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CONTEMPORARY Pediatrics

SEPTEMBER 2013
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Daytrana®:

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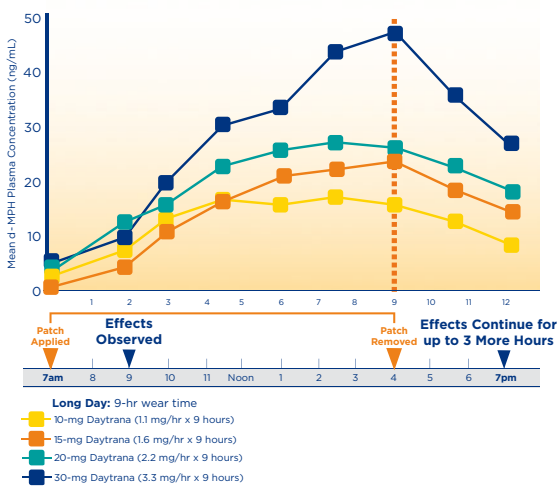
- Long-acting symptom control
- Removable to control duration

Smooth Long-Acting Symptom Control*



The Daytrana patch, as with other stimulants, is subject to abuse and dependence requiring appropriate patient selection and supervision.

INDICATION

The Daytrana® patch is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children (ages 6-12) and adolescents (ages 13-17). The efficacy of the Daytrana® patch was established in controlled clinical studies: two 7-week trials in children and one 7-week trial in adolescents. Diagnosis of ADHD is based on complete patient history and evaluation, not just DSM-IV-TR® characteristics. The Daytrana® patch is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, and social).

IMPORTANT SAFETY INFORMATION

WARNING: DRUG DEPENDENCE

Daytrana® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

CONTRAINDICATIONS: The Daytrana® patch should not be used by patients who have an allergy to methylphenidate, acrylic adhesive, or silicone adhesive; marked anxiety, tension, and agitation; glaucoma; motor tics or with a diagnosis or a family history of Tourette's syndrome; are being treated (or within 14 days after treatment) with monoamine oxidase inhibitors (MAOIs).

SERIOUS CARDIOVASCULAR EFFECTS: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. A careful patient history, including family history, and physical exam should be performed to assess the presence of cardiac disease. Stimulant products generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. Patients who develop symptoms (i.e., exertional chest pain, unexplained syncope) suggestive of cardiac disease while using or wearing the Daytrana® patch should be promptly evaluated. Use with caution in patients whose underlying medical condition might be affected by increases in blood pressure or heart rate. Use cautiously with pressor agents. Hematologic monitoring is advised during prolonged treatment.

PERIPHERAL VASCULOPATHY: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants.

PSYCHIATRIC, SEIZURES, AND GROWTH SUPPRESSION: Use with caution in patients with a history of psychosis, bipolar disorder, depression, seizures, or EEG abnormalities. New psychosis, mania, aggression, seizures, visual disturbances, and growth suppression have been associated with the use of stimulants. Growth should be monitored in children during treatment with stimulants, and patients who are not growing (gaining height or weight) as expected may need to suspend treatment with the Daytrana® patch.

CONTACT SENSITIZATION: Use of the Daytrana® patch may lead to contact sensitization. Erythema has been commonly reported and is not by itself an indication of sensitization. If contact sensitization is suspected (erythema with edema, papules and/or vesicles spread beyond the patch site and/or lack of improvement within 48 hours), treatment should be discontinued. Patients should avoid applying external heat to the Daytrana® patch; application of heat can increase the extent and rate of absorption.

MOST COMMON ADVERSE EVENTS: The most common adverse reactions associated with the Daytrana® patch (at least 5% and twice the rate of placebo-treated patients) in clinical trials were: children – decreased appetite, insomnia, nausea, vomiting, decreased weight, tics, affect lability, and anorexia; adolescents – decreased appetite, nausea, insomnia, decreased weight, dizziness, abdominal pain, and anorexia. In addition, the majority of subjects in these studies had minimal to definite skin erythema at the patch application site. Leaving the patch on for longer than the recommended 9 hours has resulted in an increased incidence of adverse events.

1. Wigal SB, Pierce DM, Dixon CM, McGough JJ. Pharmacokinetics of methylphenidate transdermal system in children with ADHD. Poster presented at: 18th Annual US Psychiatric and Mental Health Congress; November 8, 2005; Las Vegas, Nev.
2. McGough JJ, Wigal SB, Abikoff H, et al. A randomized, double-blind, placebo-controlled, laboratory classroom assessment of methylphenidate transdermal system in children with ADHD. J Atten Disord. 2006;9:47-485.

***Study 201:** Drug concentration from multiple-dose administration of Daytrana® in a randomized, double-blind, placebo-controlled laboratory pediatric classroom study. Plasma samples were obtained for pharmacokinetic analysis at predose and 2, 3, 4.5, 6, 7.5, 9, 10.5, and 12 hours after dose administration. (10 mg) n=7; (15 mg) n=32; (20 mg) n=27; (30 mg) n=8.[1,2]

Please read Important Safety Information above and Brief Summary Full Prescribing Information on next page, including **Medication Guide** and **Boxed Warning regarding Drug Dependence.**

noven THERAPEUTICS, LLC

Printed in USA DAY-2315-13 07/13

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DAYTRANA® CII (methylphenidate transdermal system) Noven Therapeutics, LLC
Brief Summary. Consult Package Insert for complete prescribing information.

WARNING: DRUG DEPENDENCE
Daytrana should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

1 INDICATIONS AND USAGE
Daytrana (methylphenidate transdermal system) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of Daytrana in patients diagnosed with ADHD was established in two 7-week controlled clinical trials in children (ages 6-12) and one 7-week, controlled clinical trial in adolescents (ages 13-17).

4 CONTRAINDICATIONS
4.1 Hypersensitivity to Methylphenidate - Daytrana is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product (polyester/ethylene vinyl acetate laminate film backing, acrylic adhesive, silicone adhesive, and fluoropolymer-coated polyester). **4.2 Agitation** - Daytrana is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms. **4.3 Glaucoma** - Daytrana is contraindicated in patients with glaucoma. **4.4 Tics** - Daytrana is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome [see Adverse Reactions (6.1)]. **4.5 Monoamine Oxidase Inhibitors** - Daytrana is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (hypertensive crises may result).

5 WARNINGS and PRECAUTIONS
5.1 Serious Cardiovascular Events ***Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems*** *Children and Adolescents:* Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug. *Adults:* Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs. ***Hypertension and Other Cardiovascular Conditions*** Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia [see Adverse Reactions (6.1)]. ***Assessing Cardiovascular Status in Patients Being Treated With Stimulant Medications*** Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation. **Peripheral Vasculopathy:** Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. **5.2 Psychiatric Adverse Events** *Pre-Existing Psychosis:* Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder. Bipolar Illness: Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. *Emergence of New Psychotic or Manic Symptoms:* Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3,482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to none in placebo-treated patients. *Aggression:* Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility. **5.3 Seizures** - There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued. **5.4 Long-Term Suppression of Growth** - Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted. **5.5 Visual Disturbance** - Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. **5.6 Contact Sensitization** - In an open-label study of 305 subjects conducted to characterize dermal reactions in children with ADHD treated with Daytrana using a 9-hour wear time, one subject (0.3%) was confirmed by patch testing to be sensitized to methylphenidate (allergic contact dermatitis). This subject experienced erythema and edema at Daytrana application sites with concurrent urticarial lesions on the abdomen and legs resulting in treatment discontinuation. This subject was not transitioned to methylphenidate. Use of Daytrana may lead to contact sensitization. Daytrana should be discontinued if contact sensitization is suspected. Erythema is commonly seen with use of Daytrana and is not by itself an indication of sensitization. However, contact sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site. Confirmation of a diagnosis of contact sensitization (allergic contact dermatitis) may require further diagnostic testing. Patients sensitized from use of Daytrana, as evidenced by development of an allergic contact dermatitis, may develop systemic sensitization or other systemic reactions if methylphenidate-containing products are taken via other routes, e.g., orally. Manifestations of systemic sensitization may include a flare-up of previous dermatitis or of prior positive patch-test sites, or generalized skin eruptions in previously unaffected skin. Other systemic reactions may include headache, fever, malaise, arthralgia, diarrhea, or vomiting. No cases of systemic sensitization have been observed in clinical trials of Daytrana. Patients who develop contact sensitization to Daytrana and require oral treatment with methylphenidate should be initiated on oral medication under close medical supervision. It is possible that some patients sensitized to methylphenidate by exposure to Daytrana may not be able to take methylphenidate in any form. **5.7 Patients Using External Heat** - Patients should be advised to avoid exposing the Daytrana application site to direct external heat sources, such as hair dryers, heating pads, electric blankets, heated water beds, etc., while wearing the patch. When heat is applied to Daytrana after patch application, both the rate and extent of absorption are significantly increased. The temperature-dependent increase in methylphenidate absorption can be greater than 2-fold. This increased absorption can be clinically significant and can result in overdose of methylphenidate [see Overdosage (10)]. **5.8 Hematologic Monitoring** - Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

6 ADVERSE REACTIONS
Detailed information on serious and adverse reactions of particular importance is provided in the Boxed Warning and Warnings and Precautions (5) sections: • Drug dependence [see Boxed Warning] • Hypersensitivity to Methylphenidate [see Contraindications (4.1)] • Marked anxiety, tension, or agitation [see Contraindications (4.2)] • Glaucoma [see Contraindications (4.3)] • Tics or a family history of Tourette's syndrome [see Contraindications (4.4)] • Monoamine Oxidase Inhibitors [see Contraindications (4.5) and Drug Interactions (7.1)] • Serious Cardiovascular Events [see Warnings and Precautions (5.1)] • Increase in Blood Pressure [see Warnings and Precautions (5.2)] • Psychiatric Adverse Events [see Warnings and Precautions (5.2)] • Seizures [see Warnings and Precautions (5.3)] • Long-Term Suppression of Growth [see Warnings and Precautions (5.4)] • Visual Disturbance [see Warnings and Precautions (5.5)] • Contact Sensitization [see Warnings and Precautions (5.6)] • External Heat [see Warnings and Precautions (5.7)] • Hematologic Monitoring [see Warnings and Precautions (5.8)] The most commonly reported (frequency ≥ 5% and twice the rate of placebo) adverse reactions in a controlled trial in children aged 6-12 included appetite decreased, insomnia, nausea, vomiting, weight decreased, tic, affect lability, and anorexia. The most commonly reported (frequency ≥ 5% and twice the rate of placebo) adverse reactions in a controlled trial in adolescents aged 13-17 were appetite decreased, nausea, insomnia, weight decreased, dizziness, abdominal pain and anorexia [see Adverse Reactions (6.1)]. The most common (≥ 2% of subjects) adverse reaction associated with discontinuations in double-blind clinical trials in children or adolescents was application site reactions15 [see Adverse Reactions (6.3)]. The overall Daytrana development program included exposure to Daytrana in a total of 2,152 participants in clinical trials, including 1,529 children aged 6-12, 223 adolescents aged 13-17, and 400 adults. The 1,752 child and adolescent subjects aged 6-17 years were evaluated in 10 controlled clinical studies, 7 open-label clinical studies, and 5 clinical pharmacology studies. In a combined studies pool of children using Daytrana with a wear time of 9 hours, 212 subjects were exposed for ≥ 6 months and 115 were exposed for ≥ 1 year; 85 adolescents have been exposed for ≥ 6 months. Most patients studied were exposed to Daytrana patch sizes of 12.5 cm2, 18.75 cm2, 25 cm2 or 37.5 cm2, with a wear time of 9 hours. In the data presented below, the adverse reactions reported during exposure were obtained primarily by general inquiry at each visit, and were recorded by the clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of events into a smaller number of standardized event categories. Throughout this section adverse reactions reported are events that were considered to be reasonably associated with the use of Daytrana based on comprehensive assessment of the available adverse event information. A causal association for Daytrana often cannot be reliably established in individual cases. Further, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

6.1 Clinical Trials Experience *Adverse Reactions Associated With Discontinuation of Treatment* In a 7-week double-blind, parallel-group, placebo-controlled study in children with ADHD conducted in the outpatient setting, 7.1% (7/98) of patients treated with Daytrana discontinued due to adverse events compared with 1.2% (1/85) receiving placebo. The most commonly reported (≥ 1% and twice the rate of placebo) adverse reactions leading to discontinuation in the Daytrana group were application site reaction (2%), tics (1%), headache (1%), and irritability (1%). In a 7-week double-blind, parallel-group, placebo-controlled study in adolescents with ADHD conducted in the outpatient setting, 5.5% (8/145) of patients treated with Daytrana discontinued due to adverse reactions compared with 2.8% (2/72) receiving placebo. The most commonly reported adverse reactions leading to discontinuation in the Daytrana group were application site reaction (2%) and decreased appetite/anorexia (1.4%). *Commonly Observed Adverse Reactions in Double-Blind, Placebo-Controlled Trials Skin Irritation and Application Site Reactions:* Daytrana is a dermal irritant. In addition to the most commonly reported adverse reactions presented in Table 2, the majority of subjects in those studies had minimal to definite skin erythema at the patch application site. This erythema generally caused no or minimal discomfort and did not usually interfere with therapy or result in discontinuation from treatment. Erythema is not by itself a manifestation of contact sensitization. However, contact sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site [see Warnings and Precautions (5.6)]. *Most Commonly Reported Adverse Reactions:* Table 2 lists treatment-emergent adverse reactions reported in ≥ 1% Daytrana-treated children or adolescents with ADHD in two 7 week double-blind, parallel-group, placebo-controlled studies conducted in the outpatient setting. Overall, in these studies, 75.5% of children and 78.6% of adolescents experienced at least 1 adverse event. *Adverse Reactions With the Long-Term Use of Daytrana:* In a long-term open-label study of up to 12 months duration in 326 children wearing Daytrana 9 hours daily, the most common (≥ 10%) adverse reactions were decreased appetite, headache, and weight decreased. A total of 30 subjects (9.2%) were withdrawn from the study due to adverse events and 22 additional subjects (6.7%) discontinued treatment as the result of an application site reaction. Other than application site reactions, affect lability (5 subjects, 1.5%) was the only additional adverse reaction leading to discontinuation reported with a frequency of greater than 1%. In a long-term open-label study of up to 6 months duration in 162 adolescents wearing Daytrana 9 hours daily, the most common (≥ 10%) adverse reactions were decreased appetite and headache. A total of 9 subjects (5.5%) were withdrawn from the study due to adverse events and 3 additional subjects (1.9%) discontinued treatment as the result of an application site reaction. Other adverse reactions leading to discontinuation that occurred with a frequency of greater than 1% included affect lability and irritability (2 subjects each, 1.2%).

Table 2 - Number (%) of Subjects with Commonly Reported Adverse Reactions (≥ 1% in the Daytrana Group) in 7-Week Placebo-controlled Studies in Either Children or Adolescents - Safety Population

	Adolescents		Children	
System Organ Class Preferred term	Placebo N = 72	Daytrana N = 145	Placebo N = 85	Daytrana N = 98
Cardiac Disorders				
Tachycardia	0 (0)	1 (0.7)	0 (0)	1 (1.0)
Gastrointestinal disorders				
Abdominal pain	0 (0)	7 (4.8)	5 (5.9)	7 (7.1)
Nausea	2 (2.8)	14 (9.7)	2 (2.4)	12 (12.2)
Vomiting	1 (1.4)	5 (3.4)	4 (4.7)	10 (10.2)
Investigations				
Weight decreased	1 (1.4)	8 (5.5)	0 (0)	9 (9.2)
Metabolism and nutrition disorders				
Anorexia	1 (1.4)	7 (4.8)	1 (1.2)	5 (5.1)
Decreased appetite	1 (1.4)	37 (25.5)	4 (4.7)	25 (25.5)
Nervous system disorders				
Dizziness	1 (1.4)	8 (5.5)	1 (1.2)	0 (0)
Headache	9 (12.5)	18 (12.4)	10 (11.8)	15 (15.3)
Psychiatric disorders				
Affect lability	1 (1.4)	0 (0)	0 (0)	6 (6.1)*
Insomnia	2 (2.8)	9 (6.2)	4 (4.7)	13 (13.3)
Irritability	5 (6.9)	16 (11)	4 (4.7)	7 (7.1)
Tic	0 (0)	0 (0)	0 (0)	7 (7.1)

* Six subjects had affect lability, all judged as mild and described as increased emotionally sensitive, emotionality, emotional instability, emotional lability, and intermittent emotional

6.2 Postmarketing Experience In addition, the following adverse reactions have been identified during the post-approval use of Daytrana. 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 Daytrana exposure. *Cardiac Disorders:* palpitation. *Eye Disorders:* visual disturbances, blurred vision, mydriasis, accommodation disorder. *General Disorders and Administration Site Disorders:* application site reactions such as bleeding, bruising, burn, burning, dermatitis, discharge, discoloration, discomfort, dryness, eczema, edema, erosion, erythema, excoriation, exfoliation, fissure, hyperpigmentation, hypopigmentation, induration, infection, inflammation, irritation, pain, papules, paresthesia, pruritus, rash, scab, swelling, ulcer, urticaria, vesicles, and warmth. *Immune System Disorders:* hypersensitivity reactions including generalized erythematous and urticarial rashes, allergic contact dermatitis, angioedema, and anaphylaxis. *Investigations:* blood pressure increased. *Nervous System Disorders:* convulsion, dyskinesia. *Psychiatric Disorders:* transient depressed mood, hallucination, nervousness. *Skin and Subcutaneous Tissue Disorders:* alopecia **6.3 Adverse Reactions With Oral Methylphenidate Products** Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur. Other reactions include: *Cardiac:* angina, arrhythmia, pulse increased or decreased. *Immune:* hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura. *Metabolism/Nutrition:* anorexia, weight loss during prolonged therapy. *Nervous System:* drowsiness, rare reports of Tourette's syndrome, toxic psychosis. *Vascular:* blood pressure increased or decreased, cerebral arteritis and/or occlusion. Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate: *Blood/lymphatic:* leukopenia and/or anemia. *Hepatobiliary:* abnormal liver function, ranging from transaminase elevation to hepatic coma. *Psychiatric:* transient depressed mood. *Skin/Subcutaneous:* scalp hair loss. *Neuroleptic Malignant Syndrome:* Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

