Contemporary PEDIATRICS®

FEBRUARY 2014
VOL. 31 | NO. 02

Expert Clinical Advice for Today's Pediatrician

ContemporaryPediatrics.com

PEER REVIEWER FEATURE

Clinical Studies

Makes Rectal Thermometers Unnecessary

1. Bahorski J, Repasky T, Ranner D, Fields A, Jackson M, Moultry L, Pierce K, Sandell M (Tallahassee Memorial Healthcare). Temperature measurement in pediatrics: a comparison of the rectal method versus the temporal artery method. In Press, Corrected Proof, Available online 24 February 2011, Journal of Pediatric Nursing (2011).
2. Batra P, Goyal S. Comparison of rectal, axillary, tympanic, and temporal artery thermometry in the pediatric emergency room. Pediatr Emerg Care. 2013 Jan;29(1):63-6. doi: 10.1097/PEC.0b013e31827b5427.
3. Batra P, Saha A, Faridi MM. Thermometry in children. J Emerg Trauma Shock. 2012 Jul;5(3):246-9.
4. Carr EA, Wilmoth ML, Eliades AB, Baker PJ, Shelestak D, Heisroth KL, Stoner KH (Akron Children's Hospital). Comparison of Temporal Artery to Rectal Temperature Measurements in Children Up to 24 Months, Journal of Pediatric Nursing, In Press, [Epub ahead of print], Jan 25, 2010.
5. Gunawan M, Soetjiningsih I (Udayana University, Sanglah Hospital, Denpasar, Indonesia). Comparison of the accuracy of body temperature measurements with temporal artery thermometer and axillary mercury thermometer in term newborns. Paediatr Indones, Vol. 50, No. 2, March 2010.
6. Kemp, C. (2013). Temporal artery thermometers may rival rectal thermometers in ED. AAP News, 34(4).
7. Reynolds M, et al. Are temporal artery temperatures accurate enough to replace rectal temperature measurement in pediatric ED patients? J Emerg Nurs. 2012 Nov 8. pii: S0099-1767(12)00329-7. doi: 10.1016/j.jen.2012.07.007. [Epub ahead of print]
8. Titus MO, Hulsey T, Heckman J, Losek JD (Medical University of South Carolina and Children's Hospital). Temporal artery thermometry utilization in pediatric emergency care. Clinical Pediatrics, Mar 2009; vol. 48: pp. 190 - 193.

Accuracy Proven for All Ages (Studies including premature neonates to infants younger than 3 months)

1. Batra P, Saha A, Faridi MM. Thermometry in children. J Emerg Trauma Shock. 2012 Jul;5(3):246-9.
2. Burdjalov et al. Non-Invasive infrared temperature assessment of the temporal artery for core temperature determination in premature neonates. American Pediatric Society and the Society for Pediatric Research, 5/1/2001
3. Carr et al. Comparison of Temporal Artery to Rectal Temperature Measurements in Children Up to 24 Months, J of Ped Nursing (2011) 26, 179–185
4. Gunawan et al. Comparison of the accuracy of body temperature measurements with temporal artery thermometer and axillary mercury thermometer in term newborns. Paediatr Indones, 50 (2) 2010.
5. Haddad et al. Comparison of temporal artery and axillary temperatures in healthy newborns. JOGNN, 41, 383-388; 2012.
6. Lee et al. Accuracy of temporal artery thermometry in neonatal intensive care infants. Adv Neonatal Care, 11(1) 62-70, 2011.
7. Reynolds M, et al. Are temporal artery temperatures accurate enough to replace rectal temperature measurement in pediatric ED patients? J Emerg Nurs. 2012 Nov 8. pii: S0099-1767(12)00329-7. doi: 10.1016/j.jen.2012.07.007. [Epub ahead of print]

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www.exergen.com/199offer

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Contemporary PEDIATRICS®

FEBRUARY 2014
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Expert Clinical Advice for Today's Pediatrician

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PEER-REVIEWED FEATURE

FIRST SEIZURE
DISPEL THE MYTHS

HOSPITAL ZONE
The State of Pediatric Hospice Care

VISION SCREENING
UPDATE & REVIEW

PUZZLER
Stumped by a bleeding umbilicus

ADVANSTAR
MEDICAL COMMUNICATIONS GROUP

FIRST SEIZURE: DISPEL THE MYTHS • THE STATE OF PEDIATRIC HOSPICE CARE • VISION SCREENING UPDATE

When assessing pediatric patients with ADHD,

Consider how ADHD symptoms impact patients throughout the day[1]

Pediatric (Aged 6 to 12) Clinical Study

Primary Endpoint: Mean Change From Baseline to Endpoint* in ADHD-RS-IV Total Score[2,3]

- Vyvanse® provided a **56%** average reduction in ADHD-RS-IV total score (from 43.9 to 19.5) for all doses combined vs a **14%** average reduction for placebo (from 42.4 to 36.6); *P*<.0001[2,3]

Find out more at Vyvansepro.com.

IMPORTANT SAFETY INFORMATION

WARNING: ABUSE AND DEPENDENCE

- **CNS stimulants (amphetamines and methylphenidate-containing products) have a high potential for abuse and dependence.**
- **Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.**

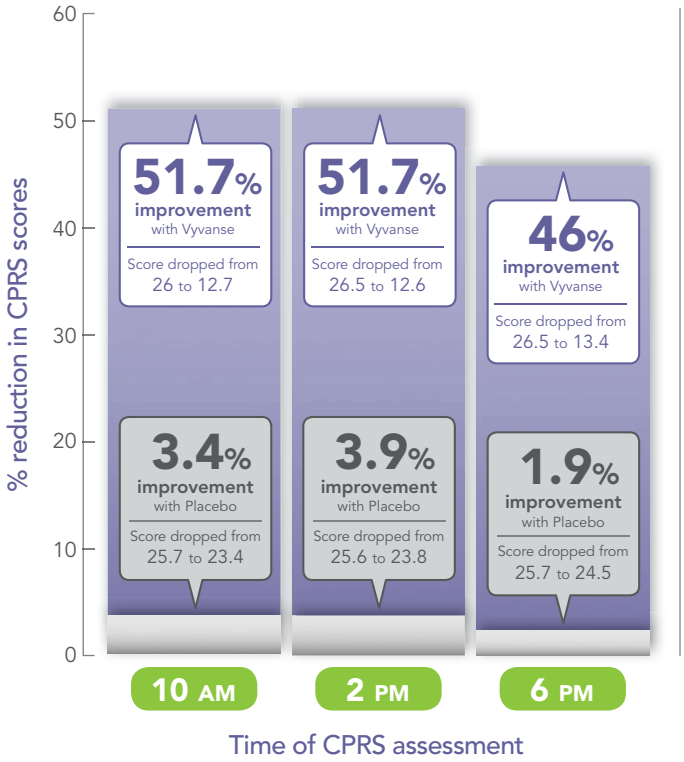
- Contraindications:
  - Known hypersensitivity to amphetamines or other ingredients in Vyvanse. Anaphylactic reactions, Stevens - Johnson syndrome, angioedema, and urticaria have been observed in postmarketing reports.
  - Concurrent administration of monoamine oxidase inhibitors (MAOI) or administration of Vyvanse within 14 days of the last MAOI dose. Hypertensive crisis can occur.
- Educate patients about abuse and periodically re-evaluate the need for Vyvanse.
- Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in children and adolescents with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Prior to treatment assess for the presence of cardiac disease. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during Vyvanse treatment.
- CNS stimulants cause an increase in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for tachycardia and hypertension.
- Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with preexisting psychosis. Clinical evaluation for bipolar disorder is recommended prior to stimulant use.
- CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Monitor weight and height in children during treatment with Vyvanse. Treatment may need to be interrupted in children not growing as expected.

Vyvanse, given once daily, significantly improved ADHD symptoms in patients aged 6–12, at 10 AM, 2 PM, and 6 PM[4]

ONCE-DAILY Vyvanse® II
(lisdexamfetamine dimesylate)
20 • 30 • 40 • 50 • 60 • 70 mg capsules

Key Secondary Endpoint: Parent-Rated Improvement Measured by Connors' Parent Rating Scale (CPRS)

Least Squares Mean Percentage Change From Baseline to Endpoint* on CPRS-ADHD Index Scores[5,6]



Study design: 4-week, double-blind, randomized, placebo-controlled, parallel-group, forced-dose titration study of 290 children aged 6 to 12 with ADHD based on *DSM-IV-TR*. The objective was to evaluate the efficacy and safety of Vyvanse (30 mg, 50 mg, 70 mg) once daily in the morning compared to placebo. Primary endpoint: Change in ADHD-RS-IV total score from baseline to endpoint.[4,7]

Vyvanse† (n=213) Placebo (n=72)

*Last post-randomization treatment week for which a valid ADHD-RS-IV total score was obtained

†Mean of all doses tested. Median daily dosing between 7:30 AM and 8:00 AM

P<.0001 for Vyvanse vs placebo at all time points assessed

DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision

IMPORTANT SAFETY INFORMATION CONTINUED

- Stimulants used to treat ADHD, including Vyvanse, are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes (e.g., numbness, pain, skin color change, or sensitivity to temperature, and rarely ulcerations and/or soft tissue breakdown) is necessary during treatment and may require further evaluation (e.g., referral).
- The most common adverse reactions (≥5% and at least twice the rate of placebo) reported in clinical trials were:
  - *Children aged 6 to 12:* decreased appetite, insomnia, upper abdominal pain, irritability, vomiting, decreased weight, nausea, dry mouth and dizziness;
  - *Adolescents aged 13 to 17:* decreased appetite, insomnia, and decreased weight;
  - *Adults:* decreased appetite, insomnia, dry mouth, diarrhea, nausea, anxiety and anorexia.

INDICATION

Vyvanse is indicated for the treatment of ADHD in patients ages 6 and above.

References

1. American Psychiatric Association. Attention-deficit/hyperactivity disorder. In: *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (*DSM-5*™). Washington, DC: American Psychiatric Association; 2013:59-65.
2. Biederman J, Krishnan S, Zhang Y, et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clin Ther.* 2007;29:450-463.
3. Data on file; LDX006; Shire US Inc.
4. Vyvanse (lisdexamfetamine dimesylate) [package insert]. Wayne, PA: Shire US Inc.
5. Lopez FA, Ginsberg LD, Arnold V. Effect of lisdexamfetamine dimesylate on parent-rated measures in children aged 6 to 12 years with attention-deficit/hyperactivity disorder: a secondary analysis. *Postgrad Med.* 2008;120(3):89-102.
6. Data on file; LDX010; Shire US Inc.
7. Data on file; NRP104-099; Shire US Inc.

Please see Brief Summary of Prescribing Information on the next pages.

Shire

Vyvanse® (lisdexamfetamine dimesylate) Capsules
20, 30, 40, 50, 60, 70 mg **CII** **Rx Only**

BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information.

WARNING: ABUSE AND DEPENDENCE

CNS stimulants (amphetamines and methylphenidate-containing products) have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

INDICATIONS AND USAGE

Vyvanse® is indicated for treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Efficacy of Vyvanse in the treatment of ADHD was established on the basis of three short-term controlled trials in children ages 6 to 12 years, one short-term controlled trial in adolescents ages 13 to 17 years, one short-term trial in children and adolescents ages 6-17 years, one maintenance trial in children and adolescents ages 6-17 years, two short-term controlled trials in adults, and one maintenance trial in adults.

DOSAGE AND ADMINISTRATION

- Recommended starting dose: 30 mg once daily in the morning in patients ages 6 and above
- Increase in increments of 10 or 20 mg at approximately weekly intervals if needed
- Maximum dose: 70 mg per day
- Prior to treatment, assess for presence of cardiac disease

CONTRAINDICATIONS

Vyvanse is contraindicated in patients with:

- Known hypersensitivity to amphetamine products or other ingredients of Vyvanse. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have been observed in postmarketing reports.
- Concurrent administration of monoamine oxidase inhibitors (MAOI) or administration of Vyvanse within 14 days of the last MAOI dose. Hypertensive crisis can occur.

WARNINGS AND PRECAUTIONS

Potential for Abuse and Dependence *(See Boxed Warning Above)*

Serious Cardiovascular Reactions

Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in children and adolescents with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during Vyvanse treatment.

Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for potential tachycardia and hypertension.

Psychiatric Adverse Reactions

Exacerbation of Pre-existing Psychosis

CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a mixed/manic episode in patients with bipolar disorder. Prior to initiating treatment, screen patients for risk factors for developing a manic episode.

New Psychotic or Manic Symptoms

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms, e.g. hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing the CNS stimulant. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in 0.1% of CNS stimulant-treated patients compared to 0% in placebo-treated patients.

Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including Vyvanse. In a 4-week, placebo-controlled trial of Vyvanse in patients ages 6 to 12 years old, there was a dose-related decrease in weight in the Vyvanse groups compared to weight gain in the placebo group. Additionally, in studies of another stimulant, there was slowing of the increase in height.

Peripheral Vasculopathy, including Raynaud's Phenomenon

Stimulants, including Vyvanse, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

ADVERSE REACTIONS

Clinical Trial Experience

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

The safety data in this section is based on data from 4-week parallel-group controlled clinical studies of Vyvanse in pediatric and adult patients with ADHD.

Adverse Reactions Associated with Discontinuation of Treatment in Clinical Trials

In the controlled trial in patients ages 6 to 12 years, 9% (20/218) of Vyvanse-treated patients discontinued due to adverse reactions compared to 1% (1/72) of placebo-treated patients. Most frequent adverse reactions leading to discontinuation (i.e. leading to discontinuation in at least 1% of Vyvanse-treated patients and at a rate at least twice that of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, insomnia, and rash [2 instances for each adverse reaction, i.e., 2/218 (1%)].

In the controlled trial in patients ages 13 to 17 years, 4% (10/233) of Vyvanse-treated patients discontinued due to adverse reactions compared to 1% (1/77) of placebo-treated patients. Most frequent adverse reactions leading to discontinuation were irritability (3/233; 1%), decreased appetite (2/233; 1%), and insomnia (2/233; 1%).

In the controlled adult trial, 6% (21/358) of Vyvanse-treated patients discontinued due to adverse reactions compared to 2% (1/62) of placebo-treated patients. Most frequent adverse reactions leading to discontinuation (i.e. leading to discontinuation in at least 1% of Vyvanse-treated patients and at a rate at least twice that of placebo) were insomnia (8/358; 2%), tachycardia (3/358; 1%), irritability (2/358; 1%), hypertension (4/358; 1%), headache (2/358; 1%), anxiety (2/358; 1%), and dyspnea (3/358; 1%).

Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) reported in children, adolescents, and/or adults were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting.

Adverse Reactions Occurring at an Incidence of 2% or More Among Vyvanse-Treated Patients in Clinical Trials

Adverse reactions reported in the controlled trials in pediatric patients ages 6 to 12 years, adolescent patients ages 13 to 17 years, and adult patients treated with Vyvanse or placebo are presented in Tables 1, 2, and 3 below.

Table 1 Adverse Reactions Reported by 2% or More of Children (Ages 6 to 12 Years) Taking Vyvanse and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial

	Vyvanse (n=218)	Placebo (n=72)
Decreased Appetite	39%	4%
Insomnia	23%	3%
Abdominal Pain Upper	12%	6%
Irritability	10%	0%
Vomiting	9%	4%
Weight Decreased	9%	1%
Nausea	6%	3%
Dry Mouth	5%	0%
Dizziness	5%	0%
Affect lability	3%	0%
Rash	3%	0%
Pyrexia	2%	1%
Somnolence	2%	1%
Tic	2%	0%

Table 2 Adverse Reactions Reported by 2% or More of Adolescent (Ages 13 to 17 Years) Patients Taking Vyvanse and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial

	Vyvanse (n=233)	Placebo (n=77)
Decreased Appetite	34%	3%
Insomnia	13%	4%
Weight Decreased	9%	0%
Dry Mouth	4%	1%

Table 3 Adverse Reactions Reported by 2% or More of Adult Patients Taking Vyvanse and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial

	Vyvanse (n=358)	Placebo (n=62)
Decreased Appetite	27%	2%
Insomnia	27%	8%
Dry Mouth	26%	3%
Diarrhea	7%	0%
Nausea	7%	0%
Anxiety	6%	0%
Anorexia	5%	0%
Feeling Jittery	4%	0%
Agitation	3%	0%
Blood Pressure Increased	3%	0%
Hyperhidrosis	3%	0%
Restlessness	3%	0%
Weight Decreased	3%	0%
Dyspnea	2%	0%
Heart Rate Increased	2%	0%
Tremor	2%	0%

In addition, in the adult population erectile dysfunction was observed in 2.6% of males on Vyvanse and 0% on placebo; decreased libido was observed in 1.4% of subjects on Vyvanse and 0% on placebo.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of Vyvanse. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events are as follows: palpitations, cardiomyopathy, mydriasis, diplopia, difficulties with visual accommodation, blurred vision, eosinophilic hepatitis, anaphylactic reaction, hypersensitivity, dyskinesia, tics, bruxism, depression, dermatillomania, aggression, Stevens-Johnson Syndrome, angioedema, urticaria, seizures, libido changes, and frequent or prolonged erections.

DRUG INTERACTIONS

Acidifying and Alkalinizing Agents

Ascorbic acid and other agents that acidify urine increase urinary excretion and decrease the half-life of amphetamine. Sodium bicarbonate and other agents that alkalinize urine decrease urinary excretion and extend the half-life of amphetamine. Adjust the dosage accordingly.

