CONTEMPORARY PEDIATRICS SEPTEMBER 2014 VOL. 31 NO. 9

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SEPTEMBER 2014
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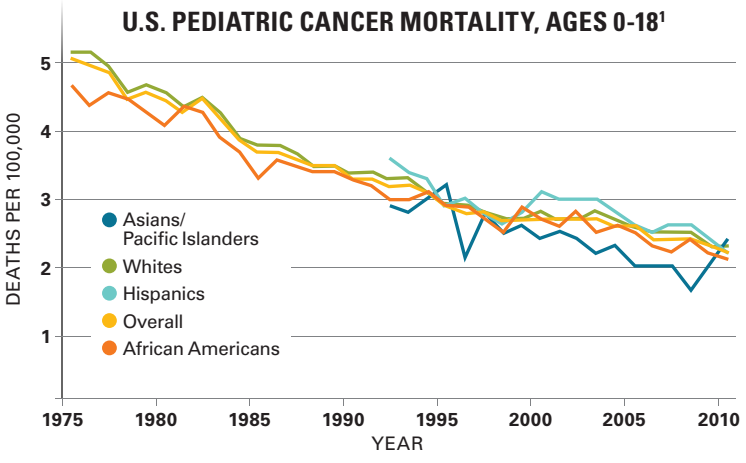

In the 30 years since the first issue of *Contemporary Pediatrics*, the mortality rate for all pediatric cancers combined has declined by more than 50%.[2] But although pediatric cancer mortality has plunged, it is still the leading disease-related cause of death for US kids. Further, some pediatric brain tumors for which no new protocols have been developed in 30 years such as brain stem gliomas and pontine gliomas, remain terminal upon diagnosis.[2]

Regrettably, this increased survival often comes at a cost. Pediatric cancer survivors face life-long health issues, termed "late effects," including serious chronic conditions and secondary cancers likely related to the very treatments that helped these children survive their cancer. More than ever, they depend upon their pediatrician not only to be the first to detect cancers' early warnings and make critical referrals, but to remain the primary sentinel for often a life-spanning monitoring of their patients' well-being and a partner on their cancer journey.

1. National Center for Health Statistics.

2. *An Analysis of the National Cancer Institute's Investment in Pediatric Cancer Research*, National Cancer Institute, U.S. Department of Health and Human Services, National Institutes of Health, September 2013.

CDC CALLS OUT PEDS ON DISMAL HPV VAX RATE

In an exclusive interview with *Contemporary Pediatrics*, Anne Schuchat, MD, assistant surgeon general in the United States Public Health Service and the director of the CDC's National Center of Immunization and Respiratory Diseases, implores pediatricians to counsel parents that the HPV vaccine is about cancer prevention, not promiscuity.

See the video at ContemporaryPediatrics.com/hpvvax

Plus, download this message-tested tip sheet for parental dialogues written with pediatricians in mind http://www.cdc.gov/vaccines/who/teens/for-hcp-tipsheet-hpv.pdf

at the podium

Be sure to catch *Contemporary Pediatrics'* own **Editorial Advisory Board Member, Jane Oski, MD, MPH, FAAP**, give her plenary session talk at next month's 2014 AAP National Conference & Exhibition in San Diego. Her not-to-be-missed topic? ***"Where There is No Psychiatrist: A Method for Addressing the Needs of Underserved Communities Using Telebehavioral Health."*** Monday, October 13, 11 am. (Session P3076)

what's trending

1. **Child with fever after foreign travel**
   ContemporaryPediatrics.com/puzzler0714
2. **Wet wraps relieve eczema in kids**
   ContemporaryPediatrics.com/wet-wraps
3. **AAP issues advice on screening teens for STIs**
   ContemporaryPediatrics.com/AAP-sti

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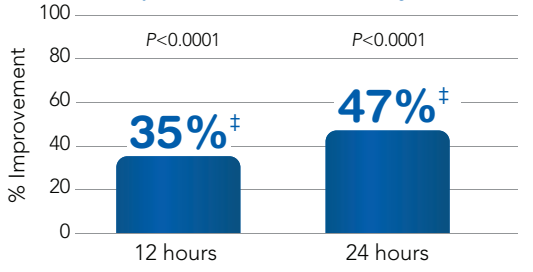

‡Efficacy and safety assessments were performed by a trained evaluator at baseline, and at 12 and 24 hours post-baseline (N=57). Subjects (2-36 months of age) must have received an "Overall Severity Score" of >1.5 as determined by evaluator at enrollment. Diaper rash severity was assessed using a 0- to 3-point scale (0=none; 3.0=severe).

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References: 1. Data on file. **2.** Brown WM, Berg JE, Li Q, Kohut BE. A clinical study to evaluate the efficacy of two marketed zinc oxide-based diaper rash ointments in children with diaper dermatitis. Poster presented at: Clinical Dermatology Conference; October 6-9, 2006; Las Vegas, NV. **3.** Product monograph. 68 FR 33377, June 4, 2003.

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To MOC or not to MOC?

editor's note

Our readers had a lot to say about our Special Report, "Maintenance of Certification: Myths, facts, and FAQs," published in the August 2014 issue. Some of you supported MOC, others had not-so-kind words to say about the program and about *Contemporary Pediatrics* for publishing this article. Some took exception to the fact that the author, Virginia Moyer, MD, MPH, is employed by the American Board of Pediatrics (a conflict of interest that has been noted online).

We thank you for the comments you sent via e-mail or posted online. We welcome the discussion, and we hope that you will keep the exchange of ideas going.

Let us know what you think about MOC, pro or con. E-mail cradwan@advanstar.com or go to http://bit.ly/1mRVqNy to read what your peers have to say and to post your own comments.

I HAVE READ MANY ONLINE POSTS ABOUT MOC, and it seems that the vast majority of doctors find MOC a waste of time and money. I completed my MOC requirements and I have to agree.

We have had CMEs that [were] not only required, but a very good idea to keep up-to-date. Any good doctor would want to maintain his or her knowledge and skills and thus competency.

MOC seems to be only busy work and costly, in time and money better spent doing good CME. I find it interesting that those who run the MOC and the Boards are the ones trying to "sell it" to the rest of us.

Also, most of the board members got themselves grandfathered in. The rest of us seem to have no choice—do MOC or not be board certified—not much of an option!

How did we all lose control of our profession?

ROBERT WIETING, MD, FAAP
Texas Children's Pediatrics
Sugar Land, Texas

I READ DR. VIRGINIA MOYER'S ARTICLE DEFENDING MOC requirements in response to several objections and critics that she has recently faced. The most important thing that many pediatricians are angry and frustrated about is that these requirements are putting too much of a burden on practicing pediatricians who do not have enough time to meet these requirements.

Second, [the American Board of Pediatrics (APB) is] trying to treat us like students [by making] us attend a secure [center] to take the exam every 10 years. It is so ridiculous.

Imagine a 60- or 70-year-old pediatrician after 20 to 30 years of practice [having] to attend a secure exam [center] and answer all the questions in a limited allowed time.

I am surprised that Dr. Moyer does not understand this stressful situation that she and her colleagues have created. They can do [the testing] through an open Internet system rather than in a secure exam center.

The recertification process should be updating, not testing. If the ABP continues these ridiculous requirements, they are going to lose more pediatricians every year.

I am one of the pediatricians who definitely will retire sooner than I should if the ABP continues to emphasize this secure board exam every 10 years.

VAHID MEHRPOUYAN, MD, FAAP
Whitesburg ARH Hospital
Whitesburg, Kentucky

To read Dr Moyer's response and other letters, go to ContemporaryPediatrics.com/mocletters

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Physicians to appeal court's affirmation of Florida law restricting gun counseling

The American Academy of Pediatrics (AAP) Florida Chapter and others plan to appeal the recent federal court decision that approves a Florida "gag" law restricting physician counseling and medical record notation about firearm ownership or presence in a patient's home.

In July, a 3-judge panel of the US Court of Appeals for the Eleventh Circuit upheld the 2011 state law that would prohibit healthcare professionals or facilities from asking questions about ownership of a firearm or ammunition; the presence of a firearm in a home; or from entering information about firearm ownership in a patient's record. The Florida chapters of the AAP, the American Academy of Family Physicians, and the American College of Physicians and others had filed a lawsuit, calling the law a restriction of free speech.

The Court decision said, "The Act recognizes that when a patient enters a physician's examination room, the patient is in a position of relative powerlessness," and that "the Act simply acknowledges that the practice of good medicine does not require interrogation about irrelevant, private matters."

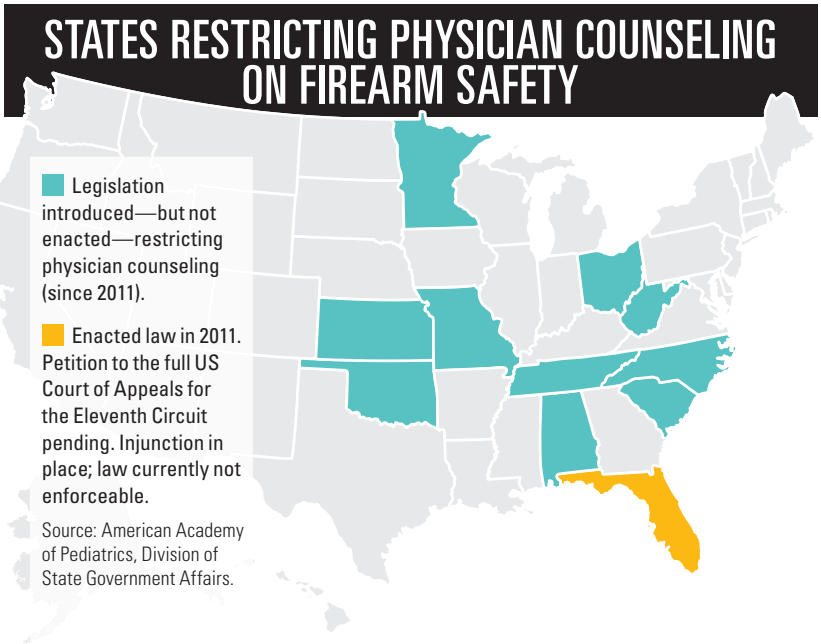
In August, Mobeen Rathore, MD, president of the Florida AAP chapter, said the organization would be asking for a hearing from the full Eleventh Circuit Court of Appeals, and, if the Court agrees to hear it, the chapter hopes that will happen in the next few months.

The Florida law does say that such questions may be asked if the practitioner or facility in good faith believes the queries are relevant to the patient's medical care or safety.

Florida's National Rifle Association (NRA) had pushed for the legislation. Marion Hammer, lobbyist for the group, said the doctor in each case is responsible for deciding when the question is relevant. "If the doctor believes that the patient is suicidal, asking about a gun, whether or not they own a gun, would certainly be pertinent to medical care. . . . If a doctor asks in a situation where it is appropriate, he or she should feel on firm ground, because the patient can only make a complaint to the medical board who is ultimately the decision maker."

Hammer and local news reports said the push for the law was inspired by the case of a woman who refused to answer when a pediatrician asked if she owned a gun and then had the doctor tell her he would no longer see her child.

There were many similar complaints, according to Hammer. The



Eleventh Circuit Court opinion said that during the legislative debate cases were described in which children separated from their mother in doctors' offices were asked if their mother owned a firearm. A state legislator, according to the Court, has been asked by a pediatrician to remove his gun from his home.

According to the National Center for Health Statistics, in 2011 there were 11 deaths by firearms in children aged younger than 1 year, 75 for children aged 1 to 4 years, and 311 for those aged 5 to 14 years.

Also, according to the Centers for Disease Control and Prevention's Web-based Injury Statistics Query and Reporting System, in 2012 there were 1322 nonfatal gunshot injuries in children aged 0 to 14 years.

A friend of the court brief filed by the American Public Health Association and others also argued that the law infringes upon the public's right to receive information, a part of free speech repeatedly recognized by the courts.

Asked about the NRA's gun safety programs, Hammer said, "When people come to NRA for gun safety training, we give them gun safety training. When people go to pediatricians for medical care, they do not expect nor do they want gun safety training."

Other groups that have signed a brief opposing the law are the American Medical Association, the American Academy of Family Physicians, the American Academy of Child and Adolescent Psychiatry, the American Academy of Orthopaedic Surgeons, the American College of Surgeons, the American College of Preventive Medicine, the American College of Obstetricians and Gynecologists, and the American Psychiatric Association.

Florida is the only state that has enacted such legislation, but 10 other states have had similar legislation introduced since 2011. What happens with the Florida case could significantly impact what other states decide to do, the AAP Florida chapter's Rathore said. ■

Go to ContemporaryPediatrics.com/alevine to listen to **Adam S. Levine, MD, JD**, discuss implications of the First Amendment challenge to the Florida "gag" law for physicians.

BY MARIAN FREEDMAN | COMMENTARY BY MICHAEL G BURKE, MD | f CONTEMPORARYPEDIATRICS

More rotavirus vaccine use leads to less diarrhea-associated healthcare

As rotavirus vaccine coverage increased from 2009 to 2011, diarrhea-associated healthcare utilization and costs continued the decline that began after the pentavalent rotavirus vaccine (RV5) and the monovalent vaccine (RV1) joined the recommended vaccine list in 2006 and 2008, respectively. An analysis of claims data for children aged younger than 5 years also showed that both vaccines provide high protection against rotavirus hospitalizations, with RV5 conferring durable protection through the fourth year of life.

By the end of 2010, RV5 and RV1 coverage rates reached 58% and 5%, respectively, among those aged younger than 5 years. In this age group, annual rates of diarrhea-associated hospitalization, emergency department (ED) visits, and outpatient visits fell significantly during each of the 4 postvaccine seasons from 2007 through 2011, except for ED and outpatient visits during the 2008-2009 season. In 2010-2011, the rate of rotavirus-related hospitalizations fell by 92% among RV5 recipients and 96% among RV1 recipients, compared with unvaccinated children.

Nonetheless, compared with prevaccine rates in 2001-2006, rotavirus-related hospitalization rates among unvaccinated children decreased by 50% in 2007-2008, 77% in 2009-2010, and 25% in 2010-2011 (Leshem E, et al. *Pediatrics*. 2014;134[1]:15-23).

commentary

If you care for hospitalized children, you could probably have guessed the results of this study. During the last 3 to 4 years, the mid- to late-winter tsunami of children with diarrheal illness has failed to materialize. That's why, despite a slight increased risk of intussusception (*N Engl J Med*. 2014;370[6]:503-512; *N Engl J Med*. 2014;370[6]:513-519), you are administering rotavirus vaccine to children in the first 6 months of life. It's nice to see measurable results of your hard work. —Michael G Burke, MD

Guidelines prompt skeletal surveys

When should a young child's fracture raise suspicion for abuse and prompt an order for a skeletal survey (SS), a series of about 20 radiographs? To answer this question, a multispecialty panel of 13 experts from key pediatric specialties, including child abuse, emergency medicine, trauma, radiology, and orthopedics, applied evidence from a literature review along with their own expertise in rating the appropriateness of performing an SS in hundreds of clinical scenarios. Of 240 scenarios, winnowed down from an initial 525, panelists agreed that SS was "appropriate" for 191, and in 175 of these 191 scenarios, appropriate but also "necessary."

According to the guidelines, SS is necessary for children aged up to 23 months with fractures from abuse or domestic violence and for children with additional injuries unrelated to the fracture, such as bruises or burns. A delay of more than 24 hours in seeking care is an indication for SS in children aged up to 11 months, regardless of type of fracture or symptoms. In children aged 12 to 23 months, such a delay calls for an SS only if the fracture is associated with significant pain or physical findings.