7 DRUG INTERACTIONS
7.1 MAO Inhibitors - Daytrana should not be used in patients being treated (currently or within the preceding two weeks) with monoamine oxidase inhibitors [see Contraindications (4.5)]. **7.2 Vasopressor Agents** - Because of a possible effect on blood pressure, Daytrana should be used cautiously with pressor agents. **7.3 Hypotension Agents** - Methylphenidate may decrease the effectiveness of drugs used to treat hypertension. **7.4 Coumarin Anticoagulants, Antidepressants, and Selective Serotonin Reuptake Inhibitors** - Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some tricyclic drugs (e.g., imipramine, clomipramine, desipramine) and selective serotonin reuptake inhibitors. Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing methylphenidate.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy: *Pregnancy Category C* - Animal reproduction studies with transdermal methylphenidate have not been performed. In a study in which oral methylphenidate was given to pregnant rabbits during the period of organogenesis at doses up to 200 mg/kg/day no teratogenic effects were seen, although an increase in the incidence of a variation, dilation of the lateral ventricles, was seen at 200 mg/kg/day; this dose also produced maternal toxicity. A previously conducted study in rabbits showed teratogenic effects of methylphenidate at an oral dose of 200 mg/kg/day. In a study in which oral methylphenidate was given to pregnant rats during the period of organogenesis at doses up to 100 mg/kg/day, no teratogenic effects were seen although a slight delay in fetal skeletal ossification was seen at doses of 60 mg/kg/day and above; these doses caused some maternal toxicity. In a study in which oral methylphenidate was given to rats throughout pregnancy and lactation at doses up to 60 mg/kg/day, offspring weights and survival were decreased at 40 mg/kg/day and above; these doses caused some maternal toxicity. Adequate and well-controlled studies in pregnant women have not been conducted. Daytrana should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **8.2 Labor and Delivery** - The effect of Daytrana on labor and delivery in humans is unknown. **8.3 Nursing Mothers** - It is not known whether methylphenidate is excreted in human milk. Daytrana should be administered to a nursing woman only if the potential benefit justifies the potential risk to the child. **8.4 Pediatric Use** - Daytrana should not be used in children under six years of age, since safety and efficacy in this age group have not been established. Long-term effects of methylphenidate in children have not been well established. Studies with transdermal methylphenidate have not been performed in juvenile animals. In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose. The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day. The clinical significance of the long-term behavioral effects observed in rats is unknown. **8.5 Geriatric Use:** Daytrana has not been studied in patients greater than 65 years of age.

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance - Daytrana is classified as a Schedule II controlled substance by federal regulation. **9.2 Abuse** - See warning containing drug abuse information [see Boxed Warning]. **9.3 Dependence** - See warning containing drug dependence information [see Boxed Warning].

Manufactured for: Noven Therapeutics, LLC. Miami, FL 33186 By: Noven Pharmaceuticals, Inc., Miami, FL 33186.
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CONTENT

TERESA MCNULTY
Content Channel Director
440.891.2728 / tmcnulty@advanstar.com

CATHERINE M RADWAN
Content Managing Editor
440.891.2636 / cradwan@advanstar.com

MIRANDA HESTER
Content Specialist

BRANDON GLENN
Digital & Interactive Content Manager
440.891.2638 / bglenn@advanstar.com

KATHRYN FOXHALL
MARIAN FREEDMAN
Contributing Editors

ROBERT MCGARR
Group Art Director

NICOLE DAVIS-SLOCUM
Art Director

KAREN LENZEN
Senior Production Manager

PUBLISHING & SALES

GEORGIANN DECENZO
Executive Vice President
440.891.2778 / gdecenzo@advanstar.com

KEN SYLVIA
Vice President, Group Publisher
732.346.3017 / ksylvia@advanstar.com

SAMANTHA ARMSTRONG
Publisher
Office: 732.346.3083 / Mobile: 914.450.0609
sarmstrong@advanstar.com

DIANE CARPENTERI
National Account Manager
732.346.3092 / dcarpenteri@advanstar.com

JOAN MALEY
Account Manager, Classified/Display Advertising
440.891.2722 / jmaley@advanstar.com

JOANNA SHIPPOLI
Account Manager, Recruitment Advertising
440.891.2615 / jshippoli@advanstar.com

DON BERMAN
Business Director, eMedia
212.951.6745 / dberman@advanstar.com

GAIL KAYE
Director, Sales Data
732.346.3042 / gkaye@advanstar.com

HANNAH CURIS
Sales Support
732.346.3055 / hcuris@advanstar.com

RENEE SCHUSTER
List Account Executive
440.891.2613 / rschuster@advanstar.com

MAUREEN CANNON
Permissions
440.891.2742 / mcannon@advanstar.com

AUDIENCE DEVELOPMENT

JOY PUZZO
Corporate Director
440.319.9570 / jpuzzo@advanstar.com

CHRISTINE SHAPPELL
Director
201.391.2359 / cshappell@advanstar.com

WENDY BONG
Manager
218.740.7244 / wbong@advanstar.com

REPRINTS
877-652-5295 ext. 121 / bkolb@wrightsmedia.com
Outside US, UK, direct dial: 281-419-5725. Ext. 121

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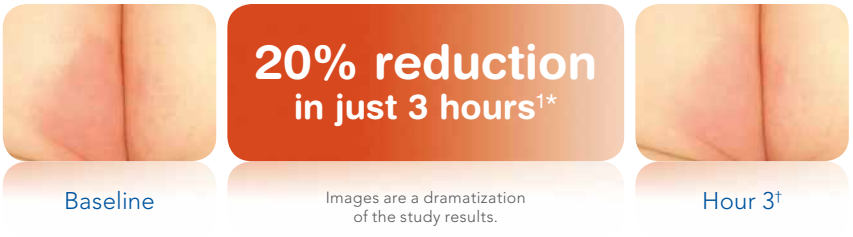
- Statistically significant reduction of erythema in just 1 diaper change[1]



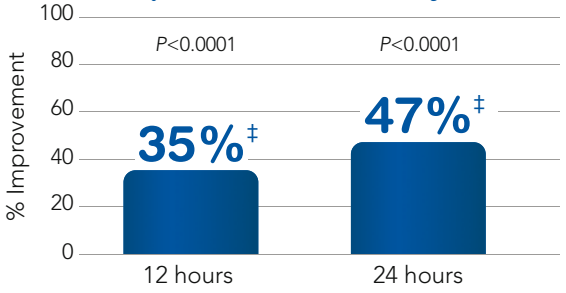
*Trial assessing the efficacy of DESITIN® Maximum Strength Original Paste for 3±1 hours in children (N=31) 3-36 months of age, with mild to moderate diaper rash, wearing diapers for 24 hours a day.[1]

†*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‡]

Significant Improvement in Diaper Rash Severity Score[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

Contains the maximum amount of zinc oxide[3] in a petrolatum and cod liver oil formula base

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—**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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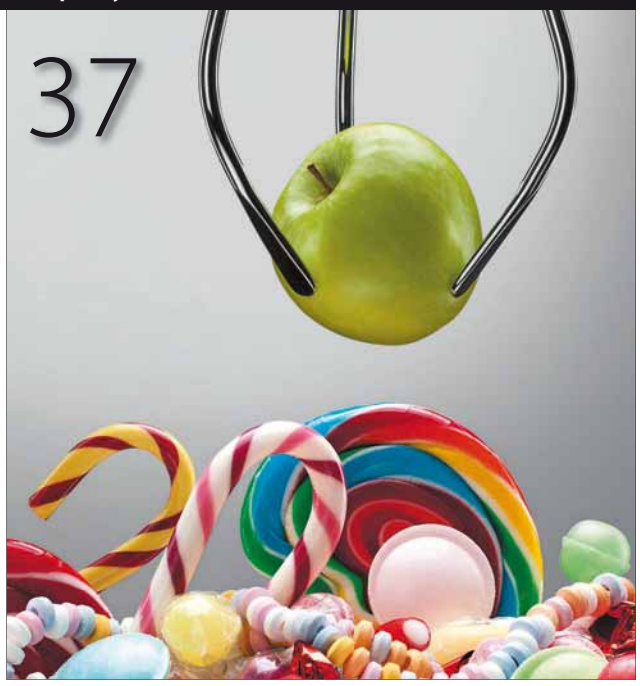

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WHEN ADHD MEDICATIONS PRESENT A NUTRITIONAL CHALLENGE, CONSIDER A NUTRITIOUS SOLUTION.

Stimulant ADHD medications can suppress a child's appetite, leading to weight loss and delayed growth.[1-4]

While you may be familiar with PediaSure® for patients with failure to thrive, it can also help with nutritional challenges for a variety of conditions, such as ADHD.

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*PediaSure SideKicks 35% less calories (150) vs PediaSure base (240 calories) and 40% less fat (5 g) vs PediaSure base (9 g) per 8 fl oz serving.

References: 1. Wigal T, Greenhill L, Chuang S, et al. Safety and tolerability of methylphenidate in preschool children with ADHD. *J Am Acad Child Adolesc Psychiatry.* 2006;45:1294-1303. **2.** Swanson J, Greenhill L, Wigal T, et al. Stimulant-related reductions of growth rates in the PATS. *J Am Acad Child Adolesc Psychiatry.* 2006;45:1304-1313. **3.** Faraone SV, Biederman J, Monuteaux M, Spencer T. Long-term effects of extended-release mixed amphetamine salts treatment of attention-deficit/hyperactivity disorder on growth. *J Child Adolesc Psychopharmacol.* 2005;15:191-202. **4.** Zachor DA, Roberts AW, Hodgens JB, Isaacs JS, Merrick J. Effects of long-term psychostimulant medication on growth of children with ADHD. *Res Dev Disabil.* 2006;27:162-174.

Abbott Nutrition

A NOTE FROM THE EDITORS

Approximately 70% of obese youth in the United States have at least 1 additional risk factor for cardiovascular disease, and about 40% have at least 2. Among families living below the federal poverty level, more than 44% of children are overweight or obese with particular impact felt in communities of color. Some researchers contend that if these trends persist, obesity could cause this generation's life expectancy to be lower than its parents'.

These statistics—alarming as they are—likely pale in comparison to the reality you encounter in your practice every day. We realize no easy answer exists when it comes to counseling your young patients and their families on weight management. Compounding the challenge is the average pediatrician's schedule. A 15-minute office visit scarcely leaves time to address rudimentary medical issues let alone a condition with such complex and far-reaching cultural and emotional tentacles.

However, against the stark backdrop of these numbers, in light of the American Medical Association's designation of obesity as a "disease," we endeavored to find pediatric peers and novel programs that have shown some promise in the treatment of overweight youngsters and their families.

As part of September's *Practical Pediatrics*, for National Childhood Obesity Awareness month, we present some targeted strategies and recommendations that are succeeding—particularly those that tap other community professionals trained in confronting this menace.

Are there techniques, resources, or programs you're finding successful in your patient care? Because this is a chronic issue, we would like to serve as a clearinghouse and forum for sharing ideas, success stories, and even anecdotal wins beyond just this issue. Please send your thoughts to tmcnulty@advanstar.com.

Alone, the scope of the problem may seem massive—both to you and to your patients. However, just as the problem itself is multifactorial, so may be its solution, and we all may have one piece to offer in solving it. CP

LETTERS

SEND YOUR LETTERS TO TMCNULTY@ADVANSTAR.COM

Help students with ADHD succeed in college

The article in the August *Contemporary Pediatrics* (Quinn PO. *Contemp Pediatr.* 2013:30[8]:14-20) concerning talking to youngsters about college was fine as a general article. It did not, however, go into specifics.

It has been my contention for years that people with ADHD . . . should NOT go to college right after high school. This is especially true for the boys, but also can pertain to the girls.

When my patients do insist on attending college, I get very specific with them as to how to increase their chances of success.

I tell them that exercising for minimally 30 minutes 3 times a week is essential for mental health and clear thinking. . . .

I also encourage them to sign up for morning classes. . . .

I give them an instruction sheet on how to study.

[I tell them that] eating a protein-filled breakfast every day is important for brain functioning.

I stress staying away from mind-altering illegal drugs and . . . continuing their medicine in a consistent manner.

Lastly, I tell them to not overload their schedules the first year. Four *B*'s are better than 5 *D*'s and *F*'s.

Whether they listen to me about any of this, I don't know. The ones that do are successful.

Joel P Sussman, MD, FAAP
Palmetto Associates for Scholastic Success
Columbia, South Carolina

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WRITTEN BY FRONTLINE PEDIATRICIANS EXPLORING NOVEL WAYS TO ADVOCATE FOR CHILDREN'S HEALTH IN THEIR COMMUNITIES.

A disruptive innovation

The way that we are currently practicing medicine for the urban poor is not working.

DAYNA LONG, MD

Obamacare is here. Although the staggered implementation schedule has many health care providers unsure of how best to serve the influx of new patients, community hospitals and primary care clinics that serve our urban poor need to be ready to implement a "disruptive innovation."

A disruptive innovation is a term usually applied to information technology. It emerges when a new idea completely and forever changes the way that we think about technology. Our medical system needs a disruptive innovation in order to systematically address our patients' lack of basic social needs (eg, unstable housing, food insecurity, lack of physical activity, and child care) within the framework of the doctor's office. If we tackle health inequities within the patient exam room by way of technology, then physicians can practice the art of medicine more effectively and efficiently. Thus, we will improve quality of care, decrease cost, and positively impact population health.

I instruct pediatricians in training at the Children's Hospital and Research Center Oakland Primary Care Clinic. Doctors in training recite patient stories and propose treatment plans. As their supervising physician, I listen and gauge their ability to make evidence-based recommendations.

Recently, I worked with a doctor in training who discussed with me a family of color—5 children and both parents—living in a 1-bedroom apartment. The walls in the kitchen and bathroom are covered in mold. The 3-year-old girl is not yet talking. The 4-year-old boy has asthma, coughs nightly, and has been to the emergency department (ED) 5 times this year. The 13-year-old brother is failing school. There is not enough food and the family is getting evicted. I could go on. This scenario occurs every day.

At our Federally Qualified Health Center (FQHC), 98% of our patients are on MediCal, which means they live under the federal poverty level. Our health care providers are dedicated and work tirelessly. Yet, as with most FQHCs, our clinics are overflowing and our EDs are oversaturated.

VIDEO

For more information about FIND and the challenges of practicing medicine among the urban poor, see our interview with Dayna Long, MD, at **ContemporaryPediatrics.com/urbanmedicine**

The poor, largely comprised of communities of color, suffer the heaviest burden of chronic disease. Prescribing treatments that target individual disease and not the health inequities that underlie illness will not cure our patients' ailments. We must demand that the system invoke real-world change, because the way that we are currently practicing medicine for the urban poor is simply not working.

A new program is being piloted in Oakland, California, that may provide one solution. The program is called the Family Information and Navigation Desk (FIND). When a family comes for a clinic visit, they

DR LONG is staff pediatrician at Children's Hospital and Research Center Oakland Primary Care Clinic, California. The clinic is designated a Federally Qualified Health Center under Section 330 of the Public Health Service Act.

will, via mobile electronic devices, be screened for their basic social needs. A positive survey will trigger the physician to refer the family to FIND. Health care professionals will be trained to understand why health inequities exist and how these inequities directly impact health.

A parent staff navigator, someone who is also a community resident, will have the technological tools to link families to community organizations and other institutions that can respond to their basic needs.

For instance, the local shelter can post open beds for homeless families. The food bank can post resources, such as a shipment of fresh produce. A family member can post that he or she received helpful instructions about accessing special education tools from the local school district. Community centers can post about local events and new projects. Regionally, community organizations jointly input and edit data. Grassroots community organizing can enter the medical home via the Web. FIND is family centered. FIND helps coordinates care.

Because of FIND, the parent navigator of the 3-year-old girl referenced in the case above was referred to a bilingual community behavioral development program. A home case manager was sent to the family's home to speak with the parents about asthma. The 13-year-old boy was given free passes to the local YMCA's Family Nights, as well as after-school tutoring programs. The parents were connected to our Medical Legal Partnership in order to mediate their eviction and the mold problem that triggered the 4-year-old boy's asthma in the first place. FIND allows me to be a better doctor.

Information technology can transform the way that we practice medicine by screening for health inequalities and galvanizing communities to work together in order to treat our patients' social determinates of health.

That's why FIND is a disruptive innovation and why I urge the technology industry to partner with safety net hospitals and clinics in order to help serve our most vulnerable citizens.

Together we can change the practice of medicine and, ultimately, the health of our nation. CP

States need more time to roll out Medicaid payment rate increases for primary care

KATHRYN FOXHALL

The 2-year bump up in rates for Medicaid primary care providers under the health care reform law has run into numerous problems. The Patient Protection and Affordable Care Act (ACA) was supposed to increase the rates for primary care physicians in 2013 and 2014 to Medicare levels. That could be significant in some cases. A 2012 survey found that for a representative sample of primary care services, the Medicaid payment averaged only 58% of that for Medicare. However, the difference varies greatly. In some cases, Medicaid rates are already higher than Medicare rates.