Monoamine Oxidase Inhibitors

Do not administer Vyvanse concomitantly with monoamine oxidase inhibitors or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C.: Risk Summary

There are no adequate and well-controlled studies with Vyvanse in pregnant women. Vyvanse should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Amphetamines are excreted into human milk. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness have been established in pediatric patients with ADHD ages 6 to 17 years. Safety and efficacy in pediatric patients below the age of 6 years have not been established.

Geriatric Use

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

DRUG ABUSE AND DEPENDENCE

Vyvanse contains lisdexamfetamine, a prodrug of amphetamine, a Schedule II controlled substance.

OVERDOSAGE

Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of overdosage. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses. Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Other reactions include arrhythmias, hypertension or hypotension, circulatory collapse, nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

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Healthy skin ***Happy patients***

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February 2014
VOL. 31 NO. 2

30 YEARS
Helping You Care for Kids

peer-reviewed article

the hospital zone

19 puzzler

39 peds v2.0

50 dermcase

departments

in addition

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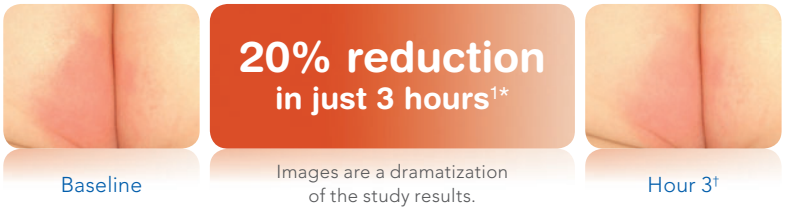
- Statistically significant reduction of erythema in just 1 diaper change[1]

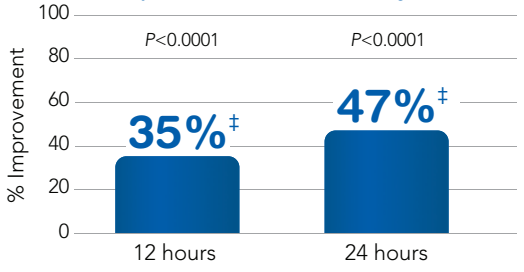


*Trial assessing the efficacy of DESITIN® Maximum Strength Original Paste for 3±1 hours in children (N=31) 3-36 months of age, with mild to moderate diaper rash, wearing diapers for 24 hours a day.[1]

†*P*=0.0001

Effective improvement in skin health

- Evaluation of erythema, papules, and dryness/scaling
- An average improvement score of **35% at 12 hours** (*P*<0.0001) and **47% at 24 hours** (*P*<0.0001)[2‡]



‡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).

Proven formula

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- Formulated to protect and help prevent recurrence—more spreadable for instant protection that lasts from diaper change to diaper change[1]
  - —**13% zinc oxide** in a mineral oil and petrolatum cream base provides an instant barrier to help seal out wetness and irritants

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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what's trending

The conversation continues all month long online.

HAS THE ACA HIT HOME YET?

37% YES
63% NO

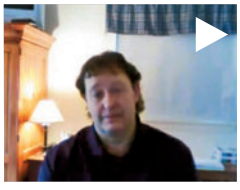
In our latest online poll, we asked if you had been dropped from any health insurance plans since enactment of the Affordable Care Act (ACA). Insurers say they must shrink their physician networks due to the billions of dollars in government payment cuts they face over the next 10 years. Some doctors who have been jettisoned are fuming about the sudden terminations, how they were communicated, the possible damage to their reputations, and the financial effect on their practices. Many even report that their patients were alerted before they were.

In response, physicians groups, including representatives from the American Academy of Pediatrics, have met with administration officials not only about their concern that new insurance plans under the ACA offer only limited networks of providers, but that that, coupled with low reimbursement rates for doctors, could make it difficult for millions of those enrolled to actually obtain health care.

Now, the *Washington Post* reports that the American Medical Association, 39 state affiliates, and 42 patient and medical specialty groups have petitioned the Obama administration to step in and compel insurers to reverse the terminations.

What about you? Has the law of unintended consequences impacted your pediatric practice in the form of an insurance plan termination notice since the health care reform law took effect? We know there's a story behind each of the data points in our poll. We'd like to hear yours. ***E-mail us at tmcnulty@advanstar.com***

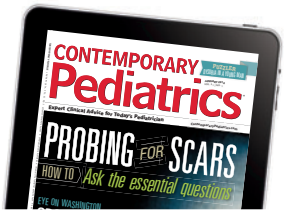
video



We recently caught up with primary care pediatrician Andrew S. Garner, MD, PhD, chair of the American Academy of Pediatrics' Leadership Workgroup on Early Brain and Child Development and coauthor of the AAP Policy Statement and Technical Report on toxic stress. Dr. Garner describes how children's response to toxic stress stimuli in their environment alters the brain, putting them at risk for a lifetime of adverse health outcomes. Pediatricians, he says, are the natural sentinels to screen and to intervene.
ContemporaryPediatrics.com/toxicstress

digital app

We reimagined the *Contemporary Pediatrics* app for the iPad and iPhone with an even more intuitive interface that serves up fresh content with a fingertip swipe. Try it free at **ContemporaryPediatrics.com/PedsApp**



1. HEEADSSS 3.0 psychosocial interview for adolescents
2. Dysuria in a young man
3. Persistent tremors and agitation in a 6-year-old girl
4. Managing chronic daily headaches
5. Apophysitis of the lower extremities

on twitter

Are you following *Contemporary Pediatrics*? Have your say in real time like these colleagues of yours did: @ContemPeds

Contemp. Pediatrics
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Onset of GI disorders can be reduced if an infant is given a probiotic during the first 3 months of life bit.ly/1aazf4g

Fernando Bula
@ferbuleh
@ContemPeds how about the best probiotic of all? Breast milk exclusively!!

Richard van Wylick
@rvanwylick
No No No. @ContemPeds : President Obama says pot no more dangerous than alcohol. Helpful message for kids to hear? yhoo.it/1mktkcV

Matt Weidman
@CountryKidsDoc
Leading causes of death for children lnkd.in/bFbQa2b @ ContemPeds via @fcpeds Homicide #4 cause for ages 1-9 yrs?! Sad commentary.

editorial

'This is what 30 looks like'

As part of our yearlong celebration of *Contemporary Pediatrics*' 30th anniversary, we are delighted to unveil a brand-new look with this issue. The magazine's fresh color palette and bold visual cues are designed to facilitate your reading and make navigating your favorite departments and features a clearer, more enjoyable experience.

We'll continue to unveil new content, features, and improvements, including a dynamic optimized app (downloadable for free at ContemporaryPediatrics.com/PedsApp) as our anniversary year progresses.

Speaking of which, turn to page 31 for the debut of our newest recurring feature, *The Hospital Zone*. Here, we'll bring you word of some of the inventive and inspiring pediatric initiatives emerging from the United States' world-class hospitals for children.

Please let us know how you like the new look—and how we are doing otherwise in our communications with you—both online and in print.

While we may have reengineered our look to launch into our third decade, our commitment remains foundational and unwavering: to assist you, the practicing pediatrician, in meeting your clinical and practice improvement information needs.

In that regard, we're old school all the way. ■

THE EDITORS

your letters

What's in a name?

I have been an avid reader of *Contemporary Pediatrics* for years and have always found the articles timely and relevant to a practicing pediatrician like myself. There is one aspect of your publication that bothers me, however, and that is not consistent with your mission statement, which is, to present practical information to office-based pediatricians.

I am referring to the persistent use of only generic names for medications discussed in your articles. Practically, we don't refer to omeprazole or lansoprazole but in reality use Prilosec or Prevacid. The same is true of fluticasone and budesonide instead of Veramyst or Pulmicort.

This may not satisfy the ivory tower academicians, but in practice we use brand names, as do our patients. It is quite annoying to have to read an article while having to employ another reference to translate the names of the drugs. Would the use of the brand name in parentheses next to the generic name offend someone's academic sensibilities?

I am the medical director of a 26-practitioner general pediatric practice, and all my colleagues feel the same way. It would make a great journal even better if you could effect that change.

DAVID WISOTSKY, MD
CEO, Medical Director
Tenafly Pediatrics PA
Tenafly, New Jersey

editor's note

Contemporary Pediatrics agrees with Dr. Wisotsky's suggestion and in the future will use both the brand names and generic names of medications in its articles. Thank you, readers, and know that we are listening to your suggestions to make this journal better.

Pediatrics, then and now

Practicing pediatricians have my sympathy.

As a pediatrician who retired after many years of solo pediatric practice and now volunteers at a clinic for the poor, I read with interest your article "5 ways your practice will change, and the 1 way it won't (*Contemp Pediatr*. 2013;30(12):24-32)" about what is causing the stress and unhappiness of many of the now-practicing pediatricians.

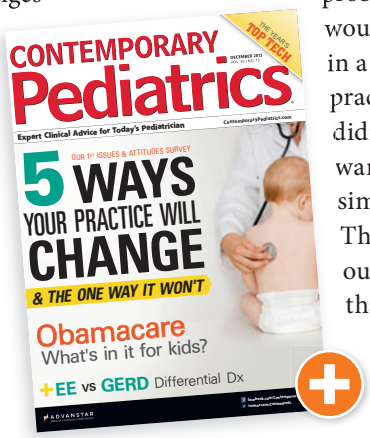
Yes, pediatrics has changed over the past 50 years. Pediatricians always were and still are underpaid and now underappreciated, while nonphysician pediatric practitioners encroach upon our specialty. Using the electronic medical record (EMR) at the clinic where I volunteer takes more time to complete than the time I spend with my patients.

However, the article left out one of the most important changes that have taken place over the years, one that has a lot to do with the current unhappiness of pediatricians in practice. The fault for this change lies with pediatricians themselves and the American Academy of Pediatrics, which is made up mainly of university professors who had (and still have) little or no insight into what goes on in the trenches and so do little if anything to make their pediatric members' lives easier or better.

Many years ago, when I finished my pediatric training under Dr. Waldo Nelson in Philadelphia, it was drummed into us daily that we would be "specialists in the care of children," taking care of almost all their problems. The few available pediatric subspecialists were so busy that they went out of their way to teach us, the general pediatricians in training, as much as they could of their own specialties so that we felt confident to handle most of the basic otolaryngologic, gastrointestinal, neurologic, orthopedic, and other subspecialty problems that we would encounter in a busy office practice. They didn't need (or want) routine, simple referrals. They sent us out confident that we truly were specialists in the care of all children. Our sick patients were treated by us, hospitalized by us, and taken care of by us. There were no "hospitalists." We took care of our own newborn patients and went to cesarean deliveries because there were no neonatologists or cesarean delivery teams of nurses and respiratory therapists.

Dr Weinberg is a retired pediatrician who volunteers at Salud Clinic, West Sacramento, California.

Were we busy? Yes. Were we tired? Yes. Were we underpaid for much of the work we did? Yes. Did our patients get excellent care? Yes! I am not at all convinced that team care—a mix of subspecialists, hospitalists, and the family general pediatrician in the background—really gives superior care to most sick children. We knew our patients, their families, and their needs, and care was not fragmented among many. Were we appreciated? Yes! Did we have status? Yes, we did! Most families rated their pediatrician just a little below their God. We were not providers but their own family pediatrician. For the most part, they loved us and appreciated everything we did, and that in itself



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*4.5 g/L vs 4.0 g/L.

Reference: 1. Data on file, Abbott Nutrition 2013.

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was rewarding, very satisfying, and made up for all the time spent being a good pediatrician.

Much of this has changed. Physicians have become providers, our child patients have become clients, and the insurance company stands between the physician and the patient. This has caused a loss of patient loyalty. If the insurance changes, often the pediatrician changes as well. It has also caused our remuneration to go down.

What caused this major upheaval in the way we practiced? It was partly the fault of the pediatricians themselves. Most of us were tired; many wanted more time off. Many were not happy with what they were doing, and so delegated more and more of their patient's care to others. They did not realize that once the interesting part of pediatrics—taking care of the sick child patient—was lost, it could never be regained. Anything the least bit complicated was referred out. Hungry pediatric subspecialists were looking for more patients and encouraging pediatricians to refer. Yes, this made more time for the pediatrician, but at the cost of job satisfaction.

So that is the here and now. When I was training new pediatric residents, it soon became obvious how things have changed. For any child seen with even a minor problem, when the resident is asked "What would you do next," the response is "We need to call the subspecialist." Will these residents, when finished with their training, be anything other than well-baby, upper-respiratory-infection, otitis-media doctors who refer out any slightly complex, but oh-so-interesting, problems or any child who is really sick and needs hospitalization? In the clinic where I mentor family practice residents in community pediatrics, when we encounter any problem and I ask a question, out comes the smartphone and the appropriate app is asked what to do. Is this a satisfying way to practice medicine? I am afraid of what will happen to the patients in the care of this new crop of physicians.

Practicing pediatricians who must battle the new government regulations have my sympathy. Yes, medicine has made many advances in the past few years. Most of these advances have been for treatment of the few, rare, really complicated medical problems and not the common, garden-variety illness that the pediatrician encounters daily. Gone are the patients with measles, chicken pox, polio, and *Haemophilus influenzae* meningitis crowding into the office in the winter months. This should have made the pediatrician's life easier, not more stressful. Sadly, that is not the case. Government regulations, the EMR, and the referral out of anything interesting now cause much of the pediatrician's unhappiness. These causes are stressful, yes, but they are not nearly as interesting as the multitude of illnesses and hospitalized patients that were *our* causes of stress. Getting efficient in the use of EMR and governmental regulations will never be as satisfying as solving a complex medical problem and having a child go home, cured.

I feel sorry for what has happened to the specialty I love, and I see no real solution that could be put into place to make the current pediatrician's life better and more meaningful. Any ideas, anyone? ■

I am not at all convinced that team care—a mix of subspecialists, hospitalists, and the family general pediatrician in the background—really gives superior care to most sick children.

HORST D WEINBERG, MD
West Sacramento, California

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BEST CHILDREN'S HOSPITALS U.S.NEWS & WORLD REPORT RANKED IN 10 SPECIALTIES 2013-14

BY KATHRYN FOXHALL |

Expect changes to CHIP as ACA ramps up

The GAO is comparing children's benefits under ACA-qualified health plans with those offered by CHIP.

A Government Accountability Office (GAO) report says there is still some uncertainty about what will or should happen with children who are currently on the Child Health Insurance Program (CHIP) as Affordable Care Act (ACA) provisions come into play.

CHIP is a joint federal-state program that covers over 8 million children living in households that had incomes too high for Medicaid, but that could not afford private health insurance, at least not before ACA implementation.

The ACA appropriated CHIP funding through October 2015, the end of the 2015 fiscal year. At that point, states without enough CHIP funding must ensure that children who would otherwise be eligible for CHIP are enrolled either in Medicaid or in a qualified health plan under the ACA, certified by the Department of Health and Human Services (HHS) as comparable to CHIP. The question is: Will those qualified health plans really be equivalent to CHIP?

To get a preview, the GAO looked at the "benchmark plans" that have been chosen in 5 states (Colorado, Illinois, Kansas, New York, and Utah) as models for benefits under the ACA. It found that although the plans were comparable to CHIP in what they covered, there were some differences. For example, the benchmark plan in Kansas did not cover hearing aids or hearing tests, although all CHIP plans cover at least 1 of those services.

"Similarly, 2 states' CHIP plans and 3 states' benchmark plans did not cover certain outpatient therapies—known as habilitative services—to help individuals attain or maintain skills they had not learned due to a disability," the GAO said.

In addition, costs to the children's families were almost always less in the 5 reviewed states' CHIP plans than they were in their state's benchmark plans for a number of services. The GAO says the cost difference was "particularly pronounced for physician visits, prescription drugs, and outpatient therapies."

The report pointed out that a specialist's office visit in Colorado would cost a CHIP enrollee $2 to $10 compared with $50 for a benchmark plan enrollee.

The GAO notes Congress must decide about funding CHIP past 2015 and HHS must decide how qualified health plans will be considered comparable to CHIP.

In the meantime, a National Center for Health Statistics (NCHS) report supplies some numbers indicating how health insurance matters for children. Only about 6.6% of children were uninsured in 2012, the report found, but for those aged 12 to 17 years, 8.7% were uninsured, as were 9.9% of American Indian or Alaska Natives; 8% of Asians; 11.1% of Hispanics or Latinos; 12.5% of Mexican or Mexican Americans; and 12% of those whose parents had less than a high school education.

About 98% of children with either private insurance or Medicaid or with another public form of insurance had a usual place for health care, but only 73% of uninsured children did, according to data for 2012 from the National Health Interview Survey. The usual site of care was a doctor's office for 85% of insured children, for 62% of publicly insured children, and for 56% of uninsured children.

Seventy-six percent of privately insured children had seen a health professional in the last 6 months. That rate was 79% for Medicaid or other public insurance but only 54% for uninsured children. Seventy percent of privately insured children had a dental visit in the last 6 months as had 63% of those with Medicaid or other health insurance, but only 35% of uninsured children had seen a dentist.

Both the GAO report and the NCHS survey are available online. ■

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

Screening rule differentiates between vasovagal and cardiac syncope

Screening children and adolescents who experience syncope using characteristics in the history, physical exam, and electrocardiogram (ECG) accurately identifies which patients require further evaluation for cardiac problems, a new study concluded. Investigators retrospectively compared data for 106 patients aged between 4 to 18 years who visited an outpatient cardiology facility or an emergency department (ED) with either vasovagal syncope (89 patients) or cardiac syncope (17 patients).

