of the presentation, “Marijuana as medicine, not as easy as it sounds,” this topic is challenging and untangling all the issues involved not easy. Essential, then, is to first clearly understand what medical marijuana is and what it is not. This includes understanding common terminology (Table 1). Further understanding is needed on how patients obtain it, including eligibility requirements based on certification from a physician and where to purchase it. Other issues involve knowing how to discuss the benefits and potential risks for patients and families who come to the clinic wanting more information on whether medical marijuana may be a good option, or for those who come to the clinic already on a medical marijuana product.

Miller underscores both the complexity and discomfort of this issue for many pediatricians, including herself. "If my experience is any indication of the majority of pediatricians, they are not comfortable overseeing medical marijuana use in their patients," she says.

In addition, Miller highlights the difficulty of talking about a potential substance for medical use for which so little evidence is available. “We’re used to knowing that new drugs have been rigorously studied,” she says. “We know the pharmacokinetics and pharmacodynamics [of drugs we prescribe], and we know the doses to give because it has been studied.”

“Medical marijuana isn’t like that,” she warns. “It is about as far away from any medicine I prescribe as possible.”

**What is medical marijuana?**

In defining medical marijuana, it is important to first define what it is not. Medical marijuana does not refer to the 3 cannabinoid medications approved by the US Food and Drug Administration (FDA) that are currently available by prescription in the United States. As shown in Table 2, 2 of these medications contain synthetic compounds of cannabis, and only 1 is derived directly from the marijuana plant. Known as cannabidiol, or CBD (Epidiolex), the drug contains a purified form of CBD and was approved in 2018 for severe forms of epilepsy (Lennox-Gastaut syndrome and Dravet syndrome) in children aged 2 years and older. As a federally controlled drug, CBD is available nationwide and dispensed through a prescription with dosing recommendations by a physician, nurse practitioner, or physician assistant.

Medical marijuana differs in several ways. None of the products are FDA approved or monitored; it is available legally only in states that have passed laws making it legal; it is dispensed through state dispensaries and not through physician offices or typical pharmacies; and there are no standard dosing or treatment duration guidelines for any specific indications. In addition, the rules and regulations on how to monitor these products for compliance of both content and contaminants vary among states, which has led to concerns by the FDA on whether label-

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**TABLE 1 COMMON TERMINOLOGY**

<table>
<thead>
<tr>
<th>Plant</th>
<th>Cannabis: source of fiber, food, oil, and medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Marijuana: dried mixture of cannabis leaves and flowers</td>
</tr>
<tr>
<td></td>
<td>Hemp: strains of cannabis subspecies containing minimal THC/CBD (&lt;0.3% THC)</td>
</tr>
<tr>
<td>Compounds</td>
<td>Cannabinoids – Class of Chemical Compounds</td>
</tr>
<tr>
<td></td>
<td>Endocannabinoid (produced naturally in animals)</td>
</tr>
<tr>
<td></td>
<td>Synthetic cannabinoid (manufactured)</td>
</tr>
<tr>
<td></td>
<td>Phytocannabinoids (naturally occurring chemicals found in cannabis plant):</td>
</tr>
<tr>
<td></td>
<td>Δ9THC—tetrahydrocannabinol</td>
</tr>
<tr>
<td></td>
<td>THCV—tetrahydrocannabidivarin</td>
</tr>
<tr>
<td></td>
<td>THCA—tetrahydocannabinolic acid</td>
</tr>
<tr>
<td></td>
<td>Δ8CBD—cannabidiol</td>
</tr>
<tr>
<td></td>
<td>CBDV—cannabidivarin</td>
</tr>
</tbody>
</table>

*Most studied compounds. From Miller EG, et al.*

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[The AAP’s 2015 policy statement] recognized that medical marijuana may be a viable option for children with life-limiting or life-threatening conditions for whom there are no other alternative treatments available.
For Miller, therefore, it is important to use a very precise definition of medical marijuana when speaking about it. “I’m defining medical marijuana as marijuana, or cannabidiol, obtained through one of the state dispensaries based on the changes in state law,” she says.

Although state laws differ regarding the conditions for which marijuana can be used for medicinal purposes, Miller says that, based on her review of state medical marijuana websites, common conditions for which pediatric patients are eligible include cancer, epilepsy, nausea, muscle spasm, and terminal condition.

Using this definition, prescribing medical marijuana under federal law is illegal. Patients gain legal access to medical marijuana through a physician’s certification that specifies the patient has a qualifying condition that may benefit from medical marijuana, says Miller. Once certification is provided, patients are registered in a state registry that allows them legal access to the state’s dispensary program (Figure).

For example, Wang says that in Colorado, minors need certification from 2 physicians to be eligible for registration on the state’s registry permitting them to obtain medical marijuana at one of the state’s dispensaries. As of May 2019, 330 minors (aged younger than 18 years) are registered, with seizures as the number one indication in children aged younger than 10 years old and severe pain for children aged 11 to 17 years (www.colorado.gov/pacific/cdphe/medicalmarijuana/).