The increase, meant to ensure there are enough primary care providers accepting Medicaid patients as the reform law rolls out, raises payments for some evaluation and management services and some vaccine administration services.

Actually making that happen has turned out to be so complicated that the funds, which were supposed to cover 2013 and 2014, were still not flowing in most instances at midyear. As of the end of July, nearly all state plans had been approved by the Centers for Medicare and Medicaid Services (CMS), but very few states had actually rolled out the program, according to Matt Salo, executive director of the National Association of Medicaid Directors (NAMD).

A big exception to the CMS approval of plans was California. A CMS spokesperson said the details of that state's plan were still being negotiated with CMS.

Salo said it's expected that states will have the program in place by September. Both CMS and Salo say the payments will be retroactive to January of this year.

Many of the problems with the rollout were related to the fact that most primary care provided under Medicaid is now under some type of managed care, and it was not readily apparent how to match those payments to Medicare payments, Salo said.

Even bigger questions are being raised about whether the 2-year increase will actually expand access to care under Medicaid and whether the program will be extended at the end of next year. Congress limited the increase to 2 years under the health care reform bill to hold down the legislation's costs, Salo said, but that action held out the question of whether a future Congress would extend the increase.

At 17 months out, it's not known whether either Congress or the states will extend the higher rates. Currently the federal government pays the full cost.

The Medicaid and CHIP (Child Health Insurance Program) Payment and Access Commission (MACPAC), which advises Congress on the programs, has noted that several states say that they are unlikely to continue the increase and they fear the drop back in 2015 may actually hurt efforts to recruit physicians to Medicaid.

The commission says that more information should be available when the program gets into day-to-day operation. However, after interviews with Medicaid officials in 6 states (Alabama, California, Indiana, Massachusetts, Oregon, and Rhode Island) and the District of Columbia, MACPAC points out that claims data that might indicate if the higher rates have succeeded in expanding access may not be ready until well after the end of next year.

MACPAC also says, "Some states interviewed indicated that the effect of the provision on access to care may be limited because the statute excludes independently practicing nonphysician practitioners. Some states rely on these providers, particularly in underserved and rural areas."

The commission says it will continue to monitor the implementation of the provision. In the meantime, eligible physicians should get the required "attestation" done to ensure they get the increase, Salo said.

The MACPAC explanation of the program, in addition to other issues, is detailed in its June report to Congress at www.macpac.gov/reports. CP

What does Auvi-Q offer my patients at risk for anaphylaxis?

I talk.

Auvi-Q is available for adults and children weighing greater than 33 lb. Features include:

- **Audio and Visual Cues** guide users step by step through the injection process
- **Press-and-Hold** injection mechanism with 5-second hold time
- **Retractable Needle** designed to help prevent accidental needle sticks
- **Unique Compact Size and Shape**

Indication
Auvi-Q™ (epinephrine injection, USP) is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to allergens, idiopathic and exercise-induced anaphylaxis. Auvi-Q is intended for individuals with a history of anaphylaxis or who are at risk for anaphylactic reactions.

Important Safety Information
Auvi-Q should **ONLY** be injected into the anterolateral aspect of the thigh. DO NOT INJECT INTO BUTTOCK OR INTRAVENOUSLY.

Epinephrine should be administered with caution to patients with certain heart diseases, and in patients who are on medications that may sensitize the heart to arrhythmias, because it may precipitate or aggravate angina pectoris and produce ventricular arrhythmias. Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease or taking cardiac glycosides or diuretics. Patients with certain medical conditions or who take certain medications for allergies, depression, thyroid disorders, diabetes, and hypertension, may be at greater risk for adverse reactions. Adverse reactions to epinephrine include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties.

Auvi-Q is intended for immediate self-administration as emergency supportive therapy only and is not a substitute for immediate medical or hospital care.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see brief summary of Prescribing Information on the next page.

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0.15 mg/0.3 mg auto-injectors
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Auvi-Q™ **Rx Only**
(epinephrine injection, USP) 0.3 mg, 0.15 mg Auto-Injector

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

Auvi-Q™ is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.

Auvi-Q™ is intended for immediate administration in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions.

Anaphylactic reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema.

Auvi-Q™ is intended for immediate self-administration as emergency supportive therapy only and is not a substitute for immediate medical care.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 EMERGENCY TREATMENT

Auvi-Q™ is not intended as a substitute for immediate medical care. **In conjunction with the administration of epinephrine, the patient should seek immediate medical or hospital care.** More than two sequential doses of epinephrine should only be administered under direct medical supervision [*see INDICATIONS AND USAGE (1), DOSAGE AND ADMINISTRATION (2) and PATIENT COUNSELING INFORMATION (17.1 in the full prescribing information)*].

5.2 INCORRECT LOCATIONS OF INJECTION

Auvi-Q™ should **ONLY** be injected into the anterolateral aspect of the thigh [*see DOSAGE AND ADMINISTRATION (2) and PATIENT COUNSELING INFORMATION (17.1 in the full prescribing information)*].

- **Do not inject intravenously.** Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine if there is such inadvertent administration.
- **Do not inject into buttock.** Injection into the buttock may not provide effective treatment of anaphylaxis. Advise the patient to go immediately to the nearest emergency room for further treatment of anaphylaxis.
- **Do not inject into digits, hands or feet.** Since epinephrine is a strong vasoconstrictor, accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area. Advise the patient to go immediately to the nearest emergency room and to inform the healthcare provider in the emergency room of the location of the accidental injection. Treatment of such inadvertent administration should consist of vasodilation, in addition to further appropriate treatment of anaphylaxis [*see ADVERSE REACTIONS (6)*].

5.3 ALLERGIC REACTIONS ASSOCIATED WITH SULFITE

Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations even though this product contains sodium bisulfite, a sulfite that may, in other products, cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons.

The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations even if the patient is sulfite-sensitive.

The alternatives to using epinephrine in a life-threatening situation may not be satisfactory.

5.4 DISEASE INTERACTIONS

Some patients may be at greater risk for developing adverse reactions after epinephrine administration. Despite these concerns, it should be recognized that the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation. Therefore, patients with these conditions, and/or any other person who might be in a position to administer Auvi-Q™ to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which epinephrine should be used.

- Patients with Heart Disease
  Epinephrine should be administered with caution to patients who have heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias [*see DRUG INTERACTIONS (7) and ADVERSE REACTIONS (6)*].
- Other Patients and Diseases
  Epinephrine should be administered with caution to patients with hyperthyroidism, diabetes, elderly individuals, and pregnant women. Patients with Parkinson's disease may notice a temporary worsening of symptoms.

6 ADVERSE REACTIONS

Adverse reactions to epinephrine include anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with hypertension or hyperthyroidism [*see WARNINGS AND PRECAUTIONS (5.4)*].

Arrhythmias, including fatal ventricular fibrillation, have been reported, particularly in patients with underlying cardiac disease or those receiving certain drugs [*see WARNINGS AND PRECAUTIONS (5.4) and DRUG INTERACTIONS (7)*].

Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease [*see WARNINGS AND PRECAUTIONS (5.4)*].

Angina may occur in patients with coronary artery disease [*see WARNINGS AND PRECAUTIONS (5.4)*].

Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area [*see WARNINGS AND PRECAUTIONS (5.2)*].

Adverse events experienced as a result of accidental injections may include increased heart rate, local reactions including injection site pallor, coldness and hypoesthesia or injury at the injection site resulting in bruising, bleeding, discoloration, erythema or skeletal injury.

7 DRUG INTERACTIONS

Patients who receive epinephrine while concomitantly taking cardiac glycosides, diuretics, or anti-arrhythmics should be observed carefully for the development of cardiac arrhythmias [*see WARNINGS AND PRECAUTIONS (5.4)*].

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

The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta-adrenergic blocking drugs, such as propranolol.

The vasoconstricting and hypertensive effects of epinephrine are antagonized by alpha-adrenergic blocking drugs, such as phentolamine.

Ergot alkaloids may also reverse the pressor effects of epinephrine.

8 USE IN SPECIFIC POPULATIONS

8.1 PREGNANCY

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well controlled studies of the acute effect of epinephrine in pregnant women.

Epinephrine was teratogenic in rabbits, mice and hamsters. Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (fetal anoxia, spontaneous abortion, or both).

Epinephrine has been shown to have teratogenic effects when administered subcutaneously in rabbits at approximately 30 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal dose of 1.2 mg/kg/day for two to three days), in mice at approximately 7 times the maximum daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal subcutaneous dose of 1 mg/kg/day for 10 days), and in hamsters at approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal subcutaneous dose of 0.5 mg/kg/day for 4 days).

These effects were not seen in mice at approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a subcutaneous maternal dose of 0.5 mg/kg/day for 10 days).

8.3 NURSING MOTHERS

It is not known whether epinephrine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Auvi-Q™ is administered to a nursing woman.

8.4 PEDIATRIC USE

Auvi-Q™ may be given safely to pediatric patients at a dosage appropriate to body weight [*see DOSAGE AND ADMINISTRATION (2)*]. However, studies in pediatric patients weighing less than 15 kg (33 pounds) have not been conducted.

8.5 GERIATRIC USE

Clinical studies of Auvi-Q™ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Epinephrine should be administered with caution in elderly individuals, who may be at greater risk for developing adverse reactions after epinephrine administration [*see WARNINGS AND PRECAUTIONS (5.4), OVERDOSAGE (10)*].

10 OVERDOSAGE

Overdosage of epinephrine may produce extremely elevated arterial pressure, which may result in cerebrovascular hemorrhage, particularly in elderly patients. Overdosage may also result in pulmonary edema because of peripheral vascular constriction together with cardiac stimulation. Treatment consists of rapidly acting vasodilators or alpha-adrenergic blocking drugs and/or respiratory support.

Epinephrine overdosage can also cause transient bradycardia followed by tachycardia, and these may be accompanied by potentially fatal cardiac arrhythmias. Premature ventricular contractions may appear within one minute after injection and may be followed by multifocal ventricular tachycardia (prefibrillation rhythm). Subsidence of the ventricular effects may be followed by atrial tachycardia and occasionally by atrioventricular block. Treatment of arrhythmias consists of administration of a beta-adrenergic blocking drug such as propranolol.

Overdosage sometimes results in extreme pallor and coldness of the skin, metabolic acidosis, and kidney failure. Suitable corrective measures must be taken in such situations.

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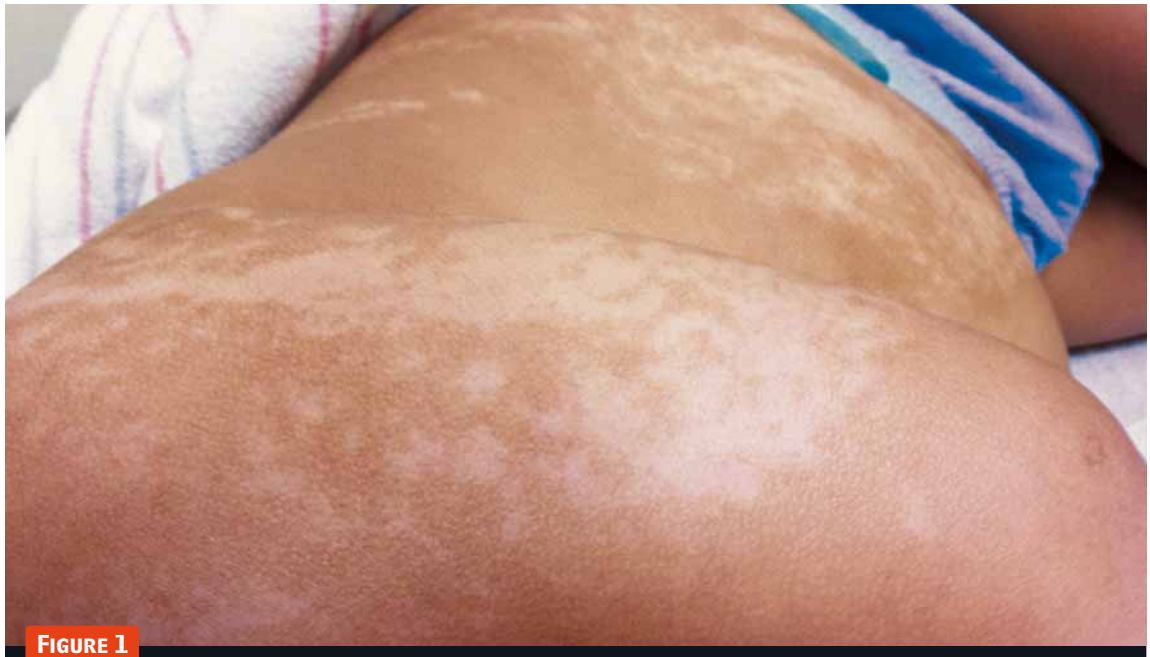

FIGURE 1
Hypopigmentation with whorl formation of the trunk

Patches of pale pigmentation in a 2-month-old boy

YOOMIE LEE, BA, MS4, AND HANAN TANUOS, MD

THE CASE

In the middle of a busy day at the pediatric clinic, you see that your next patient is a 2-month-old, full-term boy who is here for a routine checkup. You step into the examination room and see an infant in a diaper resting in his mother's arms. Immediately, you notice pale spots scattered over his body. The mother reports that the spots were present at birth but have become more distinct over the last 4 to 6 weeks.

CONTINUED ON **PAGE 49**

IMAGE CREDIT / AUTHOR SUPPLIED

MS LEE is a fourth-year medical student at Rutgers New Jersey Medical School, Newark. **DR TANUOS** is assistant professor of pediatrics, Rutgers New Jersey Medical School, Newark. The authors have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

PEDIATRIC NONALCOHOLIC FATTY LIVER DISEASE

MARY BETH NIERENGARTEN, MA; REVIEWED BY GARY L FREED, MD, MPH

The growing obesity epidemic is believed to be a main driver of the rising prevalence of nonalcoholic fatty liver disease (NAFLD) in children and adolescents. This review article provides an overview of pediatric NAFLD's unique pathophysiology and tools for diagnosis and treatment.

Nonalcoholic fatty liver disease (NAFLD) in children is increasing, with studies showing it to be the most common liver abnormality in children aged 2 to 19 years.[1] Prevalence of the disease in children and adolescents is difficult to determine given that a definitive diagnosis requires a liver biopsy and the lack of screening guidelines for pediatric NAFLD. However, a landmark study that examined the incidence of disease in 742 autopsy specimens of children who had died of an accident found that 17.3% of the children aged 15 to 19 years had the disease.[2,3] This same study showed that NAFLD was more common in boys than girls and in children of Asian descent (10.2%) and Hispanic (mostly Mexican) descent (11.8%), with the lowest rate in African Americans (1.5%), findings that have been confirmed in other studies.

The growing obesity epidemic is believed to be a main driver in the increase of pediatric NAFLD, with studies indicating that about half of obese children may have fatty liver.[1] Additional data show that overweight and obese adolescents have 4.14 and 5.98 times, respectively, the risk of NAFLD compared with adolescents of normal weight.

The need for improved diagnosis and treatment of NAFLD in children is highlighted by the multiple complications these children are at high risk of developing, including atherosclerosis and other cardiovascular complications and increased carotid intima media thickness.[4] Although prospective data are scarce on the long-term consequences of NAFLD in children, a retrospective study of 66 children with NAFLD followed for 20 years showed that 4 developed type 2 diabetes, 2 underwent liver transplantation, and 2 died of cirrhosis.

Primary care physicians and other health care professionals on the front lines of care can play an important role in identifying children and adolescents with or at risk for developing NAFLD. This review article offers a brief primer on what is currently known about

MS NIERENGARTEN, a medical writer in St. Paul, Minnesota, has over 25 years of medical writing experience, coauthoring articles for *Lancet Oncology, Lancet Neurology, Lancet Infectious Diseases*, and Medscape. **DR FREED** is an editorial board member for *Contemporary Pediatrics*. The author and the reviewer have nothing to disclose in regard to affiliations with or financial interests in any organization that may have an interest in any part of this article.

pediatric NAFLD, and provides information on the current understanding of its unique pathophysiology compared with adult NAFLD and current diagnostic and treatment approaches.

Natural history

Nonalcoholic fatty liver disease is defined as the presence of macrovesicular steatosis in greater than 5% of hepatocytes in the absence of significant consumption of alcohol, drugs, or other recognized disorders that may result in fatty liver.[2] It includes diseases that range in severity from simple steatosis to nonalcoholic stateohepatitis (NASH). Compared with NASH, simple steatosis has a benign prognosis and is characterized by the accumulation of liver fat without apparent inflammation. In contrast, NASH involves inflammation of the liver and hepatocellular damage that can progress to cirrhosis.[2,4]

Two types of NASH have been described, 1 associated with adults and the other with pediatrics.[4] Type 1 (adult) NASH is characterized by steatosis, hepatocyte ballooning, Mallory hyaline, and pericellular/sinusoidal fibrosis, most with distinct centrilobular distribution. Type 2 (pediatric) NASH is characterized by portal-based fibrosis sometimes associated with portal inflammation and without centrilobular distribution, and more strongly linked to Hispanic and Asian backgrounds and male sex. Studies have shown that 32% to 83% of children have features of both types.[4-6]

Pathogenesis

Although the pathogenesis of fatty liver in children and adolescents is not fully understood, overnutrition and a sedentary lifestyle are believed to be key contributors. Increasing attention has been given to the type of diet contributing to overnutrition and the epidemic of obesity among children, with data showing an increased intake of fructose, primarily from soft drinks, as a strong contributor.[2] Data indicate that between 1977 and 2001 the consumption of soft drinks in children and adolescents aged 2 to 19 years increased from 3.0% to 6.9%.[2] Although the effect of fructose consumption in children on NAFLD has yet to be established, studies in adults have shown that consumption of soft drinks is a risk factor for the development of NAFLD.