Panelists determined that SS is necessary in children aged up to 11 months with long-bone fractures, excluding distal radius/ulna buckle fracture, or in fracture in children aged 9 to 11 months sustained during a fall while cruising or walking. In children aged 12 to 23 months, SS is necessary for a classic metaphyseal lesion and for fractures attributed to being hit by an object. Also, SS is necessary for skull fractures in children aged up to 11 months, except for infants aged 7 to 11 months with linear, unilateral skull fractures caused by falling.

In addition, SS was deemed necessary for children aged up to 23 months with rib fractures and appropriate for infants aged 11 to 21 days with acute fractures and infants aged younger than 30 days with healing fractures. Outside the neonatal period, SS is necessary in children aged younger than 24 months with acute fractures, except for those aged 12 to 23 months with history of a fall, according to guidelines (Wood JN, et al. *Pediatrics.* 2014;134[1]:45-53).

commentary

This study is based on a bit of literature and a lot of expert opinion. Sometimes it's good to have experts' advice when you are making decisions on which children with fractures need evaluation for nonaccidental injury. The bottom line is that many, but not all, children aged younger than 24 months with a fracture should have an SS along with treatment. —Michael G Burke, MD

Does smoking e-cigarettes cut down conventional tobacco use among teens?

Although some proponents of electronic cigarettes (e-cigarettes) suggest that they may be effective as smoking cessation aids, use of e-cigarettes may actually encourage conventional cigarette use among adolescents. This conclusion emerged from analyses of survey data from a representative sample of US middle and high school students who completed the National Youth Tobacco Survey—more than 17,300 respondents in 2011 and 22,500 respondents in 2012.

Whereas in 2011 only 3.1% of the study sample had ever tried e-cigarettes, that percentage rose to 6.5% in 2012. Those who had ever smoked conventional cigarettes were more likely than those who had not to have tried e-cigarettes and to use them currently. Further, ever and currently smoking e-cigarettes highly increased the odds of experimenting with conventional cigarettes and lowered odds of abstinence from regular cigarettes. (Dutra LM, et al. *JAMA Pediatr.* 2014;168[7]:610-617).

commentary

Here's a topic we are going to need to know more about. Use of e-cigarettes or "vaping" is on the rise in both adults and children. By inhaling through these cigarette-like cylinders, users activate release of a heated, nicotine-infused vapor. These devices are being marketed heavily as "a smarter alternative" to smoking, one that can be used indoors without generating smoke or ash. Marketing has included frequent placement of advertisements on television, where advertisements for cigarettes have been banned since 1970. The US Food and Drug Administration has not acted to regulate either these devices or the many flavored nicotine solutions used with them. I am unnerved by the idea of another vehicle to introduce nicotine addiction to our teenagers. No good can come of that. Ask a few patients what they know and think about "vaping." —Michael G Burke, MD

also of note

School nursing services save money. Investigators estimated the costs and benefits of a school program delivered by full-time registered nurses to 933 Massachusetts schools with more than 477,000 students compared with having no school nursing services. The analysis showed that during the 2009-2010 school year, the services generated an estimated net benefit of $98.2 million through savings in medical procedure costs and in loss-of-productivity costs for teachers and parents (Wang LY, et al. *JAMA Pediatr.* 2014;168[7]:642-648).

puzzler

Six-year-old boy refuses to ambulate

DUSTIN PAUL, DO, MA
EBONY BEAUDOIN, MD

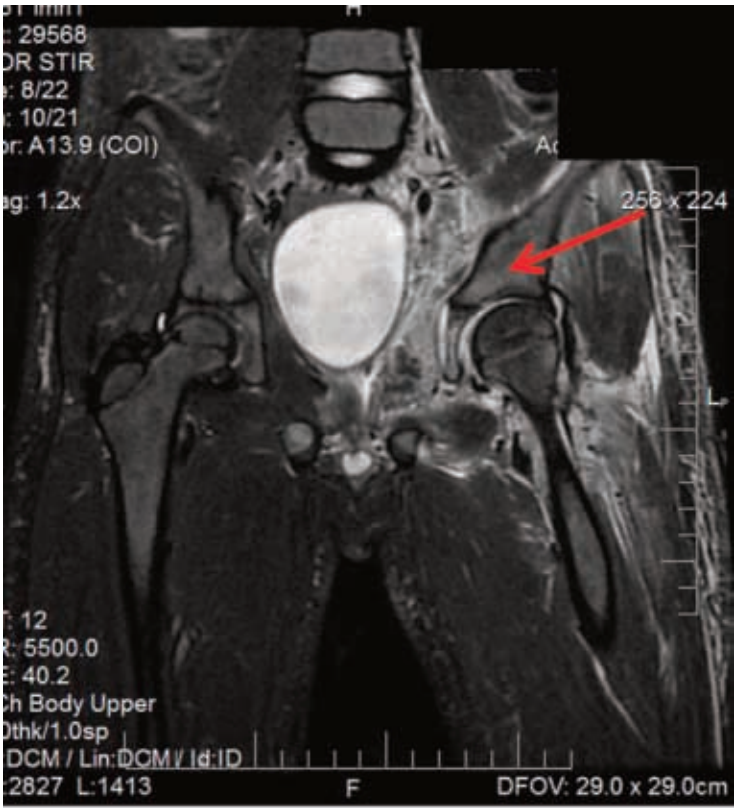


FIGURE ▶ Hip magnetic resonance imaging (with contrast) of the patient's pelvis reveals extensive multifocal areas of periosteal abscess collections.

THE CASE

A 6-year-old boy presents to the emergency department (ED) with left hip pain and refusal to ambulate. Three days earlier, he had complained of left leg pain, and on the following day had developed a notable limp. On the day prior to medical evaluation, the patient experienced fever (subjective report), rash, and testicular pain, and refused to bear weight on the affected side. TURN TO PAGE 45 ▶

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Efficacy results at 15 to 18 months of age after primary 2-dose regimen (n=3,486)[a,b]

93% protective efficacy[c]
(95% CI, 57%–98%)

After additional follow-up of 2 years and 9 months[d]

97% protective efficacy[c]
(95% CI, 72%–99.9%)
in children under 18 months

100% protective efficacy[c]
(95% CI, 24%–100%)
in children over 18 months

[a]PedvaxHIB[e] was initially evaluated in a randomized, double-blind, placebo-controlled study of Native American (Navajo) infants (n=3,486). Each infant in this study received 2 doses of either placebo or lyophilized PedvaxHIB with the first dose administered at a mean of 8 weeks of age and the second administered approximately 2 months later; DTP and OPV were administered concomitantly; [b]Protective efficacy in such high-risk populations would be expected to be predictive of efficacy in other populations. A booster dose of PedvaxHIB is required in infants who complete the primary 2-dose regimen before 12 months of age. This booster dose will help maintain antibody levels during the first 2 years of life when children are at highest risk for invasive Hib disease; [c]Estimated from person-days at risk; [d]Subjects in this portion of the study received 1 to 3 doses of PedvaxHIB; [e]A lyophilized formulation was used in the study. A later study found the antibody response of Liquid PedvaxHIB to be comparable. The antibody responses induced by each formulation of PedvaxHIB were similar.

CI=confidence interval; DTP=diphtheria and tetanus toxoids and pertussis [vaccine]; OPV=oral polio vaccine; Hib= *Haemophilus influenzae* type b.

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Indication

PedvaxHIB is indicated for routine vaccination against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2 to 71 months of age. PedvaxHIB should not be used in infants <6 weeks of age.

PedvaxHIB will not protect against disease caused by *Haemophilus influenzae* other than type b or against other microorganisms that cause invasive disease such as meningitis or sepsis.

PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 6 WEEKS OF AGE.

PedvaxHIB is administered in a 2-dose primary regimen before 14 months of age. Infants 2 to 14 months of age should receive a 0.5 mL dose of vaccine, ideally beginning at 2 months of age, followed by a 0.5 mL dose 2 months later (or as soon as possible thereafter). When the primary 2-dose regimen is completed before 12 months of age, a booster dose (0.5 mL) should be administered at 12 to 15 months, but not earlier than 2 months after the second dose.

Select Safety Information

PedvaxHIB is contraindicated in patients with hypersensitivity to any component of the vaccine. Persons who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of the vaccine.

Use caution when vaccinating latex-sensitive individuals since the vial stopper contains dry natural latex rubber that may cause allergic reactions.

The most frequently reported (>1%) adverse reactions, without regard to causality, were fever (≥101°F), irritability, sleepiness, injection-site pain/soreness, injection-site erythema (≤2.5 cm diameter), injection-site swelling/induration (≤2.5 cm diameter), unusual high-pitched crying, prolonged crying (>4 hours), diarrhea, vomiting, crying, pain, otitis media, rash, and upper respiratory infection.

As with any vaccine, vaccination may not result in a protective antibody response in all individuals given the vaccine. As with other vaccines, PedvaxHIB may not induce protective antibody levels immediately following vaccination.

Please see the adjacent Brief Summary of the Prescribing Information.

Reference: 1. Centers for Disease Control and Prevention. Catch-up immunization schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind—United States, 2013. http://www.cdc.gov/vaccines/schedules/downloads/child/catchup-schedule-pr.pdf. Accessed February 19, 2013.

MERCK

PedvaxHIB®
[Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)]

Liquid PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)]

INDICATIONS AND USAGE

Liquid PedvaxHIB is indicated for routine vaccination against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2 to 71 months of age.

Liquid PedvaxHIB will not protect against disease caused by *Haemophilus influenzae* other than type b or against other microorganisms that cause invasive disease such as meningitis or sepsis. As with any vaccine, vaccination with Liquid PedvaxHIB may not result in a protective antibody response in all individuals given the vaccine.

BECAUSE OF THE POTENTIAL FOR IMMUNE TOLERANCE, Liquid PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 6 WEEKS OF AGE. (See PRECAUTIONS in full Prescribing Information.)

Revaccination

Infants completing the primary two-dose regimen before 12 months of age should receive a booster dose (see DOSAGE AND ADMINISTRATION in full Prescribing Information).

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine or the diluent.

Persons who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of the vaccine.

PRECAUTIONS

General

As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactoid reaction occur.

Use caution when vaccinating latex-sensitive individuals since the vial stopper contains dry natural latex rubber that may cause allergic reactions.

Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

As with other vaccines, Liquid PedvaxHIB may not induce protective antibody levels immediately following vaccination.

As reported with Haemophilus b Polysaccharide Vaccine and another Haemophilus b Conjugate Vaccine, cases of Hib disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines.

There is insufficient evidence that Liquid PedvaxHIB given immediately after exposure to natural *Haemophilus influenzae* type b will prevent illness.

The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and on the etiology of the disease. The Advisory Committee on Immunization Practices (ACIP) has recommended that vaccination should be delayed during the course of an acute febrile illness. All vaccines can be administered to persons with minor illnesses such as diarrhea, mild upper-respiratory infection with or without low-grade fever, or other low-grade febrile illness. Persons with moderate or severe febrile illness should be vaccinated as soon as they have recovered from the acute phase of the illness.

If PedvaxHIB is used in persons with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

Instructions to Healthcare Provider

The healthcare provider should determine the current health status and previous vaccination history of the vaccinee.

The healthcare provider should question the patient, parent, or guardian about reactions to a previous dose of PedvaxHIB or other Haemophilus b Conjugate Vaccines.

Information for Patients

The healthcare provider should provide the vaccine information required to be given with each vaccination to the patient, parent, or guardian.

The healthcare provider should inform the patient, parent, or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination, see ADVERSE REACTIONS in full Prescribing Information.

Patients, parents, and guardians should be instructed to report any serious adverse reactions to their healthcare provider who in turn should report such events to the U. S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.

Laboratory Test Interactions

Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in urine of some vaccinees for at least 30 days following vaccination with lyophilized PedvaxHIB; in clinical studies with lyophilized PedvaxHIB, such children demonstrated normal immune response to the vaccine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Liquid PedvaxHIB has not been evaluated for carcinogenic or mutagenic potential, or potential to impair fertility.

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with PedvaxHIB. Liquid PedvaxHIB is not recommended for use in individuals 6 years of age and older.

Pediatric Use

Safety and effectiveness in infants below the age of 2 months and in children 6 years of age and older have not been established. In addition, Liquid PedvaxHIB should not be used in infants younger than 6 weeks of age because this will lead to a reduced anti-PRP response and may lead to immune tolerance (impaired ability to respond to subsequent exposure to the PRP antigen). Liquid PedvaxHIB is not recommended for use in individuals 6 years of age and older because they are generally not at risk of Hib disease.

Geriatric Use

This vaccine is NOT recommended for use in adult populations.

ADVERSE REACTIONS

Liquid PedvaxHIB

In a multicenter clinical study (n=903) comparing the effects of Liquid PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] with those of lyophilized PedvaxHIB, 1,699 doses of Liquid PedvaxHIB were administered to 678 healthy infants 2 to 6 months of age from the general U.S. population. DTP and OPV were administered concomitantly to most subjects. Both formulations of PedvaxHIB were generally well tolerated and no serious vaccine-related adverse reactions were reported.

During a three-day period following primary vaccination with Liquid PedvaxHIB in these infants, the most frequently reported (>1%) adverse reactions, without regard to causality, excluding those shown in the table, in decreasing order of frequency, were: irritability, sleepiness, injection site pain/soreness, injection site erythema (≤2.5 cm diameter, see table), injection site swelling/induration (≤2.5 cm diameter, see table), unusual high-pitched crying, prolonged crying (>4 hr), diarrhea, vomiting, crying, pain, otitis media, rash, and upper respiratory infection.

Selected objective observations reported by parents over a 48-hour period in these infants following primary vaccination with Liquid PedvaxHIB are summarized in the following table.

Fever or Local Reactions in Subjects First Vaccinated at 2 to 6 Months of Age with Liquid PedvaxHIB[a]

Reaction	No. of Subjects Evaluated	Post-Dose 1 (hr)			No. of Subjects Evaluated	Post-Dose 2 (hr)		
		6	24	48		6	24	48
		Percentage				Percentage		
Fever[b] >38.3°C (≥101°F) Rectal	222	18.1	4.4	0.5	206	14.1	9.4	2.8
Erythema >2.5 cm diameter	674	2.2	1.0	0.5	562	1.6	1.1	0.4
Swelling >2.5 cm diameter	674	2.5	1.9	0.9	562	0.9	0.9	1.3

[a]DTP and OPV were administered concomitantly to most subjects.
[b]Fever was also measured by another method or reported as normal for an additional 345 infants after dose 1 and for an additional 249 infants after dose 2; however, these data are not included in this table.

Adverse reactions during a three-day period following administration of the booster dose were generally similar in type and frequency to those seen following primary vaccination.

Lyophilized PedvaxHIB

In The Protective Efficacy Study (see CLINICAL PHARMACOLOGY in full Prescribing Information), 4,459 healthy Navajo infants 6 to 12 weeks of age received lyophilized PedvaxHIB or placebo. Most of these infants received DTP/OPV concomitantly. No differences were seen in the type and frequency of serious health problems expected in this Navajo population or in serious adverse experiences reported among those who received lyophilized PedvaxHIB and those who received placebo, and none was reported to be related to lyophilized PedvaxHIB. Only one serious reaction (tracheitis) was reported as possibly related to lyophilized PedvaxHIB and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups (9 occurred in vaccine recipients, 8 of whom also received DTP; 8 occurred in placebo recipients, 7 of whom also received DTP) and were not reported to be related to lyophilized PedvaxHIB.

In early clinical studies involving the administration of 8,086 doses of lyophilized PedvaxHIB alone to 5,027 healthy infants and children 2 months to 71 months of age, lyophilized PedvaxHIB was generally well tolerated. No serious adverse reactions were reported. In a subset of these infants, urticaria was reported in two children, and thrombocytopenia was seen in one child. A cause and effect relationship between these side effects and the vaccination has not been established.

Potential Adverse Reactions

The use of Haemophilus b Polysaccharide Vaccines and another Haemophilus b Conjugate Vaccine has been associated with the following additional adverse effects: early onset Hib disease and Guillain-Barré syndrome. A cause and effect relationship between these side effects and the vaccination was not established.