For patients and families who need or want information on how to obtain medical marijuana, it is important to educate them on where these products are purchased (at state dispensaries and not at pharmacies or doctors’ offices) as well as on their variability, because as federally unregulated products there is wide variability in terms of content, dose, and cost (see “Medical vs recreational marijuana: What’s legal, and how to get it.”)

### TABLE 2
FDA-APPROVED CANNABINOID MEDICATIONS IN THE UNITED STATES

<table>
<thead>
<tr>
<th>SYNTHETICALLY DERIVED MEDICATIONS</th>
<th></th>
<th>BOTANICAL EXTRACT FROM THE CANNABIS PLANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marinol (pill) and Syndros (solution)</td>
<td>Dronabinol (active ingredient; synthetic THC)</td>
<td>Nabilone (active ingredient; chemical structure similar to THC)</td>
</tr>
<tr>
<td>Indications:</td>
<td>Indications:</td>
<td>Indications:</td>
</tr>
<tr>
<td>▪ Stimulate appetite to counteract weight loss in patients with AIDS or cancer.</td>
<td>▪ Mitigate nausea and vomiting associated with chemotherapy.</td>
<td>▪ Mitigate nausea and vomiting associated with chemotherapy.</td>
</tr>
<tr>
<td>Cesamet</td>
<td>CBD (purified form)</td>
<td>Epidiolex (solution)</td>
</tr>
<tr>
<td>Indications:</td>
<td>Indications:</td>
<td>Indications:</td>
</tr>
<tr>
<td></td>
<td>▪ Seizures associated with severe forms of epilepsy (Lennox-Gastaut syndrome and Dravet syndrome).</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AIDS, acquired immune deficiency syndrome; CBD, cannabidiol; FDA, US Food and Drug Administration; THC, tetrahydrocannabinol.

From US Food and Drug Administration; Orange S.


![How to obtain medical marijuana for pediatric patients](image-url)
what’s not,” right).

“As states have their own rules and regulations on how to monitor these products for compliance of what the label states the products contain as well as contaminants,” says Wang, emphasizing that despite this, the FDA has published concerns about the labeling of these products. As such, he stresses the need for pediatricians and patients to be wary of false advertisement of some of these products.

The other role for pediatricians may be to certify a patient who may be a good candidate for medical marijuana. For some practices, such as Miller’s, this may be only for patients given the exception through the current 2015 policy statement (eg, children with life-debilitating or life-threatening conditions). As the evidence to date is slim on other conditions, this may be a role that emerges increasingly in the future if the data indicate a clear scientific base for it in children.

Certifying medical marijuana for children

“As pediatricians, when do we certify patients for medical marijuana?” This was a question Miller posed during her presentation.

Although the 2015 AAP policy statement opposes the medicinal use of marijuana for children outside those products approved by the FDA, it does leave open, as previously mentioned, the potential role of medical marijuana for children with life-debilitating or life-threatening conditions. Since that update, further evidence suggests additional potential roles for medical marijuana in children. A systematic review of studies of the use of marijuana for medical treatment of children and adolescents published in 2017 found that the strongest evidence for a benefit was for chemotherapy-induced nausea and vomiting, and for seizures. (Since then, the FDA approved Epidiolex for the treatment of severe seizures in children as noted above; data published in 2016 and 2017 in part led to the approval.)

For all other conditions, the data were too limited by inadequate study design with sufficient power to test efficacy. The authors noted as well that they interpreted the findings of the review in the context of the adult literature, which, they said, is more substantive.

More data is available on the potential harms of marijuana for children. Wang provided an overview of what is known about the short- and long-term effects of marijuana use in children and adolescents. Most of the information comes from exposure to recreational marijuana, which often, if not always, differs from medical marijuana in composition (see “Medical vs recreational marijuana: What’s legal, what’s not,” right).

As to short-term harm, data from a retrospective review of calls to the American Association of Poison Control Centers National Poison Data System between January 2005 and December 2011 found 985 unintentional exposures to marijuana in children aged 9 years and younger primarily through ingestion. The main symptoms, which lasted between 2 and 24 hours, were drowsiness and lethargy. Respiratory depression, bradycardia, or hypotension was found in 10 patients. Of note, the rate of exposure to marijuana increased in states that legalized marijuana.

Wang also discussed several studies documenting an increase in the labeling of these products. As of 2019, medical marijuana is legal in 33 states and Washington, DC; recreational marijuana in 10. At the federal level, marijuana remains a Schedule 1 drug, meaning that it currently has no accepted medical use and has a high potential for abuse.

This is the current legal landscape of marijuana in the United States. Dig a little deeper and it gets more complex. Laws governing the sale and dispensing of products for medicinal or recreational use vary from state to state, and what goes into products also varies. There are more than 100 cannabinoids (class of chemical compounds) in the marijuana (cannabis) plant, of which the most studied are tetrahydrocannabinol (THC, the main psychoactive constituent of cannabis) and cannabidiol (CBD). Products for medicinal or recreational use can have different combinations of these cannabinoids as well as different doses.