In particular, visceral adiposity is associated with pediatric NAFLD; data show that for every 5-cm increase in waist circumference in obese children or adolescents there is an odds ratio of 1.4 for predicting ultrasound-detected liver steatosis.[7] The central role of overnutrition and obesity, and in particular visceral adiposity, in the development of NAFLD is associated with a cascade of mechanisms associated with disease development, including insulin resistance, metabolic syndrome, change in lipogenesis, and obstructive sleep apnea.[1] Other processes suggested in the pathogenesis of disease involve mitochondrial dysfunction, which is seen as playing a key role in NASH independent of insulin resistance and its consequences, as well as the possibility of a genetic predisposition. Increasing evidence is also pointing to an association between cytokines and adipokines and the mechanism involved with liver damage and repair in fatty liver. Plasma cytokeratin-18 (CK-18), which is a marker of increased hepatocyte apoptosis, has become particularly interesting as a cytokine that may be useful as a biomarker for NASH in children.[8]

VIDEO

For more on pediatric NAFLD, see our interview with Naim Alkhouri, MD, Cleveland Clinic Children's Hospital and Digestive Disease Institute, at **ContemporaryPediatrics.com/NAFLD**

A "2-hit" model or theory has been proposed to describe the pathogenesis of NAFLD based on the recognition that steatosis can be a reversible process and that whether a patient progresses to irreversible liver damage and fibrosis is determined by whether or not they develop steatohepatitis.[9,10] In this model, the first hit in the development of NAFLD is an excessive hepatocyte triglyceride accumulation resulting from insulin resistance and the second hit involves an inflammatory injury to the liver possibly by oxidative stress, associated lipid peroxidation, and cytokines (primarily tumor necrosis factor-alpha or endotoxin).[10-12]

Diagnosis

Children with NAFLD are often asymptomatic or present with mild symptoms such as fatigue, malaise, and vague abdominal pain.[1,7] On physical presentation, some children with NAFLD may present with

TABLE Types of noninvasive biomarkers for nonalcoholic fatty liver disease

Biomarkers of hepatic inflammation	• TNF-alpha • Adiponectin • C-reactive protein • Visfatin • Resistin • Interleukin-6 • Retinol binding protein 4
Biomakers of oxidative stress	• Cytochrome P-450 • Myeloperoxidase • Nitric oxide synthase • Lipid peroxidation products (oxidized LDL, thiobarbituric acid-reactive substances)
Biomarkers of apoptosis	• Cytokeratin-18

Abbreviations: LDL, low-density lipoprotein; TNF, tumor necrosis factor.
From Widhalm K, et al.[1]

mild-to-moderate hepatomegaly with right upper-quadrant tenderness. Most children with NAFLD will present as overweight or obese, particularly with visceral adiposity, making liver palpation challenging.[4] In addition to obesity and being overweight, many children will present with acanthosis nigricans that suggests the presence of insulin resistance. Studies show that up to half of all children with NASH present with acanthosis nigricans.[1]

Currently there are no screening guidelines to help health care providers diagnose NAFLD in children. Liver biopsy remains the gold standard for making the definitive diagnosis of NASH, but it is not well suited for screening or monitoring children because of its invasive nature, cost, and complications.[4] As such, primary care physicians and other health care providers need alternative tools to help make the differential diagnosis in children, including biochemical tests and imaging studies. A number of noninvasive biomarkers of disease are also being studied for their predictive potential. Following is a brief description of these diagnostic tools.

Biochemical tests. Several biochemical tests have been evaluated to help provide information on the potential presence and severity of NAFLD in children, including liver function tests and insulin resistance tests.[1,4,7] The most common finding on laboratory studies is a mild-to-moderate elevation of serum alanine aminotransferase (ALT).[4] The use of ALT is not considered a good diagnostic marker for NAFLD, however, given its low sensitivity.[7,13] Similarly, mildly elevated levels of alkaline phosphates or gamma glutamyl transpeptidase (GGT) have been associated with NAFLD, but these do not indicate the severity of steatosis or hepatic fibrosis.[13]

Insulin resistance tests may provide information to identify children and adolescents with NAFLD, with some data suggesting that hyperinsulinemia may represent the first pathogenic hit of NAFLD.[7] As a single predictor of NAFLD, however, hyperinsulinemia is insufficient given its low specificity. Hypertriglyceridemia, atherogenic lipid profile, and uric acid all have been reported as potential biochemical markers of disease. More studies are needed to identify the best criteria for insulin resistance among the tests available and to determine the exact cutoff measures needed for standard reference.[1]

Imaging. The primary imaging tools used to diagnose NAFLD in children and adolescents are ultrasound and magnetic resonance imaging (MRI).[4] Ultrasound is used in clinical practice as well as in research studies, and shows echogenicity and frequently enlargement of the liver. Studies suggest that visceral fat measured by ultrasound may provide a way to predict the risk for NAFLD in obese adolescents, with some data showing ultrasound-detected liver involvement as frequently as 42% among prepubertal children.[1]

Magnetic resonance imaging is used primarily in research studies because of its expense and has been shown in some studies to accurately quantify fat content in the liver.[4] Computed tomography is not recommended because of the need to avoid radiation exposure in children. Although routine testing with ultrasound and MRI can detect advanced disease by signs of portal hypertension, these imaging tools are limited by the lack of sensitivity to detecting fibrosis. Other more novel imaging tools have shown accuracy in detecting liver fibrosis but are currently limited by cost (magnetic resonance spectroscopy), inability to be used in obese patients or those with ascites (transient elastography), and too little clinical data

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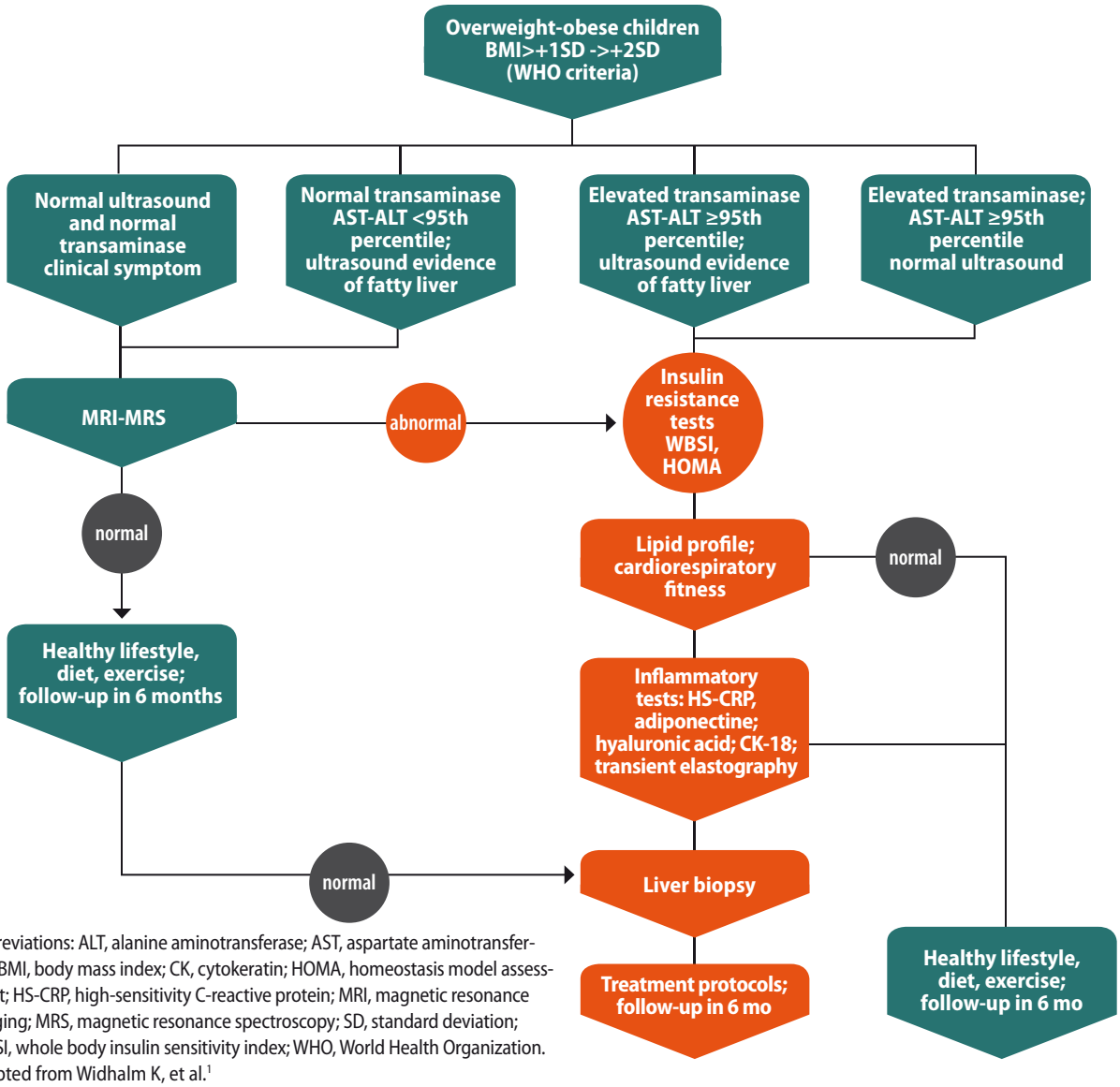
FIGURE Algorithm for diagnosis of nonalcoholic fatty liver disease



Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CK, cytokeratin; HOMA, homeostasis model assessment; HS-CRP, high-sensitivity C-reactive protein; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; SD, standard deviation; WBISI, whole body insulin sensitivity index; WHO, World Health Organization. Adapted from Widhalm K, et al.[1]

(magnetic resonance elastography).[1,4]

Noninvasive biomarkers. Three groups of noninvasive biomarkers can be used to indicate NAFLD (Table).[1] Data suggest that these biomarkers can identify NAFLD and its likely progression. Among these biomarkers, CK-18 is regarded as the most promising biomarker of NASH.[13] Data from a recent study of 201 children with biopsy-proven NAFLD showed that serum CK-18 levels were significantly higher in 140 children who had NASH compared with the other children with hepatic steatosis.[8] The study highlighted the excellent predictive value of CK-18 for diagnosing NASH and established several cutoff values to maximize sensitivity and specificity for the prediction of NASH on biopsy. Currently these biomarkers are used to diagnose NAFLD for research purposes, but it is hoped that their future role will include staging and monitoring of disease.[4]

The Figure provides an algorithm that may be useful as a guide for diagnosing NAFLD in children.[1] The algorithm recommends routine biochemical testing (liver transaminases) as well as imaging (liver

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ultrasound) in all children who are overweight or obese as defined by World Health Organization (WHO) criteria. If any of these tests suggest fatty liver, further testing is done to check the presence of insulin resistance. If insulin resistance is found, further testing for inflammatory markers is undertaken to determine the presence of fibrosis. In patients with a high suspicion of NASH, a liver biopsy is recommended.

Treatments

The first line of treatment and prevention of NAFLD focuses on lifestyle interventions.[1,2] Studies show that even very modest changes in diet and physical activity that may or may not lead to weight reduction can improve liver function tests, cytokines, and histology of NASH.[1] One study found significant improvements in markers of insulin resistance, aminotransferases, and hepatic lipid content in 68% of 84 pediatric patients with biopsy-proven NAFLD followed for 1 year in a lifestyle-intervention study.[2] Another study suggests that improvements can occur within weeks of changes to diet and physical activity.

Although there seems to be a clear benefit from modifications to diet and physical activity on obesity and associated disease mechanisms of NAFLD, getting children and adolescents to undergo and maintain these lifestyle changes remains challenging, and there are currently no standards for lifestyle changes that offer the most benefit.[1,2] Some experts recommend that children and adolescents be encouraged to follow a low-fat, low-glycemic-index diet that includes eating a minimum of 5 servings of vegetables and fruits daily, engaging in physical activity for at least 1 hour daily, and minimizing television/computer time to 2 hours daily.[2]

Other treatment approaches given the difficulty of compliance with lifestyle changes include medical therapies for NAFLD that target the metabolic syndrome (thiazolidinediones, metformin) or the hepatoprotective response (statins, vitamin E).[1,2] Two randomized clinical trials support the use of vitamin E in addition to lifestyle interventions for the treatment of NASH.[4] In the PIVENS (Pioglitazone or Vitamin E for NASH Study) 96-week study that compared pioglitazone or vitamin E with placebo in 247 adult patients with biopsy-proven NASH, significant improvements in steatosis and lobular infiltration (but not in fibrosis scores) were found in the patients in the vitamin E group compared with the placebo group. The TONIC (Treatment of NAFLD in Children) trial of 173 children with biopsy-proven NAFLD that compared vitamin E with metformin or placebo for 2 years found that neither high-dose vitamin E nor metformin significantly improved ALT versus placebo. Significant improvement in histologic findings, however, was found in the children taking vitamin E. In a subset of children with established NASH at initial biopsy, 58% receiving vitamin E showed significant histologic resolution after 96 weeks of treatment with no adverse effects noted.

Conclusion

With the increase in pediatric NAFLD, primary care physicians and other health care providers can play an important role in recognizing the signs and symptoms of early disease and intervene before the disease progresses. CP

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[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.

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

Revaccination

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

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine or the diluent.

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

PRECAUTIONS

General

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

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

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

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

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

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

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

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

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

Instructions to Healthcare Provider

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

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

Information for Patients

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

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

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

Laboratory Test Interactions

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Pregnancy

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

Pediatric Use

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

Geriatric Use

This vaccine is NOT recommended for use in adult populations.

ADVERSE REACTIONS

Liquid PedvaxHIB

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

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

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

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

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

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

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

Lyophilized PedvaxHIB

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

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

Potential Adverse Reactions

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

Post-Marketing Adverse Reactions

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

Hemic and Lymphatic System

Lymphadenopathy

Hypersensitivity

Rarely, angioedema

Nervous System

Febrile seizures

Skin

Sterile injection site abscess

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

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Pediatric practices can successfully deliver parental smoking interventions

Pediatric practices can implement a tobacco dependence intervention for parents who smoke as part of routine child health outpatient care, a new study shows. In collaboration with the Pediatric Research in Outpatient Settings (PROS) research network of the American Academy of Pediatrics, investigators recruited 22 pediatric practices in 16 states that included about 2,000 parents who smoke to participate in the randomized, controlled trial, providing half the practices with the intervention. At the conclusion of the study, investigators surveyed participants to compare levels of delivering tobacco control assistance between the practices that received the intervention and those that did not.

Investigators provided the intervention practices with training and materials to enable them to provide evidence-based assistance to parents who smoke. Training was delivered in group and individual sessions and via brief clinical counseling videos that covered likely scenarios that clinicians would encounter. Also provided was an overview of strategies for integrating tobacco cessation screening, assistance, and referrals into visits with parents. Investigators then encouraged intervention practices to supply motivational messages based on parents' own concerns as well as to exploit potential teachable moments, for example, when cued by a child's illness; to refer to quitlines; and to recommend pharmacologic treatment of tobacco dependence. Dosing information for nicotine replacement therapy and state-specific quitline referral information were also provided to the intervention practice physicians and staff.

Compared with control practices, intervention practices had a 12-fold higher rate of delivering tobacco control assistance to parents; 42.5% of intervention group participants reported discussion of methods and strategies to quit smoking, being enrolled in a quitline, or being prescribed nicotine replacement medication, compared with only 3.5% of control practice participants (Winickoff JP, et al. *Pediatrics*. 2013;132[1]:109-117).

COMMENTARY

Previous studies have shown that each component of the smoking cessation intervention is effective. Rather than restudying the interventions, this study aimed at measuring the effectiveness of a program to change the practice behaviors of physicians and their staffs, and it worked. After education and removal of barriers, the intervention practices were much more likely to actively take on the problem of parental smoking. The result may improve not only the parents' physical and financial health but also the litany of conditions worsened by passive smoke exposure in children.

—Michael Burke, MD

YOUNG MEN ARE INCREASINGLY ABUSING 2 NEW DESIGNER DRUGS

Bath salts (a synthetic form of cathinone) and synthetic marijuana (synthetic tetrahydrocannabinol, or THC) are popular new designer drugs of abuse, and exposures have been reported throughout the United States. Analysis of such exposures reported to national poison control centers from January 2011 to April 2012 showed that abuse of these drugs increased from 2009 to 2011.

Specifically, synthetic THC exposures, first reported in 2009, increased until July 2011 and have remained elevated since. THC exposures are reported more often than bath salts exposures, with totals in the first 4 months of 2012 exceeding those in the same period of 2011. Bath salts use, first reported in 2010,

DR BURKE, section editor for Journal Club, is chairman of the Department of Pediatrics at Saint Agnes Hospital, Baltimore, Maryland. He is a contributing editor for *Contemporary Pediatrics*. He has nothing to disclose in regard to affiliations with or financial interests in any organization that may have an interest in any part of this article.

steadily increased to a peak in June 2011, after which it declined until November 2011. Total bath salts exposures for the first 4 months of 2012 are lower than those for the same period in 2011.

Use of both drugs, which are generally inhaled, is most common in the Midwest and Southeast. Males are the main abusers, representing 69% of bath salts users and 74% of synthetic THC users. Bath salts exposure is most common in men aged from 20 to 29 years, while exposure to synthetic THC is highest for men aged 13 to 19 years. Intentional abuse is the most common reason for use of these drugs, although suicide attempts account for a small number of exposures (Wood KE. *J Pediatr.* 2013;163[1]:213-216).