Post-Marketing Adverse Reactions

The following additional adverse reactions have been reported with the use of the lyophilized and liquid formulations of PedvaxHIB:

Hemic and Lymphatic System

Lymphadenopathy

Hypersensitivity

Rarely, angioedema

Nervous System

Febrile seizures

Skin

Sterile injection site abscess

For more detailed information, please read the full Prescribing Information.

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New model emerges for hospital-based pediatric care

LISETTE HILTON

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.

A combination pediatric emergency department/inpatient unit is a savior for community hospital pediatric services.

In the mid-1990s, David Monroe, MD, a pediatrician in Columbia, Maryland, remembers having to admit children with common diagnoses such as appendicitis, asthma, and pneumonia to hospitals 30 or more miles away. That was because Howard County General Hospital, the community hospital in Columbia, was struggling to maintain pediatric inpatient care.

David Monroe, MD

"We tried to find a way to keep patients closer to families, keep them in our community, and still deliver good quality pediatric care," says Monroe, an assistant professor of pediatrics at Johns Hopkins, Baltimore, Maryland, and director of the Children's Care Center at Howard County.

Like many community hospitals nationwide, Howard County couldn't financially justify staffing a dedicated pediatric inpatient unit with pediatric nurses because of the unpredictable and variable nature of pediatric patient flow. Winters were busier, but summers were slow. Sometimes, according to Monroe, there weren't any patients filling those beds.

This is still a common problem today. Most community hospitals that have pediatric coverage must subsidize this care, according to Monroe.[1]

The pediatrician created a model to make the inpatient side viable by combining the pediatric emergency department (ED) with a pediatric inpatient unit, and having one staff to run both. Monroe says he figured the 5000 pediatric emergency visits the hospital had a year would drive the combination unit's financial and staffing viability. Pediatric nurses would stay because they'd be working with only pediatric patients, and more parents and caregivers would bring their children for emergency care and inpatient care to Howard County because of the specialized approach, he predicted.

He was right. The combined unit opened

at Howard County in 1997. Since then, Monroe, considered the model's founder, has published on the concept.[1]

"What we found was, first, the hospital was happy because we were viable. The unit supported the full salaries for nurses and physicians, from year one all the way to now. It continues to be on the national patient satisfaction scores—if not the highest-ranking unit in the hospital, one of the highest-ranking units in the hospital. We started with 5000 patients [a year in the ED]; we're now a little over triple that at 16,000 patients," Monroe says.

Deliveries also have increased at Howard County, which makes sense, according to Monroe. "[It is known] that the moms often decide where the whole family gets care for every problem. So, if the moms are happy with pediatric care, they're more likely to go to the same hospital for all their care. If the moms are happy with their delivery care, they're more likely to come here for pediatric care," Monroe says.

▲ **Melissa M. Sparrow, MD, clinical director, inpatient and emergency services, examines one of her young patients at the Greater Baltimore Medical Center.**

The combined unit at Howard County has been profitable for 13 to 15 years. The largest loss was $9000 out of a $2 million budget; the largest annual profit, $100,000. The losses have occurred in the last 2 years. An explanation, according to Monroe, could be an increasing number of local urgent care centers. "One of the nice things about the model is it's flexible, so we're adjusting the staff," Monroe says.

More on the need

Pediatric inpatient volume at community hospitals has been waning for some time. "With immunizations and antibiotics, the number of hospitalized pediatric patients has gotten lower over time, and those who do need to be hospitalized often have complex illnesses that need to be taken care of at tertiary care centers," according to Melissa M. Sparrow, MD, clinical director, inpatient and emergency services, Greater Baltimore Medical Center (GBMC), Maryland.

According to the Centers for Disease Control and Prevention (CDC) National Hospital Discharge Survey, pediatric admissions have gone from a high approaching 4 million annually in 1970 to about 2 million in 2009.[2]

"When you have a loss of patient volume or an unsteady volume, you can't really maintain a care structure. A hospital can't afford full-time equivalent (FTE) staff members when you have only 1 patient on a pediatric ward 1 week and 6 patients the next week," Sparrow says.

Greater Baltimore Medical Center opened its combined pediatric unit in 2004. The GBMC and MedStar Franklin Square Medical Center, also in Baltimore, were the second rung of US hospitals to open units based on Monroe's model that

BASIC NEEDS OF THE COMBINED UNIT

According to David Monroe, MD, these are the basic needs for the combined pediatric inpatient-emergency department (ED) model:

- Three ED beds
- Three Inpatient beds
- Three "swing" beds
- Single physician coverage 24/7
- Three nurses on days, 2 on nights
- Secretarial or technician coverage 8 hr/day

Monroe D. Financial incentives for physicians and hospitals. Slide presentation at: Pediatric Combined Care in the Community Hospital meeting; May 16, 2014; Baltimore, MD.

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year. Today, Sparrow teaches others about the model and in 2014 she coordinated a symposium in Baltimore for pediatricians, nurses, and community hospital administrators nationwide interested in pediatric combined care.

Pediatric units at community hospitals around the United States are having to shut down or combine with other inpatient units such as gynecology or postoperative care, Sparrow notes. Among the problems with combining pediatrics with a nonpediatric unit is the inability to sustain highly qualified pediatric nurses, she adds. "Pediatric nurses don't want to do a mixture of things when they have an area of expertise. They don't want to also take care of adult patients," she says.

Pediatric nurses, according to 1 study, find working with kids more satisfying. Researchers reported in the *Journal of Pediatric Nursing* that "pediatric nurses had more positive perceptions of unit support, workload, and overall nurse satisfaction than their colleagues working in nonpediatric facilities."[3]

"There is also the recognition that pediatric patients treated in adult-oriented EDs don't get the best care possible, often because they're not seen by pediatricians," Sparrow says. Research suggests, according to Sparrow, that children are more likely to be overadmitted and overtreated in adult EDs. "They often undergo more lab and imaging studies, like head [computed tomography] for head trauma," she points out.

Scott Krugman, MD, MS

Quality is a concern at community hospitals, says Scott Krugman, MD, MS, chairman of pediatrics, MedStar Franklin Square Medical Center. "There are concerns about the staff and training and ability to care for kids who are sick," he says. "The combined units are 1 way to maintain highly skilled, high-quality, and high-competency people because the team is regularly caring for sick children."

A statistics report published in 2012 suggests that many US hospital EDs do not have the recommended pediatric services, expertise, and supplies for treating pediatric emergencies.[4] Researchers from the CDC reported that in 2006 only 7.2% of hospital EDs had all the recommended pediatric emergency supplies. Although 66% of children's hospitals and hospitals with pediatric intensive care units had 24/7 access to a board-certified, pediatric emergency medicine attending physician, such access was uncommon among other hospital types, according to the investigators.

Still other researchers assessed EDs' pediatric preparedness in the United States and reported on a 2003 survey published in *Pediatrics* in December 2007. They wrote that 89% of pediatric (aged 0 to 14 years) ED visits occur in non–children's hospitals, and only 6% occur in a separate pediatric ED.[5] Only 6% of EDs had all recommended equipment and supplies for pediatric patients. Although hospitals often have the recommended medications for children, only half of EDs surveyed had laryngeal mask airways for children.

The concept

Six community hospitals in Maryland have since combined or are in the process of combining their

A PIVOTAL STUDY

In a study published in 2011 in *Pediatric Emergency Care*, David Monroe, MD, and colleagues obtained financial productivity and performance indicators from 2 community-based pediatric hospitalist programs from the same health system. The data included emergency department and inpatient pediatric care from July 1, 2008, to July 1, 2009.

The researchers report that, together, the combined programs generated 6079 total relative value units and collections of $244,828 annually for each full-time equivalent (FTE).

"Salary, benefits, and practice expenses totaled $235,674 per FTE. Thus, combined daily revenues exceeded expenses and provided 104% of physician salary, benefits, and practice expenses. However, 1 program generated a net profit of $329,715 ($40,706 per FTE), whereas the other recorded a loss of $207,969 ($39,994 per FTE). Emergency department throughput times and left-without-being-seen rates at both programs were comparable to national benchmarks," according to the study.

Dudas RA, Monroe D, McColligan Borger M. Community pediatric hospitalists providing care in the emergency department: an analysis of physician productivity and financial performance. *Pediatr Emerg Care*. 2011;27(11):1099-1103.

pediatric inpatient and ED units. A sprinkling of community hospitals outside the state—in Boston, Massachusetts, and in Missouri and New Jersey—have launched the model. In addition, there's a lot of interest among community hospitals still struggling to maintain inpatient pediatric services, according to Sparrow.

"I've had many people come to us because they're either in the process of arguing for [a combined pediatric unit] from the administration, or they're building one and they want to know how to apportion the rooms or how to cross-train staff. There are a lot of nurses and administrators who also come to us for questions and guidance," Sparrow says. "I'm surprised more hospitals aren't doing it. I think this is a solution to trying to maintain quality care in the community hospital with limited resources."

The combined model continues to have good outcomes at different hospitals. Not only does the model seem to reduce or eliminate the subsidies hospitals were paying hospitalists to staff independent inpatient pediatric units, but patients and staffs are more satisfied.

Krugman says that combining the ED and inpatient unit and having flex staffing for both areas gives a community hospital a more consistent census and the ability to adjust staff up and down more easily. "Not to mention, the biggest reason is to provide pediatric care for pediatric patients all in one location," he says.

Michael R. Clemmens, MD

Krugman and colleagues published a study looking at pediatric combined care at MedStar.[6]

AT-A-GLANCE BENEFITS OF THE COMBINED UNIT

- High patient satisfaction
- Quick admissions from the emergency department because it is the same staff
- More coordinated care with nurses and surgeons
- Most local children stay at the community hospital
- No "on-call" by community pediatricians
- Stable staffing

Monroe D. Financial incentives for physicians and hospitals. Slide presentation at: Pediatric Combined Care in the Community Hospital meeting; May 16, 2014; Baltimore, MD.

One of the things that was striking: the volumes increased dramatically. The community responds very positively to having an emergency room just for kids versus one where there's a stroke patient, a psych patient, a patient who has been arrested, then a kid next to them. Volumes increased—both inpatient and emergency room," Krugman says. "Another big outcome that we tracked was patient satisfaction, and our patient satisfaction actually went up. That was despite our concern about having an inpatient unit next to a [noisy, chaotic] emergency room. We have noticed a significant decrease in length of stay, which can be a good thing or a bad thing, if they come back, but they weren't coming back."

According to the study by Krugman and colleagues,[6] which compares numbers from a year before opening the combination unit at Franklin Square Hospital Center (2003) to a year after (2004), Part B billings from the 5.5 FTE pediatric hospitalists increased from $1,631,583 in 2003 to $2,967,715 in 2004—a result of increased volume of ED patients seen by pediatricians. The mean inpatient satisfaction score did not significantly change: 75.7 in 2003 and 79.0 in 2004. However, the mean pediatric ED score increased from 75.8 to 83.4, respectively. Mean scores of the efficiency measures on the survey increased significantly for pediatric ED patients, with the mean score for wait time to treatment increasing from 62.0 to 75.3. Total throughput time through the ED improved from 143 minutes to 122 minutes.

"I think that we have such a well-run efficient unit that it doesn't matter what quality measure you look at, we'll be able to succeed in doing it," Krugman says. "It's the same staff doing the same thing. We're right there talking to each other. We haven't really tracked turnaround times, from time to admission, but in general it's pretty darn quick because you just look across the hall and give someone sign-out."

Anne Arundel Health System in Annapolis, Maryland, opened its combined unit in April 2011. Michael R. Clemmens, MD, director of pediatrics, Anne Arundel Health System, says the hospital's previous inpatient pediatric unit was a drain on the bottom line.

For an extended version of this article with references, go to ContemporaryPediatrics.com/hospital-zone-0914

Living past cancer
Late effects and long-term care

PAT F BASS III, MD, MS, MPH

Dr Bass is chief medical information officer and associate professor of medicine and pediatrics, Louisiana State University Health Science Center–Shreveport. The author 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.

The pediatrician's role in cancer care for children is important first as a diagnostician and then as a watchful monitor of long-term care.

Whereas the incidence of cancer among kids is increasing, death from childhood cancer is decreasing.[1,2] As a result of increased survivorship, pediatricians need to think of cancer more like a chronic disease and develop strategies and practices to improve the health and well-being of their patients. Unfortunately, this is not a role that many physicians experienced in residency or received much formal training in since completing residency.

35,000
CHILDREN ARE CURRENTLY IN TREATMENT FOR CANCER[13]

As primary care physicians, we will play significant roles in the care of our patients throughout their cancer journey: making a diagnosis; referring patients for further workup and treatment; monitoring for late effects of the cancer and treatment; providing emotional support; following up after treatment; and assisting with palliative and end-of-life care if treatment is not successful.

Making a diagnosis

Cancer can be elusive, and it is rarely at the top of the differential for patients presenting to our outpatient offices with common complaints. An acronym from the Pediatric Oncology Resource Center outlines many of the most common symptoms that may signal a possible cancer diagnosis (Table 1).[3]

Patient barriers in cancer survivorship

Once our patients become cancer survivors and enter into long-term follow-up, a number of different barriers exist, including fragmented care, lack of education, and problems in communication.

FRAGMENTED DELIVERY SYSTEM

Pediatric cancer care is probably at bigger risk for fragmentation compared with adult patients because of specialization and regional availability of cancer services. Whereas continuity of care is extremely important, our systems have not performed well.[4] While in active treatment, the patient may see a surgeon, oncologist, radiation oncologist, and other healthcare providers in addition to the primary care physician.

Continuity of care can be thought of as ". . .the systematic assurance of uninterrupted, integrated medical and psychosocial care of the patient, in accord with the patient's wishes, from assessment of symptoms in the prediagnostic period, throughout the phase of active treatment, and for the duration of posttreatment monitoring and/or palliative care."[5]

Ultimately, poor coordination of care will lead to poor quality of care.

LACK OF KNOWLEDGE

While it is better in pediatrics compared with adult populations of cancer survivors, only 35% of 635 members in the Childhood Cancer Survivorship Study identified that previous cancer treatment could lead to a serious medical condition.[6] In that study, 45% responded negatively and nearly 20% did not know the impact. Additionally, only small numbers of patients received written summaries of their care to give to future provides to assist in their follow-up.

POOR COMMUNICATION

It appears there is a disconnect between what we as a profession want to talk to our patients about following cancer treatment and what our patients want.

I think that this is likely what happened to my colleague. He and his wife were concerned with the fear of recurrence; the impact that this experience had on their relationship with their other children; potential impacts on their ability to continue to work as they had before their child's diagnosis; and other ongoing health challenges. They did not really feel that these issues were addressed at all as part of their treatment. I also wonder how the 90 million Americans that have inadequate literacy skills deal with complicated follow-up on top of the same stresses my colleague experienced.

I RECENTLY HAD LUNCH WITH A COLLEAGUE WHOSE CHILD HAD JUST COMPLETED ACUTE CANCER TREATMENT. When I asked how things were going, I got an answer I had not really anticipated. He told me that while he and his spouse were thrilled with the care they had received and how their child had responded, he was almost more scared now than when first diagnosed. I was really floored.

I initially thought my colleague was feeling some guilt that he and his wife had not noticed their child's symptoms sooner or had initially downplayed them, but it was as if getting back to living was more difficult than the process they had just been through. With their child's diagnosis came an outpouring of support. They traveled to a specialty cancer center outside our hometown for treatment where they saw doctors every day, and then every week for a period of months. They now see doctors much less often and my colleague wonders what's next. During cancer treatment he and his wife felt as if they were fighting a war with a large group of family and providers. They returned to find their regular healthcare and life nearly as scary as going through their cancer treatment.