Products for pediatric medicinal use typically have higher concentrations of CBD and lower THC and recreational products have higher concentrations of THC, which is the psychoactive component of marijuana. All products for medicinal use are offered through recreational dispensaries, whereas those for recreational use are offered through retail.
in hospital visits, emergency departments (EDs), and urgent care (UC) centers, and regional poison centers by children unintentionally exposed to marijuana since it became legal-ized in Colorado.\textsuperscript{14,16} Data from one study, showing a significant increase in marijuana-related ED/UC visits by adolescents since legalization of marijuana, found that a significant percentage of patients presented with acute psychiatric conditions.\textsuperscript{14}

As to the long-term effects of marijuana use, Wang discussed data on adverse effects in adolescents reported in Colorado (Table 3).\textsuperscript{4,17} He underscored the many unknowns and risks remaining in understanding fully the long-term effects of marijuana in children/adolescents.

### Summary

With the growing interest in and availability of marijuana for medicinal use, pediatricians need to know how to talk to patients and families about what medical marijuana is, how it is obtained, what it is indicated for, the current evidence on its efficacy and safety in children, and other challenging issues around a topic that is evolving state-by-state. For pediatricians such as Miller and Wang, the lack of scientific evidence warrants caution but challenges pediatricians to recognize when medical marijuana may be a viable option for select children/adolescents. “The evidence for marijuana as medicine for all the things it is touted as and used for is not there,” says Wang. “There still needs to be a lot more research about the potential benefits and potential harms for the use in children.”

Recognizing, however, that some patients may already be using marijuana for a medical reason, Wang emphasizes the importance of not alienating these patients. “For community pediatricians, keep an open line of communication with patients,” he says. “We can’t alienate them from their medical homes for using these products, but we have to make sure they are informed of the risks and benefits of them.”

Miller underscores that medical marijuana is not the latest quick fix hoped for by many. She stressed the importance to remember that “right now, for every disease and symptom, there is an alternative available with better evidence than medical marijuana.”

### TABLE 3

**ADVERSE EFFECTS OF MARIJUANA IN ADOLESCENTS**

- **Weekly marijuana use:** Associated with impaired learning, memory, math, and reading—even 28 days after use; associated with high school dropout and may be associated with failure to attain a college degree.
- **Daily/near daily use:** Associated with developing a psychotic disorder such as schizophrenia in adulthood.
- **Youth who use marijuana are more likely to experience psychotic symptoms, such as hallucinations, paranoia, delusional beliefs, and feeling emotionally unresponsive.**
- **Associated with future tobacco and illicit drug use and high-risk of alcohol.**

From Miller EG; Colorado Department of Public Health and Environment.\textsuperscript{17}
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AI in Pediatrics: past, present, and future

Adopting technologies with artificial intelligence (AI) will change patient care in many ways. Here’s where AI has been, where it is now, and what it holds for the future of Pediatrics.

ANDREW J SCHUMAN, MD, FAAP

For many, the expression “artificial intelligence” (AI) conjures up images of a dystopian future in which humans are ruled by malevolent computers or androids. In our real-world, not-quite-dystopic lives, AI is responsible for driving autonomous vehicles, powering intelligent assistants such as Alexa and Siri, and placing annoying advertisements on the web pages we frequently view. Yet, AI is also improving many aspects of pediatric medicine, and in the not-too-distant future AI will dramatically change the way we practice.

AI, machine learning, and deep learning

Simply stated by Merriam-Webster, artificial intelligence is the “capability of a machine to imitate intelligent human behavior.” It is a generic term, and it is important to understand that computers—machines—can be programmed with a series of “if-then” statements that give the appearance of “intelligence.” A good example would be web- or software-based programs used to prepare taxes. There is nothing natively “intelligent” about these programs, but they accomplish something that a human—eg, an accountant—does routinely.

Machine learning (ML) is a subset of AI, with its programs utilizing algorithms to modify themselves by responding to inputted data (Figure 1). Such ML programs can be presented with labeled data and perform “supervised learning,” or be taught to extract data from unlabeled data, which is to perform “unsupervised” learning. Supervised ML can detect faces, identify objects in images, transcribe speech to text, and classify text as spam. Unsupervised ML can compare documents for keywords, detect anomalies in images, and predict changes in health status. Whereas ML programs are capable of some autonomy, human programmers need to modify code when errors occur.

Deep learning (DL) is a subset of ML that is dependent on the development of neural networks. These networks consist of layered sets of algorithms, modeled after the human brain, to recognize patterns within data. Thus, DL systems can modify their algorithms independent of human programming. The layers are made of computational nodes that determine which information should be passed on to subsequent nodes (Figure 2). The more data provided to DL systems, the better they become at doing what they were designed to do. Over the last 10 to 20 years, DL systems have evolved significantly. In the past they beat humans at chess, on the game show “Jeopardy,” and most...
recently at the Chinese game of Go, which requires many magnitudes of calculations more than chess.