Investigators compared a wide range of characteristics of those with vasovagal syncope versus those with cardiac syncope, including circumstances surrounding the syncopal event, signs and symptoms during the event, medical history, and cardiology evaluation findings. They found 4 characteristics that are far more likely in patients with cardiac syncope than in patients with more benign vasovagal syncope:

- Syncope related to activity (identified in 65% of those with cardiac syncope vs 18% of those with vasovagal syncope);
- Family history of cardiac disease or sudden cardiac death (41% vs 25%, respectively);
- Abnormal findings on the physical examination supporting a cardiac diagnosis (29% vs 0%, respectively);
- Abnormal findings on ECGs (76% vs 0%, respectively).

Screening for cardiac disease using any 1 of these 4 characteristics had a sensitivity of 100% and specificity of 60%. About 60% of patients in the study with vasovagal syncope would not have been referred to cardiology had this screening rule been applied, the investigation determined (Tretter JT, et al. *J Pediatr.* 2013;163[6]:1618-1623).

commentary

Worrisome cardiac syncope is much less common than vasovagal syncope. In this study, researchers collected data on 89 patients with vasovagal syncope by evaluating 1 year's referrals to their cardiology clinic. To find 17 patients with cardiac syncope, they reviewed charts from 10 years of visits to their ED, inpatient service, and cardiology clinic. The findings of this study may allow you to avoid a cardiology referral for most of the children you see after what seems to you to be a simple vasovagal fainting episode. *—Michael Burke, MD*

Insights into racial differences in vitamin D levels

Compared with whites, blacks consistently have lower levels of total vitamin D (25-hydroxyvitamin D) and elevated levels of parathyroid hormone (considered a sensitive marker of vitamin D deficiency), often leading to a diagnosis of vitamin D deficiency. Yet blacks have higher bone mineral density (BMD) than whites. A new investigation into racial differences in vitamin D-binding protein genotypes and concentrations of circulating vitamin D-binding protein suggests that racial differences in the prevalence of common genetic variants in the vitamin D-binding protein gene may explain this paradox.

Investigators measured levels of total vitamin D, vitamin D-binding protein, and parathyroid hormone as well as BMD in more than 2,000 black and white study participants. They examined participants for 2 common variants in the vitamin D-binding protein gene and estimated levels of

bioavailable vitamin D.

As expected, BMD was higher in blacks than in whites, and levels of parathyroid hormone increased as levels of total or bioavailable vitamin D decreased. Levels of vitamin D-binding protein were lower in blacks than in whites, probably because of the high prevalence of genetic variants, which seemed to explain 79.4% of the variation in vitamin D-binding levels between blacks and whites. These genetic variants also accounted for 9.9% of differences in total vitamin D between blacks and whites. Alhough blacks had significantly lower levels of *total* vitamin D than whites, they had equivalent levels of *bioavailable* vitamin D, which seemed to be associated with their lower levels of vitamin D-binding protein (Powe CE, et al. *N Engl J Med.* 2013;369[21]:1991-2000).

commentary

The last 5 years have seen a flurry of studies describing the prevalence of vitamin D deficiency and its association with everything from diabetes mellitus to asthma to mental illness. We may now need to take a step back to look at these findings through the lens of this study, considering that what is a normal vitamin D level for one person may be abnormal for another. *—Michael Burke, MD*

New tool helps monitor asthma symptoms

The new Asthma Symptom Tracker (AST), which rests on weekly (instead of traditional monthly) use of the Asthma Control Test (ACT), facilitates monitoring of patients' symptoms and rapid recognition and response to warning signs of deterioration in asthma control, a new study found. The investigation looked at 210 children aged from 2 to 18 years who were hospitalized for asthma, then followed for more than 6 months after discharge, while using the AST tool.

The AST includes user instructions on answering the ACT questionnaire and calculating and plotting the child's score on a graphic display, which also provides color-coded zones indicating the asthmatic's level of symptom control, using the standard ACT cutoff points. A "decision support" section includes 3 color-coded boxes that show when asthma control scores fall within the green zone (well controlled), or yellow or red zones (not well controlled), which are expected to prompt a follow-up physician visit.

For comparison purposes, investigators also administered the Asthma Control Questionnaire (ACQ). The ACT and ACQ both assess levels of asthma control, but higher scores on the ACT (and hence the AST) indicate better symptom control, whereas higher scores on the ACQ indicate the reverse—more severe symptoms.

A decrease in AST scores (meaning less symptom control) was associated with an increase in use of oral steroids and unscheduled acute care visits (Nkoy FL, et al. *Pediatrics.* 2013;132[6]:e1554-e1561).

commentary

The point of this study is to allow patients and families to systematically monitor asthma symptom severity and then to intervene before deterioration leads to a full-blown asthma attack. In the words of the researchers, "Most asthma exacerbations are preventable because they rarely occur without warning." In a family that is organized and energized enough to use this tool on a weekly basis, this may prove to be a practical approach to effectively managing asthma. *—Michael Burke, MD*

also of note

Vaccine-hesitant parents respond to strong provider recommendations. An analysis of 111 vaccine discussions, half of which involved parents with concerns about having their children vaccinated, found that parents were significantly more likely to resist vaccine recommendations if the provider initiated recommendations in a participatory manner (eg, "What do you want to do about shots?") rather than presumptively (eg, "Well, we have to do some shots"). In addition, when providers pursued vaccine recommendations presumptively in the face of parental resistance, almost half of initially resistant parents accepted the recommendation (Opel DJ, et al. *Pediatrics.* 2013;132[6]:1037-1046).

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

Protective efficacy demonstrated against *Haemophilus influenzae* type b in a high-risk population

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

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

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

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

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PedvaxHIB[c] 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.

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.

[a]Estimated from person-days at risk.

[b]Subjects in this portion of the study received 1 to 3 doses of PedvaxHIB.

[c]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.

- ✓ **3-dose series can spare baby a shot[1]**
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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.

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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.

Manufactured and distributed by: Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.**

MERCK

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VACC-1068000-0000 02/13

puzzler

Stumped by a bleeding umbilicus

STACY B PIERSON, MD
PARTH MEHTA, MD, MPH

THE CASE

It is a beautiful, sunny afternoon in the state of Florida. You are making your rounds in the local tertiary children's hospital when you receive a call from the emergency department (ED). You are told that a 10-day-old white male has been transferred from an outlying ED and is being admitted for further evaluation of unremitting umbilical stump bleeding despite multiple interventions.

Naturally, you ask what interventions have been attempted to stop the bleeding. You are told that the umbilical stump has been reclamped several times. Chemical cauterization with silver nitrate, as well as application of Gelfoam impregnated with thrombin, has not worked. Despite putting pressure on the site for 10 minutes at a time, blood continues to ooze from the site. Intrigued, you anxiously await the arrival of the patient to the floor so that you can obtain more history. TURN TO PAGE 35 FOR THE DIAGNOSIS ▶

First seizure: Dispel the myths

SARAH C DOERRER, CPNP, AND ERIC H KOSSOFF, MD

When a child experiences a seizure for the first time, frantic parents turn to their pediatrician for answers about what just happened and what to do next. The conversation should begin by discussing exactly what a seizure is and what it is not.

There are few things more terrifying for parents than witnessing their child having a seizure. Clinicians who work with these families can attest to the fact that one of the most commonly heard fears following a seizure is, "I thought my child stopped breathing and was going to die." In many cases, these children are transported emergently to the hospital, have a computed tomography (CT) scan of the brain, have blood drawn, are observed for a few hours, and are then discharged home with instructions to follow up with their pediatrician. The parents, searching for answers, turn to their pediatrician for help and ask, "Now what do we do?" Meanwhile, the pediatrician may be wondering the same thing.

Following a first seizure, the pediatrician's primary role is to provide accurate information, dispel myths, and address parental anxiety as quickly as possible. For children with a first unprovoked (nonfebrile, nontoxin-induced) seizure, a child neurologist consultation is warranted, but a 5-minute conversation with the pediatrician can prevent hours of worry. The conversation should begin by discussing exactly what a seizure is and what it is not.

What is a seizure?

A seizure is defined as a clinical (or subclinical) event caused by abnormal and excessive firing of neurons in the brain. We will often provide the analogy of "static on your television" to help children understand. Epilepsy, simply put, is diagnosed after 2 or more unprovoked (nonfebrile) seizures.[1] Parents should be reassured right from the beginning that having a single seizure is *not* the same as having epilepsy, although sometimes epilepsy is diagnosed after a single seizure if the electroencephalogram

GETTY IMAGES/DORLING KINDERSLEY (BRAIN); THINKSTOCK/ISTOCK/VOLODYMYR GRINKO (CONNECTIONS)

(EEG) is abnormal and suggests a high likelihood of seizure recurrence. Inevitably, parents will ask what caused the seizure and often the answer to this question is unknown.

Many seizures are "idiopathic" and presumed to be genetic in etiology, with genetic factors accounting for 80% of idiopathic epilepsies.[2] Parents will frequently worry that the seizure was brought on by a brain tumor. They should be reassured that a seizure alone is an extremely rare presentation for most tumors. They may also worry that their child stopped breathing during the seizure or was close to death, an understandable fear given that many children become cyanotic during a convulsion, with a blue tinge to the lips and eyelids. Caregivers should be reassured that although seizures are frightening and it appeared that their child was not breathing, there is no evidence that seizures lasting less than 30 minutes cause anoxic brain injury.

After the trauma of witnessing a seizure, it can be difficult for parents to view their child as "normal." Parents need to hear that their child can, and should, resume normal activities. This means that the child should sleep alone in his or her own bed (but not on the top bunk), should still be in school, can play video games (unless photic stimulation on an EEG elicits events, which is rare) and watch movies, and should still take out the trash and do chores.

Children who have experienced a seizure can safely participate in almost all activities, with the exceptions being scuba diving, sky diving, and activities involving projectile weapons such as guns and bows and arrows. The concern regarding these sports stems from the possibility of harm to not only the child but also to another person in the case of a seizure. Most sports are fine as long as proper protective equipment is worn, such as harnesses when rock climbing, and a child can safely ride a bike as long as he or she is wearing a helmet. Parents should be informed that swimming is also safe as long as the child is fully supervised by an adult who is aware that the child has had a seizure.[3]

It is *not uncommon* for children to experience a *single unprovoked seizure* and never have another.

Evaluation

Following an unprovoked (nonfebrile) seizure, children often undergo an extensive workup, although it may not always be warranted. In 2000, the Quality Standards Subcommittee of the American Academy of Neurology published a practice parameter evaluating a first nonfebrile seizure in children to help guide clinical decision making and prevent unnecessary testing.[4] A review of the literature showed that there was insufficient evidence to support performing routine laboratory testing on every child following a first unprovoked seizure. Blood studies, however, were recommended in children exhibiting other concerning clinical findings, specifically vomiting, diarrhea, dehydration, or failure to return to baseline alertness. Toxicology screenings are also recommended in infants, children, and teenagers when a toxic ingestion or exposure is in question. Finally, lumbar puncture was found to be of limited usefulness and is recommended only when there is concern for meningitis or encephalitis.

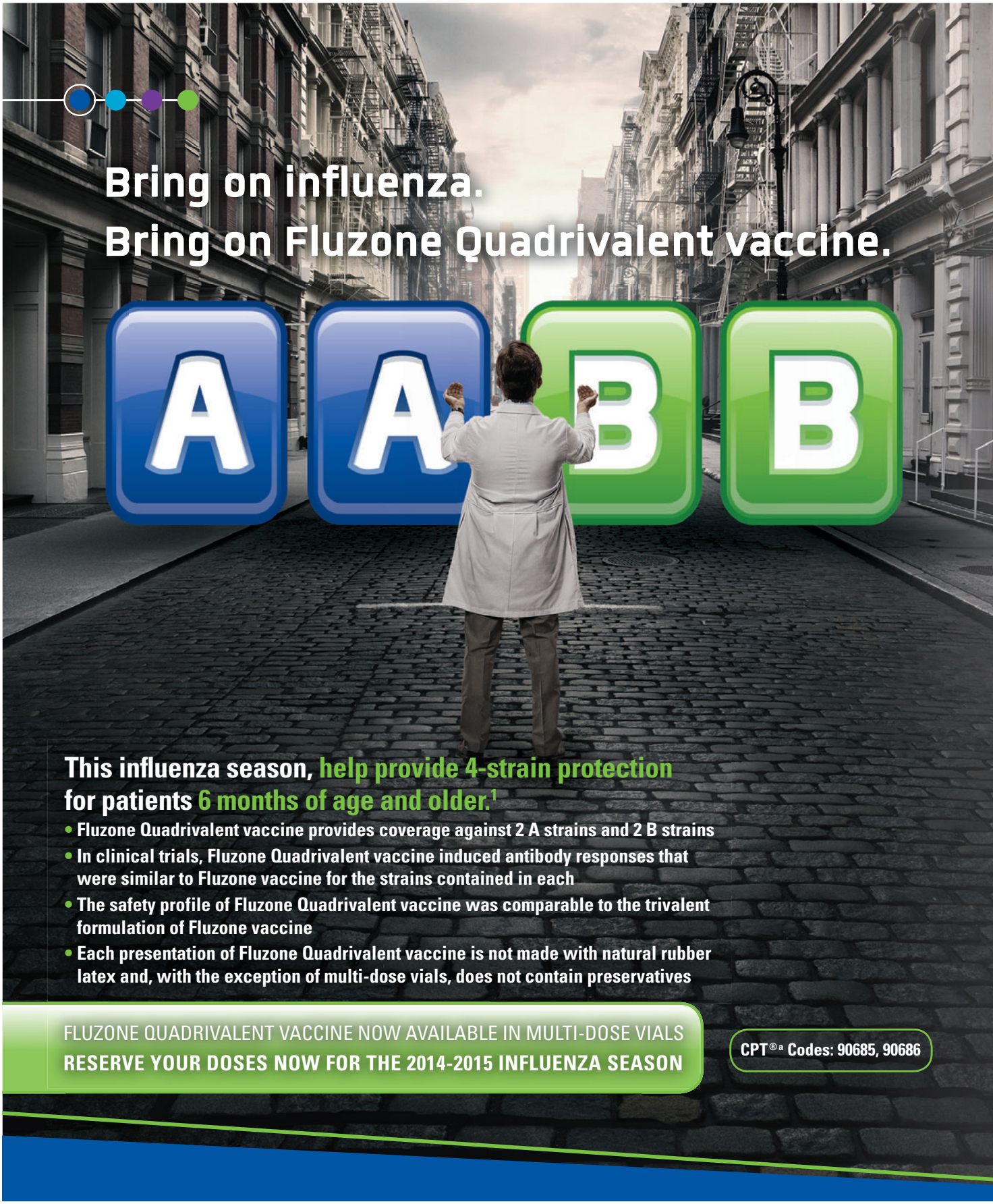
The utility of imaging studies was also assessed. Emergent neuroimaging (ie, CT) should be performed on any child who exhibits a prolonged postictal focal deficit (Todd's paresis) or fails to return to baseline within several hours of the seizure.[4] Nonurgent imaging should

CONTINUED ON ***PAGE 26***

CASE 1

Nathan, a 15-year-old boy, was found by his mother at 6 AM having a full body convulsion after he had been up late playing Halo on his Xbox. He was taken to the emergency department (ED) where his urine toxicology screen was negative. The ED physician started him on levetiracetam (Keppra) 500 mg twice daily and told the family to follow up with their doctor. At their follow-up visit, the anxious parents want to know why it happened and if they should continue the medication.

Outcome: *Nathan underwent an EEG, which showed high-amplitude, generalized 4–6Hz polyspike-wave complexes, consistent with a diagnosis of juvenile myoclonic epilepsy. The family was told that the risk of future seizures was very high and that remaining on medication was wise. Because Nathan was itching to get his driver's license, both he and his parents chose to continue the levetiracetam.*



This influenza season, help provide 4-strain protection for patients 6 months of age and older.[1]

- Fluzone Quadrivalent vaccine provides coverage against 2 A strains and 2 B strains
- In clinical trials, Fluzone Quadrivalent vaccine induced antibody responses that were similar to Fluzone vaccine for the strains contained in each
- The safety profile of Fluzone Quadrivalent vaccine was comparable to the trivalent formulation of Fluzone vaccine
- Each presentation of Fluzone Quadrivalent vaccine is not made with natural rubber latex and, with the exception of multi-dose vials, does not contain preservatives

FLUZONE QUADRIVALENT VACCINE NOW AVAILABLE IN MULTI-DOSE VIALS

RESERVE YOUR DOSES NOW FOR THE 2014-2015 INFLUENZA SEASON

CPT®[a] Codes: 90685, 90686

SANOFI PASTEUR. Discovery Drive. Swiftwater, Pennsylvania 18370. www.sanofipasteur.us

IMPORTANT SAFETY INFORMATION

INDICATION

Fluzone Quadrivalent vaccine is an inactivated quadrivalent influenza virus vaccine indicated for the prevention of influenza disease caused by influenza subtype A and type B viruses contained in the vaccine. Fluzone Quadrivalent vaccine is approved for use in persons 6 months of age and older.