COMMENTARY

Even if you haven't yet seen these drugs, they may soon be coming to a neighborhood near you. This research reports on about 19,000 calls to poison centers about these substances and this is likely the tip of the iceberg. Many emergency department physicians and hospitalists are now all too familiar with these drugs and their effects. Bath salts, sometimes called "plant food," may cause panic attacks, hallucinations, paranoia, self-mutilation, hyperthermia, tachycardia, and hypertension. Severe cardiac, central nervous system, and musculoskeletal complications have been described. Synthetic THC, sold as K2 or spice, may cause a broad array of psychiatric symptoms, tachycardia, hypertension, and seizures. Know what's out there.

—Michael Burke, MD

HOMICIDE RATES DECLINED AMONG YOUNG PEOPLE FROM 2000 TO 2010

To examine trends in homicides among those aged 10 to 24 years, the Centers for Disease Control and Prevention analyzed National Vital Statistics System data on such deaths for the period 1981 to 2010 and described trends by sex, age, race/ethnicity, and mechanism of injury. Here are the major findings:

- Homicide rates varied substantially during the study period, with a sharp rise from 1985 to 1993, followed by a decline that has slowed since 1999.
- Throughout the 30-year study period, homicide rates for individuals aged 20 to 24 years remained the highest and rates for those aged 10 to 14 years were the lowest.
- In 2010, among the entire age range (10 to 24 years), the homicide rate was 7.5 per 100,000, the lowest rate in the 30-year study period.
- Nearly 80% of all homicides in the overall study period were attributable to firearms, with the rate of firearm homicide on average 3.7 times that of nonfirearm homicide.
- The highest rates of homicide over the entire study period were among males, those aged 20 to 24 years, and blacks (David-Ferdon C, et al. *MMWR Morb Mortal Wkly Rep.* 2013;62[27]:545-548).

COMMENTARY

It is good to be reminded that, even with recent decreasing rates in those aged 10 to 24 years, homicide is consistently a leading cause of death in adolescents and young adults. As advocates of children, we need to continue thinking of ways to change these statistics through our actions in the office, the community, and the statehouse.

—Michael Burke, MD

Also of Note

Do sick-visit immunizations dampen parental incentive to return for missed well-baby examinations? Apparently not, according to an examination of subsequent immunization levels and routine well-baby visits when sick visits for acute otitis media took the place of routine well-baby visits at 2, 4, or 6 months of age among a health plan population. No differences were detected in immunization rates or well-baby visits through 24 months of age between infants who received sick-visit immunizations and those who did not (Robison SG. *Pediatrics.* 2013;132[1]:44-48).

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TREATING INFECTION IN BURNS

KATRINA B MITCHELL, MD; NICOLE E LEAHY, RN, MPH; AND **JAMES J GALLAGHER, MD**

Most pediatric burns are small and can be managed by primary care physicians. However, knowing when to contact a local burn center for assessment and treatment of burn injuries can minimize adverse outcomes and optimize care for the burn-injured child.

If all types of burns are considered, there is scarcely a child who has not been burned. Burns most commonly occur during routine activities of daily living and play. Sources of injury include scalds, fire, chemicals, radiation, electricity, and hot objects.[1] Scald burns (hot foods or drinks, showers, or tubs) are the most common type of burn among children aged younger than 5 years; older children, adolescents, and teens may be more likely to suffer a burn from fire (candles, matches, lighters, and house fires). Fortunately, most burns are small, heal spontaneously, and can be adequately managed in the outpatient setting by the general pediatric practitioner. Some burns, however, can be large or associated with infections and long-term sequelae such as scarring. Therefore, all providers should be familiar with the assessment and treatment of burns to minimize the risk of adverse outcomes. This article focuses on burns and infections relevant to primary care pediatric practice.

Initial assessment of a burn injury

When a child presents with a burn, it is important to obtain a detailed account of the circumstances and mechanism of the burn injury from the adult caregiver and the child (when possible). Important details to note are the etiology of injury, time interval from the injury to medical treatment, steps used to clean and treat the wound before the evaluation, and presence of other injuries. Should any suspicion of abuse or neglect arise, the patient should be considered for referral to the local child protection authorities. Such cases could include those in which the reported circumstances of injury are unclear, vary when recounted, or are inconsistent with the clinical presentation. Other warning signs include a previous burn injury, delay in seeking care, presence or suspicion of other injuries, and specific patterns such as cigarette burns or scald burns with well-demarcated borders and/or absence of marks to surrounding areas.[2]

DR MITCHELL is chief resident in general surgery, New York-Presbyterian Hospital/Weill Cornell Medical Center, New York. **MS LEAHY** is manager, Community Outreach and Professional Education Program, William Randolph Hearst Burn Center, New York-Presbyterian/Weill Cornell Medical Center. **DR GALLAGHER** is assistant professor of surgery and assistant attending burn surgeon, William Randolph Hearst Burn Center, New York-Presbyterian Hospital/Weill Cornell Medical Center. The authors have been active in developing a pediatric burn unit at New York-Presbyterian Hospital/Weill Cornell Medical Center's partner hospital in Tanzania, East Africa. They 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.

NEED FOR REFERRAL

At initial presentation, all burns should be evaluated for anatomic location, size, and depth. These factors are important both individually and synergistically to help determine the appropriate treatment, including referral to a burn center if needed.[3] In particular, pediatricians should refer the patient to a burn center when burns involve the face, hands, feet, genitalia, perineum, or major joints; when partial-thickness burns cover more than 10% of the body surface area; and for any third-degree burn. Children with preexisting medical conditions or burns that will require long-term rehabilitation and social service coordination should be referred to a burn center. Finally, any burn injury involving an electrical, chemical, or inhalational source should be managed in a burn center and not by the primary care pediatrician (Table 1).

BURN DEPTH

Burns can present as first, second, third, and fourth degree and involve layers from the epidermis through the deep dermis and underlying tissue (Table 2).[4] Commonly, burns are of mixed depth, and clinical judgment remains the best tool for determining wound depth and the need for skin grafting.[2] To ensure the most accurate assessment of wound size and depth, the burned areas should be thoroughly cleaned and patted dry before visualization. Once dry, the wounds should be inspected for the extent of injury, the development of moisture, and the presence of pain. It is commonly agreed among burn surgeons that the more exudate is present, the higher the likelihood that the wound is superficial and will heal spontaneously. The drier the wound, the more likely it is to be deep and require further intervention. Pain associated with the wound can also provide insight into the depth; significant pain is characteristic of superficial to middermal wounds, whereas minimal pain or absence of pain can indicate nerve damage consistent with deep-partial or full-thickness injury.[4]

BURN SIZE

Burn size can be estimated using various tools, including the "rule of nines," the Lund and Browder chart, or the use of the palmar surface of the patient's hand to represent approximately 1% of the total body surface area.[4] Regardless of the tool used, estimates of burn size should include only areas of skin loss and exclude areas of first-degree injury.[2] Although estimates of burn size often vary among providers of different training levels and backgrounds, burns that are less than 10% of the total body surface area pose a low risk of mortality to the patient in most cases.[1]

TABLE 1 **Advanced Burn Life Support (ABLS) burn center referral criteria**

- Partial-thickness burns >10% of total body surface area
- Burns on face, hands, feet, genitalia, perineum, or major joints
- Third-degree burns in any age group
- Electrical burns, including lightning burns
- Chemical burns
- Inhalation burns
- Burn injury in patients with preexisting medical conditions that could complicate management, prolong recovery, or affect mortality
- Any patient with burns and concomitant trauma (eg, fractures) in which the burn injury poses the greater risk of morbidity or mortality. If trauma poses the greater immediate risk, the patient may be stabilized in a trauma center before transfer to a burn unit. Physician judgment in these cases should reflect the regional medical control plan and triage protocols.
- Children with burns in hospitals without qualified personnel or equipment for pediatric care
- Burn injury in patients who will require social, emotional, or rehabilitative interventions

Adapted from American Burn Association.[3]

Caring for the burn wound

The goals of wound care are to remove dead tissue and promote healing while minimizing the risks of infection and scarring.

CLEANING AND DEBRIDEMENT

Basic wound care performed in the outpatient clinic setting should include gentle debridement (use of antimicrobial or mild soap on cotton gauze) as a first step to gently remove loose skin and any existing topical application before wound evaluation. Blisters should be allowed to remain intact.[5] If large or interfering with function, blisters are best treated by unroofing and gentle cleansing. Burns should then be evaluated for size, depth, presence

TABLE 2 Clinical presentation of burns based on burn depth

Burn depth	Clinical presentation
First degree	• Damage to the epidermal layer only • Painful, erythematous • Heals spontaneously within several days • No scarring
Second degree/ partial thickness	• Damage to the dermis • Erythematous, painful • Blisters • Pink/red/shiny to pale/mottled • Heals by reepithelialization from structures within dermis • May lead to (significant) scarring based on level of dermal involvement
Third degree/ full thickness	• Damage through the dermis • Hard, dry eschar • Painless • Heals by skin grafting surgery • Significant scarring
Fourth degree	• Damage to structures and tissue below the skin

Gallagher JJ, et al.[4]

of infection, and appropriate topical antimicrobial treatment.

TOPICAL AND ANTIMICROBIAL THERAPY

Silver sulfadiazine (SSD) offers broad-spectrum coverage and is most often used for middermal to full-thickness wounds with necrosis and in areas distant from mucous membranes (Table 3; go to ContemporaryPediatrics.com/infection-burns).[4-7] Topical antibiotic ointments such as bacitracin are recommended for treatment of superficial burns, burns to the face or areas near mucous membranes, or burns in patients with sulfa allergies who are unable to tolerate SSD.[4,5,8] These agents do not provide the antimicrobial coverage offered by SSD but are cost effective and can be purchased over the counter.[4-6,8]

Once the topical agent has been applied, the affected area should be wrapped using a minimal amount of petrolatum emulsion-soaked gauze (eg, Adaptic) or nonstick pads and cotton wrap dressings (eg, Kerlix, Kling) to absorb the exudate while keeping the topical application in contact with the wound and protecting the area.[4-6] The parent should be taught this routine and then continue this care twice daily until the follow-up visits when the provider judges the skin to have reepithelialized. Wounds that do not heal within 14 to 21 days or those that appear to be full thickness should be referred for grafting, preferably at a burn center.[5]

As an alternative to a twice-daily wound care regimen, multiday dressings can be used for uncomplicated burn injuries. Adherent occlusive dressings can be used safely for several days in superficial wounds. Such products include Duoderm and Opsite, which cover the wound but do not offer antimicrobial protection.[4,5] Clinical experience shows that these dressings are well suited for placement onto a wound that has a border of intact skin to anchor the dressing.

Newer to the dressing-care market are multiday antimicrobial dressings (such as Mepilex Ag, Aquacel Ag, and Acticoat), which are put onto a clean, superficial to middermal burn wound and left in place to maintain the moist environment, thereby facilitating antimicrobial delivery. Each dressing should be kept in place for several days according to the manufacturer's recommendations. These dressings obviate the need for daily wound care and thereby reduce pain.[7,9]

Regardless of the wound care regimen used, patients, families, and providers must be aware that an evaluation by the clinician is indicated if signs and symptoms of wound infection occur. If the wound develops purulent discharge, a change in color or odor, or erythema, the child should return for further evaluation and treatment.[7]

Infectious complications: What to look for and when to treat

The burning process itself kills bacteria on the skin surface. In the absence of clinical signs of infection, the routine use of antibiotics is not recommended.[5,10]

FEVER

Fever is commonly present after burn injury, although the mechanism is poorly understood. Elevated temperature cannot be relied upon as a sole indictor of infection, even among children with minor burns.[11] Only sustained fever for more than 48 hours was significantly associated with infectious complications. In addition,

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INDICATIONS AND USAGE

MOXEZA® Solution is a topical fluoroquinolone anti-infective indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms: *Aerococcus viridans*, Corynebacterium macginleyi*, Enterococcus faecalis*, Micrococcus luteus*, Staphylococcus arlettae*, S. aureus, S. capitis, S. epidermidis, S. haemolyticus, S. hominis, S. saprophyticus*, S. warneri*, Streptococcus mitis*, S. pneumoniae, S. parasanguinis*, Escherichia coli*, Haemophilus influenzae, Klebsiella pneumoniae*, Propionibacterium acnes, Chlamydia trachomatis** (*efficacy for this organism was studied in fewer than 10 infections).

Dosage and Administration:

Instill 1 drop in the affected eye(s) 2 times daily for 7 days.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions:

- Topical ophthalmic use only.
- Hypersensitivity and anaphylaxis have been reported with systemic use of moxifloxacin.
- Prolonged use may result in overgrowth of non-susceptible organisms, including fungi.
- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis.

Adverse Reactions:

The most common adverse reactions reported in 1-2% of patients were eye irritation, pyrexia, and conjunctivitis.

For additional information please refer to the accompanying brief summary of prescribing information on adjacent page.

Reference: 1. MOXEZA® Solution package insert.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

MOXEZA® solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:
Aerococcus viridans, Corynebacterium macginleyi*, Enterococcus faecalis*, Micrococcus luteus*, Staphylococcus arlettae*, Staphylococcus aureus, Staphylococcus capitis, Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus hominis, Staphylococcus saprophyticus*, Staphylococcus warneri*, Streptococcus mitis*, Streptococcus pneumonia,*
Streptococcus parasanguinis, Escherichia coli*, Haemophilus influenzae, Klebsiella pneumoniae*, Propionibacterium acnes, Chlamydia trachomatis**

*Efficacy for this organism was studied in fewer than 10 infections.

DOSAGE AND ADMINISTRATION

Instill 1 drop in the affected eye(s) 2 times daily for 7 days.

DOSAGE FORMS AND STRENGTHS

4 mL bottle filled with 3 mL of sterile ophthalmic solution of moxifloxacin hydrochloride, 0.5% as base.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Topical Ophthalmic Use Only
NOT FOR INJECTION. MOXEZA® solution is for topical ophthalmic use only and should not be injected subconjunctivally or introduced directly into the anterior chamber of the eye.

Hypersensitivity Reactions
In patients receiving systemically administered quinolones, including moxifloxacin, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported, some following the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to moxifloxacin occurs, discontinue use of the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

Prolonged Use
As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

Contact Lens Wear
Patients should be advised not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described below reflect exposure to MOXEZA® solution in 1263 patients, between 4 months and 92 years of age, with signs and symptoms of bacterial conjunctivitis. The most frequently reported adverse reactions were eye irritation, pyrexia and conjunctivitis, reported in 1-2% of patients.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category C. Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day (approximately 25,000 times the highest recommended total daily human ophthalmic dose); however, decreased fetal body weights and slightly delayed fetal skeletal development were observed. There was no evidence of teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (approximately 5,000 times the highest recommended total daily human ophthalmic dose). An increased incidence of smaller fetuses was observed at 100 mg/kg/day. Since there are no adequate and well-controlled studies in pregnant women, MOXEZA® solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Moxifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when MOXEZA® solution is administered to a nursing mother.

Pediatric Use
The safety and effectiveness of MOXEZA® solution in infants below 4 months of age have not been established. There is no evidence that the ophthalmic administration of moxifloxacin has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

Geriatric Use
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

Microbiology
The antibacterial action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, aminoglycosides, or tetracyclines. Therefore, moxifloxacin may be active against pathogens that are resistant to these antibiotics and these antibiotics may be active against pathogens that are resistant to moxifloxacin. There is no cross-resistance between moxifloxacin and the aforementioned classes of antibiotics. Cross-resistance has been observed between systemic moxifloxacin and some other quinolones. *In vitro* resistance to moxifloxacin develops via multiplestep mutations. Resistance to moxifloxacin occurs *in vitro* at a general frequency of between 1.8×10^{-9} to $< 1 \times 10^{-11}$ for Gram-positive bacteria.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed. Moxifloxacin was not mutagenic in four bacterial strains used in the Ames *Salmonella* reversion assay. As with other quinolones, the positive response observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was obtained in the same assay when v79 cells were used. Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity *in vivo* in a micronucleus test or a dominant lethal test in mice. Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 25,000 times the highest recommended total daily human ophthalmic dose. At 500 mg/kg orally there were slight effects on sperm morphology (head-tail separation) in male rats and on the estrous cycle in female rats.

PATIENT COUNSELING INFORMATION

Patients should be advised not to touch the dropper tip to any surface to avoid contaminating the contents. Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis. Systemically administered quinolones, including moxifloxacin, have been associated with hypersensitivity reactions, even following a single dose. Patients should be told to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction.

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the presence of fever should not automatically mandate an investigation for infection or prescription of an antibiotic. However, in daily practice, providers should be aware of common generalized signs of worsening infection, such as mental status changes, tachypnea, decreased oral intake, decreased urine output, increased pain, and changes in the wound as described below.

TETANUS

As a matter of routine, a burn-injured patient should be considered for administration of tetanus toxoid if the date of the last dose received is unknown or if the patient's last dose of toxoid or booster was more than 3 years or 10 years ago, respectively.[7]

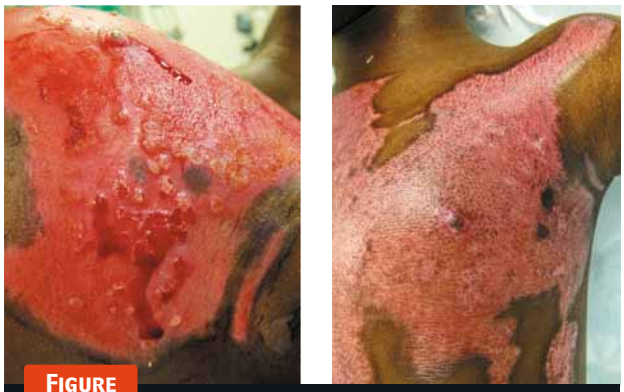
BURN WOUND ERYTHEMA VERSUS CELLULITIS

Burn wound erythema can be a normal part of burn pathophysiology. This painless, benign erythema characteristically occurs 3 to 5 days after the initial injury, surrounds the injury to within 2 cm of the burn edge, and subsides spontaneously.[7] Recognition of this entity is important to decrease the unnecessary use of antibiotics and to differentiate it from burn wound cellulitis.