IBM, creator of Watson, the AI system that communicates with users via human-like speech, has coined the alliterative term “cognitive computing” to encompass AI, ML, and DL. The term was adopted to give a human spin on the use of AI systems, representing IBM’s belief that Watson and its offspring will complement human judgement and experience rather than replace them. Other AI experts suggest replacing the term “artificial intelligence” with “augmented intelligence” to convey a similar message.

**AI’s history in medicine and Pediatrics**

One of the first AI programs with medical implications was the MYCIN project developed in the 1970s at Stanford University, Stanford, California. It was an expert system that queried a physician regarding patients with severe infections. The program delivered a list of possible causative bacteria and recommended antibiotics with the dosage based on the patient’s body weight. The program performed better than expert physicians but was never used in practice.

A more familiar example of AI currently used in medical practice is voice recognition/dictation software. James and Janet Baker founded Dragon Systems in 1982 to commercialize speech recognition software based on statistical predictive models. Today, the current incarnation of Dragon—Nuance (Burlington, Massachusetts)—boasts a vocabulary of 300,000 words and integrates vocabularies for 90 medical specialties. By integrating DL into the software, the software learns the nuances of one’s speech patterns and improves over time, achieving 99% accuracy.

My first experience with AI in pediatric technology was in 2010 when I wrote about digital stethoscopes and a program from the former Zargis Medical called “CardioScan” that used DL to analyze recorded heart sounds and identify murmurs that should be investigated with an echocardiogram. This technology was called computer-assisted auscultation (CAA), and CardioScan performed much better than pediatricians in identifying potentially pathologic murmurs. The CAA technology is available today via a program called SensiCardiac (Diacoustic Medical Devices; Stellenbosch, South Africa). It has become popular in third-world countries where pediatric cardiologists are in short supply.

**Current state and future implications**

Much research is ongoing in AI and healthcare, and many studies (Figure 3) have important implications for pediatric care. Despite the abundance of research that demonstrates how AI can improve healthcare, relatively few products/devices have been granted US Food and Drug Administration (FDA) approval. In April 2019, the FDA issued its recommendations for a new approval process for clearing medical devices that use AI algorithms to assist in diagnosis. According to the FDA, devices that utilize ML algorithms have the potential to adapt and optimize performance over time. To respond to this regulatory challenge, the FDA has proposed adoption of a “predetermined changed control plan” in all premarket submissions of medical devices that utilize ML algorithms. This would require that manufacturers provide periodic updates to the FDA as their devices and algorithms change over time.

Cognitive computing is poised to change healthcare in many ways. It will impact our ability to expedite identification of biomarkers to more effectively treat cancers; facilitate mental health diagnoses; accelerate drug development; promote patient safety; predict how environmental change will affect short-term and long-term health; and much, much more.

The process from the inception of a healthcare DL algorithm to implementation can take years. First, studies need to demonstrate the efficacy of a healthcare algorithm, and once perfected these must undergo clinical validation before FDA approval becomes possible. It would take a much longer article to detail the science, math, and programming re-
practice improvement

sensible for healthcare DL neural networks, but I will describe some recent developments in healthcare AI relevant to Pediatrics that are quite exciting.

**ELECTROPHYSIOLOGY**

In 2017, AliveCor (Mountain View, California) received FDA approval for marketing the KardioMobile portable device that records 1-lead electrocardiograms (EKGs) and detects atrial fibrillation via a Bluetooth connection to a smartphone. One year later, Apple received its own FDA approval and integrated atrial fibrillation detection into the Apple Watch series 4. Although atrial fibrillation is rare in Pediatrics, both devices can be used for recording brief EKGs in children with palpitations and sharing these with their pediatricians or pediatric cardiologists.

In the coming months, AliveCor is releasing an upgraded device that will perform a 6-lead EKG called the KardioMobile XL. In addition, the Zio XT patch (iRhythm Technologies; San Francisco, California) is an EKG monitoring system that has a 2-week storage capability. The device was developed using a deep neural network (DNN) and trained on a data-set of 91,232 EKG records from some 53,549 patients to accurately recognize 10 arrhythmia types including supraventricular tachycardia. The Zio XT patch is currently used by pediatric cardiologists when a traditional Holter monitor will not suffice.

There have been several studies indicating that DL algorithms are capable of reading and interpreting electroencephalograms (EEGs), but these have yet to be developed and integrated into routine practice.

**RADIOLOGY**

Several companies (Aidoc [Tel Aviv, Israel], Neural Analytics [Los An-
犊es, California], MaxQ-AI [Andover, Massachusetts], Viz.ai [San Francisco, California], and Imagen [New York, New York] have received FDA approval for marketing adjuncts to radiology software, commonly referred to as “picture archiving and communication systems” (PACS). These expedite diagnoses of intracranial bleeding, multiple sclerosis, traumatic brain injury, pulmonary embolisms, and wrist fractures. There are even ultrasound systems now available for expediting stroke diagnosis for elderly patients by emergency medical technicians in the field. A study published just a few months ago showed that a DL algorithm could perform bone-age assessments better than radiologists.