SAFETY INFORMATION

The most common local and systemic adverse reactions to Fluzone Quadrivalent vaccine include pain (tenderness in young children), erythema, and swelling at the injection site; myalgia, malaise, headache, and fever (irritability, abnormal crying, drowsiness, appetite loss, and vomiting in young children). Other adverse reactions may occur. Fluzone Quadrivalent vaccine should not be administered to anyone with a severe allergic reaction (eg, anaphylaxis) to any vaccine component, including egg protein, or thimerosal (the multi-dose vial is the only presentation containing thimerosal) or to a previous dose of any influenza vaccine.

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of previous influenza vaccination, the decision to give Fluzone Quadrivalent vaccine should be based on careful consideration of the potential benefits and risks. Vaccination with Fluzone Quadrivalent vaccine may not protect all individuals.

Before administering Fluzone Quadrivalent vaccine, please see accompanying brief summary of full Prescribing Information on next page.

To order Fluzone Quadrivalent vaccine for the 2014-2015 influenza season or learn about the Fluzone Partners Program, log onto **VaccineShoppe.com**® or call **1-800-VACCINE** (1-800-822-2463).

[a] CPT (Current Procedural Terminology) is a registered trademark of the American Medical Association.
Fluzone and Fluzone Quadrivalent vaccines are manufactured and distributed by Sanofi Pasteur Inc.

Reference: 1. Fluzone Quadrivalent vaccine [Prescribing Information]. Swiftwater, PA: Sanofi Pasteur Inc.; 2013.

Fluzone® Quadrivalent
INFLUENZA VIRUS VACCINE

SANOFI PASTEUR

Fluzone® Quadrivalent (Influenza Virus Vaccine) Suspension for Intramuscular Injection

2013-2014 Formula

℞ only

BRIEF SUMMARY: Please consult package insert for full prescribing information.

INDICATIONS AND USAGE

Fluzone® Quadrivalent is an inactivated quadrivalent influenza virus vaccine indicated for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Fluzone Quadrivalent is approved for use in persons 6 months of age and older.

DOSAGE AND ADMINISTRATION

• For intramuscular use only

Dose and Schedule

The dose and schedule for Fluzone Quadrivalent are presented in Table 1.

Table 1: Dose and Schedule for Fluzone Quadrivalent

Age	Dose	Schedule
6 months through 35 months	One or two doses[a] , 0.25 mL each	If 2 doses, administer at least 4 weeks apart
36 months through 8 years	One or two doses[a] , 0.5 mL each	If 2 doses, administer at least 4 weeks apart
9 years and older	One dose, 0.5 mL	-

[a]1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines
"-" Indicates information is not applicable

Administration

Inspect Fluzone Quadrivalent visually for particulate matter and/or discoloration prior to administration. If any of these defects or conditions exist, the vaccine should not be administered. Before administering a dose of vaccine, shake the prefilled syringe or single-dose vial. Withdraw the vaccine using a sterile needle and syringe. The preferred sites for intramuscular injection are the anterolateral aspect of the thigh in infants 6 months through 11 months of age, the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in persons 12 months through 35 months of age, or the deltoid muscle in persons ≥36 months of age. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk. Do not administer this product intravenously, intradermally, or subcutaneously. Fluzone Quadrivalent vaccine should not be combined through reconstitution or mixed with any other vaccine.

DOSAGE FORMS AND STRENGTHS

Fluzone Quadrivalent is a suspension for injection. Fluzone Quadrivalent is supplied in 3 presentations: 1) Prefilled single-dose syringe (yellow syringe plunger rod), 0.25 mL, for persons 6 months through 35 months of age. 2) Prefilled single-dose syringe (purple syringe plunger rod), 0.5 mL, for persons 36 months of age and older. 3) Single-dose vial, 0.5 mL, for persons 36 months of age and older.

CONTRAINDICATIONS

Do not administer Fluzone Quadrivalent to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or to a previous dose of any influenza vaccine.

WARNINGS AND PRECAUTIONS

Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an elevated risk of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated.† If GBS has occurred within 6 weeks of previous influenza vaccination, the decision to give Fluzone Quadrivalent should be based on careful consideration of the potential benefits and risks.

Preventing and Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of Fluzone Quadrivalent.

Altered Immunocompetence

If Fluzone Quadrivalent is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the expected immune response may not be obtained.

Limitations of Vaccine Effectiveness

Vaccination with Fluzone Quadrivalent may not protect all recipients.

ADVERSE REACTIONS

In children 6 months through 35 months of age, the most common (≥10%) injection-site reactions were pain (57%)[a] or tenderness (54%)[b], erythema (37%), and swelling (22%); the most common solicited systemic adverse reactions were irritability (54%)[b], abnormal crying (41%)[b], malaise (38%)[a], drowsiness (38%)[b], appetite loss (32%)[b], myalgia (27%)[a], vomiting (15%)[b], and fever (14%). In children 3 years through 8 years of age, the most common (≥10%) injection-site reactions were pain (67%), erythema (34%), and swelling (25%); the most common solicited systemic adverse reactions were myalgia (39%), malaise (32%), and headache (23%). In adults 18 years and older, the most common (≥10%) injection-site reaction was pain (47%); the most common solicited systemic adverse reactions were myalgia (24%), headache (16%), and malaise (11%). In adults 65 years of age and older, the most common (≥10%) injection-site reaction was pain (33%); the most common solicited systemic adverse reactions were myalgia (18%), headache (13%), and malaise (11%).

[a]Assessed in children 24 months through 35 months of age
[b]Assessed in children 6 months through 23 months of age

Clinical Trials Experience

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

Children 6 Months Through 8 Years of Age

Study 1 (NCT01240746, see http://clinicaltrials.gov) was a single-blind, randomized, active-controlled multi-center safety and immunogenicity study conducted in the US. In this study, children 6 months through 35 months of age received one or two 0.25 mL doses of either Fluzone Quadrivalent or one of two formulations of a comparator trivalent influenza vaccine (TIV-1 or TIV-2), and children 3 years through 8 years of age received one or two 0.5 mL doses of either Fluzone Quadrivalent, TIV-1, or TIV-2. Each of the trivalent formulations contained an influenza type B virus that corresponded to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). For participants who received two doses, the doses were administered approximately 4 weeks apart. The safety analysis set included 1841 children 6 months through 35 months of age and 2506 children 3 years through 8 years of age. Among participants 6 months through 8 years of age in the three vaccine groups combined, 49.3% were female (Fluzone Quadrivalent, 49.2%; TIV-1, 49.8%; TIV-2, 49.4%), 58.4% Caucasian (Fluzone Quadrivalent, 58.4%; TIV-1, 58.9%; TIV-2, 57.8%), 20.2% Black (Fluzone Quadrivalent, 20.5%; TIV-1, 19.9%; TIV-2, 19.1%), 14.1% Hispanic (Fluzone Quadrivalent, 14.3%; TIV-1, 13.2%; TIV-2, 14.7%), and 7.3% were of other racial/ethnic groups (Fluzone Quadrivalent, 6.8%; TIV-1, 8.0%; TIV-2, 8.5%). Table 2 and Table 3 summarize solicited injection-site and systemic adverse reactions reported within 7 days post-vaccination via diary cards. Participants were monitored for unsolicited adverse events for 28 days after each dose and serious adverse events (SAEs) during the 6 months following the last dose.

Table 2: Study 1[a]: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Children 6 Months Through 35 Months of Age (Safety Analysis Set)[b]

	Fluzone Quadrivalent (N°=1223)			TIV-1[c] (B Victoria) (N°=310)			TIV-2[d] (B Yamagata) (N°=308)		
	Any (%)	Grade 2[f] (%)	Grade 3[g] (%)	Any (%)	Grade 2[f] (%)	Grade 3[g] (%)	Any (%)	Grade 2[f] (%)	Grade 3[g] (%)
Injection-site adverse reactions									
- Pain[h]	57.0	10.2	1.0	52.3	11.5	0.8	50.3	5.4	2.7
- Tenderness[i]	54.1	11.3	1.9	48.4	8.2	1.9	49.7	10.3	0.0
- Erythema	37.3	1.5	0.2	32.9	1.0	0.0	33.3	1.0	0.0
- Swelling	21.6	0.8	0.2	19.7	1.0	0.0	17.3	0.0	0.0
Systemic adverse reactions									
- Fever (≥100.4° F)[i]	14.3	5.5	2.1	16.0	6.6	1.7	13.0	4.1	2.0
- Malaise[h]	38.1	14.5	4.6	35.2	14.8	4.7	32.4	12.8	6.8
- Myalgia[h]	26.7	6.6	1.9	26.6	9.4	1.6	25.0	6.8	2.7
- Headache[h]	8.9	2.5	0.6	9.4	3.9	0.0	12.2	4.7	0.0
- Irritability[i]	54.0	26.4	3.2	52.8	20.1	3.1	53.5	22.9	2.8
- Crying-abnormal[i]	41.2	12.3	3.3	36.5	8.2	1.9	29.9	10.4	2.1
-Drowsiness[i]	37.7	8.4	1.3	32.1	3.8	0.6	31.9	5.6	0.7
- Appetite loss[i]	32.3	9.1	1.8	33.3	5.7	1.9	25.0	8.3	0.7
- Vomiting[i]	14.8	6.2	1.0	11.3	4.4	0.6	13.9	6.3	0.0

[a]NCT01240746
[b]The safety analysis set includes all persons who received at least one dose of study vaccine
[c]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed
[d]Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed
[e]N is the number of participants in the safety analysis set
[f]Grade 2 - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site tenderness: cries and protests when injection-site is touched; Injection-site erythema, Injection-site swelling: ≥2.5 cm to <5 cm; Fever: >101.3°F to ≤103.1°F (6 months through 23 months); ≥101.2°F to ≤102.0° F (24 months through 35 months); Malaise, Myalgia, and Headache: some interference with activity; Irritability: requiring increased attention; Crying abnormal: 1 to 3 hours; Drowsiness: not interested in surroundings or did not wake up for a feed/meal; Appetite lost: missed 1 or 2 feeds/meals completely; Vomiting: 2 to 5 episodes per 24 hours
[g]Grade 3 - Injection-site pain: incapacitating, unable to perform usual activities; Injection-site tenderness: cries when injected limb is moved, or the movement of the injected limb is reduced; Injection-site erythema, Injection-site swelling: ≥5 cm; Fever: >103.1°F (6 months through 23 months); ≥102.1°F (24 months through 35 months); Malaise, Myalgia, and Headache: Significant; prevents daily activity; Irritability: inconsolable; Crying abnormal: >3 hours; Drowsiness: sleeping most of the time or difficult to wake up; Appetite lost: refuses ≥3 feeds/meals or refuses most feeds/meals; Vomiting: ≥6 episodes per 24 hours or requiring parenteral hydration
[h]Assessed in children 24 months through 35 months of age
[i]Assessed in children 6 months through 23 months of age
[j]Fever measured by any route

Table 3: Study 1[a]: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Children 3 Years Through 8 Years of Age (Safety Analysis Set)[b]

	Fluzone Quadrivalent (N°=1669)			TIV-1[c] (B Victoria) (N°=424)			TIV-2[d] (B Yamagata) (N°=413)		
	Any (%)	Grade 2[f] (%)	Grade 3[g] (%)	Any (%)	Grade 2[f] (%)	Grade 3[g] (%)	Any (%)	Grade 2[f] (%)	Grade 3[g] (%)
Injection-site adverse reactions									
- Pain	66.6	15.8	2.1	64.6	9.5	2.0	63.8	11.6	2.8
- Erythema	34.1	2.9	1.8	36.8	3.4	1.2	35.2	2.5	1.8
- Swelling	24.8	2.8	1.4	25.4	1.5	1.2	25.9	2.5	1.8
Systemic adverse reactions									
- Fever (≥100.4° F)[h]	7.0	2.1	2.1	7.1	2.2	1.2	7.6	2.8	0.8
- Headache	23.1	6.8	2.2	21.2	5.1	2.7	24.4	7.5	2.0
- Malaise	31.9	11.2	5.5	32.8	11.4	5.6	33.4	10.8	5.0
- Myalgia	38.6	12.2	3.3	34.1	9.0	2.7	38.4	11.1	2.8

[a]NCT01240746
[b]The safety analysis set includes all persons who received at least one dose of study vaccine
[c]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed
[d]Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed
[e]N is the number of participants in the safety analysis set
[f]Grade 2 - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site erythema, Injection-site swelling: ≥2.5 cm to <5 cm; Fever: ≥101.2°F to ≤102.0°F; Headache, Malaise, and Myalgia: some interference with activity
[g]Grade 3 - Injection-site pain: incapacitating, unable to perform usual activities; Injection-site erythema, Injection-site swelling: ≥5 cm; Fever: ≥102.1°F; Headache, Malaise, and Myalgia: Significant; prevents daily activity
[h]Fever measured by any route

Among children 6 months through 8 years of age, unsolicited non-serious adverse events were reported in 1360 (47.0%) recipients in the Fluzone Quadrivalent group, 352 (48.0%) recipients in the TIV-1 group, and 346 (48.0%) recipients in the TIV-2 group. The most commonly reported unsolicited non-serious adverse events were cough, vomiting, and pyrexia. During the 28 days following vaccination, a total of 16 (0.6%) recipients in the Fluzone Quadrivalent group, 4 (0.5%) recipients in the TIV-1 group, and 4 (0.6%) recipients in the TIV-2 group, experienced at least one SAE; no deaths occurred. Throughout the study period, a total of 41 (1.4%) recipients in the Fluzone Quadrivalent group, 7 (1.0%) recipients in the TIV-1 group, and 14 (1.9%) recipients in the TIV-2 group, experienced at least one SAE. Three SAEs were considered to be possibly related to vaccination: croup in a Fluzone Quadrivalent recipient and 2 episodes of febrile seizure, 1 each in a TIV-1 recipient and a TIV-2 recipient. One death occurred in the TIV-1 group (a drowning 43 days post-vaccination).

Adults

In study 2 (NCT00988143, see http://clinicaltrials.gov), a multi-centered randomized, open-label trial conducted in the US, adults 18 years of age and older received one dose of either Fluzone Quadrivalent or one of two formulations of comparator trivalent influenza vaccine (TIV-1 or TIV-2). Each of the trivalent formulations contained an influenza type B virus that corresponded to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The safety analysis set included 570 recipients, half aged 18-60 years and half aged 61 years or older. Among participants in the three vaccine groups combined, 67.2% were female (Fluzone Quadrivalent, 68.4%; TIV-1, 67.9%; TIV-2, 65.3%), 88.4% Caucasian (Fluzone Quadrivalent, 91.1%; TIV-1, 86.8%; TIV-2, 87.4%), 9.6% Black (Fluzone Quadrivalent, 6.8%; TIV-1, 12.1%; TIV-2, 10.0%), 0.4% Hispanic (Fluzone Quadrivalent, 0.0%; TIV-1, 0.5%; TIV-2, 0.5%), and 1.7% were of other racial/ethnic groups (Fluzone Quadrivalent, 2.1%; TIV-1, 0.5%; TIV-2, 2.2%). Table 4 summarizes solicited injection-site and systemic adverse reactions reported within 3 days post-vaccination via diary cards. Participants were monitored for unsolicited adverse events and SAEs during the 21 days following vaccination.

Table 4: Study 2[a]: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 3 Days After Vaccination in Adults 18 Years of Age and Older (Safety Analysis Set)[b]

	Fluzone Quadrivalent (N°=190)			TIV-1[c] (B Victoria) (N°=190)			TIV-2[d] (B Yamagata) (N°=190)		
	Any (%)	Grade 2[f] (%)	Grade 3[g] (%)	Any (%)	Grade 2[f] (%)	Grade 3[g] (%)	Any (%)	Grade 2[f] (%)	Grade 3[g] (%)
Injection-site adverse reactions									
- Pain	47.4	6.8	0.5	52.1	7.9	0.5	43.2	6.3	0.0
- Erythema	1.1	0.0	0.0	1.6	0.5	0.0	1.6	0.5	0.0
- Swelling	0.5	0.0	0.0	3.2	0.5	0.0	1.1	0.0	0.0
- Induration	0.5	0.0	0.0	1.6	0.5	0.0	0.5	0.0	0.0
- Ecchymosis	0.5	0.0	0.0	0.5	0.0	0.0	0.5	0.0	0.0
Systemic adverse reactions									
- Myalgia	23.7	5.8	0.0	25.3	5.8	0.0	16.8	5.8	0.0
- Headache	15.8	3.2	0.5	18.4	6.3	0.5	18.0	4.2	0.0
- Malaise	10.5	1.6	1.1	14.7	3.2	1.1	12.1	4.7	0.5
- Shivering	2.6	0.5	0.0	5.3	1.1	0.0	3.2	0.5	0.0
- Fever (≥100.4° F)[h]	0.0	0.0	0.0	0.5	0.5	0.0	0.5	0.5	0.0

[a] NCT00988143

[b] The safety analysis set includes all persons who received study vaccine

[c] 2009-2010 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

[d] 2008-2009 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Florida/04/2006 (Yamagata lineage), licensed

[e] N is the number of participants in the safety analysis set

[f] Grade 2 - Injection-site pain: Some interference with activity; Injection-site erythema, Injection-site swelling, Injection-site induration, and Injection-site ecchymosis: ≥5.1 to ≤10 cm; Fever: ≥101.2°F to ≤102.0°F; Myalgia, Headache, Malaise, and Shivering: some interference with activity

[g] Grade 3 - Injection-site pain: Significant; prevents daily activity; Injection-site erythema, Injection-site swelling, Injection-site induration, and Injection-site ecchymosis: >10 cm; Fever: ≥102.1°F; Myalgia, Headache, Malaise, and Shivering: Significant; prevents daily activity

[h] Fever measured by any route

Unsolicited non-serious adverse events were reported in 33 (17.4%) recipients in the Fluzone Quadrivalent group, 45 (23.7%) recipients in the TIV-1 group, and 45 (23.7%) recipients in the TIV-2 group. The most commonly reported unsolicited non-serious adverse events were headache, cough, and oropharyngeal pain. In the follow-up period, there were two SAEs, 1 (0.5%) in the Fluzone Quadrivalent group and 1 (0.5%) in the TIV-2 group. No deaths were reported during the trial period.