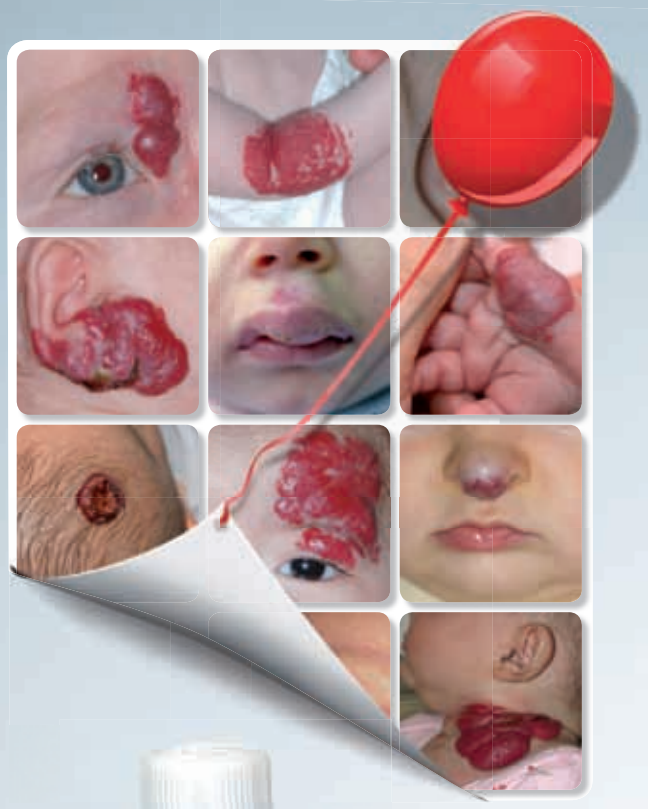
They find themselves wondering if every headache, runny nose and other common ailment is a cancer recurrence. They express significant concerns about coordination of care and communication between multiple subspecialists, and they are incredibly worried that their child will get lost in a complicated health system.

Our patients are not the only ones who can get lost in the shuffle. As primary care physicians we also experience a number of barriers to cancer care.

Our patients are not the only ones who experience barriers. We often experience the same fragmentation in attempting to get advice or records from multiple providers and centers. Often we are not reimbursed adequately to ensure delivery of comprehensive, coordinated care for complicated patients such as pediatric cancer survivors. Additionally, most of us have not had formal education in cancer survivorship, and often there are no standards related to survivorship care. However, there is something we can do to overcome some of these barriers.

Survivor care plan

Much like an asthma care plan for asthmatics, our cancer survivors



80% of hemangioma growth is complete at 3 months.[1]

Up to 69% of infantile hemangiomas leave residual lesions when left untreated.[2]

Proven efficacy

as shown in a phase II/III clinical trial.

60.4% of complete or nearly complete resolution by six months *versus* placebo 3.6%.

88% of patients showed improvement at week 5 of treatment.

Safety profile

The most common adverse reactions (occurring ≥10% of patients) were sleep disorders, aggraved respiratory tract infections, diarrhea, and vomiting.

Fewer than 2% of treated patients discontinued treatment due to safety concerns.

Hemangeol™

(propranolol hydrochloride) oral solution **4.28 mg/mL**

The only FDA approved drug for infantile hemangioma

There is no therapeutically equivalent drug.

Indication

Hemangeol™ (propranolol hydrochloride) is indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy.

TREAT EARLY*

*Initiate treatment at ages 5 weeks to 5 months.

1. Tollefson M & Frieden IJ. Pediatrics 2012;130:e314.
2. Bauland CG et al. Plast Reconstr Sur. 2011;12:1643–8.

See important safety information on the following page.

HEM-14225

Pierre Fabre Pharmaceuticals, Inc.

Pierre Fabre DERMATOLOGIE

Important safety information

Hemangeol™ (propranolol hydrochloride) oral solution is contraindicated in the following conditions: • Premature infants with corrected age <5 weeks • Infants weighing less than 2 kg • Known hypersensitivity to propranolol or any of the excipients • Asthma or history of bronchospasm • Heart rate <80 beats per minute, greater than first degree heart block, or decompensated heart failure • Blood pressure <50/30 mmHg • Pheochromocytoma.

Hemangeol™ prevents the response of endogenous catecholamines to correct hypoglycemia and masks the adrenergic warning signs of hypoglycemia, particularly tachycardia, palpitations and sweating. Hemangeol™ can cause hypoglycemia in children, especially when they are not feeding regularly or are vomiting; withhold the dose under these conditions. Hypoglycemia may present in the form of seizures, lethargy, or coma. If a child has clinical signs of hypoglycemia, parents should discontinue Hemangeol™ and call their health care provider immediately or take the child to the emergency room.

Concomitant treatment with corticosteroids may increase the risks of hypoglycemia. Hemangeol™ may cause or worsen bradycardia or hypotension. Monitor heart rate and blood pressure after treatment initiation or increase in dose. Discontinue treatment if severe (<80 beats per minute) or symptomatic bradycardia or hypotension (systolic blood pressure <50 mmHg) occurs.

Hemangeol™ can cause bronchospasm; do not use in patients with asthma or a history of bronchospasm. Interrupt treatment in the event of a lower respiratory tract infection associated 4 with dyspnea and wheezing.

Hemangeol™ may worsen circulatory function in patients with congestive heart failure or increase the risk of stroke in PHACE syndrome patients with severe cerebrovascular anomalies. Investigate infants with large facial infantile hemangioma for potential arteriopathy associated with PHACE syndrome prior to Hemangeol™ therapy.

Hemangeol™ will interfere with epinephrine used to treat serious anaphylaxis.

The most frequently reported adverse reactions to Hemangeol™ (occurring ≥10% of patients) were sleep disorders, aggravated respiratory tract infections, diarrhea, and vomiting. Adverse reactions led to treatment discontinuation in fewer than 2% of treated patients.

The most common (>3% more often on Hemangeol™ than on placebo) adverse reactions reported in a total of 424 patients treated with Hemangeol™ 1.2 mg/kg/day or 3.4 mg/kg/day were sleep disorder (17.5%; 16.1%), bronchitis (8%; 13.4%), peripheral coldness (8%; 6.7%), agitation (8.5%; 4.5%), diarrhea (4.5%; 6.3%), somnolence (5%; 0.9%), nightmare (2%; 6.3%), irritability (5.5%; 1.3%), decreased appetite (2.5%; 3.6%), and abdominal pain (3.5%; 0.4%), respectively.

Adverse events such as cardiac disorders, urticaria, alopecia, decreased blood glucose, and decreased heart rate occurred in less than 1%.

Safety and effectiveness for infantile hemangioma have not been established in pediatric patients greater than 1 year of age.

Indication

Hemangeol™ is indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy.

Please see Full Prescribing Information on www.hemangeol.com

HEM-14225

TABLE 1 COMMON SYMPTOMS OF CANCER DIAGNOSIS

- **C**ontinued, unexplained weight loss
- **H**eadaches, often with early morning vomiting
- **I**ncreased swelling or persistent pain in bones, joints, back, or legs
- **L**ump or mass, especially in the abdomen, neck, chest, pelvis, or armpits
- **D**evelopment of excessive bruising, bleeding, or rash
- **C**onstant infections
- **A** whitish color behind the pupil
- **N**ausea that persists or vomiting without nausea
- **C**onstant tiredness or noticeable paleness
- **E**ye or vision changes that occur suddenly and persist
- **R**ecurrent or persistent fevers of unknown origin

From Feist P.[3]

need a survivorship care plan (SCP). This is a written document that patients can have and take with them. An SCP outlines their diagnosis, treatment, and possible consequences of their cancer. Many times the transition back to a primary care physician can be chaotic, much like what I have described about my colleague. If he were not a physician, I wonder how he would know:

- How often does his child need to follow up with his primary care physician (PCP)?
- How often does his child need to go back and see his cancer specialist?
- What tests should be performed as part of the postcancer treatment plan?
- How will his child be monitored?
- How will care be coordinated between the cancer specialist and the PCP?

Whereas SCPs are becoming more common, they are not commonly used. It seems reasonable to ask for an SCP from our consultants or have the patient ask for such a document.

An SCP can help bridge this gap of care (Table 2).

Having SCPs may help prevent our patients from falling through the cracks, provide a plan of care, and help us anticipate therapies and screenings they need. These SCPs are very important because patients are less likely as adults to tell doctors about pediatric cancer and they do not often have discussions with their doctors about their cancers as adults.[7] In addition, SCPs provide families with reassurance because they know the long-term complications for which their child is at risk and how the child will be screened for them. Examples of care plans can be downloaded from the Memorial Sloan Kettering Cancer Center.

Late effects of cancer

With the improved survival of pediatric cancer, we are going to see as many as 75% of patients develop late effects (either a treatment-related toxicity or complications from the primary cancer).[8,9] Late effects will be dependent on the patient's treatment—one reason why developing an SCP is important. Recommendations for follow-up and screening based on the patient's treatment may be obtained from the Children's Oncology Group's website, www.survivorshipguidelines.org/. In general, the younger the patient is when he or she begins treatment, the more risk he or she has for many late effects. Some of the late effects may include:[8]

GROWTH AND DEVELOPMENT

Chemotherapy or radiation can lead to a number of problems. Growth failure and delayed sexual development can result from either chemotherapy or radiation and are more common the younger the age at which treatment begins. If growth hormone deficiency is suspected, obtain a bone age x-ray, consider other causes of growth problems such as hypothyroidism, and refer to an endocrinologist if abnormal.[8,9]

25%

OF ALL KIDS WHO ARE DIAGNOSED WITH CANCER DIE[13]

Female prepubertal cancer survivors may experience a spectrum of gonadal dysfunctions depending on their treatment, ranging from delayed puberty to premature menopause. Yearly Tanner staging is recommended until the patient is sexually developed. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol are recommended at age 13 years and with any clinical indication such as irregular menses. Male survivors whose treatment increases risk for urologic/

reproductive problems need yearly follow-up to assess pubertal and hormone status. Testosterone, FSH, and LH are recommended yearly with endocrinology follow-up for abnormalities.[8]

Learning issues and developmental problems such as attention-deficit/hyperactivity disorder have been attributed to cranial radiation.[9-11] Besides a heightened awareness, monitoring will primarily be the same as screening other patients through history and physical exam.

With the improved survival of pediatric cancer, we are going to see as many as 75% of patients developlate effects. [8,9]

OBESITY AND UNDERWEIGHT

While obesity is increasing in both noncancer and cancer survivors and there may be a genetic variation predisposing survivors to obesity, many cancer survivors will be underweight as adults.[9] Obesity is associated with the development of a number of chronic diseases and recurrence of some cancers. It is a particular complication for patients surviving acute lymphoblastic leukemia (ALL) and cranial tumors as well as a cancer diagnosis between ages 5 to 9 years. Obesity is also associated with metabolic syndrome, which is associated with a number of cardiac complications.

On the other hand, a number of other cancers such as Hodgkin disease, Wilms tumor, and non-Hodgkin lymphoma were associated with being underweight. Underweight survivors are more likely to experience adverse health and medical complications. Weights should be monitored annually and lab testing done every other year to monitor glucose and lipids.[8]

CARDIAC

A common adverse effect of treatment with anthracyclines, cardiac problems are among the most common late effects with chemotherapy. Left untreated, asymptomatic left ventricular dysfunction can lead to congestive heart failure (CHF). Patients exposed to possible chemotherapy agents leading to these late effects will receive periodic echocardiograms and electrocardiograms.[9,12]

However, it may be possible to risk stratify some patients. Patients receiving low cumulative doses of anthracyclines (<250 mg/m2) have low risk of developing CHF compared with patients receiving higher doses (>250 mg/m2) and may be able to be screened less often.[12]

LIVER

Both radiation and chemotherapy can potentially damage the liver. Blood tests to evaluate the liver should be obtained when entering long-term follow-up along with a yearly exam to check for liver enlargement.[8]

PULMONARY PROBLEMS

If a patient received certain treatments such as bleomycin or busulfan, there may be an increased risk of pulmonary complications, especially if he or she was younger when treated or is exposed to secondhand smoke. Yearly history and exam are indicated as well as chest x-ray and pulmonary function tests 2 years after completing treatment to see if there are any problems that are not immediately apparent.[8]

BONE PROBLEMS

Osteoporosis, osteopenia, and osteonecrosis result from failing to reach peak bone mass. These conditions are being more commonly identified in cancer survivors and

TABLE 2 SURVIVORSHIP CARE PLAN FOR PATIENTS

The Survivorship Care Plan (SCP) bridges the gap of care between the cancer specialist and the primary care physician. It includes:

- Basic information about the type of cancer the patient had, such as stage, diagnosis date, location, and histology
- Specific treatments the patient received for the cancer, including chemotherapy, radiation, and surgery
- Late effects or toxicities for which the patient may be at risk, as well as monitoring needed for those toxicities
- Who will be responsible for the patient's follow-up care
- Psychosocial issues that may impact the patient
- Preventive behaviors that can allow the survivor to thrive, such as exercise, immunizations, and diet

can result in a number of problems such as fractures, spine deformities (kyphosis, lordosis, scoliosis), abnormal gait, or pain in bone/muscle.[8,9] Periodic screening is performed with dual energy x-ray absorptiometry (DEXA) scans.

ORAL HEALTH

Chemotherapy or radiation can lead to a number of dental problems following cancer treatment. Both treatments may lead to increased risk for cavities and problems with enamel, absence of teeth, or tooth development. Treatment beginning before age 5 years or a longer treatment course increases risk of these problems.[8] Radiation may also increase risk of tooth sensitivity, xerostomia, alterations in taste, temporomandibular joint dysfunction, or periodontal disease.

FERTILITY

Women surviving pediatric cancer have a number of pregnancy-related problems. They are less likely to get pregnant than their siblings and their infants are more likely to be preterm and low birth weight. However, babies of survivors of pediatric cancer are not at increased risk for congenital malformations.[9]

THYROID

Primary hypothyroidism (resulting from damage or removal of the thyroid gland), central hypothyroidism (resulting from damage to the hypothalamus or pituitary gland), or compensated hypothyroidism are common in childhood cancer survivors.[8] Thyroid problems primarily affect patients receiving radiation near the thyroid gland and may occur years after treatment. Radiation affecting the thyroid gland also increases risk for thyroid nodules and thyroid cancer.

Patients receiving radiation to the head are at increased risk for central hypothyroidism. The younger a patient is when treated, the more likely he or she is to develop thyroid problems.[8] In addition to examining the thyroid during a yearly exam, yearly checking of TSH and T4 is indicated in at-risk children. During times of rapid growth, screening may be recommended more frequently. Additionally, it is important to have thyroid levels checked before becoming pregnant.

Poor coordination of [cancer] care will lead to poor quality of care.

KIDNEYS

It is recommended that pediatric survivors have their kidney function and electrolytes monitored at their first long-term monitoring visit and for a period of 2 years. Additionally, it is recommended that blood pressure and urinalysis be monitored yearly.[8]

SECOND AND RECURRENT CANCERS

A second malignancy is the most common cause of death in patients who survive longer than 15 years. These cancers generally fall into 2 groups: 1) solid tumors related to radiation treatment; and 2) myelodysplasia and acute myelogenous leukemia related to chemotherapy.[9] It is important for parents and caregivers to realize they need to report any of the following (Table 3).