**DERMATOLOGY**

Artificial intelligence systems can be trained to recognize skin cancer, and a large study published last year demonstrated that AI can identify malignant melanoma as well as a panel of 58 dermatologists. As of yet there are no FDA-cleared products for skin cancer detection, but BlueScan Labs (San Francisco, California; www.bluescanlabs.com) is inviting clinicians to share images of suspect lesions with the company, with the intention of building a large-enough dataset to develop an accurate skin cancer detection system.

**OPHTHALMOLOGY**

The FDA cleared the autonomous IDx-DR device (IDx Technologies; Coralville, Iowa) in 2018, which facilitates detection of retinopathy in diabetic patients aged 22 years and older, without an ophthalmologic examination. The system is intended for use in optometry and primary care offices. In addition, there are now telemedicine photo systems that enable detection of retinopathy of prematurity (ROP) in premature infants who are cared for in remote neonatal intensive care units that may not have access to pediatric ophthalmologists. A study published last year demonstrated that DL algorithms could be used to accurately screen for ROP via telemedicine.

**GENETICS**

DeepGestalt is a community-driven phenotyping platform trained on a dataset of more than 17,000 images representing 200 syndromes. It has been shown to achieve an accuracy of 91% in syndrome identification. Pediatricians can subscribe to the Face2Gene project (Boston, Massachusetts; www.face2gene.com) and utilize its smartphone application to identify a patient’s syndrome while enlarging the project’s dataset.

**CLINICAL DECISION SUPPORT**

Earlier this year, American pediatricians collaborated with pediatricians in China to extract information from the Guangzhou Women and Children’s Medical Center electronic health record (EHR) system to develop a “clinical decision support system” (CDSS) tool. In total, 101.6 million data points from 1,362,559 EHRs were extracted from free-text EHR notes using natural language processing algorithms. When tested, the study’s CDSS tool bested “junior pediatricians” but not “senior pediatricians” in diagnosing cases of asthma, encephalitis, gastroenteritis, pneumonia, sinusitis, upper-respiratory infections, and psychiatric diseases. Overall, the system was able to produce accurate diagnosis 90% of the time and no worse than 79% of the time.

CONTINUED ON PAGE 45

**WHY AI NOW?**

Over the past 10 years, there has been a remarkable expansion in the use of deep learning (DL) systems in healthcare. Although artificial intelligence (AI) had its origins well over 50 years ago, we are now at a time in human history that may well be considered the “AI Renaissance.” This has come into being because of a perfect storm resulting from advances in technology and computer science as well as adoption of smartphones and the ability to extract data from a variety of resources.

Firstly, graphic processing units (GPUs), used to power high-resolution video games, have improved significantly over the last decade to the point where they include hundreds of cores and can perform millions of computations per second. Cluster GPUs in servers or place them in the cloud and you have an incredible amount of computer power that can be leveraged to perform DL analysis efficiently and inexpensively.

In addition, much information has become digitized, and paper records are becoming obsolete. Google and Apple enable the collection of information about where we go, what we buy, what we view, and much more. We now have healthcare sensors and connected devices that communicate remotely via the Internet. Because data is digitized, information exists in expansive labeled datasets that facilitate training of DL systems.

Lastly, there have been advances in “image detection systems” such that computers can analyze images—for example, X-rays—as well as advances in “natural language processing” so that DL programs can scrub and extract data from organized databases as electronic health records (EHRs). As a consequence, DL programs are now used extensively in finance, government, education, and business, as well as in healthcare.

—ANDREW J. SCHUMAN, MD, FAAP
new therapies can prevent functional or life-threatening complications.

Q. What are some of the subtle signs or diagnostic tip-offs and clues community pediatricians need to know and at what point should they refer a patient to a specialist?

A. That is such a good question. In the last few months, actually in January of this year, a “Clinical Practice Guideline for the Management of Infantile Hemangiomas” by Daniel Krowchuk and colleagues was published in Pediatrics, which goes over that very issue. What are the signs we look for? Which are the ones that we have to worry about? We know that some are known to be higher risk, long term, and we need to look for those.

Which ones are high risk? Sometimes they’re pretty subtle. Sometimes just more than 5 little hemangiomas anywhere on the body can be a concern because those can be associated with liver hemangiomas, internal hemangiomas, and can be a problem long term for the baby. So, any child who has 5 or more hemangiomas, even if they look tiny—and often they are very tiny in this particular subset disorder—those children need to be evaluated, and often we get an ultrasound of the liver.

The other thing that presents subtly is the child has had some little hemangiomas on the face in what we call the beard area around the chin, the neck, right in front of the ears, and sometimes those hemangiomas are quite small and seem inconsequential, while other times they are more apparent. They don’t look that big or worrisome, but they can be associated with airway hemangiomas that can be a big problem for those kids. Often the mom will come in and say: “Well, my son has had these little spots. I wasn’t worried about them, but he gets croup and he’s had croup 3 or 4 times in the last 6 months, but when he gets steroids he gets better.” Well, the astute clinician will know that the croup that baby is getting is actually an internal hemangioma blocking his airway—1 or more growing in the airway. Every time that child gets steroids, it shrinks those lesions and therefore he does better, but the hemangiomas will keep growing every time the steroids are stopped.