Geriatric Adults

In Study 3 (NCT01218646, see http://clinicaltrials.gov), a multi-center, randomized, double-blind trial conducted in the US, adults 65 years of age and older received one dose of either Fluzone Quadrivalent, or one of two formulations of comparator trivalent influenza vaccine (TIV-1 or TIV-2). Each of the trivalent formulations contained an influenza type B virus that corresponded to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The safety analysis set included 675 recipients. Among participants in the three vaccine groups combined, 55.7% were female (Fluzone Quadrivalent, 57.3%; TIV-1, 56.0%; TIV-2, 53.8%), 89.5% Caucasian (Fluzone Quadrivalent, 87.6%; TIV-1, 89.8%; TIV-2, 91.1%), 2.2% Black (Fluzone Quadrivalent, 4.0%; TIV-1, 1.8%; TIV-2, 0.9%), 7.4% Hispanic (Fluzone Quadrivalent, 8.4%; TIV-1, 7.6%; TIV-2, 6.2%) and 0.9% were of other racial/ethnic groups (Fluzone Quadrivalent, 0.0%; TIV-1, 0.9%; TIV-2, 1.8%). Table 5 summarizes solicited injection-site and systemic adverse reactions reported within 7 days post-vaccination via diary cards. Participants were monitored for unsolicited adverse events and SAEs during the 21 days following vaccination.

Table 5: Study 3[a]: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Adults 65 Years of Age and Older (Safety Analysis Set)[b]

	Fluzone Quadrivalent (N°=225)			TIV-1[c] (B Victoria) (N°=225)			TIV-2[d] (B Yamagata) (N°=225)		
	Any (%)	Grade 2[f] (%)	Grade 3[g] (%)	Any (%)	Grade 2[f] (%)	Grade 3[g] (%)	Any (%)	Grade 2[f] (%)	Grade 3[g] (%)
Injection-site adverse reactions									
- Pain	32.6	1.3	0.9	28.6	2.7	0.0	23.1	0.9	0.0
- Erythema	2.7	0.9	0.0	1.3	0.0	0.0	1.3	0.4	0.0
- Swelling	1.8	0.4	0.0	1.3	0.0	0.0	0.0	0.0	0.0
Systemic adverse reactions									
- Myalgia	18.3	4.0	0.4	18.3	4.0	0.0	14.2	2.7	0.4
- Headache	13.4	1.3	0.4	11.6	1.3	0.0	11.6	1.8	0.4
- Malaise	10.7	4.5	0.4	6.3	0.4	0.0	11.6	2.7	0.9
- Fever (≥100.4° F)[h]	1.3	0.0	0.4	0.0	0.0	0.0	0.9	0.4	0.4

[a] NCT01218646

[b] The safety analysis set includes all persons who received study vaccine

[c] 2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

[d] Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

[e] N is the number of participants in the safety analysis set

[f] Grade 2 - Injection-site pain: some interference with activity; Injection-site erythema and Injection-site swelling: ≥5.1 to ≤10 cm; Fever: ≥101.2°F to ≤102.0°F; Myalgia, Headache, and Malaise: some interference with activity

[g] Grade 3 - Injection-site pain: Significant; prevents daily activity ; Injection-site erythema and Injection-site swelling: >10 cm; Fever: ≥102.1°F; Myalgia, Headache, and Malaise: Significant; prevents daily activity

[h] Fever measured by any route

Unsolicited non-serious adverse events were reported in 28 (12.4%) recipients in the Fluzone Quadrivalent group, 22 (9.8%) recipients in the TIV-1 group, and 22 (9.8%) recipients in the TIV-2 group. The most commonly reported adverse events were oropharyngeal pain, rhinorrhea, injection-site induration, and headache. Three SAEs were reported during the follow-up period, 2 (0.9%) in the TIV-1 group and 1 (0.4%) in the TIV-2 group. No deaths were reported during the trial period.

Post-Marketing Experience

Currently, there are no post-marketing data available for Fluzone Quadrivalent vaccine.

The following events have been spontaneously reported during the post-approval use of the trivalent formulation of Fluzone. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to Fluzone.

- *Blood and Lymphatic System Disorders:* Thrombocytopenia, lymphadenopathy
- *Immune System Disorders:* Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)
- *Eye disorders:* Ocular hyperemia
- *Nervous System Disorders:* Guillain-Barré syndrome (GBS), convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), dizziness, paresthesia
- *Vascular Disorders:* Vasculitis, vasodilatation/flushing
- *Respiratory, Thoracic and Mediastinal Disorders:* Dyspnea, pharyngitis, rhinitis, cough, wheezing, throat tightness
- *Skin and Subcutaneous Tissue Disorders:* Stevens-Johnson syndrome
- *General Disorders and Administration Site Conditions:* Pruritus, asthenia/fatigue, pain in extremities, chest pain
- *Gastrointestinal Disorders:* Vomiting

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with Fluzone Quadrivalent. It is also not known whether Fluzone Quadrivalent can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fluzone Quadrivalent should be given to a pregnant woman only if clearly needed.

Sanofi Pasteur Inc. is conducting a prospective pregnancy exposure registry to collect data on pregnancy outcomes and newborn health status following vaccination with Fluzone Quadrivalent during pregnancy. Healthcare providers are encouraged to enroll women who receive Fluzone Quadrivalent during pregnancy in Sanofi Pasteur Inc.'s vaccination pregnancy registry by calling 1-800-822-2463.

Nursing Mothers

It is not known whether Fluzone Quadrivalent is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Fluzone Quadrivalent is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Fluzone Quadrivalent in children below the age of 6 months have not been established. Safety and immunogenicity of Fluzone Quadrivalent was evaluated in children 6 months through 8 years of age.

Geriatric Use

Safety and immunogenicity of Fluzone Quadrivalent was evaluated in adults 65 years of age and older. Antibody responses to Fluzone Quadrivalent are lower in persons ≥65 years of age than in younger adults.

REFERENCE

1. Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barre´ syndrome and the 1992-1993 and 1993-1994 influenza vaccines. N Engl J Med 1998;339:1797-802.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Single-dose, prefilled syringe (yellow plunger rod), without needle, 0.25 mL (NDC 49281-513-00) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-513-25).

Single-dose, prefilled syringe (purple plunger rod), without needle, 0.5 mL (NDC 49281-413-88) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-413-50).

Single-dose vial, 0.5 mL (NDC 49281-413-58) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-413-10).

Storage and Handling

Store all Fluzone Quadrivalent presentations refrigerated at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard if vaccine has been frozen.

Do not use after the expiration date shown on the label.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information). Inform the vaccine recipient or guardian:

- Fluzone Quadrivalent contains killed viruses and cannot cause influenza.
- Fluzone Quadrivalent stimulates the immune system to protect against influenza, but does not prevent other respiratory infections.
- Annual influenza vaccination is recommended.
- Report adverse reactions to their healthcare provider and/or to the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967.
- Sanofi Pasteur Inc. is conducting a prospective pregnancy exposure registry to collect data on pregnancy outcomes and newborn health status following vaccination with Fluzone Quadrivalent during pregnancy. Women who receive Fluzone Quadrivalent during pregnancy are encouraged to contact Sanofi Pasteur Inc. directly or have their healthcare provider contact Sanofi Pasteur Inc. at 1-800-822-2463.

Vaccine Information Statements must be provided to vaccine recipients or their guardians, as required by the National Childhood Vaccine Injury Act of 1986 prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

Product information as of June 2013.

Manufactured by:
Sanofi Pasteur Inc.
Swiftwater PA 18370 USA

Printed in USA

MKT26489

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CONTINUED FROM ***PAGE 21***

be considered for a child with an unexplained cognitive or motor delay, focal neurological deficits, partial (focal) seizures, and EEG that does not represent a benign epilepsy of childhood, or in children aged younger than 1 year (Table 1).[4] If imaging is warranted magnetic resonance imaging (MRI), not a CT, should be ordered. More detail regarding brain structure is available from an MRI compared with a CT (and the former does not involve radiation).

Finally, the evidence supported obtaining an EEG on almost all children after a first unprovoked seizure.[4] The EEG was found to be useful in predicting seizure recurrence (54% vs 25% in children with abnormal EEGs vs normal EEGs, respectively) and determining the need for subsequent neuroimaging studies. An EEG was also helpful in differentiating seizures from other nonepileptic events and critical for diagnosing an epilepsy syndrome. Obtaining the EEG in a center with pediatric epilepsy expertise is best.

Epilepsy syndromes

An epilepsy syndrome is defined as "a complex of signs and symptoms that define a unique epileptic condition."[5] Epilepsy syndromes have a specific presentation, both clinically and electrographically (on EEG), which includes the clinical signs of the events, the timing of the episodes, and the age at onset. A diagnosis of an epilepsy syndrome can be incredibly useful in determining the need for additional testing (eg, whether an MRI is truly needed), helping to guide treatment decisions, and allowing the clinician to provide a long-term prognosis to the family. Thus, when evaluating a child for seizures, assessing whether or not a child fits a particular syndrome is a good place to start.

TABLE 1
INDICATIONS FOR MRI AFTER A SEIZURE

- Significant cognitive or motor impairment with unknown etiology
- Unexplained abnormalities on neurologic exam
- Partial-onset seizure with or without secondary generalization
- Abnormal EEG that does not represent a benign epilepsy of childhood or a primary generalized epilepsy
- Children aged <1 year

Abbreviations:
EEG, electroencephalogram;
MRI, magnetic resonance imaging.
Hirtz D, et al.[4]

Although many epilepsy syndromes exist, there are 3 common syndromes frequently encountered by pediatricians about which they need to be aware: benign rolandic epilepsy (also known as benign epilepsy with centrotemporal spikes [BECTS]), childhood absence epilepsy (CAE)/juvenile absence epilepsy (JAE), and juvenile myoclonic epilepsy (JME). Representative EEGs are shown in the Figure.

Benign epilepsy with centrotemporal spikes

Benign rolandic epilepsy, or BECTS, is the most common idiopathic epilepsy syndrome seen in school-aged children.[6] The majority of seizures (~80%) occur out of sleep or on awakening, but seizures may also occur during the day. Seizures are characterized by drooling and unilateral facial twitching of the tongue, lip, and cheek. Consciousness is generally preserved and the child may attempt to communicate, although speech arrest is common. The child may report full memory of the event, which can at times lead to confusion about whether the event was a true seizure.

Seizures can sometimes secondarily generalize, particularly in children aged younger than 5 years. Age at seizure onset can be anywhere between 3 and 13 years, with a median age of 7 years. This syndrome has an excellent prognosis, with 95% of children showing complete seizure resolution by 14 years. It is important to note that BECTS has been associated with cognitive, behavioral, and, particularly, language difficulties, which means that the child may require extra support in the form of an individualized education plan or 504 plan.[7] The child may also benefit from neuropsychologic testing, if available.[6] Academic progress may not be the most sensitive indicator of education-related problems, so further questioning about learning may be needed to diagnose these problems.

Treatment with medication for BECTS is not always required because many children experience only a handful of seizures before outgrowing them. However, if the seizures become frequent, if developmental or academic difficulties emerge, or if extreme parental

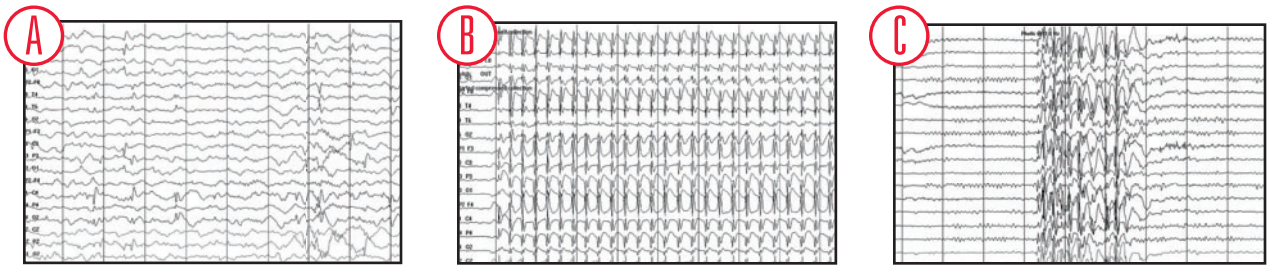

FIGURE Electroencephalograms of A benign rolandic epilepsy, B childhood absence epilepsy, C juvenile myoclonic epilepsy.

anxiety is present (eg, "I NEVER want to see a seizure ever again!"), anticonvulsant drugs are an option. Most medications are very effective in controlling seizures, with useful first-line agents being levetiracetam and oxcarbazepine (Trileptal).[8]

Absence epilepsy

Absence seizures, historically referred to as "petit mal" seizures, are characterized by brief, 5- to 20-second episodes of staring and unresponsiveness, and can occur up to hundreds of times a day.[9] A key feature that differentiates absence seizures from other types of staring seizures, such as complex partial seizures, is the lack of a postictal state, with children experiencing absence seizures returning immediately to baseline following the event. Children with absence epilepsy may also experience generalized tonic-clonic seizures, with approximately 30% of children presenting with a convulsion. Absence seizures can be safely diagnosed in the office by having the child hyperventilate (eg, by blowing on a pinwheel). This is absolutely safe and can lead to a rapid diagnosis.

Childhood absence epilepsy, or CAE, occurs in developmentally normal children aged between 4 and 10 years, with the peak incidence between 6 and 8 years. The prognosis is good and seizures are outgrown in approximately 80% of children by adolescence.[9] It is important to note, however, that children with CAE have a greater risk of long-term cognitive, behavioral, and linguistic comorbidities as compared with children without epilepsy, making prompt diagnosis and treatment critical.[10]

Juvenile absence epilepsy, or JAE, on the other hand, is not usually outgrown, and spontaneous remission of seizures occurs far less frequently as compared with CAE, with the presence of generalized tonic-clonic seizures being a predictor of poorer outcome.[9] Peak onset for JAE is between 10 and 12 years of age and is more strongly associated with photosensitivity than CAE. In JAE, seizures are most prominent on awakening, and generalized tonic-clonic seizures, often precipitated by sleep deprivation, are common.

First-line treatment for CAE is ethosuximide (Zarontin), followed by valproic acid (Depakote) and lamotrigine (Lamictal).[11] Because of teratogenic effects, valproic acid is rarely used as the initial anticonvulsant in girls aged older than 10 years, with zonisamide (Zonegran) or topiramate (Topamax) being good alternatives.

Juvenile myoclonic epilepsy

In JME, the most common idiopathic epilepsy syndrome presenting in adolescents and adults,[12] a teenager typically presents after experiencing a generalized

CASE 2

Jayden, a 7-year-old boy, stumbled into his parents' bedroom at 11 PM with the right side of his lip and cheek twitching. The parents report that he was completely awake and trying to talk but couldn't. His terrified parents are now asking you, "Are you sure it isn't a stroke or a tumor?"

Outcome: *Jayden underwent an EEG the following week, which revealed centrotemporal spikes during sleep, suggesting a diagnosis of benign rolandic epilepsy. The family was reassured that Jayden did not have a tumor or a stroke and that neither a CT scan nor an MRI was needed. The family was also told that because some children have only 1 or 2 seizures, Jayden did not need to start daily medication. A few months later, his mother called to say that Jayden had another 30-second episode of facial twitching, but this time she wasn't nearly as scared because of the reassurance you provided at their last visit.*

CASE 3

Charlotte, a 6-year-old girl, presents today because of slipping grades and teacher reports of frequent "daydreaming" episodes.

Outcome: *Charlotte underwent an EEG that revealed generalized high-amplitude 3 Hz spike- and slow-wave complexes during hyperventilation, consistent with a diagnosis of childhood absence epilepsy (CAE). At the clinic visit, her parents were reassured that CAE generally responds well to medication and that her seizures would likely be outgrown. The family walked out the door looking incredibly relieved. She was placed on ethosuximide and a week later, Charlotte was seizure free.*

CASE 4

Makayla, a 5-year-old girl, was found convulsing in her bed with a blue tinge to her lips and her eyes deviated sharply to the left. Her parents gave her cardiopulmonary resuscitation and called 911. Her CT scan was normal and her lab work was unremarkable. An EEG was also obtained, which was normal as well. Today, her mother wants to know if the seizure may have caused brain damage.

Outcome: *Makayla had an MRI a few days later, which, like her EEG, was also normal. Her mother was told that the risk of seizure recurrence was only about 40% and for this reason first seizures are rarely treated. No medication was started and Makayla never had another seizure.*

tonic-clonic seizure on awakening. After careful questioning, the adolescent may also report morning myoclonic jerks that resolve by breakfast. For example, he or she might report losing control of a spoon or toothbrush. This epilepsy syndrome rarely, if ever, remits without medication, but usually responds favorably to anticonvulsants. The most commonly used drugs are levetiracetam, valproic acid, lamotrigine, and zonisamide. Although medication is seldom started in children who have experienced a single seizure, adolescents with a diagnosis of JME are often an exception because of safety concerns such as driving and the high likelihood of recurrence.