Burn wound cellulitis presents with advancing erythema, warmth, and tenderness, which must be distinguished from the initial blanching appearance of burn wound erythema. The most common organism is *Staphylococcus aureus,* and appropriate antibiotics should be initiated with close follow-up.[7] If the cellulitis does not respond to oral antibiotics or affects a large area, if additional infection is suspected, or if the patient and family are unable to secure follow-up care, the burn-injured child should be transferred to a burn center. A wound with surrounding cellulitis should not be considered for a multiday dressing; instead, twice-daily wound care with washing and topical ointments is the preferred treatment for these burns. The clinical suspicion of infection should be addressed as soon as possible because inadequate treatment of a burn wound infection can lead to adverse systemic consequences and deepen the wound, thereby increasing the likelihood of scarring and possibly the need for surgery.

SEVERE INFECTIONS

More severe forms of burn wound infection are commonly limited to large burns, which require the expertise of a burn center. Some atypical forms of burn wound infections, however, may present in small and superficial burns; for example, herpes simplex virus.[12] In these cases, inspection will show an atypical pattern, with the burn wound healing edges scalloped with visible vesicles. A careful history should reveal previous herpes simplex infection in the child. Appropriate antiviral therapy should allow normal healing (Figure).



FIGURE

Lateral left chest of a child with scald injury on day 10 after the burn. Scalloped epithelial edges are characteristic of viral infection.

Appearance of wound after 7 days of treatment with antiviral therapy.

Toxic shock syndrome (TSS) from toxic shock toxin-1–producing *Staphylococcus aureus* is a rare but serious complication of burn infection that primarily affects young children because of their lower levels of protective antibodies.[13] Clinical TSS presents with a variety of symptoms, including rash, irritability or lethargy, pyrexia, and shock.[7,13] A common scenario of TSS involves a young child with a small burn who experiences rapid deterioration; the condition can become life threatening within hours unless it is recognized and treated promptly.[13] Mortality is a significant risk.[7] Children with bacterial sepsis deteriorate over 12 to 24 hours, and in most cases respond to antibiotics[13] (Table 4[7,14]; go to ContemporaryPediatrics.com/infection-burns). In contrast, children with TSS can deteriorate in 1 to 2 hours and are unresponsive to antibiotics alone.[13]

The development of shock and suspected sepsis always requires that the wound be considered as a

IMAGE CREDIT/ AUTHOR SUPPLIED

possible source. However, clinicians should keep in mind that in the case of small and moderate burns, the burn wound itself is not the most common source of infection. Other sources of sepsis, such as recent urinary catheterization, should be considered. In addition, children with burns are part of the general pediatric population, and they can develop a second problem such as appendicitis, respiratory infection, or gastroenteritis.

MANAGEMENT OF PAIN AND ITCHING

Most burns can be extremely painful. To treat the pain associated with minor burns, options include narcotics, acetaminophen, or other nonsteroidal anti-inflammatory agents (barring the possibility of surgery) as needed, especially for use as a premedication before wound care.[5,15] As the areas heal, itching becomes extremely common among children. This may last 18 months or longer after the burn and may result in scratching to the point of injury and infection of the regenerating tissue.[15] First-line treatments include liberal use of a mild lotion (cocoa butter, Elta, Lubriderm, Nivea) or oatmeal baths. Pharmacologic options can include antihistamines given orally or topically.[15,16]

Care of the healed areas

Areas of healed burns may remain sensitive for months after the initial injury and more prone to traumatic reinjury than areas of uninjured skin. Rough play or specific activities should be limited to prevent tears of the regenerated tissue.[16] Although all areas of the body should be protected from the sun with sunscreen, healed burn sites require vigilant use of sunscreen and ultraviolet protective clothing to prevent permanent scarring of those areas. Loose-fitting cotton clothes are preferred to tight-fitting clothes, belts, and elastic-waist pants, which can rub and cause blisters. Patients and families should expect that the color of the healed skin will change over time depending on the child's original pigmentation, injury depth, and other factors.

Conclusion

The vast majority of burns sustained by children can be managed by primary care pediatricians. However, if the pediatrician is unsure about management at any stage, or if the burn is deep or developing an infection, he or she should contact the local burn center to arrange transfer for the child. In many cases, the primary care pediatrician can be assisted by a discussion with a burn surgeon who has reviewed a good-quality photograph of the burn injury. Together, they can formulate a plan for optimal care of the burn-injured child.

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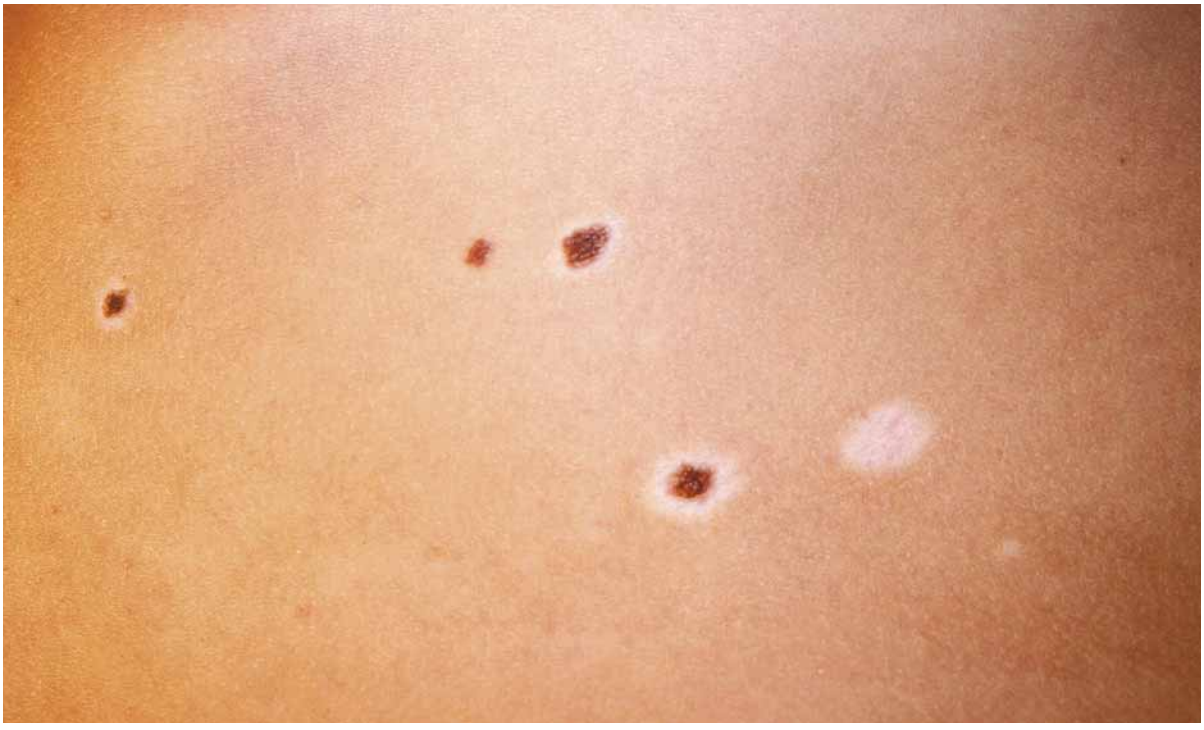

Rings around the nevi

CHLOE ETZLER, MD

THE CASE

A panicked mother of an 11-year-old girl brings her daughter to your office for evaluation of changing moles that she noted when they returned from the family beach vacation last weekend. What's the diagnosis?

FOR DISCUSSION SEE PAGE 36

TELL US ON FACEBOOK

Have you seen a puzzling skin condition in a pediatric patient? How did you arrive at your diagnosis? We'd like to hear from you. Share your story with us and our readers on Facebook.
facebook.com/ContemporaryPediatrics

DR ETZLER is a resident at Albert Einstein Medical Center, Philadelphia, Pennsylvania. She will begin a 3-year residency in dermatology at Hahnemann University Hospital, Philadelphia, in 2014. **DR COHEN**, the section editor for Dermatology: What's Your Dx?, is director, Pediatric Dermatology and Cutaneous Laser Center, and associate professor of pediatrics and dermatology, Johns Hopkins University School of Medicine, Baltimore, Maryland. The author and section editor have nothing to disclose regarding affiliations with or financial interests in any organization that may have an interest in any part of this article. Vignettes are based on real cases that have been modified to allow the author and editor to focus on key teaching points. Images also may be edited or substituted for teaching purposes.

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DIAGNOSIS:

Halo nevus

CLINICAL FEATURES

Halo nevus, also termed leukoderma acquisitum centrifugum or Sutton nevus, is a benign pigmented melanocytic nevus surrounded by a depigmented ring.[1,2] Halo nevi have an incidence of 1% in the general population. The mean age of onset is 15 years, and they occur equally in males and females. The nevus itself is most commonly acquired, but rarely develops around congenital nevi. Patients may have 1 or multiple halo nevi, and the most common location is on the trunk.

Halo nevi have 4 clinical stages of development.[1,2] In the first stage, a pigmented nevus is present surrounded by the characteristic halo of depigmentation. Stage 2 occurs when the nevus loses its pigmentation, leaving a skin-colored macule or papule surrounded by depigmentation. In stage 3, the papule or macule in the center vanishes completely, with only an oval or round patch of depigmentation remaining. In the final stage, repigmentation of the area occurs, resulting in the disappearance of the halo nevus completely. Each individual halo nevus may go through all 4 stages or may cease development at any stage. Nevi that do progress through the fourth stage may take years or even decades to completely repigment.[1]

Halo nevi may be seen more frequently in patients with Turner syndrome and vitiligo.[2] About 20% of children and adults with vitiligo have halo nevi, and those with multiple halo nevi are more likely to have concurrent vitiligo. Although the causes of both vitiligo and halo nevi are poorly understood, both are most commonly believed to be an immune-mediated process resulting from damage or destruction of melanocytes.[2,3] Family history may be positive for halo nevus, vitiligo, atopic dermatitis, and autoimmune disorders, most commonly Hashimoto thyroiditis.[2]

ETIOLOGY AND PATHOLOGY

While the precise etiology is unknown, autoimmune phenomenon is believed to play a role in the development of halo nevi.[2,4] Skin biopsy shows a mononuclear infiltrate comprised primarily of macrophages, cytotoxic T cells, and Langerhans cells surrounding the nevus at the epidermal-dermal junction and within the papillary dermis.[3] Histology of the halo of depigmentation demonstrates a decrease in the number of melanocytes and melanophages, as well as a decrease in pigment within keratinocytes.[4]

DIFFERENTIAL DIAGNOSIS AND TREATMENT

The differential diagnosis for a halo nevus should include malignant melanoma, atypical nevus, and postinflammatory hypopigmentation.[1,3] Although the risk of melanoma developing in conjunction with halo nevi is rare, the presence of a nevus with changing color or border requires careful evaluation. The central nevus should be examined closely, and a biopsy performed if warranted. Benign-appearing halo nevi warrant observation and periodic reexamination (eg, annually).

OUR PATIENT

The nevi in the centers of our patient's halos appeared to be quite stable, and at a follow-up visit 6 months later they appeared unchanged. Photographs were obtained for continued monitoring, and her mother was reassured. CP

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WEIGHTY MATTERS

LISETTE HILTON

Pediatricians are at the front lines of the pediatric obesity epidemic, charged with helping to get America's children back to healthy weights, but which tools and programs truly make a difference?

Overview: childhood overweight and obesity

Recent statistics suggest childhood obesity rates may be leveling off.[1] The problems associated with childhood overweight and obesity, however, continue to be a heavy burden on the minds, health, and pocketbooks of society, parents and children, and pediatricians.

FAST FACT Only about 8% of adolescents aged 12 to 15 years get 60 minutes of daily physical activity (Troiano RP, et al. *Med Sci Sports Exerc*. 2008;40[1]:181-188).

Childhood obesity is the number one health concern among parents in the United States, topping drug abuse and smoking[2]—and with good reason. Excess weight at young ages is associated with higher and earlier death rates in adulthood.

Because of obesity, today's pediatricians are witness to an onslaught of pediatric patients with adult-like physical and mental health problems. Obesity in children and adolescents is associated with multiple comorbidities, including metabolic, cardiovascular, gastrointestinal, pulmonary, orthopedic, and psychological disorders. In fact, cardiovascular and metabolic impairments in childhood and adolescence constitute major risk factors for developing cardiovascular disease in adulthood.[3]

And obese children are more likely to become obese adults.[4-6] Also, if children are overweight, obesity in adulthood is likely to be more severe.[7]

Obesity's financial toll is staggering. Treating obesity and obesity-related conditions costs billions each year. One estimate suggests the United States spent $190 billion on obesity-related health care expenses in 2005, which is twice previous estimates.[8]

FAST FACT In some communities children "account for almost half of new cases of type 2 diabetes [which had previously been adult onset]" (Frieden TR, et al. *Health Aff [Millwood]*. 2010;29[3]:357-363).

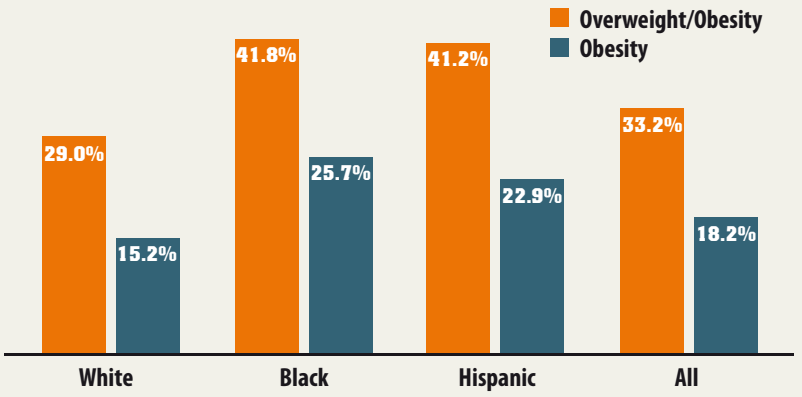
Pediatricians who spend their days treating these patients say the old paradigm of dictating to kids and their parents that they need to eat less and exercise more doesn't work in this new age.

Treatment starts with a conversation

Eliana M. Perrin, MD, MPH, associate professor of pediatrics, University of North Carolina School of Medicine, Chapel Hill, conducts extensive research looking at pediatrician-parent communication about weight and body mass index (BMI) screening. Some of the research suggests that parents and pediatricians are not happy with

MS HILTON is a medical writer in Boca Raton, Florida. She has nothing to disclose in regard to affiliations with or financial interests in any organization that may have an interest in any part of this article.

FIGURE 1 Percentages of overweight/obesity or obesity by race/ethnicity, ages 6-19 years



their communication about weight, and there's reason to believe these conversations often do not take place.

In a study of nearly 5,000 children aged 2 to 15 years with BMIs in the 85th percentile or higher, Perrin and colleagues asked parents if their doctors or health care providers had ever told them their children were overweight. They found that fewer than one-quarter of parents of overweight children said they had been told their children were overweight.[9]

Then, there's parental perception.

"Many parents of healthy weight children think their children are too skinny, particularly for ages 3 to 8,

FAST FACT Hospitalizations of obese children and adolescents aged 2 to 19 years nearly doubled between 1999 and 2005 for obesity-related conditions such as asthma, diabetes, gallbladder disease, pneumonia, skin infections, pregnancy complications, depression, and other mental disorders (Trasande L, et al. *Health Aff [Millwood]*. 2009;28[4]:W751-W760).


Dr Perrin

when that BMI takes a natural dip. And communication of the children's BMI can help reassure parents and keep them from actively working to fatten them up," Perrin says.

According to Perrin, parents of overweight children rarely know their children are overweight. This is especially true of younger children, when a healthier dietary pattern and more physical activity could make the most difference, she says.

Jamie Jeffrey, MD, medical director, Children's Medicine Center and HealthyKids Pediatric Weight Management Program at Charleston Area Medical Center, West Virginia, uses the 5210 Let's Go! toolkit for health care providers (www.letsgo.org/programs/healthcare/toolkits/), which includes motivational interviewing techniques aimed at creating more effective conversations between health care providers and families.

"The 5210 motivational interviewing is part of the well-child check. It's a collaborative approach. It's starting with, 'Can I please talk with you about Johnny's BMI today?'" Jeffrey says.

The take-home for pediatricians, according to Perrin, is that effective communication can be pivotal in the care of these children.

FAST FACT Defined as body mass index (BMI) ≥1.2 times the 95th percentile or an absolute BMI ≥35 kg/m, severe obesity is estimated to affect about 5% of the US pediatric population (Kelly AS. *J Pediatr*. 2013;163[1]:6-8).

"Parents expect us to talk with them, and as long as we do that in a motivating, health-focused, and sensitive manner, those conversations will likely go very well. We should communicate BMI screening to parents (using color-coded charts) but make the rest of the conversation about health and recommendations about healthy activity and dietary behaviors," Perrin says. "We shouldn't talk about diets or dieting, because this is a common pathway into restrictive eating disorders and actually obesity!"

Obesity is a complex problem

Effectively treating obesity requires more than addressing the obvious, some experts say.

The complexities of overweight and obesity include the roles of ethnicity, socioeconomics, and more. Pediatricians should take into consideration families' cultural and socioeconomic backgrounds and offer families a menu of realistic options so they can choose what works best for them, according to Perrin.