How would I know that looking at that baby? Those sometimes inconspicuous hemangiomas that are in the beard distribution, in front of the ears, along the neck, along the chin line are other subtle lesions that often portend a more significant problem. Any lesion on the face we need to take seriously, no matter how small it is, because it can leave a mark that may be worrisome to the family, even if they never caused a medical issue.

Also concerning are hemangiomas around the eyes or nose or mouth. A small hemangioma around the eyes can enlarge significantly over a 3- to 6-month period and can obstruct vision, and sometimes, unfortunately, leave children with permanent visual disabilities because the hemangiomas are obstructing vision at a very important time of visual development.

Again, this Clinical Practice Guideline actually lays out the higher-risk areas and the higher-risk lesions, as I’ve talked about: Lesions on the beard area are perhaps related to underlying airway problems; multiple lesions on the body might be related to liver hemangiomas; any hemangiomas that could obstruct vision or could cause a problem with eating or distorting the nose or lips are a potential issue, as are those in the genital areas. If you have a hemangioma in the genital area or the perianal area, it often will erode from friction and cause a significant degree of pain for the baby.

“There’s a window, in the first 1 to 3 months, that if you get in there and intervene you can prevent [hemangiomas] from getting bigger and becoming more of a problem.”
—SHEILA FALLON FRIEDLANDER, MD
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One of the main goals for the guideline is to recognize these high-risk lesions and get them in for appropriate evaluation and treatment. There’s a window, in the first 1 to 3 months, that if you get in there and intervene you can prevent these lesions from getting bigger and becoming more of a problem.

Q. When hemangiomas do need to be treated, what are some of the treatment guidelines for which pediatricians should be aware?

A. The most effective treatment that we’re now clear about, and it shows a chart delineating that propranolol is the treatment of choice for worrisome hemangiomas. That doesn’t mean that every child who comes in to your office with a hemangoma gets propranolol, but for those lesions where you are significantly concerned about an untoward outcome, propranolol is the drug of choice at a dose of 2 mg to 3 mg per kilogram.

Now there are some concerns with propranolol. Kids who are on this drug need to be fed. If they do not eat or absorb food for a prolonged period, they can become hypoglycemic. In addition, because propranolol is a beta-blocker, you don’t want to put a child with bad asthma or reactive airway disease on the drug because it may make that worse. Certainly you want to know that the patient doesn’t have cardiac problems or any significant central nervous system (CNS) or cranial vascular problems, but often if the cardiac, blood pressure, pulmonary, and general exam are within normal limits, those kids will do very well on propranolol.

We do, however, always warn the families that if your child stops eating, has diarrhea and vomiting, is sick, or if is there anything untoward going on with his health, then we want you to withhold the treatment. However, other than that, most kids will do absolutely fine, even though one would think propranolol is going to drop their blood pressure. The effect propranolol has on blood pressure in a healthy child is minimal, and in a healthy child on the right dose it doesn’t usually lead to any significant problems.

One serious issue, though, is that as soon as this baby starts to get better and his hemangioma shrinks, the families want to discontinue the drug. They’re so happy he started it and they’re so excited about stopping it. Yet we know it’s extremely important that the family understands that if we want to prevent recurrence or rebound growth of the hemangioma, that child needs to be on medication for a minimum of 6 months and most often up to 10 to 12 months. So I tell my patients, your child is going to be on this drug probably for at least 10 months. If you tell them out of the gate that that’s the case, they’re much better able to deal with the long duration of treatment. Pediatricians can handle much of this follow-up, and we dermatologists can work with our primary care docs in following up on these kids so that it’s a shared responsibility during their treatment.

Q. Any other aspects of aftercare that community pediatricians should know about?

A. I was just thinking that one other treatment we use a lot is topical timolol. The 0.5% gel-forming solution is a beta-blocker as well and works very similarly to propranolol, but it has the advantage of being a topical formulation. You don’t have to give it by mouth, and therefore, when used appropriately, the systemic exposure is less than that of oral propranolol. We have used this for hemangiomas that aren’t really that deep or problematic, and it’s very useful. It appears to help short-circuit the growth cycle so that it will often lead to lightening of the lesion and sort of an abrupt arrest in growth. Most experts don’t want to use more than 1 to 2 drops twice a day, but it appears to be a very safe drug when used in the right amount on children. It is important, though, to monitor response, because if it is ineffective, propranolol may need to be initiated.

Timolol is something that pediatricians can feel comfortable with. I do think that if a child comes in to the office and has a small lesion on the forehead, for example, and the family’s concerned, you know that the lesion is not going to interfere with vision but it’s a cosmetic issue for them. For a thinner lesion, in the first month or 2 of life, start the topical timolol—1 or 2 drops twice a day—and it really can hold things at bay. Primary care providers can feel comfortable with this plan if they monitor response to the treatment. If there is an issue or if the lesion starts to grow, they can involve the dermatologist at that point.