After a first seizure, the issue of driving is often on the forefront of both the teenager's and the parents' minds. The family should be told that epilepsy does not necessarily preclude the teenager from driving, but that he or she must be seizure free to obtain and keep a driver's license. Clinicians who work with patients with seizures should know the driving laws of their state that pertain to epilepsy, as well as the process for reporting their diagnosis to the state motor vehicle administration.

A frank conversation with teenagers about lifestyle factors is essential in helping them remain seizure free and feeling a sense of control over their epilepsy. Common seizure triggers in patients with JME are sleep deprivation, alcohol use, and, of course, failing to take medication. "But I forgot!" is an all-too-frequent explanation for breakthrough seizures, and teenagers should be given concrete strategies to minimize the chance of seizure recurrence. For example, placing the medication next to his or her toothbrush can be a good reminder, and for those mornings when he or she forgets, medication can be kept in the nurse's office if permitted by the school. In addition, although schoolwork, extracurricular activities, and part-time jobs can make getting 9 to 10 hours of sleep a night seem impossible, the importance of getting sufficient sleep should be strongly emphasized. Finally, avoidance of alcohol and drugs, including illegally obtained prescription drugs, should be a key part of the discussion.

To treat or not to treat?

After a first seizure, many parents worry that starting medication is inevitable. They should be informed that treatment of a single seizure is rare (with the major exceptions of CAE, JAE, and JME as noted). Several prospective studies have found no evidence that treatment of the first seizure affects long-term prognosis, and there is consensus that it is not necessary to prescribe daily antiepileptic drug treatment after a single unprovoked epileptic seizure.[13] In addition, it is not uncommon for children to experience a single unprovoked seizure and never have another, with most children having a 40% to 50% chance of recurrence (even if the first seizure was an episode of status epilepticus). Risk of recurrence depends on multiple factors including an abnormal EEG, seizure while asleep, Todd's paresis, and history of febrile seizures.[14]

The decision to treat is made when the risks of treating are outweighed

LATEST GUIDANCE FROM AAP ON THE MANAGEMENT OF GER

Avoid medications in otherwise healthy infants with reflux

#1 REGURGITATION FORMULA RECOMMENDED MOST BY PEDIATRICIANS*

AAP recommends thickened formulas as an option for formula-fed infants with reflux[1]

TRUST ENFAMIL A.R.®—PROVEN IN A PUBLISHED CLINICAL TRIAL TO REDUCE REGURGITATION DUE TO REFLUX BY >50%[2†]

GER = gastroesophageal reflux

* of pediatricians recommending a specific brand; regurgitation formula is defined as a rice-thickened formula

† Based on a published, double-blind, randomized, controlled trial of Enfamil A.R. with infants who spit up frequently (5 or more spit-ups per day) comparing frequency and volume of spit-up after feeding Enfamil A.R. to the same infants at the beginning of the study

References: 1. Lightdale JR et al. *Pediatrics.* 2013;131:e1684-e1695. **2.** Vanderhoof JA et al. *Clin Pediatr (Phila).* 2003;42:483-495.

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Mead Johnson Nutrition

by the risks of not treating.[15] Every drug carries with it some risk that must be balanced against the risk of harm, both physical and emotional, from seizure recurrence. Treatment with medication is also initiated when risk of seizure recurrence is high, based on the history and the abnormalities on EEG. In some cases, medicine may be started after a first seizure if the EEG clinches a diagnosis of an epilepsy syndrome such as JME.

Primary care provider as 'hero'

After a first seizure, the pediatrician, armed with some basic knowledge, can be the hero! Providing reassurance and easing parental anxiety is an essential part of managing a child after a first seizure, and the act of doing so can be incredibly rewarding for the pediatrician. Seizure first aid should be discussed with the family, including when to call 911 (Table 2). Having brochures and printed-out information from websites ready to distribute to families can also be very helpful. If the child has had a seizure lasting longer than 5 minutes, the clinician may want to consider prescribing rectal diazepam (Valium). It is safe and easy to prescribe, and with proper parental counseling can prevent unnecessary trips to the emergency department.

Also, when referring a child to a neurologist, consider ordering the EEG in advance, ideally at the center where the child will be seen. If this is not possible, then the closest institution that cares for pediatric patients is acceptable. Note that EEGs that capture sleep tracings are preferable; families should be told to keep the child up late the night before the EEG or instructed to schedule the test during a young child's naptime. It is important to be aware that the EEG does not need to be done immediately. Although the EEG is more likely to be abnormal within the first 24 hours after a seizure, it will often remain abnormal in children with epilepsy syndromes, and obtaining a good-quality, sleep-deprived EEG is often worth the wait in some cases.[16,17]

Finally, do not hesitate to ask for help from the child neurologist with whom the child has an appointment, particularly if the child's case is perceived as urgent. Most neurologists will offer advice, including when to watch and when to worry. ■

TABLE 2 SEIZURE FIRST AID

- Position the child on his or her side to help clear the airway. Sometimes children will drool excessively or vomit during a seizure.
- Move the child away from ledges, hard or sharp objects, and other dangerous places.
- Loosen tight clothing.
- Place something soft underneath the head (eg, pillow or blanket).
- Do not try to restrain the child.
- Do not put anything in the child's mouth. This includes fingers. The child will not swallow his/her tongue.
- Time the seizure. Call 911 for a seizure lasting >5 min. For children with epilepsy, consider prescribing rectal diazepam for emergency use at home to avoid the need for ED transport.
- Stay calm and comfort the child as he or she regains consciousness.

Abbreviation: ED, emergency department.

HELPFUL WEBSITES FOR PARENTS

Visit these websites for valuable information and epilepsy resources to pass along to your patients' parents.

- **www.epilepsy.com**
- **www.epilepsyfoundation.org**
- **www.webmd.com/epilepsy**
- **www.cdc.gov/epilepsy**

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

Program gives children with life-limiting conditions quality of life

LISETTE HILTON

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Providing quality-of-life care for the sickest of children was a passion for pediatrician Gary Ceneviva, MD. As a critical care physician, he was troubled by what he saw. "Unfortunately when children die, they typically die within an [intensive care unit (ICU)]," Ceneviva says. So in true pediatrician fashion, he did something about it.

Ceneviva started a program aimed at helping children with life-threatening conditions and their families to navigate the health care system, coordinate care, and support decision making, as well as meet their physical, spiritual, and psychosocial needs. Today, as medical director of the Hummingbird Program, Penn State Hershey Children's Hospital, Hershey, Pennsylvania, Ceneviva and Deana Deeter, CRNP, CHPPN, CPON, Hummingbird Program manager, oversee a team of highly trained, committed professionals charged with ensuring that these kids and their families have not only the medical care they need, but also quality of life.

"We take care of children from birth to the end of life," says Ceneviva, who is also boarded in hospice and palliative care.

Children in the program have a number of conditions, including chromosome anomalies, cancer, complex heart disease, severe pulmonary problems, genetic conditions, neurologic diseases, and more.

editor's note

This new recurring feature will showcase novel hospital-based programs, innovations, and outreach initiatives that are meeting children's health care needs in unique ways. Propose your story for *The Hospital Zone* via cradwan@advanstar.com

"[For example,] we see a number of patients with either genetic or neurologic issues. These patients often develop respiratory problems," Ceneviva says. "Our program will assist in the medical and technologic management of these symptoms. During our discussions with the family, we converse on the pros and cons of various treatments and technologies and assist guiding the patient and family in complex decision making in accordance with their values, beliefs, and wishes."

A growing need

As health care advances, so does the length of the lives of children with life-threatening illnesses. What's often lacking, say doctors at the Hummingbird Program, is care that specifically takes their unique health circumstance into account.

"When I first started [developing] this back in the early 2000s, there were about half a million children estimated to have life-threatening conditions," Ceneviva says. "The number now is approaching 1 million. These children have grown in complexity and grown in number."[1,2]

Dr. Ceneviva

In the past, these children only rarely received hospice or palliative care services.

"In 2001, the Children's International Project on Palliative/Hospice Services (now the Children's Project on Palliative/Hospice Services) estimated that 8,600 children would be eligible for palliative care services on any given day; however, only 5,000 of the 53,000 children who died that year received hospice services, and usually only for a brief period of time," according to a 2009 document by the National Hospice and Palliative Care Organization (NHPCO).[3]

▲ **The Program's mascot, Hummy.**

While it's still true today that most children with complex chronic conditions die in the hospital setting, this is changing. Innovations in technology and changes in reimbursement are enabling an increasing number of medically fragile children to live their last days at home. Just over 10% of children aged 0 to 19 years died at home in 1989, versus about 18.2% in 2003.[3]

"Further breakdown of the data reveals that the odds of dying at home are reduced for black and Hispanic children. Geography also matters, as death at home is more likely in the West versus the northeastern United States," according to NHPCO.[3]

Bumps on an already rocky road

Problems occur for these kids and their families especially during and after transitions of care, according to Ceneviva. Children might transition in a hospital among floor units, step-down units, and the ICU, or

"The hummingbird is one of life's tiny miracles, just like our patients. A hummingbird's heart beats faster than any other bird. Its wings fly in the shape of a figure eight, the symbol of infinity. Hummingbirds are magical, mystical, and make our world a more beautiful place. In Native American traditions, the hummingbird has represented a messenger between worlds, helping to maintain the balance between nature and spirit. It is a creature that opens the heart and teaches others to appreciate the magic of being alive. The same lessons can be learned from the patients we are privileged to care for."

—Penn State Hershey Children's Hospital Hummingbird Program website

from hospital to home and back. Staff at the Hummingbird Program help children and families adjust.


Dr. O'Hara

"Having a strong care coordination component to this care is a lifeline for families," says Nicole C. Hahnlen, RN, CHPPN, Hummingbird Program nurse coordinator. "Physicians often don't have the opportunity to interact with patients and families quite as in-depth as I have the opportunity to. So, families have a real comfort level knowing they can pick up the phone and call and have a conversation with me, and I can certainly find a physician to address their needs."

Christopher O'Hara, MD, who splits his time as a hospitalist at Penn State Hershey Children's Hospital and as a pediatrician in the Hummingbird Program, says the program addresses potential care gaps. "Because of time constraints, some pediatricians are hesitant to care for these children. With a program like ours, whether it's the family or the pediatrician, we can be contacted to move things along," O'Hara says.

Getting to goals

One of the key focuses of the Hummingbird Program is to help children and families identify, achieve, and reassess their goals.


Ms. Hahnlen

"We did a study, looking at goals in 50 children with complex conditions," Ceneviva says. "We found that, for most families, their desire was for their child to come home. Another desire was to have the child develop as fully as possible, whether emotionally, socially, or intellectually. Our role is often to assist in helping those families achieve those goals. If they're in-house [and their goal is to go home], we would try to get them home and work with nursing agencies, hospices, durable medical equipment companies, and others to get these children home and make sure they have adequate staffing to keep them home."[4]

A pediatric partnership

While the Hummingbird Program and pediatric palliative care programs like it are uniquely positioned to provide a valuable bridge for patients' families, its founders stress that in no way are they intended to take the place of community-based pediatricians and other non-hospital-affiliated programs.

"We're not here to usurp any of

RESOURCES FOR PEDIATRIC PALLIATIVE/HOSPICE CARE PROGRAMS

There are many organizations devoted to establishing a standard scope of services so that the designation of "pediatric palliative care program" will come to have a uniform meaning across all such care sites in order to ensure the highest quality of care. These organizations, some of which also offer resources helpful for initiating such programs on a local level, include:

National Hospice and Palliative Care Organization:
- **www.nhpco.org/**

Education in Palliative and End-of-life Care for Pediatrics (EPEC):
- **www.epec.net/epec_pediatrics.php?curid=6 and modules at www.epec.net/documents/EPEC-PEDs_CurriculumListing_Objectives.pdf**

National Hospice and Palliative Care Organization: *NHPCO Facts and Figures: Pediatric Palliative and Hospice Care in America:*
- **www.nhpco.org/sites/default/files/public/quality/Pediatric_Facts-Figures.pdf**

Archive of Children's Project on Palliative/Hospice Services (ChIPPS) newletters:
- **www.nhpco.org/chipps-newsletters**

The Initiative for Pediatric Palliative Care (IPPC):
- **www.ippcweb.org/about.asp**

American Academy of Pediatrics Statement on Palliative Care for Children:
- **http://pediatrics.aappublications.org/content/106/2/351.full**

the primary care from the pediatrician," Ceneviva says. "We encourage the primary care physicians to maintain that valuable bond that they have with families."

It's imperative that a program such as this maintain a relationship with all health care providers, whether they're within the hospital or within the community, Ceneviva notes. "When [children are] making the transition from within the hospital to the community, one of our primary roles [often is] care coordination. That takes not only the work of our team but also the care providers within the hospital and, of course, the pediatrician," he says.

Dr. Ostrov

The frequency of services provided by the Hummingbird Program, which varies with each patient and family, is one practical factor in making pediatrician collaboration essential, adds Barbara Ostrov, MD, vice chair of pediatrics and pediatrician-in-chief, Penn State Hershey Children's Hospital.

"Our program doesn't always provide continuous care. Sometimes, there are consultations once or twice a year to help guide the primary care. Our program also provides consultations to help people understand what their wishes are for their child for end-of-life discussions. Some of those are more consultative because of the expertise," Ostrov explains.

In-hospital and community-based pediatricians play a pivotal role in seeking out patients and families for the programs. "We rely on pediatricians to make referrals to our program when they can or think they should," says Ceneviva.

In his position as a hospitalist, O'Hara makes it a point to recognize children with complex life-limiting issues and let them and their families know about the program as a potential resource.

Like O'Hara, say the program founders, pediatricians in the community who might not be part of such a program themselves will hopefully familiarize themselves with the resource so that they, in turn, can share word of it when families in their care have occasion to confront end-of-life circumstances with their children. ■

ADDITIONAL READING

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HOSPICE CARE BY THE NUMBERS

Gravely ill children, their families, and their pediatric providers in central Pennsylvania richly benefit from the presence of the Penn State Hershey Children's Hospital Hummingbird Program in the community and its palliative care expertise garnered in the decade since its inception. How available are similar programs in your locale?

Programs focused on providing consulting services, coordination of care, and more for children with very complex medical needs exist around the United States, but they vary considerably from hospital-based programs to community agency or long-term care facility-based programs, according to the National Hospice and Palliative Care Organization (NHCPO).[1] Designated pediatric palliative and/or hospice care units in hospitals also are rare.

To read the complete article, go to **ContemporaryPediatrics.com/pediatrichospicecare**

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STUMPED BY A BLEEDING UMBILICUS

The story

You are told that the patient has made it to the floor, so you quickly make your way to the room for further evaluation. When you enter, you notice that the intern is already there, so you sit back and listen to the story.

The patient was born 10 days ago at 39 weeks' gestation by spontaneous vaginal delivery to a 25-year-old primagravida white female. Birth weight was 7 pounds, 12 ounces. Pregnancy was uncomplicated. History was negative for immune thrombocytopenia or infection, and the infant received intramuscular vitamin K in the nursery. He was discharged after 48 hours. The mother is breastfeeding only. The only other complication he has had after birth is that he had trouble latching on, which was believed to be due to ankyloglossia. Frenulectomy was performed on day-of-life 5 by his pediatrician. There were no bleeding complications at that time and breastfeeding immediately resumed without any further problems.

The patient had been doing well until the day prior to admission, when the mother began noticing during each diaper change that there would be blood on the top edge of the diaper, but no active bleeding from the stump. While feeding the patient in a sitting position earlier this morning, she started seeing active bleeding from the umbilical stump that continued for 1 hour despite repeated application of pressure with gauze.

Upon presentation to the outlying ED, multiple interventions were attempted without success. The umbilical stump was reclamped twice. Silver nitrate was applied, but it only seemed to make the bleeding worse. Finally, Gelfoam impregnated with thrombin was applied, but the oozing continued. It was decided to transfer the patient to your hospital's ED for further testing and evaluation. Prior to transfer the patient was given a shot of vitamin K.

History and physical examination

The family history was negative for bleeding disorders or connective tissue disorders. The patient has been breastfeeding normally. Stools have been pigmented and without apparent blood. The mother denies using any medications or home remedies on herself or the patient. On arrival to the ED, physicians obtained a complete blood count (CBC) and blood chemistries. They also obtained a prothrombin time/activated partial thromboplastin time (PT/aPTT), which can be difficult to interpret because they are usually prolonged at this age. The ED physicians finally contact the on-call hematologist/oncologist who asks them to obtain a von Willebrand disease panel as well as a Factor XIII level, and admit the patient to your general pediatric service for further observation.

After obtaining the history, you do the physical exam with the intern, hoping that the findings will be not only educational but also conclusive. Unfortunately, a thorough exam turns up no new clues. General exam shows a nontoxic-appearing male who is afebrile. Examination of the skin shows no bruising. Nares and oral cavity are negative for any bleeding. Joints show no signs of swelling. The patient moves all extremities with no signs of a deficit. Other than the bleeding umbilicus, the rest of the physical exam shows a healthy, happy 10-day-old boy.

It won't stop bleeding

One hour later, you are sitting in your office when you receive an urgent but calm call from the floor nurse that you'd better get to the treatment room because there is a problem. When you arrive, you notice numerous blood-soaked gauze pads around the infant. The nurse is holding pressure on the patient's umbilicus and calmly states, "In my 20 years I have never seen a baby bleed so much from the belly button." She again puts pressure on the area for 10 minutes without hemostasis. Repeated applications of thrombin spray are also ineffective. Pressure bandage is placed by the senior resident and we decide to retreat to the workroom to figure out how to work up this patient.