Efforts to provide culturally and

linguistically appropriate care, family-based treatment programs, and support services that aim to uncouple socioeconomic factors from adverse health outcomes could improve obesity care for racial/ethnic minority children.[10]

The primary things health providers need to look at when treating these children are barriers, according to Lori Fishman, PsyD, an attending psychologist at the Optimal Weight for Life program at Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts.

"What are the barriers or obstacles for these families to be healthy? Sometimes, access is an issue. Is there a financial limitation? Is there a cultural limitation that prevents a good understanding of the nutrition education that we're trying to provide? Sometimes the barrier is about parenting and parenting style," says Fishman.

Best practices

In December 2007, *Pediatrics* published "Expert Committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report.[11]

While those guidelines, as well as others, especially focus on how to screen, today's guidelines fall short, according to Stephen Pont, MD, MPH, assistant professor of pediatrics at University of Texas Southwestern-Austin and medical director, Texas Center for the Prevention and Treatment of Childhood Obesity. Pont also chairs the American Academy of Pediatrics (AAP) Section on Obesity.

FAST FACT Today, about 1 in 3 American kids and teenagers is overweight or obese, nearly triple the rate in 1963 (American Heart Association; 2013).

RESOURCES FOR KIDS

Nexercise interactive fitness game *(iTunes, Google play)*

WakeMyMojo health tracker game *(iTunes)*

LiVe sets nutrition goals *(iTunes)*

Pick Chow! virtual plate *(www.zisboombah.com)*

"One thing that is not as well described is what to do with outcomes of the screening," Pont says.

Dr Pont

Pont, who is part of the FOCUS on a Fitter Future initiative, says more information is on the way. In 2008, the National Association of Children's Hospitals and Related Institutions (NACHRI) formed FOCUS on a Fitter Future. FOCUS on a Fitter Future's aim is to articulate the role of children's hospitals in combating pediatric obesity while building consensus on performance measurement and quality improvement. One of the group's projects, according to Pont, is a soon-to-be published consensus on treatment algorithms.

However, for most children, it's not about dieting and losing weight, but rather encouraging the children to "grow into" their weight, Perrin says. "That's one reason we encourage pediatricians to track BMI and communicate with families so that we can note concerning weight trajectories early on, before unhealthy habits are entrenched and before there is a need to lose weight," she says. "Involving a nutritionist and other support systems (ie, psychology) can be helpful as well, if they are available in your community."

The pediatrician is but one part of what it takes to help children with weight issues. Obese children often suffer psychological issues, such as depression, anxiety, low self-esteem, social isolation, teasing, binge-eating disorder, and night-eating syndrome, according to Fishman.

FAST FACT In 2007, the average person consumed 400 more calories a day than in 1985, and 600 calories more a day than in 1970 (Wallinga D. *Health Aff [Millwood].* 2010;29[3]:405-410).

University of California, Los Angeles, researchers analyzed data on more than 43,000 children, aged 10 to 17 years, to study associations between weight status and 21 indicators of general health. They concluded: "Obese children have increased odds of worse reported general health, psychosocial functioning, and specific health disorders. Physicians, parents, and teachers should be informed of the specific comorbidities associated with childhood obesity to target interventions that could enhance well-being."[12]

PODCAST

Click **ContemporaryPediatrics.com/jeffrey** to hear more from our interview with Dr Jeffrey.

Fishman says having a behavioral component is crucial when treating obese and overweight patients. "That's beyond just giving behavioral recommendations, but also thoroughly assessing for mental health concerns," she says.

FAST FACT Recent data show that Hispanic and black high school children have obesity rates of 16.6% and 18.3%, respectively, which is significantly higher than their white counterparts (10.8%) *(Trust for America's Health; 2009)*. The same disparities exist for younger children (Bethell C, et al. *Health Aff [Millwood]*. 2010;29[3]:345-356).

There also is the psychosocial component. Overweight and obese children are often teased and ostracized by their peers, so they don't have as many places to go, socially. They tend not to be as active as other kids their ages, ending up home more, with food as their comfort, according to Fishman.


Dr Fishman

At the Optimal Weight for Life program, the core health care team includes a physician who specializes in obesity, a dietician, and a mental health professional. In short, treatment is a "team sport" requiring involvement of all stakeholders. "What does not work is parents who are not invested and have expectations that children are going to do this on their own," Fishman says.

PODCAST

Click **ContemporaryPediatrics.com/fishman** to hear more from our interview with Dr Fishman

Similarly, pediatricians can't talk just to children about behavior change because parents are responsible for cooking, grocery shopping, getting their kids to activities, and more.

Understanding obesity at a deeper level

In 1999, Robert A. Pretlow, MD, a pediatrician in Seattle, Washington, started a Web site called Weigh2Rock.com for obese and overweight teenagers and preteens. At the time, he says, he thought it might provide a safe communication haven for children who are often ostracized, even by their doctors, about their weight.

". . . [W]ithin a couple of years, I had 100,000 kids a month visiting this site from all over the world. It's still at about that level with about 100,000 kids a month," Pretlow says.

The next logical step, Pretlow thought, was to use the site to teach those on it conventional wisdom about healthy eating and exercise. The educational component, coupled with the site's peer support, would surely help them lose weight and maintain healthier weights. Or so he thought.

FAST FACT Almost 17% of children were obese in 2009–2010 (Ogden CL, et al. *NCHS Data Brief*. 2012;[82]:1-8).

"That just didn't happen. . . . Many continued to gain weight, much to their angst. I was dumbfounded as to why," Pretlow says.

Through subsequent surveys and monitoring the site, Pretlow says he learned the kids didn't think health-eating education helped. In fact, they felt overdosed on that information, he says.

"What they said they needed help with was cravings. The level of human misery that is expressed in what these kids write in chat rooms is just appalling," Pretlow says.

In 2009, Pretlow published the book *Overweight: What Kids Say* (CreateSpace; 2009), based on 134,000 anonymous bulletin board messages posted over 10 years. "What they said was it wasn't a healthy eating problem. It was something very similar to an addiction. They even called it that: an addiction," Pretlow says.

FAST FACT Percentage of adolescents aged 12-19 years who are obese: 18.4% (2009-2010) (Ogden CL, et al. *NCHS Data Brief*. 2012;[82]:1-8).

Pretlow then published findings in *Eating Disorders*,[13] where he wrote about the data he and his colleagues gathered from Weigh2Rock: "Many respondents, ages 8 to 21, exhibited DSM-IV substance dependence (addiction) criteria when describing their relationship with highly pleasurable foods. Further research is needed on possible addiction to highly pleasurable foods in youth. Incorporating substance dependence methods may improve the success rate in combating the childhood obesity epidemic."

For today's providers, there is an extensive eCare system contained in the Weigh2Rock.com Web site, where providers may follow and manage their overweight patients remotely. Simultaneously, the children receive peer and educational support from the site.

"The children weigh in on their secure individual charts on the site, via the eCare system, and the provider[s] may monitor the weight charts of their patients and post secure supportive and educational messages to the child in each child's individual 'e-Room,'" says Pretlow.


Dr Pretlow

Jeffrey uses Weigh2Rock.com to keep in touch with children who have completed an intensive 8-week program at her clinic. The children can log in their weights and e-mail providers at the center with questions, problems, and challenges.

"The kids that do Weigh2Rock on a regular basis seem to do better. I don't have absolute data—I can just tell you that they are more likely to come to their appointments. They are more likely to stay on track with their nutritional and activity goals," Jeffrey says.

There is, however, a dilemma with using apps and computer games and gadgets to help kids lose weight. That dilemma: screen time, says Fishman.

"We focus a lot on one particular behavioral strategy for managing weight, which is limiting screen time," Fishman says. "So, we're cautionary about using apps or asking people to use screens as part of this because we're spending so much time encouraging kids to get outside, play sports, and be active."

FAST FACT Percentage of children aged 2-5 years who are obese: 12.1% (2009-2010) (Ogden CL, et al. *NCHS Data Brief.* 2012;[82]:1-8).

Models for change

The care of obese children is evolving, says Jeffrey. "The whole reason I started the HealthyKids Pediatric Weight Management Program was the primary care setting couldn't adequately take care of these kids. I don't think my tertiary care setting can take care of them, either. I think we really have to go with the chronic care model and have the village take care of the kids," she says.

There is hope for better access to obesity-related health care services and better reimbursement. The American Medical Association's designation of obesity as a disease, has not impacted reimbursement for childhood obesity and overweight, but it's a move in the right direction, according to Pont. Health reform could be another positive step in the care of these children, he adds.

"Health reform . . . does recognize that everyone should be able to see their doctor once a year for a health visit, and that would be heavily subsidized or without a copay. Talking about weight could be a part of that visit," Pont says. "However, for kids, there are so many things we need to cover in that visit . . . that to think there is also going to be time to specifically address all the factors that have led to a child being overweight is unrealistic. We need to have the ability to see them back for future visits."

FAST FACT Most obese children and adolescents are not low income (below 130% of the poverty level). Childhood obesity prevalence decreases as the education of the head of household increases, but the relationship is not consistent across race and ethnicity groups (Ogden CL, et al. *NCHS Data Brief.* 2010;[51]:1-8).

In some ways, health care reform is going to prioritize preventive care, which is very important in this discussion, according to Perrin. "For now, we need to make sure we are having efficient, sensitive, motivating conversations with families regarding obesity prevention and treatment," she says. "I think the provider can be very influential. Parents with an accurate assessment of their children's weight are more likely to make weight-related behavior changes."

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

RESOURCES FOR PARENTS

Download these helpful PDFs for your patients' families to take home:

We Can! Families Finding the Balance: A Parent Handbook (English) www.nhlbi.nih.gov/health/public/heart/obesity/wecan_mats/parent_hb_en.pdf

We Can! Families Finding the Balance: A Parent Handbook (Spanish) www.nhlbi.nih.gov/health/public/heart/obesity/wecan_mats/parent_hb_sp.pdf

Online clinical support: Medical information at your fingertips

In this month's article, we take a look at the many online and mobile resources that help us provide our patients with the best care.

There was a time not that long ago when, if we had a patient care question, we'd simply pull a book off the bookshelf, locate the appropriate topic, and find the solution to our clinical conundrum. For the majority of questions arising in routine clinical practice, this process would prove more than adequate. Rarely, when we were stumped and desperate, we would "phone a friend," usually a pediatric specialist who would provide useful advice for managing our complicated patient.

Times have changed a bit, and between trying to see all our patients and completing our electronic health record (EHR) charting, pediatricians have little extra time to devote to researching clinical questions. Another obstacle to providing the most up-to-date care is that many busy pediatricians find it difficult to keep up with the current pediatric literature and may not be familiar with the latest evidence-based practice guidelines and recommendations.

Unless you're a recent graduate, much of the "stuff" we learned in medical school and residency has become outdated, and we must continue to reeducate ourselves regarding appropriate workup and management of routine issues. While I try to learn just 1 new thing every day I'm in practice, I'm sure there are many conditions I see so infrequently that they are no more than distant memories. In this month's Pediatrics V2.0 article, we'll look at the many online and mobile resources that help pediatricians provide our patients with the best care.

Favorite resources

A typical pediatrician keeps copies of 2 resource texts always close at hand. These would be the *Harriet Lane Handbook: A Manual for Pediatric House Officers* (now in its 19th edition) and the American Academy of Pediatrics (AAP) *Red Book Atlas of Pediatric Infectious Diseases (*aka, the *Red Book)* with the latest edition published in 2012. These trusted resources have helped pediatricians care for generations of infants and children.

The *Harriet Lane Handbook* provides a quick resource for drug dosages and normal lab values, and the book is also great at guiding workups for common clinical issues such as hematuria, anemia, goiter, limp, and innumerable other problems. For an infectious disease and immunization reference, there has never been a more thorough and comprehensive resource than the *Red Book*.

I would also add to this list of handy books our favorite pediatric textbook. For most of us, this would likely be the *Nelson Textbook of Pediatrics*, although the AAP *Textbook of Pediatric Care* is a close rival. Reading sections of either textbook in the context of a clinical case provides a welcome review while providing guidance and direction for patient management.

DR SCHUMAN is adjunct associate professor of pediatrics at the Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire. He is also section editor for Pediatrics V2.0 and an editorial advisory board member for *Contemporary Pediatrics*. He has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

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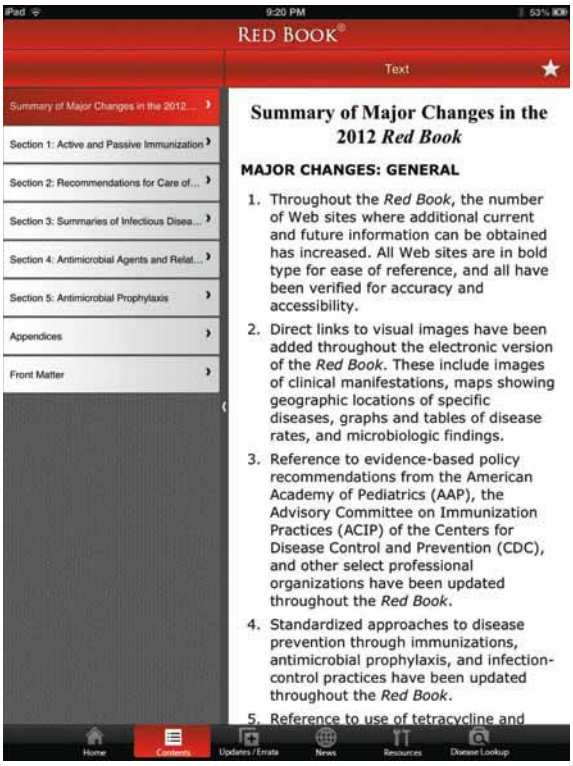


Red Book: AAP's trusted disease and immunization reference; tablet version.

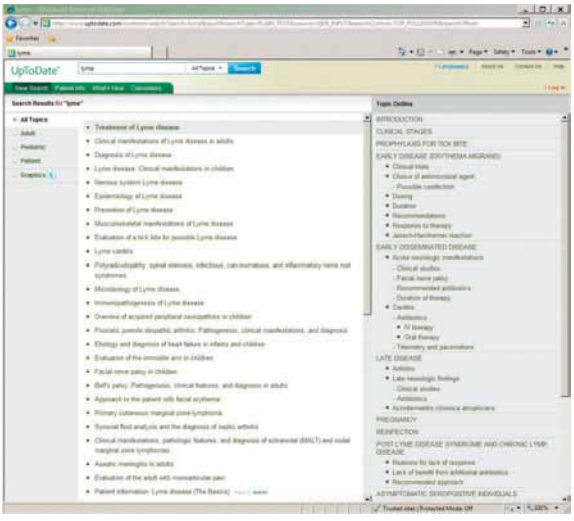
There are electronic versions of these resources, of course, that often offer additional features, quick navigation, and enhancements. For example, the online version of the *Red Book* features an extensive visual library illustrating examples of many conditions discussed in the text as well as infectious disease-related news items. Tablet versions of these resources are also available. One can get the *Red Book* and the *Textbook of Pediatric Care* directly from the AAP online bookstore as e-books, and both the *Harriet Lane Handbook* and *Nelson Textbook of Pediatrics* are available if you subscribe to MD Consult from Elsevier. Note that the AAP's *Textbook of Pediatric* Care can be accessed for free by subscribing to Pediatric Care Online.

Call me old fashioned, but I've been using the real world texts for so many years that I will likely never give up the bound versions of these resources. However, if clinical questions come up when I round at the hospital, when I'm in an exam room with a patient, or when I am on call at home, clinical information is always just a personal computer or smart device-connection away.

Clinical knowledge support systems

When time permits, I review additional information from several clinical knowledge support systems as well. Reading recommendations from a number of sources always gives me confidence that I am using the best clinical-care strategies for my patients. In comparison to online versions of trusted pediatric reference textbooks and manuals, many physicians nowadays utilize 1 or more online clinical knowledge support systems.