The other thing is, with any lesion we need to observe and have vigilance about it because these lesions can start out and look a little smaller but then get more of a life of their own in the first 3 to 4 months of life. Follow-up’s really important, and the pediatrician, dermatologist, or chronic care doc can all work together to take care of these families.
**Is there anything else that community pediatricians need to know?**

**A.** I think that they need to remember that although the vast majority of these lesions will not cause a medical harm to the children who have them, they often can leave a scar that is a psychological issue, so for any hemangioma that’s in a cosmetically important area, and that includes the face and the hands and the neck, those kids are worthy of monitoring and therapeutic intervention. Many of them will respond to topical timolol treatment. If they have large, rapidly enlarging lesions, or for those that pose a significant risk in a problematic site, then they may need systemic propranolol. We now can stop the cycle and make a big difference in the eventual outcome medically and often cosmetically for these kids.

**Ms Hilton** is a medical writer who has covered health and medicine for 25 years. 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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**AI in Pediatrics**

We do not have a CDSS released for general pediatric use yet, but it is just a matter of time before CDSS tools are integrated into our EHRs. These can guide physicians to the most likely diagnosis, order the most cost-effective tests, and prescribe the least-expensive antibiotics while reducing medical errors.

**Beware the ‘black box’**

According to Wikipedia, a “black box” is a system that “can be viewed in terms of its inputs and outputs, without any knowledge of its internal workings.” Therefore, most AI applications in healthcare function as a “black box” system. That is, their implementation is considered “opaque” to those utilizing the system. There are many physicians who believe—as I do—that medicine is more art than science and cannot be reduced to “cookbook” algorithms. As DL systems will improve with use, the dilemma we face is explaining to colleagues and patients why DL-derived recommendations are made. Now more than ever there is a growing emphasis on changing DL systems to be more “transparent.”

**Conclusion**

This discussion of AI’s applications in Pediatrics should convince pediatricians that cognitive computing has the potential for improving pediatric practice. It is unlikely that computers will become “self-aware” and compete with pediatricians for patients. Pediatricians should keep an open mind to adopting AI technologies that will improve care while reducing the hassles associated with pediatric practice.

**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.

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**FIGURE 3 NUMBER OF PUBLICATIONS RELATING TO AI IN PEDIATRICS**

Abbreviation: AI, artificial intelligence.

Adapted from Kokol P, et al.

**Q.** Is there anything else that community pediatricians need to know?

**A.** I think that they need to remember that although the vast majority of these lesions will not cause a medical harm to the children who have them, they often can leave a scar that is a psychological issue, so for any hemangioma that’s in a cosmetically important area, and that includes the face and the hands and the neck, those kids are worthy of monitoring and therapeutic intervention. Many of them will respond to topical timolol treatment. If they have large, rapidly enlarging lesions, or for those that pose a significant risk in a problematic site, then they may need systemic propranolol. We now can stop the cycle and make a big difference in the eventual outcome medically and often cosmetically for these kids.

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For reference, go to ContemporaryPediatrics.com/infantile-hemangiomas
The differential diagnosis for IDF includes periungual fibromas, supernumerary digits, and acral fibrokeratomas.

Periungual fibromas are pink to skin-colored papules that develop from the proximal nail fold.\(^1,8\) They are associated with tuberous sclerosis and von Recklinghausen disease.\(^8\) In fact, approximately 50% of patients with tuberous sclerosis have multiple periungual fibromas, also known as Koenen tumors.\(^1\) However, solitary periungual fibromas can also be seen in the general population.\(^8\) They can produce pressure on the nail matrix, resulting in a longitudinal groove in the nail plate.\(^1\)

Supernumerary digits are soft tissue growths that lack a skeletal component.\(^1\) They can appear as fleshy or verrucous-like papules, or present as larger, pedunculated nodules. Supernumerary digits are present at birth and often found bilaterally, with the most common location being the lateral aspect of the fifth finger.

Acral fibrokeratomas, also known as acquired digital fibrokeratomas, are relatively rare, benign skin growths.\(^1,9\) They present as skin-colored to pink, faintly keratotic papulonodules. Acral fibrokeratomas are typically solitary and tend to occur on the fingers and toes of middle-aged adults. They also can be seen on the palms and soles.\(^9\)

Management
Currently, there is no agreed-upon treatment approach for IDFs. Surgical excision is a viable option; however, recurrence is common with an estimated recurrence rate between 61% to 74%.\(^3\) Therefore, surgical excision is typically reserved for symptomatic cases causing pain or functional impairment.

Nonsurgical options include topical steroids, intralesional triamcinolone, or intralesional 5-fluorouracil (5-FU).\(^3\) However, these nonsurgical approaches have not been studied extensively, given the rarity of this condition. Eypper and colleagues recently proposed a management algorithm for IDFs: If symptomatic, proceed to surgical excision; if asymptomatic but greater than 1 cm, treat with intralesional triamcinolone or intralesional 5-FU; if asymptomatic and less than 1 cm, continue to monitor.