TABLE 3
SYMPTOMS OF SECOND AND RECURRENT CANCERS

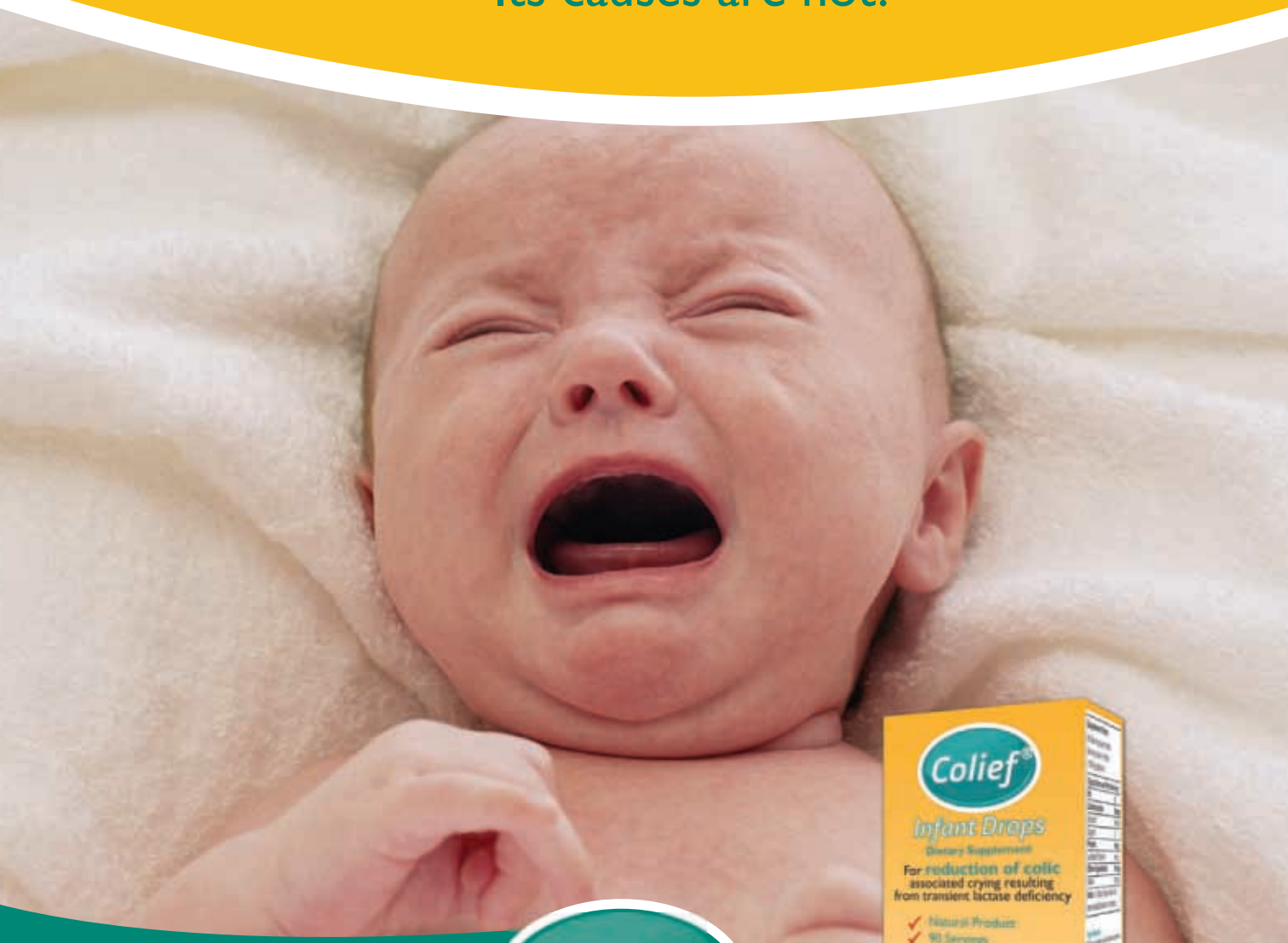
- Easy bruising or bleeding
- Abnormal fatigue
- Bone pain
- Lesions that do not heal
- New lumps or bumps that do not resolve
- Blood in stool or urine
- Painful defecation or urination
- Persistent abdominal pain
- Shortness of breath
- Persistent headaches or vision changes
- Early morning vomiting

Additionally, all patients should avoid cancer-promoting habits such as smoking. Patients should be encouraged to exercise and adopt dietary habits such as increasing fruits and vegetables that may decrease cancer risk.

MENTAL HEALTH

Survivors of pediatric cancer experience a number of adverse mental health symptoms. Compared with their siblings, pediatric survivors are more likely to report depressive symptoms, somatic complaints, and posttraumatic stress disorder. As pediatric survivors grow into adulthood, they are more likely

Crying is obvious.
Its causes are not.



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1. Kanabar D, Randhawa M, Clayton P. Improvement of symptoms in infant colic following reduction of lactose load with lactase. J Hum Nutr Diet. 2001;14(5):359-363

*Defined by Wessel's Rules of 3: crying that lasts 3 hours a day, for at least 3 days in a week, for 3 weeks

†These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

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to report suicidal ideation compared with the general population. Additionally, there are a number of life situations that can potentially lead to or contribute to mental health symptoms. Pediatric survivors report increased problems related to employment (more unemployment, underemployment, and job discrimination) and marriage (less likely to marry, but no difference in divorce) compared with their siblings.[9]

treatments, and support families in the decisions they make.

After the completion of treatment, we will need to participate not only in monitoring the late effects of cancer treatment, but also in monitoring for secondary cancer and cancer recurrence. I have experienced parents who sometimes want significant amounts of testing for seemingly nonserious complaints. Surprising to me, I have found very little written about this other than the previously mentioned studies that indicate we may be able to screen for cardiac conditions less frequently.

Facing a parent who is concerned that a cancer has returned when I think their child just has a regular headache is a scary thing. I don't want to miss a recurrence, but I also don't want to irradiate a child needlessly. Making the best clinical decision I can, trying to explain my reasoning to the parents, and providing them with close follow-up is all I know to do. Finally, I think it is important that we are available if treatment fails and parents want advice about palliation and end-of-life care.

Our role in pediatric cancer care is important first as a diagnostician, then in monitoring after treatment, and finally at the end of life. Most of our training was likely deficient in at least one of these areas, so let's make it a point to improve our skills in this important aspect of what we do. ■

As a result of increased survivorship, pediatricians need to think of cancer more like a chronic disease and develop strategies and practices to improve the health and well-being of their patients.

Pediatricians' role in cancer care

Whereas specific cancer treatment will be provided by other specialists, pediatricians will remain involved in the care of cancer survivors. We will likely make a diagnosis or refer patients for testing that will reveal a potential diagnosis. During treatment we need to be available to support families, act as a confidant to discuss alternative

40%

OF CHILDHOOD CANCER SURVIVORS HAVE SEVERE ILLNESSES OR DIE FROM SUCH ILLNESSES[13]

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Tumor classification using molecular signatures

MARY BETH NIERENGARTEN, MA

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A new genomics approach is building a stronger bridge to personalized medicine for both childhood and adult malignancies.

Classifying malignant tumors has typically relied on pathologic criteria from the tissue site of origin with histologic and other clinical characteristics of the tumor determining the target and type of therapeutic intervention.[1] This approach to classifying cancer, however, is slowly being rethought as a more precise understanding of the molecular characteristics of tumors is emerging from several large-scale genomics projects.

Two primary observations emerging from the molecular analysis of cancer are that 1) cancers from the same organ are often distinct from each other, and 2) cancers of different organs share many of the same features.[2,3] These emerging insights are paving the way for the potential to better target the specific pathologic pathways underlying disease and build a stronger bridge toward personalized medicine in oncology.

This article briefly describes the ongoing research and recent findings that are reshaping the classification of cancer and leading, it is hoped, to better, more precise treatments. Focus is on the extensive work being done by The Cancer Genome Atlas (TCGA) Research Network and TCGA Pan-Cancer Initiative, which are providing the foundation for the molecular analysis of tumors.[2,3] The article also briefly describes genomic research under way in childhood cancers, highlighting one of several genomic initiatives over the past 5 years aimed at cataloging all the genomic lesions in childhood cancer.

TCGA Research Network and TCGA Pan-Cancer Initiative

In 2006, the TCGA Research Network project was initiated with a goal of collecting and profiling tumor samples from at least 20 tumor types to discover molecular aberrations at the genetic and epigenetic levels.[1,2] To date, the TCGA Research Network has identified 12 primary tumor types (Table 1).[3]

Two primary observations emerged from the molecular analysis of cancer: 1) cancers from the same organ are often distinct from each other, and 2) cancers of different organs share many of the same features.[2] Researchers have identified, for example, a number of important

TABLE 1 PRIMARY TUMORS PROFILED BY TCGA RESEARCH NETWORK

- Glioblastoma multiforme
- Serous ovarian carcinoma
- Colon and rectal adenocarcinomas
- Lung squamous cell carcinoma
- Lung adenocarcinoma
- Breast cancer
- Acute myelogenous leukemia
- Endometrial cancer
- Renal cell carcinoma
- Bladder urothelial adenocarcinoma
- Head and neck squamous cell carcinoma

Abbreviation: TCGA, The Cancer Genome Atlas.
From The Cancer Genome Atlas Research Network.[3]

similarities among tumor subtypes from different organs (Table 2).

To help coordinate and provide a systematic foundation from which to discover differences, commonalities, and emergent themes across tumor lineages, the TCGA Pan-Cancer Initiative was launched in 2012 with the specific aim of comparing the first 12 tumor types identified through the TCGA Research Network.[3] The initiative involves over 250 collaborators from 30 institutions using the same data set to work on over 60 different research projects.[4]

In 2013, the first findings of this initiative were published.[2,5] A study by Ciriello and colleagues found that tumors comprise 2 major genomic categories independent of tumor tissue type or tissue of origin. Tumors had either a large number of copy number alterations or they had a large number of somatic mutations.[2] Furthermore, the study found that tumors across several tissue types share the same oncogenic signature. Based on these findings, the investigators derived a hierarchical classification in terms of oncologenic signatures of thousands of tumors from the 12 tumor types.

A second study by Zack and colleagues, also published in 2013, provides insight into the mechanisms of generation and functional consequences of cancer-related somatic copy number alterations (SCNAs), which play a critical role in activating oncogenes and inactivating tumor suppressors.[5] The investigators identified common patterns of SCNAs across cancer type and found significant recurrent focal SCNAs in 140 genomic regions. Among these regions, 102 did not have known oncogene or tumor suppressor gene targets and 50 regions had a significant number of mutated genes.

In a commentary accompanying the studies, John Weinstein, MD, PhD, University of Texas MD Anderson Cancer Center, Houston, and colleagues said that "shared molecular patterns will enable etiologic and therapeutic discoveries in one disease that can be applied to another. Importantly, integrative interpretation of the data will help identify how the consequences of mutations vary across tissues, with important therapeutic implications."[3]

"Relatively rare cancers, such as childhood malignancies in particular, stand to benefit from such an approach," the researchers said in the commentary.[3]

In the most recent study published in 2014, Hoadley and colleagues further examined the molecular alterations of the 12 tumor types to see which alterations are shared across cancers arising from different tissues.[1] They also looked at whether disease subtypes previously identified do span multiple tissues of origin.

To test their hypothesis that molecular signatures provide a distinct molecular taxonomy relative to the current classification of tumors by tissue of origin, the investigators used a multiplatform integrative analysis of thousands of cancers from the 12 tumor types.[1]

Using the data from multiple assay platforms, the investigators identified 11 major subtypes.[1] Most subtypes were identified by tissue of origin features, but several distinct cancer types converged into common subtypes. One subtype typified by TP53 alterations, TP63 amplifications, and high expression of immune and proliferation pathway genes included lung squamous cancers, head and neck cancers, and a subset of bladder cancers. The most heterogeneous malignancy was bladder cancers that split into 3 primary subtypes.

Overall, the study found that about 10% of cases were reclassified by the molecular taxonomy, indicating that 1 in 10 patients would be classified differently by the new molecular taxonomy versus using just the current tissue of origin system of classifying tumors.[1]

The implication of these findings is the potential to better target therapy by improving the ability to more precisely subtype cancers. "If used to guide therapeutic decisions, this reclassification would affect a

significant number of patients to be considered for nonstandard treatment regimens," state the investigators. "In addition to identifying several new genomic and pathway insights between and within tissue-of-origin tumor types, this TCGA study provides a public resource compendium of individuals and integrated data sets . . . enabling researchers to explore new questions and analytical approaches that will perpetuate this discovery process."[1]

Looking for molecular signatures for childhood cancers

Over the past 5 years, a number of large genomic initiatives have been started to catalog all the genomic lesions present in childhood cancer. Among these is a project through the National Cancer Institute (NCI) called Therapeutically Applicable Research to Generate Effective Treatments (TARGET) managed by the Office of Cancer Genomics and Cancer Therapy Evaluation Program. Genomic data generated from the TARGET initiative is available to the research community with the broad aim of facilitating the discovery of therapeutic targets for childhood cancers and translating this into clinical application. Current projects include research that is examining the genomes, transcriptions, and/or epigenomes of selected childhood cancers including acute lymphoblastic leukemia, acute myeloid leukemia, kidney tumors, neuroblastoma, and osteosarcoma.

According to Malcolm A. Smith, MD, PhD, associate branch chief, Pediatrics, in the Clinical Investigations Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI, Bethesda, Maryland, enormous progress has been made over the last 5 years as a result of the large-scale initiatives that together have sequenced thousands of childhood cancer genomes. One major insight that has emerged is the recognition that diseases previously thought to be relatively homogenous actually represent multiple molecularly distinctive subtypes. For example, he said, it is now recognized that there are 4 distinctive subgroups within medulloblastoma that have different demographic and prognostic characteristics, different genomic lesions, and different potentials for being treated with specific targeted therapies.

"We need to adjust our thinking about how we approach medulloblastoma diagnostically and eventually how we treat it," said Smith, adding that the information gathered from genomic research is being used in the development of medulloblastoma clinical trials. Similar molecularly defined subtypes have been identified for other cancers and are being incorporated into clinical trials conducted by clinical trial groups such as the Children's Oncology Group.

Saying that genomic information will be increasingly used over the next years, Smith emphasized that this information will serve to complement the information gleaned from histology and other clinical characteristics but is unlikely to replace tissue-of-origin classification of disease. "Tissue of origin is still important, and the genomic

TABLE 2 SIMILARITIES AMONG TUMOR SUBTYPES

COMMON MOLECULAR MUTATION	TUMOR TYPE	IMPLICATION
TP53 mutations	○ High-grade serous ovarian carcinoma ○ Serous endometrial and basal-like breast carcinoma	Share a global transcriptional signature that involves activation of a similar oncogenic pathway
ERBB2-HER2 mutation or amplification	Found in subsets of the following cancers: ○ Glioblastoma ○ Gastric ○ Serous endometrial ○ Bladder ○ Lung	Response to HER2-targeted therapy in some cases
Inherited and somatic inactivation of BRCA1-BRCA2 pathway	○ Serous ovarian cancer ○ Basal-like breast cancers ○ Microsatellite instability in colorectal and endometrial tumors	

From Ciriello G, et al.[2]

MORE ON CANCER AS A GENOMIC DISEASE

Understanding Cancer	A tutorial that provides a comprehensive review of cancer and its molecular causes	**www.cancer.gov/cancertopics/understandingcancer/cancer**
Understanding Cancer Genomics	A tutorial that provides an introduction to genomics and how genomic technologies are applied to the study of cancer	**www.cancer.gov/cancertopics/understandingcancer/cancergenomics**
The Cancer Genome Atlas (TCGA) Data Portal	Contains clinical information, genomic characterization data, and high-throughput sequencing analysis of over 20 different cancers. Search, download, and analyze data sets generated by TCGA.	**http://cancergenome.nih.gov/**
Cancer Genome Anatomy Project (CGAP)	Contains a wide range of genomics data on cancerous cells. Accessible through easy-to-use online tools. Researchers, educators, and students can find "in silico" answers to biological questions through the CGAP website.	**http://cgap.nci.nih.gov/cgap.html** Learn to navigate the website via a free copy of the CGAP Website Virtual Tour available from **ocg@mail.nih.gov**
SNPs and Cancer	Information on single nucleotide polymorphisms (SNPs) and how they can influence a person's health, and in particular cancer.	**www.cancer.gov/cancertopics/understandingcancer/geneticvariation**
Cancer Genome Anatomy Project SNP500Cancer Database	Part of CGAP, the goal of the SNP500Cancer project is to resequence 102 reference samples to find known or newly discovered SNPs that are of immediate importance to molecular epidemiology studies in cancer.	**http://snp500cancer.nci.nih.gov/**

National Cancer Institute, Office of Cancer Genomics. Available at: https://ocg.cancer.gov/programs/target/resources. Accessed August 26, 2014.

information will complement, extend, and enrich it to potentially point to specific treatments in some cases and in other cases to provide prognostic information that can help guide treatment," he said.