The workup

Could this be a bleeding disorder? As you start your research, you learn that you have to determine if it is a problem with primary hemostasis

TABLE DIFFERENTIAL DIAGNOSIS OF BLEEDING DISORDERS IN THE NEWBORN PERIOD

- Hypofibrinogenemia
- Factor XIII deficiency[a]
- Mild von Willebrand disease[a]
- Mild factor deficiencies, heterozygous carriers (Factor VIII, IX, XI)[a]
- Acquired qualitative platelet disorders (uremia, medications)[a]
- Inherited qualitative platelet disorders[a]
- Vascular disorders (hereditary hemorrhagic telangiectasia, allergic purpura, etc)[a]
- Dysfibrinogenemia[a]
- Hemorrhagic disease of the newborn
- Hemophilia A and B
- Moderate to severe Factor VIII and IX deficiencies

[a] Normal prothrombin time/activated partial thromboplastin time.
From Lippi G, et al[1]; Sharathkumar AA, et al[2]; Bolton-Maggs H, et al[3]; Brown DL[4]; Peyvandi F, et al[5]; Inbal A, et al.[6]

or secondary hemostasis. Primary hemostasis is the "formation of the primary platelet plug, which involves platelets, blood vessel components, and von Willebrand factor (vWF)."[1]

Secondary hemostasis involves coagulation of blood that stabilizes the primary platelet plug. Unfortunately, you also learn that obtaining a thorough history and physical examination is usually low in diagnostic yield when it comes to evaluation of bleeding disorders. To avoid wasting time, most clinicians suggest that you develop a systematic high-yield approach to evaluating patients for blood disorders (Table[1-6]).

First you review the CBC and peripheral smear that were obtained in the ED because they allow you to look at the platelet count and morphology. The platelet morphology and CBC are found to be normal for age, but these do not necessarily reflect all components of primary hemostasis such as platelet function and/or adhesion, or vWF function or number. Because you know that the vWF disease panel has been ordered and the platelet count is normal, you decide to turn your attention to possible disorders of platelet function.

You learn that platelet dysfunction is usually divided between acquired and congenital disorders. Acquired disorders are much more common and are associated with use of medications such as "antiepileptic medications (eg, valproic acid), antidepressants, aspirin, and nonsteroidal anti-inflammatory drugs. Systemic disorders such as uremia, liver failure, leukemia, and congenital heart disease can lead to platelet function defects."[2]

Since this patient is otherwise healthy (normal physical exam and normal chemistry panel), and there is no medication use in either the mother or patient, an acquired disorder is essentially ruled out. That leaves you with congenital disorders of platelet function as a possible cause. You decide to wait for the hematologist's consultation before doing any further workup.

Next you focus on the results of the PT/aPTT as indicators of the health of the coagulation pathway and secondary hemostasis. Because they were normal for age, you can tentatively rule out any abnormality of the extrinsic or intrinsic pathway of coagulation, with the 2 most common disorders of coagulation being Factor VIII and Factor IX deficiencies. Now the only tests you have pending are the von Willebrand disease panel and Factor XIII level.

In the meantime, you also consider whether this could be an abnormally patent vessel that just hasn't closed correctly, so you decide to obtain a surgical consult for further evaluation.

The surgery

The patient is seen by the surgical service the next day. After discussion with the primary service, it is decided to take the patient to surgery for exploration of the umbilical stump. The patient is found to have a patent umbilical artery that is subsequently sutured. Believing that you have found the source of bleeding, the patient is eventually discharged the next day once his vWF disease panel comes back normal. The patient is to follow up with surgery in 2 weeks.

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More problems?

Two days later, the patient is readmitted to the surgery service after oozing from the umbilical site returns and persists for several hours despite attempts to stop the bleeding. Repeat umbilical stump exploration reveals that although the patient has a hematoma over the umbilical artery, blood continues to ooze around the clot. The area is cauterized and the umbilical artery is resutured. The patient is then kept overnight to monitor for continued bleeding. The next day, hematology/oncology service contacts the surgery service with some amazing news—the patient's Factor XIII level is severely low at <3%!

Factor XIII deficiency

Now looking back, you did wonder why the hematologist ordered a Factor XIII assay if the PT/aPTT was normal. You learn that Factor XIII deficiency is a very rare (1 in 1 to 5 million), autosomal recessive or acquired bleeding disorder.[3]

Also known as fibrin stabilizing factor, Factor XIII's primary job is to cross-link fibrin strands, thus strengthening the fibrin plug. It is a part of secondary hemostasis, and because it acts at the end of the coagulation pathway, affected patients would be expected to have a normal PT/aPTT.

Because the patient is unable to maintain the fibrin plug, you can see the usual clinical manifestations such as umbilical stump bleeding (80% of the cases)[3,4]; delayed wound healing; intracranial hemorrhaging (25% to 30%); and a lifelong tendency for ecchymosis, hematomas, and prolonged bleeding following trauma.[3-5]

Diagnosis can be made either by using a commercially available test to measure the activity of the Factor XIII or doing a clot solubility test using thrombin to form the clot and dissolving it in a 2% acetic acid suspension. Treatment for the patient consists of receiving Factor XIII concentrate, fresh frozen plasma (FFP), or cryoprecipitate. Factor XIII and FFP are preferred to cryoprecipitate. All patients should receive infusions when the level is below 1%, but infusion should also be considered in those at a level below 4%.[3]

Because Factor XIII has a long circulating half-life of 7 to 10 days, 10 to 20 units per kg of Factor XIII concentrate, 15 to 20 ml per kg of FFP, or 1 bag of cryoprecipitate per 10 kg of body weight every 4 weeks should be sufficient to prevent the majority of patients from experiencing spontaneous hemorrhaging.

A new recombinant human Factor XIII A-subunit was approved for use by the US Food and Drug Administration in December 2013.[6] It is dosed at 35 IU/kg/month and study results show decreased rates of bleeding episodes and rare development of anti-Factor XIII antibodies.

Finally, a diagnosis and treatment

By the time the hematology/oncology service contacted the surgeons, the patient was noted to have some postoperative bleeding under his dressing. He was given an infusion of FFP with reapplication of his pressure dressing and was observed for another night. Because he did not have a reoccurrence of the bleeding, he was discharged home to follow up with hematology/oncology. The patient is currently doing well and is seen every month for prophylactic FFP infusions. ■

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ANDREW J SCHUMAN, MD
SECTION EDITOR

Instrument-based vision screening: Update and review

RICHARD H SCHWARTZ, MD, FAAP; ANDREW J SCHUMAN, MD, FAAP; AND LISA L WEI, MD, FAAO, FAAPOS

In late 2012, the American Academy of Pediatrics (AAP) Section on Ophthalmology and Committee on Practice and Ambulatory Medicine joined the American Academy of Ophthalmology, the American Association for Pediatric Ophthalmology and Strabismus (AAPOS), and the American Association of Certified Orthoptists in issuing a policy statement endorsing the use of instrument-based vision screening in the pediatric population.[1]

This was the subject of the inaugural article in the Peds v2.0 series in January 2013 (*Contemp Pediatr.* 2013:30(1):41-44). We now revisit the topic because insurance companies are beginning to compensate pediatricians for performing photoscreening, billed under Current Procedural Terminology (CPT) code 99174. We applaud the efforts of the many pediatricians, pediatric ophthalmologists, and state chapters of the AAP who have aggressively petitioned insurance companies to cover this important service for our patients.
—Andrew J Schuman, MD, Section Editor

Amblyopia, defined as poor vision caused by abnormal development of visual areas of the brain, occurs in as many as 2% to 4% of children.[2] It is associated with complete or partial lack of clear visual input to 1 eye (unilateral/anisometropic refractive amblyopia), or, less often, to both eyes (bilateral refractive amblyopia), or to conflicting visual inputs to the 2 eyes (strabismic amblyopia). Less-common causes include ptosis, congenital cataract, and corneal injury or dystrophy. According to the US Preventive Services Task Force (USPSTF), amblyopia is regarded as a disease of childhood; however, its effects are irreversible if left untreated, and it is the most common cause of monocular vision loss among adults aged 20 to 70 years.[3]

Unfortunately, only a minority of young children are screened for this disabling condition. One study reported that in a sample of 102 private pediatric practices in the United States, vision screening was attempted on only 38% of 3-year-old children and 81% of 5-year-old children.[4] The study also showed that only 21% of children failing the AAP vision screening guidelines were referred for a professional eye examination.

38%

OF 3-YEAR-OLD CHILDREN IN THE UNITED STATES HAD VISION SCREENING ATTEMPTED ON THEM.

TABLE 1 RISK FACTORS FOR AMBLYOPIA

CONDITION	DESCRIPTION
Strabismus (strabismic amblyopia)	○ Ocular misalignment; most common cause of amblyopia
Anisometropia (anisometropic amblyopia)	○ Asymmetric refractive error between the 2 eyes, which causes image suppression in the eye with the larger error
Astigmatism	○ Blurred vision at any distance because of abnormal curvature of the cornea or lens
Hyperopia	○ Farsightedness; visual images come to focus behind the retina
Media opacity (deprivation amblyopia)	○ Opacities of the clear refractive media of the eye such as the cornea, anterior chamber, lens, and vitreous humor may cause acute visual loss as manifested by blurry vision or reduced visual acuity

From USPSTF[3]; Mansouri B, et al.[7]

Vision screening in pediatric practice

Vision and amblyopia screening should be viewed as a continual process beginning in mid-infancy and repeated annually throughout early childhood.[5] Vision screening for infants, toddlers, and preschool children is traditionally performed by primary care physicians and nurses, using a rechargeable, battery-powered ophthalmoscope to test pupil position, equality, size, steadiness, and reaction to bright light; extraocular muscle function; ocular deviation during a cover-uncover test; and presence of unequal red reflexes in a darkened room.

Many of the major risk factors for amblyopia are poorly detected during a traditional vision screening examination. Vision acuity testing in children aged younger than 3 years in a medical office can be challenging because few children this age can be screened with a vision chart. From ages 3 to 5 years, screening is possible with Snellen charts, Tumbling E charts, or picture tests such as Allen Visual Acuity Cards, but this is time consuming and can lead to inconsistent or erroneous results.

Amblyopia: the problem

Amblyopia remains treatable until age 60 months, with rapid decline of effective treatment after age 5 years.[5,6] The goal of vision screening in infants and young children, therefore, must be the *early* detection of high severity (magnitude) amblyopia risk factors (ARFs), including moderate or severe astigmatism, anisometropic myopia, high hyperopia, severe strabismus, and opacities in the visual axis, including retinoblastoma or other ocular entities that cause opacities that interfere with transmission of light to and from the retina (Table 1[3,7]). Any media opacity (including the retina) greater than 1 mm in size is potentially amblyogenic and should be detected with photoscreening.

The relationship between refractive error and the likelihood of the development of amblyopia depends on the child's age, the magnitude of blurred vision, and other factors.[5] For children aged 3 years and younger, the prevalence of amblyopia correlates with the severity of anisometropia (unequal refractive power between each eye).[8] In this age group, high-magnitude amblyopia risk factors increase the likelihood of overt amblyopia. Many children with mild amblyopia from anisometropic amblyopia or strabismic amblyopia improve with spectacle (eyeglasses) treatment alone.[9] Treatment options for children in whom spectacles are not appropriate or are not effective include patching the better-seeing eye or using atropine drops to blur vision in the better-seeing eye.

In 2013, the AAPOS Vision Screening Committee revised its criteria for instrument-based vision screening because "many children with low-magnitude ARFs do not develop amblyopia, and those who do often respond to spectacles alone."[5] They noted that referral criteria for vision photoscreening instruments should have high specificity for ARFs in young children (to minimize false positive referrals) and high sensitivity to detect amblyopia risk factors in older children (when children are approaching an age when treatment becomes less effective). See Table 2 for the current age-related thresholds recommended by the AAPOS.[5] Note that the detection of higher magnitude

anisometropia (>3.0 diopters), even in children in the 31- to 48-month age group, should be highly sensitive because it is associated with amblyopia that continues to deepen over time.

Visually significant media opacities such as cataracts, infantile glaucoma, persistent hyperplastic primary vitreous, and retinoblastoma must be detected accurately at all ages.[7]

Benefits of photoscreening

In primary care pediatric and family medicine offices, photoscreening for high refractive errors and other ARFs is recommended for infants, toddlers, and preschool-aged children. Even in primary grades, such

TABLE 2 AMERICAN ASSOCIATION FOR PEDIATRIC OPHTHALMOLOGY AND STRABISMUS' RECOMMENDED AMBLYOPIA RISK FACTOR TARGETS

REFRACTIVE RISK FACTOR TARGETS				
Age, months	Astigmatism	Hyperopia	Anisometropia	Myopia
12-30	>2.0 diopters	>4.5 diopters	>2.5 diopters	>-3.5 diopters
31-48	>2.0 diopters	>4.0 diopters	>2.0 diopters	>-3.0 diopters
>48	>1.5 diopters	>3.0 diopters	>1.5 diopters	>-1.5 diopters
NONREFRACTIVE RISK FACTOR TARGETS				
All ages	Media opacity >1 mm Manifest strabismus >8 prism diopters in primary position			

From Donahue SP, et al.[5]

TABLE 3
REASONS TO USE VISION PHOTOSCREENING FOR CHILDREN

- Age 6 months to 72 months
- Poor cooperation with Snellen wall chart or Allen cards
- Intellectual disability
- Unable to read letters
- Fear of occluder used to block vision from nontested eye
- Hyperactive child
- Autistic spectrum disorder
- Exam area with insufficient length for wall chart
- Verification of abnormal Snellen refraction test
- Screening accomplished quickly

technology offers advantages over traditional Snellen wall charts or Allen cards because it is less time consuming, more efficient, and provides much more specific information (Table 3).[1] In the Vision in Preschoolers Study, published in 2004, it was found that visual acuity testing (using eye charts) of more than 2,500 preschool children had a 77% sensitivity for detecting conditions associated with amblyopia, while photoscreener devices had a sensitivity of 81% to 88%.[10] Note that the use of photoscreeners not only improves detection of eye pathology but also does so in a fraction of the time required to perform testing with eye charts.

How to photoscreen

Regardless of the device used to screen patients, testing should be done in a darkened room with lights off and, if necessary, window shades drawn. If the room is too dark, the room door may be opened a small amount. The child's pupils should be level. Head tilting produces off-center pupils that can produce false positive results for refraction and astigmatism problems. The child's pupil size must be at least 4 mm in diameter to aim the light beam into the plane of the visual axis. If the subject's pupil size is too small for the light beam to penetrate well, the instrument will state: "pupils too small." Children from many Asian countries have epicanthic folds or partial ptosis, which require them to open their eyelids as wide as possible for the light beam to penetrate into their pupils.

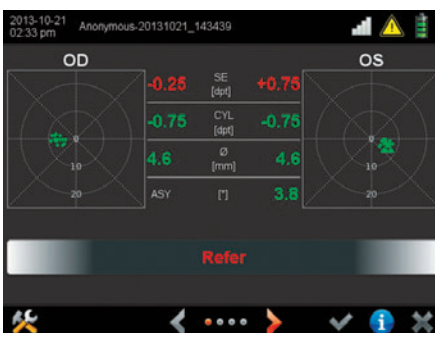
Photoscreening devices

Pediatricians interested in incorporating photoscreening technology into routine practice have a number of devices to choose from. Dr. Schuman detailed several of these devices in the January 2013 article. We provide a brief description of popular photoscreeners here along with some new devices that either are presently available or will be in the near future. Note that many insurance companies are now covering photoscreening under the CPT code 99174 ("ocular photoscreening with interpretation and report, bilateral"), paying usually $25 to $30 per screen.

Plusoptix (Atlanta, Georgia), a German company, introduced its 4th-generation vision screener

▲ **Plusoptix S12C vision screener detects amblyopia.**

last year—the portable **Plusoptix model S12C.** Patient information is inputted with a touch-screen interface, and then pushing a trigger button activates the camera. The device produces a warbling sound to attract the child's attention and gaze toward the smiling face displayed on the patient side of the device. The child's eyes are positioned in a white rectangle on the viewing screen and moved until a green line is drawn between the pupils. Once positioned, the device takes 36 pictures of both eyes and performs measurements regarding pupil sizes, corneal reflexes, and refraction, which are displayed on the screen along with an indication whether the child passed the screening. The device records the patient data as a pdf file on a secure digital card that can be transferred to a computer to print the result for incorporation into



▲ **Plusoptix device takes pictures and measurements of a child's eyes.**

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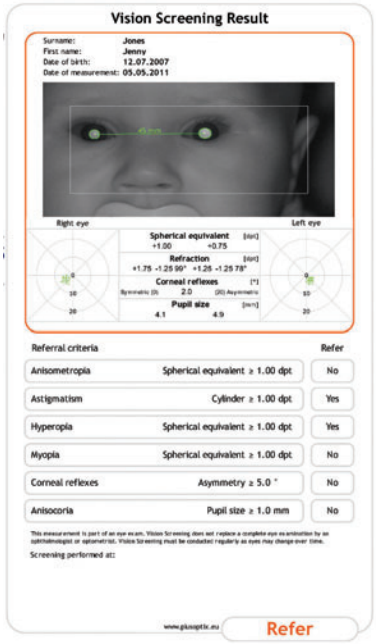

▲ **Plusoptix vision screener records patient data as a PDF file.**

the patient record. It connects wirelessly to a Zebra printer to print an abbreviated version of the results. According to Plusoptix, the device can detect the amblyopia with a sensitivity as high as 92% and specific-

▲ **Spot vision screener finishes testing in less than 1 second.**

ity as high as 88%. The S12C device sells for $7,385 each. A smaller version of the Plusoptix portable device, **model S12R,** doesn't have the wireless printing capability or data storage capability of the model C, but is priced at $5,875.