Patient outcome
A shave biopsy confirmed the diagnosis of IDF in this infant girl. The growth continued to rapidly enlarge, causing slight distortion of the distal interphalangeal joint. Surgical excision was performed at the age of 14 months without complication. However, at age 3 years the patient returned to the clinic for evaluation of a new growth on the dorsolateral aspect of her distal left fourth finger, clinically consistent with IDF. There also was evidence of recurrence of the previously excised IDF on her left fifth finger.

Given the small size of these growths (both less than 1 cm), clinicians opted to closely monitor the patient and prescribed clobetasol 0.05% cream to be used 2 times daily on the affected areas.

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

For references, go to ContemporaryPediatrics.com/dermcase-0719

Diffuse rash spreads from infant’s scalp to extremities
The infant has begun to scratch it.
ContemporaryPediatrics.com/dermcase-0519

Hypopigmented lesions in a teenaged girl
Multiple ovoid macules appeared on her bilateral anterior thighs.
ContemporaryPediatrics.com/dermcase-0419

Fuzzy brown spots on a healthy 3-year-old
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An otherwise healthy 5-month-old girl presents with an asymptomatic, rapidly growing, firm, smooth nodule on the side of her left fifth finger since she was 2 months of age (Figure).

**FIGURE** On the patient’s left fifth finger there is a rapidly growing, firm, smooth, pink nodule.

**INFANTILE DIGITAL FIBROMA (IDF)**

**Discussion**

Infantile digital fibromas (IDFs), also known as inclusion body fibromatosis or recurring digital fibrous tumors of childhood, are rare, benign, fibromatous tumors most commonly located on the dorsolateral aspects of the fingers and toes.1 These fibromas typically develop during the first year of life; however, they are present at birth in up to one-third of cases.2,3 In rare circumstances, they can appear during adulthood.4

Infantile digital fibromas initially exhibit a period of slow growth, which is followed by a rapid growth phase over 10 to 14 months.2 They can ultimately reach sizes ranging from 3 mm to 35 mm.2 They subsequently regress without treatment within 2 to 3 years.6

These fibromas classically appear as single to multiple, smooth, firm, skin-colored to pink nodules on the dorsolateral aspects of the fingers and toes.1,7 Interestingly, the thumbs and great toes are typically spared.1,2,7

**Histopathology**

Histopathologic examination reveals proliferations of spindle-shaped myofibroblasts admixed with collagen bundles within the dermis.1,2 The presence of eosinophilic inclusions arranged in a perinuclear fashion within the myofibroblast cytoplasm is pathognomonic for IDF. Masson’s trichrome stains these inclusions red, whereas phosphotungstic acid-hematoxylin (PTAH) stains them purple.1

FOR MORE ON THIS CASE, TURN TO PAGE 46.
Hemangiomas in Pediatrics

This month, Contemporary Pediatrics focuses on Dermatology—to be specific, pediatric hemangiomas—and talks with Sheila Fallon Friedlander, MD, professor of Dermatology and Pediatrics at the University of California-San Diego School of Medicine (UCSD) and former Director of the Dermatology Fellowship Training Program at Rady Children’s Hospital-San Diego. Dr. Friedlander trained at the University of Chicago and the University of California, Los Angeles (UCLA) Medical Center and is board certified in Pediatrics and Dermatology, with subspecialty training in Infectious Diseases. She is a member of the Academy of Clinician Scholars at UCSD, past-president of the Society for Pediatric Dermatology, and an elected member of the American Academy of Dermatology Board of Directors. Dr. Friedlander says that some older views about pediatric hemangiomas are outdated in the light of just-published guidelines that will help pediatricians quickly identify these lesions in children and begin what could possibly be life-saving intervention.

Q. Dr. Friedlander, what is the one key dermatologic condition or disease state that you believe community pediatricians should be especially vigilant about, either because it’s trending upward in severity or frequency or is being missed or underdiagnosed?

A. I think that infantile hemangiomas pose a challenge for clinicians. They are sometimes very subtle and oftentimes don’t need to be treated, but a significant minority can be functionally and/or life-threatening for patients. They occur in about 5% of newborns, so this is something that pediatric clinicians see a lot and therefore can be challenged by what’s the way to approach them and how important are they. I think that we have an increased amount of knowledge in the last few years in terms of how to diagnose them, when they’re a problem, and what is the best plan in terms of treating them.

Q. Are there some key misconceptions or data gaps that you believe some pediatricians may hold about pediatric hemangiomas?

A. Yes, and having been a pediatrician before I was a dermatologist I remember clearly that we were incorrectly taught that hemangiomas generally are nothing to worry about—they’ll grow and then they’ll go away without any sequelae. However, we now know that even the smallest hemangiomas can leave parchment-like or sometimes disfiguring scars, so that even though they didn’t obstruct vision, they didn’t risk this baby’s life, they may leave this child with a permanent mark. We now have treatments that can help decrease the chance of leaving a significant mark for these kids. More important,
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