Building the bridge to personalized medicine

All this research points to finding a better way to tailor treatment and provide the best care possible to people with cancer. "The hope is that investigations across tumor type such as the Pan-Cancer project will ultimately inform clinical decision making," according to Weinstein and colleagues.[3] "We hope [such studies] will enable discovery of novel therapeutic agents that can be tested clinically—perhaps in novel adaptive, biomarker-based clinical trials that cross tumour boundaries."

Success in using genomic information already has been seen with the development of recent cancer treatments that specifically target molecular changes now recognized in specific cancers.[6] These targeted therapies include imatinib that inhibits an altered enzyme found in patients with chronic myelogenous leukemia; trastuzumab that targets human epidermal growth factor receptor 2 (HER2) mutations in patients with HER2-positive breast cancer; and gefitinib and erlotinib that target epidermal growth factor receptor (EGFR) mutation in patients with EGFR-positive lung cancer.

In addition, genomics research provides a better understanding of which patients will likely not benefit from selected therapies, and thereby helps to avoid unnecessary treatment and adverse effects.[6] This can be seen with cetuximab and panitumumab, both targeted therapies that do not benefit colon cancer patients with tumors that have a mutation in a gene called KRAS.

The broad aim of collaborative efforts by initiatives such as the Pan-Cancer project and TARGET is to increasingly expand the molecular analysis of cancers to more tumor types with the long goal of developing more target-specific treatments and, ultimately, offering patients more precise personalized medicine. ■

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

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References: 1. US Dairy Export Council. *Reference Manual for US Whey and Lactose Products*. June 2004. **2.** HPLC analysis. Data on file. Nestlé. 2002. **3.** Florendo KN et al. Growth in preterm infants fed either a partially hydrolyzed whey or an intact casein/whey preterm infant formula. *J Perinatol*. 2009;29:106-111. **4.** Cooke R et al. High protein pre-term infant formula: effect on nutrient balance, metabolic status and growth. *Pediatr Res*. 2006;59:265-270. **5.** American Academy of Pediatrics. Committee on Nutrition. *Pediatric Nutrition Handbook*. 6th ed. 2009.

Phase I clinical trials test new therapies for kids' cancers

LISETTE HILTON

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Early phase pediatric cancer trials offer hope to children whose cancer defies standard therapy.

Children's cancer treatment has come a long way. Pediatric oncology is one of the biggest success stories in medical, and certainly cancer, research, says Stacey L. Berg, MD, pediatric oncologist at Texas Children's Cancer Center and professor of pediatric hematology and oncology at Baylor College of Medicine, Houston, Texas.

Stacey L. Berg, MD

"The very good news is somewhere over 80% of the children who are diagnosed with cancer are actually able to be cured with the therapies we have now," Berg says.

In fact, a drastic improvement in the overall outlook for children with cancer has occurred in the last half century. In 1975, slightly more than half of children diagnosed with cancer before age 20 years survived at least 5 years.[1] In 2004 to 2010, more than 80% of children diagnosed with cancer before age 20 years survived at least 5 years.[2] Yet there's more work to be done.

"[The] significant, unintended, late effects of current curative therapies result in serious chronic morbidity in 2 out of every 3 survivors of childhood cancer.[3] For children and adolescents who experience a recurrence or relapse of cancer, many will die as the result of progression of cancer that is unresponsive to current therapies," says Elizabeth Fox, MD, associate professor of pediatrics, Perelman School of Medicine at the University of Pennsylvania, and head of the developmental therapeutics program for childhood cancer research at the Children's Hospital of Philadelphia.

Uncovering new options with early phase research

Although most newly diagnosed children with cancer participate in phase III studies, which test standard treatments against promising alternatives, the phase I and II trials stand to help the 20% or so of children who aren't cured or whose cancer returns. The goal of phase I trials is to evaluate dosages and treatment safety. Phase

II studies identify which tumors respond favorably to the new drug or treatment.

The earliest an oncology drug would become available to patients is in the context of a phase I trial, according to Berg.

Elizabeth Fox, MD

There are thousands of pediatric cancer patients who run out of treatment options each year, given that an estimated 15,780 children and adolescents will have been diagnosed with cancer in 2014.[4] Although cancer in children is rare, it is the leading cause of death by disease past infancy among children in the United States. Nearly 2,000 US children and adolescents will die of the disease in 2014.

"Early phase clinical trials are one of those things where we're . . . trying [in order] to put ourselves out of business, by getting into a situation where standard therapies can help everybody. That's not the case right now," Berg says. "There's a big need for developing new drugs and new treatments that will let us help children that we don't have good therapy for right now. And then hopefully in the future, these new therapies will become standard and help people at the time of diagnosis."

The curability of pediatric cancers is uneven. While the cure rate for some kinds of leukemia is as high as 95%, cures are much less likely for other cancer types.

According to the American Cancer Society, the most common types of cancer diagnosed in children and adolescents are leukemia; brain and central nervous system tumors; lymphoma; rhabdomyosarcoma; neuroblastoma; Wilms tumor; retinoblastoma; and bone cancer.[5]

"One of the most difficult groups of cancer for us to treat is some kinds of brain tumors," Berg says. "Other tumors that are difficult to treat are solid tumors that either have spread widely throughout the body at the time of diagnosis or that recur or return after initial treatment. Those are areas where there is a lot of activity in terms of research to develop new therapies."

Early phase pediatric cancer research has its success stories. One example of a novel therapy developed for children with cancer is dinutuximab, a chimeric antibody that targets the ganglioside D2 molecule found on the surface of neuroblastoma cells, according to Fox.

"High risk neuroblastoma occurs in young children and is characterized by wide dissemination of disease at diagnosis. [These children] have very poor prognosis even with intensive multimodality therapy," Fox says. "Dinutuximab was developed as a collaboration of physician-scientists in pediatric oncology research teams, the National Cancer Institute (NCI; Bethesda, Maryland), the Children's Oncology Group (COG), and the pharmaceutical industry (United Therapeutics; Silver Springs, Maryland). By combining dinutuximab with other drugs that stimulate the immune system, the 2-year event-free survival for selected children with high-risk neuroblastoma improved from 46% to 66%."[6]

Research trends

A primary trend in today's cancer research is the study of molecular targeted agents, with the goal of matching a molecularly targeted agent to the genomic alterations that a particular child has in his or

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Operations Director
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Fax: 626-445-4334
E-mail: tbeeles@childrensoncologygroup.org
www.childrensoncologygroup.org/index.php/phase-1-home

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NATIONAL CANCER INSTITUTE (NCI):
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www.ClinicalTrials.gov

NCI'S CANCER THERAPY EVALUATION PROGRAM (CTEP):
Childhood cancer research resources:
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Stacey L. Berg, MD, Director of Clinical Research and staff
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A SNAPSHOT OF CHILDHOOD CANCER SURVIVAL

- Mortality from childhood cancer fell 52% from 1975-1977 to 2007-2010.
- The greatest percentage declines in mortality were for Hodgkin lymphoma (82%) and gonadal tumors (83%). Declines higher than 50% have been seen in leukemias, renal tumors, and non-Hodgkin lymphoma.
- Survival improvements are not as dramatic for neuroblastoma, where mortality has declined 43%, and for brain tumors (29%) and bone tumors (36%).
- Researchers noted the smallest declines in liver tumors and for tumors of the "soft tissue, including the heart," according to a study published in August 2014 in *Cancer.*

Smith MA, Altekruse SF, Adamson PC, Reaman GH, Seibel NL. Declining childhood and adolescent cancer mortality. Cancer. 2014;15:120(16):2497-506.

her cancer, according to Malcolm A. Smith, MD, PhD, associate branch chief for pediatrics in the Cancer Therapy Evaluation Program, NCI.

"This is the concept of precision medicine, in which we try to find the right drug for the right patient," Smith says. "We have trials that we have conducted or are conducting in which we have a targeted agent that acts to inhibit a particular cancer driver inside the cancer cells. If we have patients who have the cancer gene driver turned on, the agent can be quite effective."

Malcolm A. Smith, MD, PhD

One example, according to Smith, is the agent crizotinib, an anaplastic lymphoma kinase (ALK) inhibitor. "[It's] an effective treatment for the approximately 5% of lung cancer patients who have a genomic alternation in the ALK gene, which makes them especially sensitive to crizotinib," Smith says. "Within the pediatric population, we have a group of patients with anaplastic large cell lymphomas who also have genomic alterations in the ALK gene. When these patients were treated with crizotinib in a phase I trial, among the 9 patients treated with this diagnosis, 8 showed a high degree of tumor regression.[7] That's a very promising result."

This potential breakthrough would make a big difference in the lives of some children with anaplastic large cell lymphoma, according to Peter C. Adamson, MD, professor of pediatrics and pharmacology at the University of Pennsylvania, Children's Hospital of Philadelphia.

"[For] over 20 years, we've known the molecular cause [of anaplastic large cell lymphoma] but haven't been able to take that molecular cause and find a new treatment. Historically, it has been treated with relatively intensive chemotherapy. Despite numerous variations in that intensive chemotherapy, we still only have 70% of children who are 5-year event-free survivors. In essence, 30% of children with anaplastic large cell lymphoma, despite our efforts, would succumb to the disease," Adamson says.

In addition to crizotinib, another drug is showing promise in treating children with the cancer type who have relapsed, according to Adamson. It's a conjugated antibody called brentuximab vedotin.

"[In an ongoing phase II trial,] children are being randomized to receive chemotherapy plus 1 of the 2 drugs because both drugs appear very effective in the relapse setting. One goal is to determine whether we can combine the new drugs with effective chemotherapy but, more importantly, another goal is to find out if addition of a targeted new agent is going to be able to push the needle away from the 70% event-free survival rate that we've been stuck at for too long," Adamson says.

Immunotherapy includes novel therapies that modify the child's own T-cells to fight cancer, according to Fox. "There is a growing number of clinical trials evaluating chimeric antigen receptor (CAR) T-cell therapies in leukemia and solid tumors in children and adolescents. In addition, vaccines for childhood cancer therapy and oncolytic virus therapies have been evaluated as new therapeutic approaches," he says.

As new agents become more specific and target molecular characteristics of specific cancers, clinical trial enrollment may be restricted to children with relapsed cancer that harbor selected mutations, according to Fox.

"We may need a change in thinking about caring for children and adolescents with cancers that are metastatic at diagnosis, have high-risk clinical phenotypes, or have

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a high likelihood of recurring or being refractory to standard therapy," Fox says. "For these children and adolescents, discussions about future therapeutic options are never premature. Early discussion may help patients, families, and primary care physicians sort through the vast amount of information available on the Internet. Preliminary discussions may help preserve options for patients in the future or facilitate referral for enrollment, if needed."

Access to early trials

Phase I pediatric cancer trials are generally small, with approximately 20 to 30 participants in each trial. However, they're complex, difficult to administer, and expensive, so most (if not all) of these early phase trials are conducted in large children's or academic hospitals. One of the reasons that pediatric phase I trials are relatively small is that dosing begins at levels very close to the recommended adult dose. Hence, only 1 or 2 higher dose levels typically need to be evaluated, according to Smith.

The NCI directly supports phase I pediatric cancer research primarily through 2 avenues: the COG Phase I and Pilot Consortium, and the Pediatric Brain Tumor Consortium. The NCI also provides funding for early research to New Approaches to Neuroblastoma Therapy (NANT).

"One of the goals of those 2 groups was to be able to spread, somewhat geographically, the availability of early phase clinical trials," says Berg, who is vice chair for regulatory affairs of the COG's Phase I and Pilot Consortium.

The COG Phase I and Pilot Consortium, launched in 2002, is made up of 21 pediatric oncology programs in the United States that were selected in a peer review process, according to the COG website, www.ChildrensOncologyGroup.org. The COG's Phase I and Pilot Consortium is part of the larger COG, which conducts all phases of pediatric cancer research and has more than 8,000 experts worldwide and nearly 100 active clinical-translational trials open at any given time. More than 90% of US children and adolescents diagnosed with cancer each year are cared for at COG member institutions, according to the website.

The NCI formed the Pediatric Brain Tumor Consortium in 1999 to improve primary brain tumor treatment in children. Its primary goal is to rapidly conduct novel phase I and phase II clinical evaluations of new therapeutic drugs, new biological therapies, treatment delivery technologies, and radiation treatment strategies in children from infancy to age 21 years.

"One of the reasons for having small consortia is that these studies are extremely hard to do," Berg says. "They take a lot of expertise by the doctors, research staff, and the institutions themselves. They also take a huge amount of resources. You have to have a whole dedicated research staff. It's very helpful to have a special kind of research unit in the hospital. You have to have regulatory staff who know how to do all the paperwork properly, because, for safety and ethical reasons, this is very highly regulated research." He continues, "Although the National Cancer Institute does pay the institutions to some extent to support the research that's being done, there's also a big contribution from the institution. [T]hat's not in reach of every institution."

Funding sources

Phase I pediatric cancer trials are primarily funded by government institutions that do the research and philanthropy, according to Berg.

INSTITUTIONS PARTICIPATING IN THE PEDIATRIC BRAIN TUMOR CONSORTIUM

- Children's Hospital Los Angeles (California)
- Children's National Medical Center (Washington, DC)
- Children's Memorial Hospital (Chicago, Illinois)
- Cincinnati Children's Hospital Medical Center (Ohio)
- Duke University (Durham, North Carolina)
- Lucile Packard Children's Hospital Stanford (California)
- Memorial Sloan-Kettering Cancer Center (New York, New York)
- National Cancer Institute (Bethesda, Maryland)
- St. Jude Children's Research Hospital (Memphis, Tennessee)
- Texas Children's Cancer Center (Houston, Texas)
- University of Pittsburgh (Pennsylvania)

Source: Pediatric Brain Tumor Consortium website, www.pbtc.org/public/gen_info.htm.

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PHASE I COUNSEL HOPES, EXPECTATIONS, AND TRADE-OFFS

When talking with patients and families about phase I pediatric cancer trials, the biggest issue for the pediatrician is to try to set realistic expectations, according to Benjamin Wilfond, MD, director, Treuman Katz Center for Pediatric Bioethics, Seattle Children's Hospital, University of Washington.

Benjamin Wilfond, MD

Phase I trials are done when current therapies have such limited opportunities for success that parents and children might be willing to try these other things. However, the therapy in the trial might not work, and it could be harmful, according to Wilfond.

"Most children in phase I trials ultimately die because of where they are in the disease," Wilfond says. "When the family decides to do it, it's . . . because their motivation and hope is that it will work."

The biggest issue for pediatricians is to distinguish between hope and expectations, according to Wilfond. "The hope for the family is that it will help, but the likelihood, in general, is very small," he says.

Another message from pediatricians should be the importance of early phase cancer trials for children and how being in them is an opportunity to give back, according to Wilfond. The message, he says, is: All the therapy that kept their child alive until that date was possible because other parents who were facing similar circumstances made the decision to have their children in early trials.

A third issue to raise is the question of a trade-off. It's a trade-off to enter into a phase I trial for pediatric cancer research, whether doing it for the patient or anyone else versus what family and patients want for the end of life.