Spot Vision Screener from PediaVision (Lake Mary, Florida) is a photoscreener that is battery powered, lightweight (2.5 pounds), and features a portable infrared camera that, like the Plusoptix S12C, combines autorefraction and video retinoscopy. The rechargeable battery is designed to supply sufficient power for an entire day of screening children. Spot makes 23 images of the retina by shooting infrared light

▲ **2WIN photoscreener records and displays readings in 7 seconds.**

through a 4-mm or greater pupillary aperture. The light beam is directed to the retina but may be blocked by lesions in the cornea, lens, vitreous, and retina itself. In the absence of opacified lesions in the visual axis, the light beam is reflected off the retina and returns to the instrument. A software program analyzes the result and compares it to internal norms that can be modified for the child's age.

Physicians familiar with digital cameras find the Spot easy to use. After inputting identifying information, one aims the device toward the child and positions the child's

▲ **iScreen Vision Screen 3000 sends test results for interpretation.**

face on a display. The device indicates whether you are too close or too far from the subject and then initiates the screening sequence, which is completed in less than a second. The screen displays the pupillary size, distance, alignment, and complete refraction information for both eyes and indicates whether the child needs to be referred to a pediatric ophthalmologist. Additionally, the device can connect to a wireless printer to facilitate printing a complete report for parents or for inclusion in the medical record. The Spot Vision Screener sells for $7,495. Those pediatricians who purchased the Spot more than 9 months ago need to reset the device's threshold to those listed in Table 2 to avoid overreferrals to ophthalmologists.[5]

The **2WIN binocular refractometer and photoscreener** is new to the American market, produced by an Italian company called Adaptica (Padova, Italy). It is comparable in size to the small Plusoptix S12R. According to the manufacturer, 2WIN has a rechargeable battery; records and displays readings in as little as 7 seconds; and has wireless and infrared printer connectivity. The device is priced at $6,950.

The **iScreen Vision Screen 3000** from iScreen Vision Inc

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ALASKA BLIND CHILD DISCOVERY BRINGS VISION SCREENING TO ALASKA'S PRESCHOOLERS

There is no such thing as a "brief" conversation with Robert W. Arnold, MD, pediatric ophthalmologist, when the topic is preschool vision screening. He originated the Alaskan Blind Child Discovery (ABCD) program in his beloved state of Alaska in the early 1990s. Its goal was to test every young child in Alaska for amblyopia.

▲ **Dr. Arnold tests patients for amblyopia.**

Arnold began with a handful of photoscreener devices that he provided to pediatricians, public health nurses, and ophthalmologists. Later, he gained philanthropic support provided by local Lions, Kiwanis, and Shriners organizations and launched vision screening clinics throughout the state.

Along the way, Arnold found the time to perform many investigations that helped refine and ultimately define the current state-of-the-art regarding vision screening for young children. He has published extensively and is a coauthor of the 2013 AAPOS guidelines for automated preschool vision screening.[5]

From 1996 through today, the ABCD project has screened over 60,000 children. The project's website, www.abcd-vision.org/, has a wealth of information regarding pediatric vision screening that can assist pediatricians interested in starting their own vision programs. There also are numerous informative videos, with many demonstrating the photoscreeners discussed in this article.

(Cordova, Tennessee), is yet another photoscreener that takes pictures of the pupillary and red reflex to screen for amblyopia. In contrast to the automatic computer analysis of the photos of the red reflex performed by the Plusoptix and PediaVision devices, the iScreen Vision Screen 3000 connects by a network cable to your office network and transfers each patient screening test to a "professional" who interprets the test (with computer assistance) and provides information regarding whether the patient is at risk for amblyopia and needs referral to a pediatric ophthalmologist. Results are transmitted to the office e-mail within minutes of receipt, so the parents can be apprised of the results before the visit is done. The iScreen Vision Screen 3000 sells for $4,200, and each test costs $6.

New screening technologies coming soon

If there is a limitation to photoscreeners, it is that they can still miss a child with amblyopia, and there is a substantial overreferral rate associated with these devices. Hence, it is important that screening is performed yearly at well-child checks, and when a child is referred to an ophthalmologist, parents must be reminded that there is a possibility that no pathology will be discovered. David Hunter, MD, chief of ophthalmology at Boston Children's Hospital, has developed a new device called the **Pediatric Vision Scanner** (PVS) that uses polarized laser light to test eye orientation at the retinal level to detect amblyopia in children with sensitivities and specificities much higher than those associated with photoscreeners. The new technology is called "retinal birefringence scanning," and Hunter has formed a company called REBIScan to commercialize its use. The PVS is currently being evaluated by the US Food and Drug Administration and, following approval, will be available for use by

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▲ **Pediatric Vision Scanner tests via retinal birefringence scanning.**

pediatricians this year.

Lastly, a new company called Gobiquity (Aliso Viejo, California) will soon introduce an iPhone application called **GoCheck Kids** that uses the camera built into the smartphone to photograph a child's eyes. The application will subsequently analyze the photograph in much the same way as photoscreeners do, generating a report that will indicate whether the child passes or needs referral to a pediatric ophthalmologist. Initial data indicate that the GoCheck Kids application produces results comparable to those of currently available photoscreeners. The cost of the application and pricing model for screening has not yet been determined as of this writing.

Conclusion

Author Richard Schwartz, MD, has been using the Spot instrument in his practice since May 2013, and has been able to screen young and often uncooperative children for refractive errors or amblyopia risk factors. It has paid for itself in this time and has detected several children with significant refractive errors as well as a cataract and posterior vitreous disease. He reports that insurance companies are reimbursing for photoscreening in Virginia.

Author Andrew Schuman, MD, has trialed both the Plusoptix S12C and the Spot and has found them easy to use—both providing readings in seconds. He notes that parents are very impressed that their children can be screened so easily, and using either device is a huge time-saver in his pediatric office. In his state of New Hampshire, all insurance carriers, including Medicaid, are currently reimbursing for photoscreening. He advises that before you purchase, you contact your insurance companies to see if they will reimburse for CPT code 99174.

Practices should challenge rejected claims by providing copies of the new AAP policy and/or the USPSTF policy statement, and when necessary ask the state chapter of the AAP to petition insurance companies to cover this important service as well. ■

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▲ **GoCheck Kids app uses a smartphone for vision screening.**

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SCREENING / TESTS

CONTINUED FROM PAGE 50

dermcase } BOY WITH WORST-CASE DERMATITIS

Clinical findings

Eczema herpeticum (EH) is a disseminated herpes simplex virus (HSV) infection usually affecting patients suffering from atopic dermatitis (AD), contact dermatitis, or other primary dermatoses.[1] Although most patients show serologic evidence of HSV exposure, EH affects only about 3% of patients with AD.[2]

Predisposing factors may include compromised host defenses such as those seen in severe AD, leukemia, lymphoma, bone marrow transplantation, chemotherapy, and previous topical corticosteroid use.[1] However, recent studies have shown little evidence to substantiate the latter, and in many children with AD, their skin disease may be relatively well controlled when EH erupts.[3,4] A recent study by Aronson and colleagues confirmed this and found that use of oral corticosteroids increased average length of hospitalization in patients with EH by 18%.[5]

Classic findings of primary infection include fever; lymphadenopathy; exquisite pain in the affected area; and clusters of disseminated, monomorphic, vesicular, and dome-shaped vesicles, pustules, and crusts. The most commonly affected areas are the head, neck, and upper trunk.[3] Unlike other primary or recurrent HSV eruptions, lesions in EH are usually disseminated, but if the clinician looks carefully, he or she may still be able to define clustering of discrete and confluent lesions.

Patients with head, neck, or large body-surface-area involvement, or early-onset AD, have higher risks of EH.[6,7] Although unusual, more serious systemic involvement occurs particularly in patients with primary infection and immunosuppression.[1] Rarely, patients can develop keratoconjunctivitis, meningoencephalitis,[8] disseminated intravascular coagulation, bronchial hemorrhage, and even adrenal hemorrhage.[9] The infection typically resolves within 2 to 3 weeks, but recurrences are common. Although recurrences tend to be milder than primary disease,[1] they can disrupt normal day care, school, and sports activities.

Differential diagnosis

Eczema herpeticum may resemble varicella, disseminated varicella zoster virus (VZV) infection, and impetigo. Varicella tends to be uniformly disseminated on skin and mucous membranes. In disseminated VZV in the immunocompromised host, one can usually identify more than 20 vesicles outside the area of primary or adjacent dermatomes.[10] In bullous impetigo, the clustered initial vesicles tend to expand and vary in size. The typical appearance of characteristic lesions as well as a history of AD or other cutaneous dermatoses should raise the clinical suspicion for EH. Because secondary bacterial infection complicating EH is common, bacterial and viral cultures should be sent when both are suspected.[6]

More recently, enteroviral infection with coxsackievirus A6 has been recognized as a trigger of a disseminated eruption similar to EH. However, at the time of diagnosis, affected children are usually afebrile and clinically appear well, and the eruption tends to be symmetric with a predilection for involvement of the distal extremities, diaper area, and perioral skin. Cultures for HSV are negative.[11]

In severe EH, particularly in those who are immunocompromised, early diagnosis is critical. Mortality in the latter as high as 50% has been reported, although between 6% to 10% is the more accepted number.[4,6] Studies before the use of acyclovir quoted mortality rates upward of 10% to 50%.[12] Although the current mortality rate of EH has not been reported, the mortality rate of hospitalized children with EH is low.[13]

Eczema herpeticum is a clinical diagnosis that can be confirmed from blister fluid by polymerase chain reaction for viral DNA.[3] The diagnosis is supported by Tzanck test, which also may be done on blister fluid. A less sensitive method is viral culture, and a less specific method is serologic testing.

Dr Santos-Arroyo is a second-year dermatology resident, University of Puerto Rico School of Medicine, San Juan.
Mr Nevares-Pomales is a fourth-year medical student, University of Puerto Rico School of Medicine, San Juan. The authors and section editor have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article. Vignettes are based on real cases that have been modified to allow the authors and editor to focus on key teaching points. Images also may be edited or substituted for teaching purposes.

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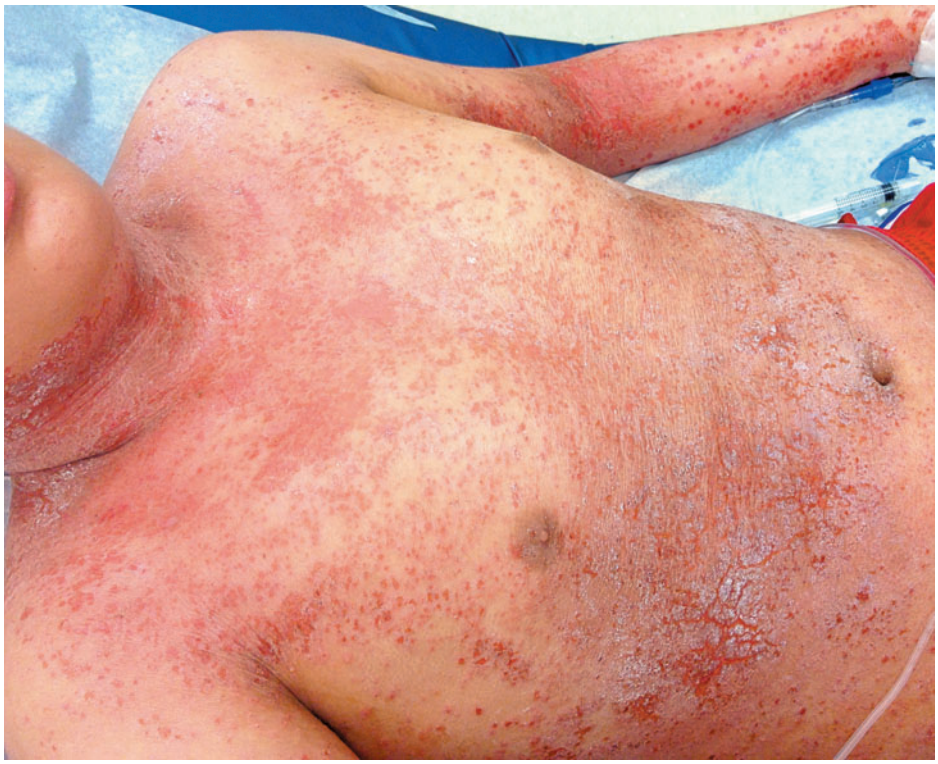

Clusters of disseminated monomorphic, vesicular, and dome-shaped vesicles, pustules, and crusts affect the patient's head, neck, and upper trunk.

Boy with worst-case dermatitis

AILEEN E SANTOS-ARROYO, MD, AND OSCAR W NEVARES-POMALES, MS4, BA

THE CASE

You are called to the emergency room to see an ill-looking, 13-year-old boy with a severe flare of his atopic dermatitis associated with fever, malaise, and chills, which started a week ago. FOR MORE ON THIS CASE TURN TO PAGE 49 ▶

Have you seen a case such as this one in your practice? How did you reach your diagnosis? We'd like to hear from you. Share your Dermcase with us and with your colleagues on Facebook. facebook.com/ContemporaryPediatrics

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DERMCASE *diagnosis* } ECZEMA HERPETICUM

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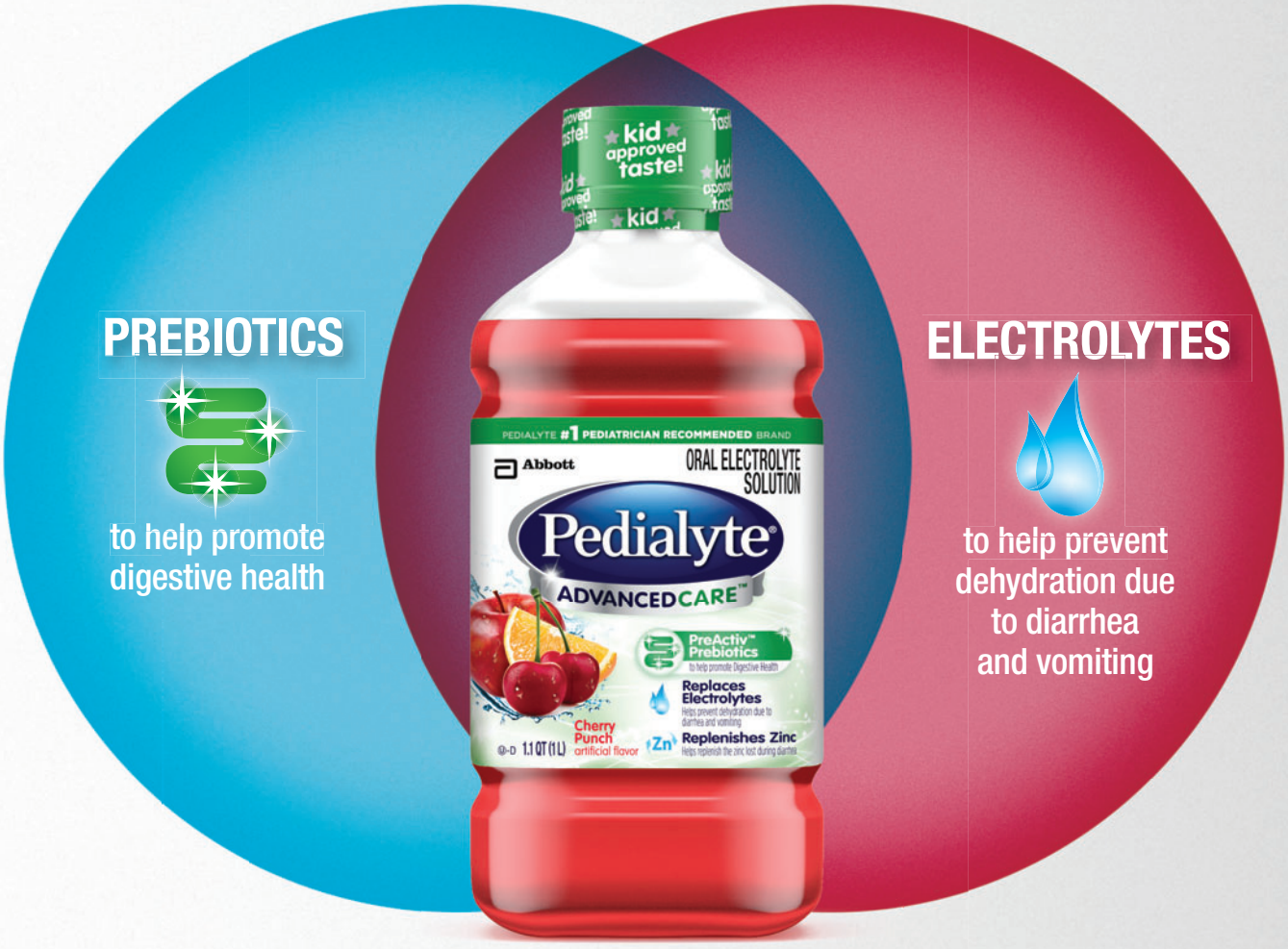

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