Pediatricians should make it clear to parents that this is a choice they can make. They can make the choice about whether or not they want their child's life to play out in a phase I trial. They may be required to stay in the hospital. They might have to drive far away. Their child might not live out his or her last days at home.

"The pediatrician should let them know that not all families do this," Wilfond says. "It's a personal choice, not a requirement."

"We were very fortunate to become funded as what's called a developmental therapeutic center of excellence by Alex's Lemonade Stand Foundation. There are currently 4 of those centers in the country," Berg says.

Government funding for phase I pediatric cancer trials has been stable over the last few years, with some modest increases, according to Smith.

Private industry is less likely than these other sources to finance early childhood cancer trials. "If you only look at the purely economic reasons to develop new drugs just for children with cancer, you might say it's not that big a market, so big pharma wouldn't be that interested. Recognizing this problem, Congress (over the last 20 years) enacted a series of bills that provide incentives for industry to develop drugs for children," Berg says.

The legislation, including such laws as the Best Pharmaceuticals for Children's Act, provides financial incentives for companies to allow their new drugs to be tested in children with various illnesses. In return, the companies benefit with things such as patent extensions, according to Berg.

The incentives might not be enough, however. "The rarity of childhood cancer means that industry is not going out and developing a drug for children with cancer. There is not an economic model for doing that. There are regulatory and financial incentives that may help, but the fact of the matter is industry does not set out to develop a drug first for children with cancer," Adamson says.

Robin Norris, MD

Barriers to pediatric research

Doctors who conduct phase I pediatric cancer trials say one of the biggest barriers is being able to study drugs in children that have shown promise in adult cancers. "That is partly because of the regulatory burden and partly because the companies can be very conservative in their plans for moving new drugs into pediatrics," Berg says.

For an extended version of this article with references, go to ContemporaryPediatrics.com/cancer-clinical-trials

puzzler } NO AMBULATION

CONTINUED FROM PAGE 16

The patient had no significant medical history and had been in good health. He was current on immunizations and yearly checkups. He was born full term by spontaneous vaginal delivery without complications during pregnancy or after birth. No upper respiratory tract infection (URI) or trauma was present in the weeks preceding the ED visit.

Physical examination

Physical exam was significant for fever and an 8-cm erythemic rash along the lateral aspect of the left iliac crest that was associated with tenderness and warmth on palpation. Abdominal exam revealed suprapubic tenderness with possible abdominal mass. The left hip was found to be held in external rotation with limited passive range of motion secondary to extreme pain. Edema was present in the left hip and left knee with tenderness to palpation. The left hip was warm to the touch. Scrotal edema was present, as was testicular tenderness and a 1.5-cm tender inguinal lymphadenopathy.

Labs demonstrated a normal white blood cell (WBC) count with a left shift (WBC count, 9.9; 74% neutrophils); bandemia (9 bands); elevated erythrocyte sedimentation rate (62 mm/hr); and a high C-reactive protein (10.6 mg/dL). Plain films were negative for acute abnormalities, but ultrasound showed left hip joint effusion.

Differential diagnosis

Based on the initial presentation and workup, the patient was believed to have a serious condition, but the identity or extent of disease had not been determined. Given the patient's good health and the absence of URI or trauma preceding his presentation, infectious causes were more likely than other etiologies (Table 1).[1-3] Septic arthritis and osteomyelitis were the most likely culprits. However, differential diagnosis required further diagnostic workup and consultation with orthopedics.

Further testing

The patient was taken to the operating room for debridement. The initial washout was unable to fully assess the extent of disease. The patient continued to be febrile (103°F to 104°F) and in severe pain. Magnetic resonance imaging (MRI) was subsequently ordered and revealed multifocal areas of periosteal abscess collections throughout the pelvis, with adjacent myositis and osteomyelitis of the left ischium and quadrilateral plate, and abscess formation within the body of piriformis muscle (Figure). A diagnosis of septic arthritis was made.

Discussion

Septic arthritis, also known as pyogenic arthritis, occurs when there is bacterial invasion of the synovium and joint space, which triggers inflammatory response. An estimated 10 to 25 cases per 100,000 children occur annually, with twice as many affected boys than girls. Children who are immunocompromised or who have

TABLE 1 DIFFERENTIAL DIAGNOSIS FOR LIMP IN A CHILD

INFECTIOUS
- Abdominal abscess
- Appendicitis
- Bursitis
- Cat scratch disease
- Gonorrhea
- Intracranial abscess
- Lyme disease
- Osteomyelitis
- Parvovirus
- Septic arthritis
- Spinal cord abscess
- Toxic synovitis

MALIGNANCY
- Acute lymphoblastic leukemia
- Ewing sarcoma
- Neuroblastoma
- Osteoid osteoma
- Osteosarcoma

RHEUMATOLOGIC
- Juvenile idiopathic arthritis
- Systemic lupus erythematosus
- Rheumatic fever
- Reactive arthritis

STRUCTURAL
- Apophyseal avulsion fractures
- Avascular necrosis of the femoral head
- Child abuse
- Femur fracture
- Hip dysplasia
- Hip fracture
- Legg-Calvé-Perthes disease
- Patella fracture
- Parvovirus
- Slipped capital femoral epiphysis

OTHER
- Hip effusion
- Sickle cell disease
- Hemophilia
- Heavy metal toxicity
- Insect bites
- Osgood-Schlatter disease
- Osteochondritis dissecans
- Osteonecrosis

From Brady M[1]; Mathison DJ, et al[2]; Gill KG.[3]

sickle cell disease are more susceptible to septic arthritis than healthy children. Peak incidence occurs between ages 2 to 3 years.

Patients with septic arthritis often present with pain, edema, limp, and refusal to ambulate or move the affected joint (pseudoparalysis). These symptoms tend to rapidly progress over a short time. The majority of cases involve the lower extremity joints, with the knee being most commonly affected.

Septic arthritis of the hip is especially difficult to assess because physical exam findings are often mild. When the patient presents with hip involvement and physical exam reveals findings such as scrotal edema, testicular tenderness, and suprapubic tenderness, further assessment of complications and extent of involvement is warranted.[4] Standard imaging studies may indicate increased joint space (x-ray) and joint effusion (ultrasound). However, MRI should be performed without delay to assist in the diagnosis and management. Timely diagnosis of septic arthritis of the hip is critical because pressure on the precarious vascular supply of the femoral head makes it highly susceptible to avascular necrosis of the femoral head and physeal damage leading to late angular deformities, hip dislocations, growth disturbances, gait abnormalities, limb length discrepancies, pseudarthrosis, joint dislocations, and other bony and joint deformities. In the absence of MRI, the gold standard for diagnosis is the evaluation of aspirated joint fluid (Table 2). It should be noted, however, that up to 70% of septic arthritis cases in children are culture negative.[5]

Positive cultures typically reveal infection by a single pathogen. Outside the neonatal population, the most common organism detected is *Staphylococcus aureus,* followed by respiratory pathogens *Streptococcus pyogenes, Streptococcus pneumoniae, Haemophilus influenzae type B,* and *Kingella kingae*. Among children aged younger than 4 years, *K kingae* is the predominant cause of osteoarticular infections. Advances in culturing and polymerase chain reaction (PCR) methodology have increased *K kingae* detection.[6]

Patients with sickle cell disease appear to be particularly susceptible to *Salmonella* species, whereas neonates are more likely to acquire *Streptococcus agalactiae* infections.[7]

The vascular nature of the synovial membrane makes hematogenous seeding of bacteria the customary mechanism of infection. Septic arthritis may also develop from direct adjacent spread from osteomyelitis, which may have been the case in this patient. In younger children, infection is known to extend from metaphysis of adjacent bone through transphyseal vessels. Lack of a limiting basement membrane allows the infection to spread into the joint.

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TABLE 2 DIAGNOSTIC CONSIDERATIONS FOR SEPTIC ARTHRITIS

MARKERS OF INFLAMMATION/INFECTION
- C-reactive protein
- Erythrocyte sedimentation rate
- Procalcitonin
- White blood cell count

IMAGING STUDIES
- Plain x-ray
- Ultrasound
- Magnetic resonance imaging

PATHOGEN IDENTIFICATION
- Blood cultures
- Synovial fluid aspirate
- Gram stain

Medical management includes initiation of antibiotic therapy after blood and synovial cultures have been obtained. Antibiotics have been proven to reach high concentrations in synovial fluid.[8] Antimicrobial therapy should be directed toward common pathogens of the patient's age group. A first-generation cephalosporin or clindamycin covers methicillin-sensitive *S aureus*, *S pyogenes*, *S pneumoniae*, and *Kingella*.[9] Vancomycin is primarily used for areas with high methicillin-resistant *S aureus* (MRSA) prevalence. Note that *Kingella* is resistant to clindamycin and vancomycin but susceptible to cephalosporins and penicillins.

Duration of antibiotic therapy ranges from 2 to 6 weeks, with a minimum of 1 week of intravenous therapy. In the modern treatment era, a shorter length of treatment may be possible. A recent randomized clinical trial compared a 10-day versus a 30-day antibiotic regimen for children with septic arthritis.[10] Treatment was initiated with 2 to 4 days of parenteral antibiotics and followed by enteral therapy for the remainder of the treatment course. No difference in outcomes was seen, but further studies are necessary to assess long-term outcomes. In practice, duration of treatment should be guided by clinical improvement.

Emerging evidence suggests that dexamethasone may be a useful adjunct to antibiotic therapy. More rapid amelioration of symptoms, a shorter duration of parenteral antibiotic therapy, and decreased length of hospital stay were observed with a 4-day course of dexamethasone versus placebo in a recent randomized, controlled trial that enrolled children with septic arthritis.[11]

The pain and fever associated with septic arthritis are generally managed with nonsteroidal anti-inflammatory drugs. Surgical debridement may not be necessary in all cases. Patients presenting early in the course of the disease have recovered uneventfully without surgery. The chance of a favorable outcome lessens if symptoms have been present for longer than 5 days. Surgery is indicated if the patient is persistently febrile, has elevated circulating levels of inflammatory markers, and demonstrates little-to-no clinical improvement.

Complication rates for septic arthritis remain high, with approximately 40% of septic hips and 10% of septic knees developing growth plate damage and some degree of functional loss.[12] The likelihood of complications increases in cases of MRSA infection. It is crucial to consider septic arthritis in children who present with unexplained joint maladies.

Treatment outcome

The patient was transferred to a facility that offered expertise in hip pathology. A pediatric orthopedic surgeon performed additional surgical debridement. Infectious disease was consulted to assist with pathogen identification. The patient was bacteremic with MRSA, which most likely seeded in the left hip. No portal of entry for the etiologic agent was identified.

The patient was treated with 4 weeks of parenteral clindamycin therapy. Pain was managed initially with morphine and transitioned to acetaminophen and ibuprofen prior to discharge. Physical and occupational therapy were provided at a rehabilitation facility. The patient had returned to baseline at the 6-month follow-up visit with no residual effects of his disease.

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Dr Beaudoin is assistant professor of pediatrics, Department of Pediatrics, University of Texas Medical School, UT Health, Houston. The authors have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

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Pediatric practice and the bottom line

Whether you are an employed physician or in private practice, to survive and thrive in the era of healthcare reform you need to optimize your bottom line and maximize productivity while continuing to provide quality care.

Although pediatricians enjoy caring for patients, there is no disputing the fact that a medical practice is a business that must be run efficiently and profitably. We must learn to become shrewd businesspeople in order to keep our doors open. This edition of Peds v2.0 discusses financial concerns important to both independent physicians and those employed by hospitals or large health systems.

More and more pediatricians are abandoning private practice because they believe that medical practice has become too burdensome. The Medical Group Management Association reports that two-thirds of physicians were independent practitioners in 2005. By 2008, the majority (52%) were employees.[1] According to a recent survey (2012) conducted by Accenture, a medical industry consultative group, only 39% of physicians remain independent.[2]

According to the Accenture survey, there are many reasons why physicians are leaving private practice[2]:

- Medical practice is growing more complicated and many fear that healthcare reform will drive most physicians out of practice.
- Most doctors see joining a hospital or health system organization as safeguarding their salaries at least for the near future.
- More than half of doctors cited electronic health record (EHR) requirements as a main reason for leaving private practice.

When you become employed, you have done so because you have a firm belief in the concept of "safety in numbers." However, as an employee you give up your autonomy. This means that you use the EHR system chosen by the institution, and follow policies established by managing physicians. You may have the ability in such a situation to express opinions and influence decisions, but unlike in private practice, change comes very slowly and policies are often reactive rather than proactive.

So, if you are in private practice, how do you maximize revenue and control costs to ensure that you remain independent? If you are an employed physician, how do you provide quality care and maximize your productivity? Here are my suggestions regarding some best practices that will help you thrive in an era of uncertainty and healthcare reform. You should take comfort

Don't miss Dr. Andrew Schuman, *Contemporary Pediatrics'* tech guru, as he presents the best new technologies for your practice at the American Academy of Pediatrics' National Conference and Exhibition in San Diego. Interactive Group Forum Sessions, #I3137 Must-have gadgets, gizmos, and technology for the pediatric office; Monday, October 13, 2014; 4:00-5:30 pm; Convention Center. For more information, go to www.aapexperience.org.

in the fact that the need for primary care physicians is expected to increase over the next few years, and those who can prove they provide quality care—whether an employed physician or in private practice—will be in the best position to negotiate contracts with insurance companies or negotiate compensation with their employers.

Improve efficiency

No matter if you are an employed physician or in private practice, to survive and thrive in the era of healthcare reform you need to scrutinize your workflow and that of your staff to optimize daily patient throughput. This has been the subject of previous Peds v2.0 articles, and it requires challenging yourself and staff to think "inside" the box.

It means simplifying the check-in process by shortening patient intake or registration questionnaires; mailing new patient registration forms or using patient portals; and using secure e-mails or online services to remind patients of their appointments.

It means using technology to improve office-based care and screening. Chief among these technologies are photoscreeners and otoacoustic emissions automated screeners to test vision and hearing in your young patients, and office diagnostic tests such as rapid strep tests and rapid influenza testing.

It means that your staff should take vital signs in exam rooms, document the chief complaint, and update medication lists and problem lists so providers can focus on patient care rather than on electronic housekeeping. To facilitate office efficiency, all exam rooms should be equipped with computers running your EHR and printers.

You need to adopt workflow practices that allow you to maximize quality time with patients so you have time to reinforce recommendations.

Optimize coding, billing, and collection

As I discussed in the February 2013 article "Level 4 office-visit coding," pediatricians are very timid when it comes to coding for the services we provide patients. By simply learning the nuances of documenting to support the level of service provided, you will improve your bottom line and be able to survive any insurance company audit. Studies have shown that physicians tend to undercode office visits: 99214 visits are generally reimbursed $30 to $50 more than 99213 visits. These 99214 visits require moderate medical decision making and should be considered when patients present with:

- One or more chronic illnesses with mild exacerbation, progression, or adverse effects of treatment (eg, asthma exacerbation, attention-deficit/hyperactivity disorder not responding to medication).
- Two or more stable chronic illnesses (asthma, enuresis).
- Undiagnosed new problem with uncertain prognosis (eg, blood in the stool).
- Acute illness with systemic symptoms (eg, pyelonephritis, pneumonitis, colitis).
- Acute complicated injury (eg, head injury with brief loss of consciousness).
- Conditions that require prescription drug management (otitis media, urinary tract infection, strep pharyngitis).

Cash flow is the lifeblood of any practice. If insurance companies delay payment, or if you have a slow month, a decline in cash flow may threaten the viability of any

IMPROVE YOUR BOTTOM LINE

IMPROVE EFFICIENCY

- Simplify registration
- Computer workstations in all exam rooms
- Take vital signs in exam rooms
- Have staff update EHR information
- Use patient portals and/or reminder services

OPTIMIZE CODING, BILLING, AND COLLECTIONS

- Avoid undercoding for office visit services
- Collect copays and deductibles at time of service
- Consider credit card charge agreements
- Provide incentives for coders and billers for achieving benchmarks
- Challenge denied claims
- Keep a mindful eye on accounts receivable

REDUCE OVERHEAD

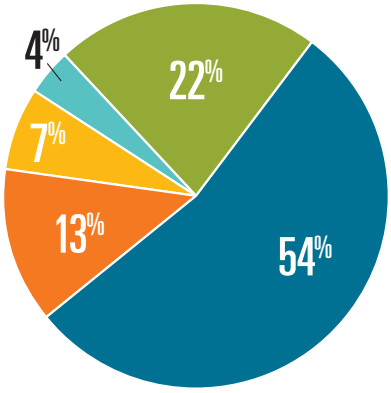
- Staff appropriately
- Consider joining a buying service
- Transition to a free EHR
- Lease expensive equipment

Abbreviation: EHR, electronic health record.

practice. To prevent this, you need to optimize cash flow by using an effective billing service or employing experienced coders and billers. Pay your coders and billers well and consider providing cash incentives for hitting certain collection thresholds. Remember that most patients have high deductible insurance plans, so collect payments from parents who have yet to meet their deductibles at the time of service and consider providing a discount when patients pay by cash or check. When in question, always verify patient eligibility via the insurance company's website. This usually takes less than 2 minutes.

Many practices have patients sign an agreement enabling the practice to charge a credit card for their portion of the bill once the submitted claim has been processed by the insurance company. Electronic claims should be submitted within 7 days of service for a busy practice and posted within 2 to 3 days upon receipt. Patient bills should be generated within a week's time of posting. Do not use paper claims because they can significantly prolong the collection process.

Billing services allow you to outsource your billing, but they collect a percentage of payments or charge per claim processed (or a hybrid of both) whether the bill is paid or not. Many pediatricians prefer to keep billing and collections in-house so they can monitor cash flow and react to problems sooner rather than later. Keep a very close eye on your cash receivables. In general, for a private primary care practice, 54% of your receivables should be in the 0-to-30-day category; 13% in the 30-to-60-day category; 7% in the 60-to-90-day category; 4% in the 90-to-120-day category; and 22% in the over-120-day category.



OPTIMAL RECEIVABLES AGING TARGETS IN DAYS

- <30 days
- 30-60 days
- 60-90 days
- 90-120 days
- >120 days

Never be reluctant to challenge denied claims for charges you believe are appropriate. This is often the case when insurance companies begin to make payments for new services that your practice is beginning to offer, such as developmental screening or visual screening using photoscreeners. It is always helpful to attach American Academy of Pediatrics (AAP) policy statements that support your appeal letters. When you have questions, do some research. A great resource has always been the listserv run by the AAP's Section on Administration and Practice Management.

Some pediatricians are not aware that you can charge for a well visit as well as a sick visit when your coders use modifiers correctly and you provide 2 notes to provide documentation of your service. This can be done when a patient is discovered to have an ear infection, sore throat, or pneumonia at a well visit, or a new significant problem (eg, blood in stool, palpitations) that will need to be worked up.

It is also important to keep a substantial cash reserve on hand to keep your practice running for several months should collections or productivity decline. If this is not possible, establish a line of credit with a bank that can be used in times of need and paid off in times of plenty.

Keep overhead down

While it behooves all independent pediatricians to be good minders of practice financials, all pediatricians—those employed as well as those in private practice—will benefit if they take measures to reduce practice overhead.

There are many ways a medical practice can reduce costs. Electronic health record systems are extremely expensive, so if you are displeased with your EHR, don't be reluctant to transition your EHR to Practice Fusion, a free cloud-based EHR that integrates with both cloud-based billing services and desktop billing software. You can reduce your need to send out claims, registration forms, and notices for upcoming patient appointments by using patient portals and/or appointment reminder services. These dramatically reduce overhead, saving postage and time by automating many of the tedious processes that can occupy much of your staff's time. Most patient portals facilitate payment of bills via the portal itself.

For an extemded verision of this article and references, go to ContemporaryPediatrics.com/bottom-line

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Pathogenesis, epidemiology, and classification

Infantile hemangiomas are benign vascular tumors that result from the proliferation of endothelial-like cells that express high levels of glucose transporter isoform 1 (GLUT1) and placenta-associated vascular antigens.[1] They develop early in life in 4% to 5% of infants.[2,3] There is a higher prevalence in females, non-Hispanic whites, premature infants (<37 weeks gestational age), infants of low birth weight (<2500g), and infants of multiple gestations.[4] There also seem to be associations with older maternal age (≥30 years), placenta previa, and preeclampsia during the prenatal period.

Hemangiomas are often classified morphologically as superficial, deep, or mixed.[5,6] A superficial hemangioma is red, nodular, and raised above the normal skin. A deep hemangioma presents as a subcutaneous skin-colored nodule or tumor with overlying bluish discoloration, with or without associated telangiectasia. Mixed hemangiomas contain both superficial and deep components.

Hemangiomas can be focal (localized and usually round or oval and relatively small); multifocal (same as focal but multiple hemangiomas); and segmental (covering a specific territory and usually large).[6]

Segmental hemangiomas are more likely to be associated with developmental abnormalities, including PHACE syndrome (**p**osterior fossa malformations, large segmental **h**emangiomas, and **a**rterial/**c**ardiac/**e**ye abnormalities).[7] Therefore, these children require more intensive monitoring; are more likely to require medical therapy; and tend to have more complications (eg, ulceration) than children with localized hemangiomas.[6]

TABLE 1 COMPARISON OF VASCULAR LESIONS OF INFANCY

	HEMANGIOMAS OF INFANCY	VASCULAR MALFORMATIONS
Types of conditions	○ Infantile hemangioma ○ Congenital hemangioma	○ Capillary malformations (salmon patch, port-wine stain) ○ Venous malformations ○ Lymphatic malformations ○ Arteriovenous malformations ○ Mixed malformations
Occurrence	○ Commonly present shortly after birth (infantile hemangiomas)	○ Present at birth
Location	○ Frequently involves head and neck but can involve any area	○ Common on limbs but can involve any area
Course	○ Rapid growth during infancy and slow, spontaneous involution (self-limited) ○ Lesions proliferate within predetermined anatomic boundaries	○ Growth in proportion to overall growth and no spontaneous regression ○ Lesions may fluctuate at puberty ○ Lesions are infiltrative and destructive

Adapted from Chang LC, et al[8]; Richter GT, et al[9]; Habif TP.[10]

Natural course

The natural progression of hemangiomas includes 2 phases: proliferation and spontaneous involution. The average hemangioma will reach 80% of its full size by 3 months with the majority of growth completed by 5 months of age.[8] Following proliferation, the majority of hemangiomas begin to regress by 1 year of age. Hemangiomas must be distinguished from vascular malformations. A hemangioma is a vascular neoplasm that grows by cellular hyperplasia; a vascular malformation is a result of defective vascular morphogenesis.[9] The differences are outlined in Table 1.[8-10]

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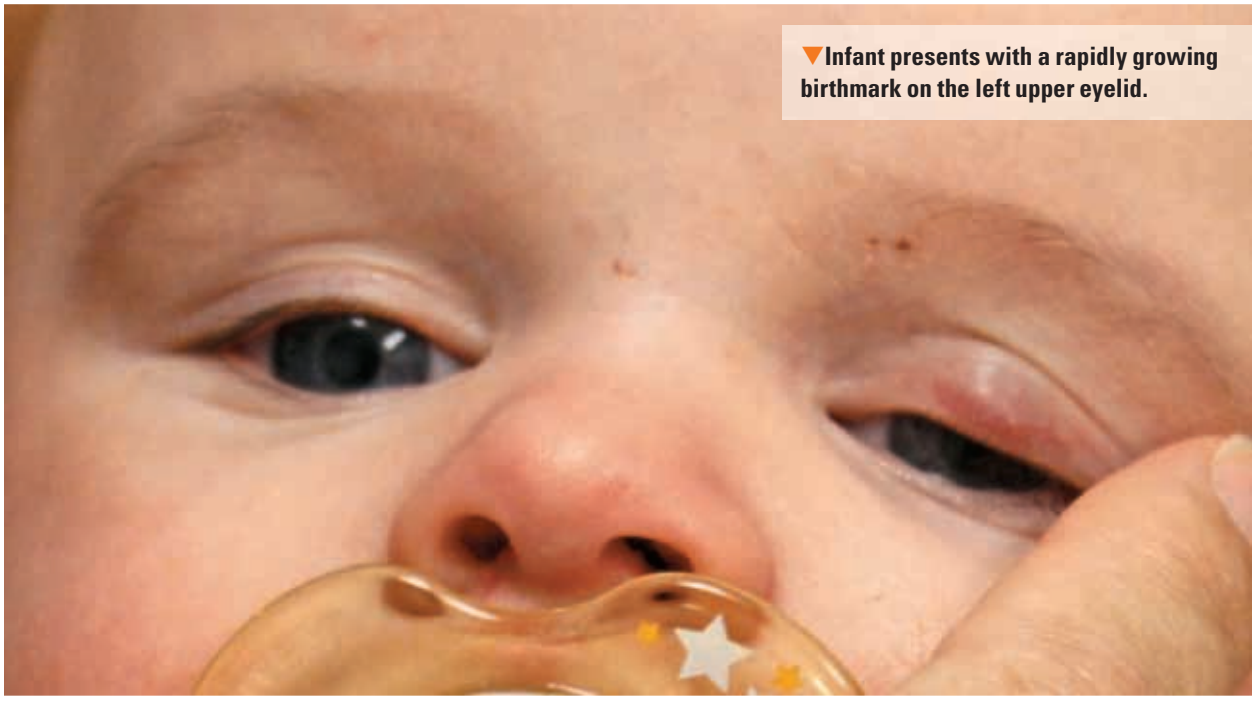
The authors have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

For an extended version of this article with references, go to ContemporaryPediatrics.com/dermcase0914

BERNARD A COHEN, MD
SECTION EDITOR



▼Infant presents with a rapidly growing birthmark on the left upper eyelid.

Infant's growing birthmark causes blurry vision

JINA CHUNG, BS, MS4
BERNARD A COHEN, MD

THE CASE

You are asked to see a healthy 3-month-old boy with a rapidly growing lump on his left upper eyelid. At birth there was a red macule that was diagnosed as a small port-wine birthmark. The infant was seen by a pediatric ophthalmologist who noted significant astigmatism of the left eye. FOR MORE ON THIS CASE, TURN TO PAGE 57. ▶

IMAGE CREDIT / AUTHOR SUPPLIED

DERMCASE *diagnosis* } INFANTILE HEMANGIOMA

EpiPen® 0.3 mg EPINEPHRINE AUTO-INJECTOR EpiPen Jr® 0.15 mg EPINEPHRINE AUTO-INJECTOR

BRIEF SUMMARY. See package insert for full Prescribing Information.

CONTRAINDICATIONS: There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS: EpiPen and EpiPen Jr Auto-Injectors should **only** be injected into the anterolateral aspect of the thigh. DO NOT INJECT INTO BUTTOCK. Injection into the buttock may not provide effective treatment of anaphylaxis. Advise the patient to go immediately to the nearest emergency room for further treatment of anaphylaxis.

Since epinephrine is a strong vasoconstrictor, accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area. Treatment should be directed at vasodilation in addition to further treatment of anaphylaxis. Advise the patient to go immediately to the nearest emergency room and to inform the healthcare provider in the emergency room of the location of the accidental injection.

DO NOT INJECT INTRAVENOUSLY. Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine if there is such inadvertent administration.

Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may, in other products, cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations even if the patient is sulfite-sensitive.

Epinephrine should be administered with caution in patients who have heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, e.g., digitalis, diuretics, or anti-arrhythmics, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. It should be recognized that the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation.

PRECAUTIONS:

(1) General

EpiPen and EpiPen Jr Auto-Injectors are not intended as a substitute for immediate medical care. In conjunction with the administration of epinephrine, the patient should seek immediate medical or hospital care. More than two sequential doses of epinephrine should only be administered under direct medical supervision.

Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs, and other allergens as well as idiopathic and exercise-induced anaphylaxis should be carefully instructed about the circumstances under which epinephrine should be used. It must be clearly determined that the patient is at risk of future anaphylaxis.

The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors.

Some patients may be at greater risk of developing adverse reactions after epinephrine administration. These include: hyperthyroid individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women, pediatric patients under 30 kg (66 lbs.) body weight using EpiPen Auto-Injector, and pediatric patients under 15 kg (33 lbs.) body weight using EpiPen Jr Auto-Injector.

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with these conditions, and/or any other person who might be in a position to administer EpiPen or EpiPen Jr Auto-Injector to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which epinephrine should be used.

(2) Drug Interactions

Patients who receive epinephrine while concomitantly taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias.

The effects of epinephrine may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines, notably chlorpheniramine, tripelennamine and diphenhydramine.

The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta-adrenergic blocking drugs, such as propranolol. The vasoconstricting and hypertensive effects of epinephrine are antagonized by alpha-adrenergic blocking drugs, such as phentoloamine. Ergot alkaloids may also reverse the pressor effects of epinephrine.

(3) Carcinogenesis, Mutagenesis, Impairment of Fertility

Epinephrine and other catecholamines have been shown to have mutagenic potential *in vitro* and to be an oxidative mutagen in a *WP2* bacterial reverse mutation assay. Epinephrine had a moderate degree of mutagenicity, and was positive in the DNA Repair test with *B. subtilis* (REC) assay, but was not mutagenic in the *Salmonella* bacterial reverse mutation assay.

Studies of epinephrine after repeated exposure in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted. This should not prevent the use of epinephrine under the conditions noted under **INDICATIONS AND USAGE.**

(4) Usage in Pregnancy

Pregnancy Category C: There is no study on the acute effect of epinephrine on pregnancy. Epinephrine has been shown to have developmental effects when administered subcutaneously in rabbits at a dose of 1.2 mg/kg daily for two to three days (approximately 30 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis), in mice at a subcutaneous dose of 1 mg/kg daily for 10 days (approximately 7 times the maximum daily subcutaneous or intramuscular dose on a mg/m^2 basis) and in hamsters at a subcutaneous dose of 0.5 mg/kg daily for 4 days (approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis). These effects were not seen in mice at a subcutaneous dose of 0.5 mg/kg daily for 10 days (approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis). Although, there are no adequate and well-controlled studies in pregnant women, epinephrine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known if epinephrine passes into breast milk.

ADVERSE REACTIONS: Adverse reactions to epinephrine include transient, moderate anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with hypertension or hyperthyroidism. Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease or certain drugs **[see PRECAUTIONS, Drug Interactions]**. Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease. Angina may occur in patients with coronary artery disease. The potential for epinephrine to produce these types of adverse reactions does not contraindicate its use in an acute life-threatening allergic reaction.

Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area **(see WARNINGS).** Adverse events experienced as a result of accidental injections may include increased heart rate, local reactions including injection site pallor, coldness and hypoaesthesia or injury at the injection site resulting in bruising, bleeding, discoloration, erythema or skeletal injury.

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IMPORTANT SAFETY INFORMATION

EpiPen Auto-Injectors should only be injected into the anterolateral aspect of the thigh. DO NOT INJECT INTO BUTTOCK, OR INTRAVENOUSLY.

Epinephrine should be used with caution in patients with certain heart diseases, and in patients who are on drugs that may sensitize the heart to arrhythmias, because it may precipitate or aggravate angina pectoris and produce ventricular arrhythmias. Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease or taking cardiac glycosides or diuretics. Patients with certain medical conditions or who take certain medications for allergies, depression, thyroid disorders,

IMPORTANT SAFETY INFORMATION (CONTINUED)

diabetes, and hypertension, may be at greater risk for adverse reactions. Other adverse reactions include transient moderate anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties.

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