I depend almost exclusively on 2 reliable online resources to complement my textbook resources. I would speculate that most physicians are familiar with the UpToDate subscription service. Priced at a reasonable $500 per year, UpToDate provides an expansive catalog of disease conditions that can help expedite diagnosis and treatment. One merely enters the symptom or diagnosis and the search yields appropriate items for review. References to clinical studies supporting the authors' recommendations are plentiful, and diagnosis is usually cross-referenced to related topics in the database. All topics are reviewed and updated by section editors on a regular basis, so you can be assured that information is current. I recently found the section on idiopathic thrombocytopenic purpura (ITP) very helpful in managing a patient. Algorithms, photos, and illustrations are often provided and frequently can facilitate a workup even if you don't have time to read through the discus-



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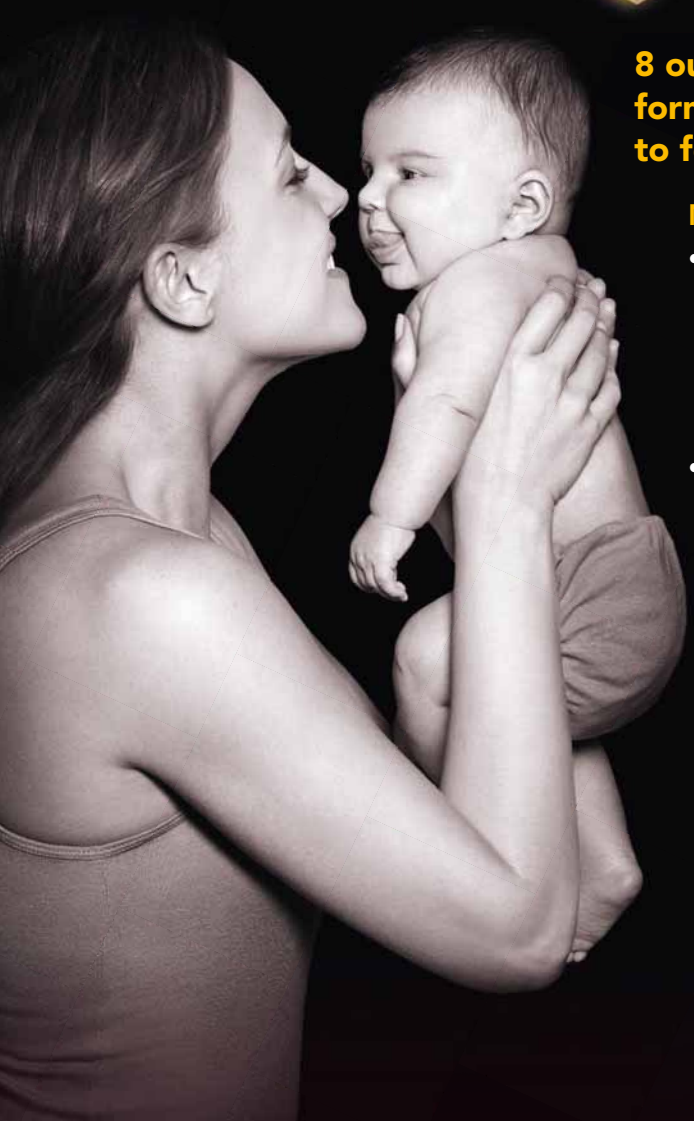

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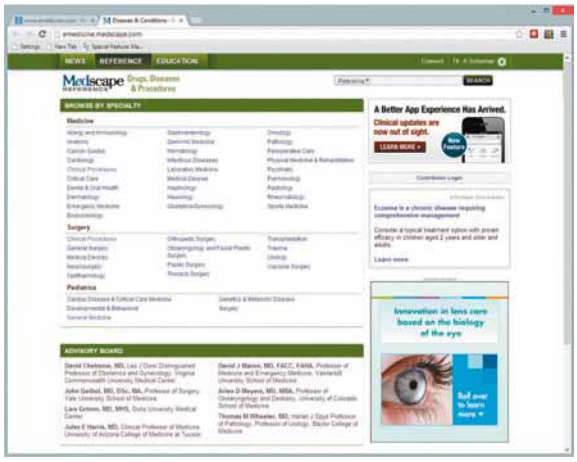


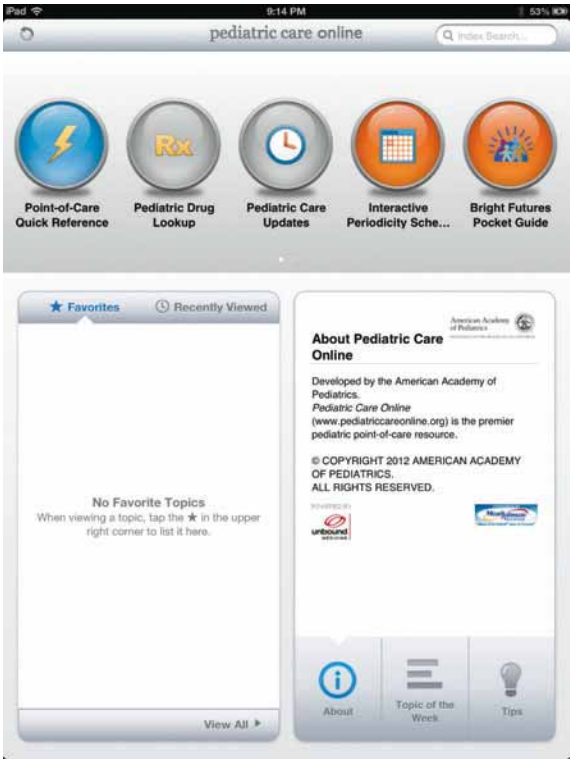
Medscape eMedicine: Free online service has a multimedia library for a wide range of topics.

sion. Additionally, educational materials are available for a limited number of disease conditions allowing you to share information with your patients when appropriate.

The free alternative to UpToDate is eMedicine, now an online service provided by Medscape. Originally conceived in 1996 as an online emergency medicine textbook, the service grew rapidly and became a resource trusted by clinicians. A search entry is entered and then one can quickly drill down to the appropriate sections. Topics are organized into Overview, Presentation, Differential Diagnosis, Workup, Treatment, and Medication, with subsections for each topic. The organization makes it quite easy to focus on the section you need (eg, medication) while ignoring unneeded material. The eMedicine sections also include a multimedia library with illustrations, charts, and photos. Patient handouts are not available, but eMedicine integrates nicely with WebMD's Medscape News and Reference resources and provides lots of free continuing medical education material covering a wide range of topics.

While UpToDate and eMedicine are my personal favorites, competition is fierce between online medical resource providers. DynaMed from EBSCO features a spartan, uncluttered interface and is priced right at $400 per year. The AAP's version of a clinical knowledge support system is Pediatric Care Online, which costs $259 for AAP members. Information supplied by Pediatric Care Online is nicely summarized and organized with information presented from AAP policy statements, the *Red Book*, or the *Textbook of Pediatric Care*. Pediatric Care Online also has a multimedia library and displays current AAP news in addition to a wide variety of clinical support tools and the complete AAP library of patient handouts. The feature set is great and the tablet version is extremely easy to navigate (the *Textbook of Pediatric Care* is only available to read with the online version, however). The last Web site I would recommend bookmarking is Merck Medicus, a free clinical support service, with information presented largely from the current edition of the *Merck Manual*. Patient information handouts are available for free.

Note that these services provide detailed summaries of medical conditions and appropriate references for all their recommendations. One can use other services such as $500-per-year MD Consult (soon to be replaced by Elsevier's new service called ClinicalKey) to read references, if you have an interest.

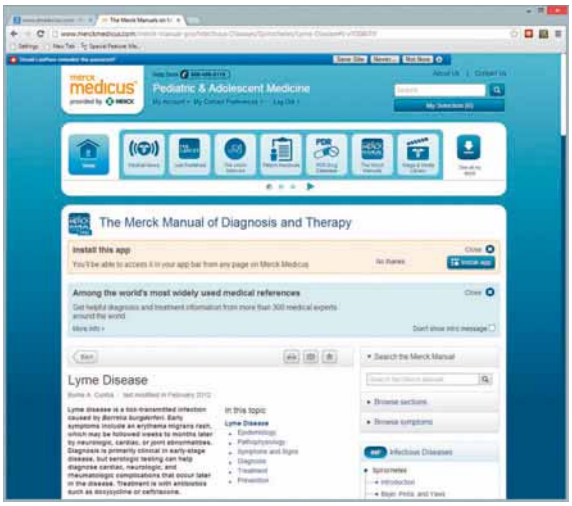


Pediatric Care Online: Digital library of parent handouts; tablet version.

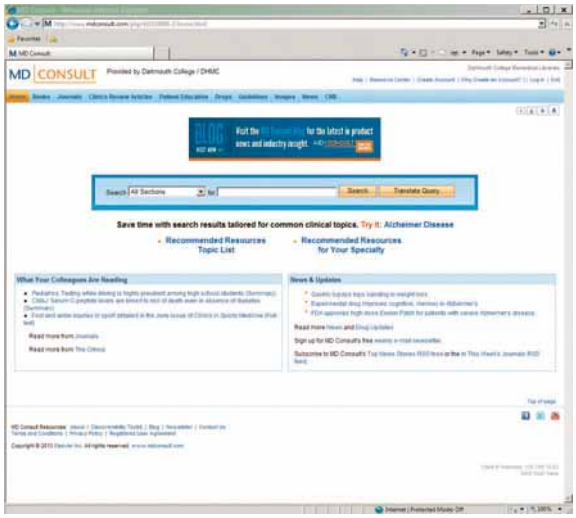
Parents are becoming experts

One situation that we did not face in the pre-Internet days is concerned parents who have a wealth of resources available to them on the Web. It is not uncommon for parents to research a subject and come in with a laundry list of questions and their own requests for tests they'd like performed and specialists they'd like to see. If possible, it is always prudent to steer patients toward trusted resources such as those provided by the AAP or the Centers for Disease Control and Prevention (CDC). The AAP's free site for patient information, HealthyChildren.org, provides thorough discussions of dozens of common preventive care and common acute illness conditions. In addition, the CDC's site has an incredibly extensive library of diseases and conditions. Even Wikipedia usually provides accurate information and is a resource with which most parents are familiar.

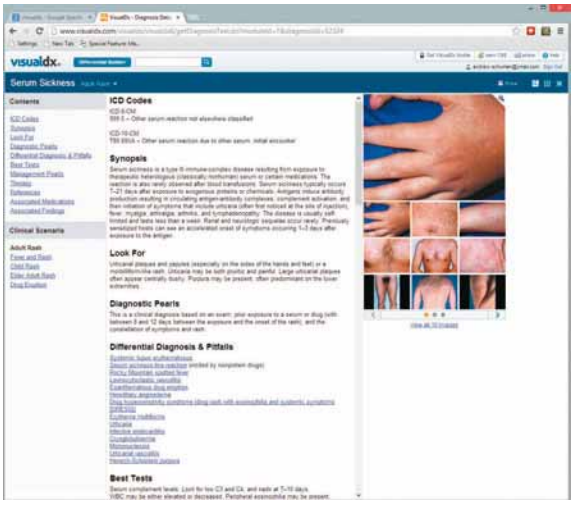
As discussed previously in the Pediatrics V2.0 series, your practice's patient portal should include access to information sheets regarding many common pediatric problems, and this should be promoted as your patient's parents' home base for information. When you'd like to maintain a digital library of handouts that can be



Merck Medicus: Free online service for the current version of the *Merck Manual.*



MD Consult: Detailed summaries of medical conditions with references; by subscription.



VisualDX: Uses symptoms to provide possible diagnoses associated with rashes.

printed and handed to parents, you can subscribe to either Pediatric Care Online or to the AAP Patient Education Online service ($225 per year for members).

Are there new guidelines for this?

It seems that every time you pick up a pediatric journal you discover new guidelines for common pediatric illnesses (vision screening, *Clostridium difficile* infections, otitis media with effusion, sinusitis, gonorrhea, and more), and not all new guidelines originate from the AAP. Pediatricians can review AAP guidelines via its Web site's section on policy, but the best resource for discovering if a new guideline or policy has been issued by any organization while you were sleeping is to visit guidelines.gov. Input a search item and, voila, any policies or guidelines will appear for review.

The future: clinical decision support systems

While the above resources are currently more than adequate for providing helpful patient management information that is merely a mouse click or a finger tap away, health care information technology experts expect that our EHRs will eventually be augmented with clinical decision support systems. Using complex algorithms, software integrated into "approved" EHRs will facilitate diagnosis by examining a patient's symptoms and signs and will suggest a diagnosis and appropriate workup. Many such support systems are currently available and being tested at academic health care facilities around the country.

A good example of a clinical decision support system is VisualDx, available for just $99 per year for pediatricians. VisualDX is designed to help pediatricians identify rashes associated with a variety of clinical conditions. Unlike clinical knowledge support systems where one inputs a diagnosis to retrieve information, with VisualDx one inputs symptoms or clinical findings and the online system presents a list of diagnoses (all associated with rashes) to assist with your diagnosis. A tablet version of VisualDx is available as well. Note that a rudimentary version of a clinical decision support system is available via the Pediatric Care Online Web site as a "signs and symptoms" input tool. As the name suggests, you input descriptive phrases such as "fever," "rash," or "arthralgia" and the online tool suggests possible diagnoses and provides resources to review.

At this point, I remain a bit skeptical about clinical decision support systems. Although I don't mind a little help doing my job, I continue to believe that medicine is often more art than science, and my gut feelings and intuition have over years proven themselves invaluable with patient care. These clinical skills will never (hopefully) be replicated in software. CP

PUZZLER CONTINUED FROM PAGE 13

On physical examination, the patient is awake, alert, and active. The anterior fontanel is open and flat. There is a positive red reflex and pupils are equal, round, and reactive to light. There are vesicular breath sounds with no wheezes, rales, or rhonchi. The S1 and S2 are normal, with regular rate and rhythm and no murmurs. He has normoactive bowel sounds, a nontender abdomen with no organomegaly. He is Tanner stage I with descended testes. Skin findings include hypopigmented macules scattered over his body, involving the trunk and bilateral upper and lower extremities. Skin has no erythema, scaling, or hyperpigmented lesions. There are no focal neurologic deficits and the infant meets age-appropriate milestones. The patient has no history of seizures, abnormal behavior, or any developmental concerns. The family history is only remarkable for 2 maternal nieces with congenital deafness. Otherwise, there are no family members with similar skin findings, epilepsy disorder, birth defects, or mental retardation. There is no known consanguinity between parents.

Birth and medical histories

You review the patient's chart and recall that the 39-year-old mother received adequate prenatal care and that the prenatal screen was within normal limits. Due to advanced maternal age, the mother received genetic counseling. The mother denied amniocentesis, but a level 2 ultrasound was within normal limits. The patient was born at 39 weeks' gestation by spontaneous vaginal delivery with no complications. After birth, the patient weighed 3,225 g (50th-70th percentile) and there were no abnormal skin findings at the time. He failed an initial hearing screening in the nursery, but a repeat test at 2 weeks was within normal limits. He was discharged home with the mother at 2 days of age. At the routine 1-month visit, you found a low-lying sacral dimple and a salmon patch that was not overlying the dimple. A subsequent spinal ultrasound yielded normal findings and there was no sonographic evidence for a tethered cord.

Differential diagnosis

You recall different causes of hypopigmented skin lesions in your mind (Table[1-6]). You recall a multisystemic disorder called incontinentia pigmenti, a genodermatosis in which distinctive skin lesions are associated with ophthalmologic, central nervous system, and musculoskeletal abnormalities.[6] An inflammatory red urticarial and vesicular eruption in the newborn along the lines of Blaschko are followed by the development of warty papules, then hyperpigmented macules, and finally subtly atrophic hypopigmented linear macules.[7] Although your patient presents with hypopigmented skin lesions, esotropia, and hypotonia, you rule out this disorder because it is found primarily in females and only rarely in males, and the patient's skin lesions did not evolve through the various stages of evolution. Moreover, there is no evidence of atrophy in the skin lesions.

Another possibility that runs through your mind is nevus depigmentosus, or isolated hypomelanotic nevi that are fixed from birth and present as a single, well-defined area of hypopigmentation.[8] The classic

TABLE Differential diagnosis for hypopigmentation

Hypopigmented skin lesions	Age at onset	Diagnosis
Diffuse pigmentary dilution	Birth or infancy	Angelman syndrome, Hermansky-Pudlak syndrome, oculocutaneous albinism, Chédiak-Higashi syndrome, Griscelli syndrome
Circumscribed areas of hypopigmentation	Birth or infancy	Vitiligo, piebaldism, Waardenburg syndrome, tuberous sclerosis, Blaschkoid hypopigmentation, nevus depigmentosus
Circumscribed hypopigmentation	Childhood	Vitiligo, pityriasis alba, atopic dermatitis, lichen striatus, pityriasis lichenoides chronica, lichen sclerosus, postinfectious hypopigmentation (ie, following varicella infection), posttraumatic (ie, cryotherapy or thermal burn)

From: Orlow SJ[1]; Bolognia JL[2]; Spritz RA[3]; Józwiak S, et al[4]; Loomis CA[5]; Ehrenreich M, et al.[6]

lesion is an ovoid or irregular patch that breaks apart into smaller macules in the periphery, resembling a splash of paint.[9,10] However the lesions of your patient manifest as multiple streaks, whorls, and patches of hypopigmentation, so the pattern does not fit.

Other possible lesions of hypopigmentation in children include vitiligo, which is classically divided into segmental and generalized types, in which segmental vitiligo has a unilateral distribution usually involving the face, whereas generalized vitiligo is fairly symmetric and is distributed over the periorificial areas, hands, wrists, elbows, axillae, knees, and feet.[11] Tuberous sclerosis, in which the lesions consist of ash leaf spots and "confetti" macules, does not follow the lines of Blaschko.[12] Lesions of piebaldism are present at birth, remain stable, consist of islands of hypopigmented and normally pigmented skin, and favor the ventral trunk while sparing the hands and feet.[11] Pityriasis alba presents as ill-defined, scaly areas of hypopigmentation on the cheeks of children. Inflammatory or infectious processes such as atopic dermatitis and pityriasis versicolor can result in hypopigmentation as well. Lastly, another possibility is pigmentary demarcation lines, the natural boundaries of pigmentation that occur in racially pigmented skin.[8] From your standpoint, you conclude that this patient is healthy and you refer the patient to dermatology.

Dermatology consultation

Five days later you receive a call from the dermatologist with the "most likely" diagnosis of hypopigmentation along the lines of Blaschko that is consistent with genetic mosaicism. He will see the patient again in his office and return the patient to you for long-term care. He recommends regular follow-up to monitor for developmental delays and referrals to a pediatric neurologist and ophthalmologist to screen for abnormalities.

On repeat examination in your office, you note the linear and reticulated hypopigmented macules along the lines of Blaschko on the chest, abdomen, and back (Figure 1). On the left and right upper extremities, there are linear hypopigmented patches and macules along the lines of Blaschko (Figure 2). On the lower extremities and buttocks, there are similar macules (Figure 3). With the exception of these hypomelanotic lesions of the skin, the physical examination at this visit is unremarkable. You give the patient's mother referrals for genetics, pediatric neurology, and pediatric ophthalmology; arrange another appointment with the dermatologist; and tell her to return to your office for another appointment next week.

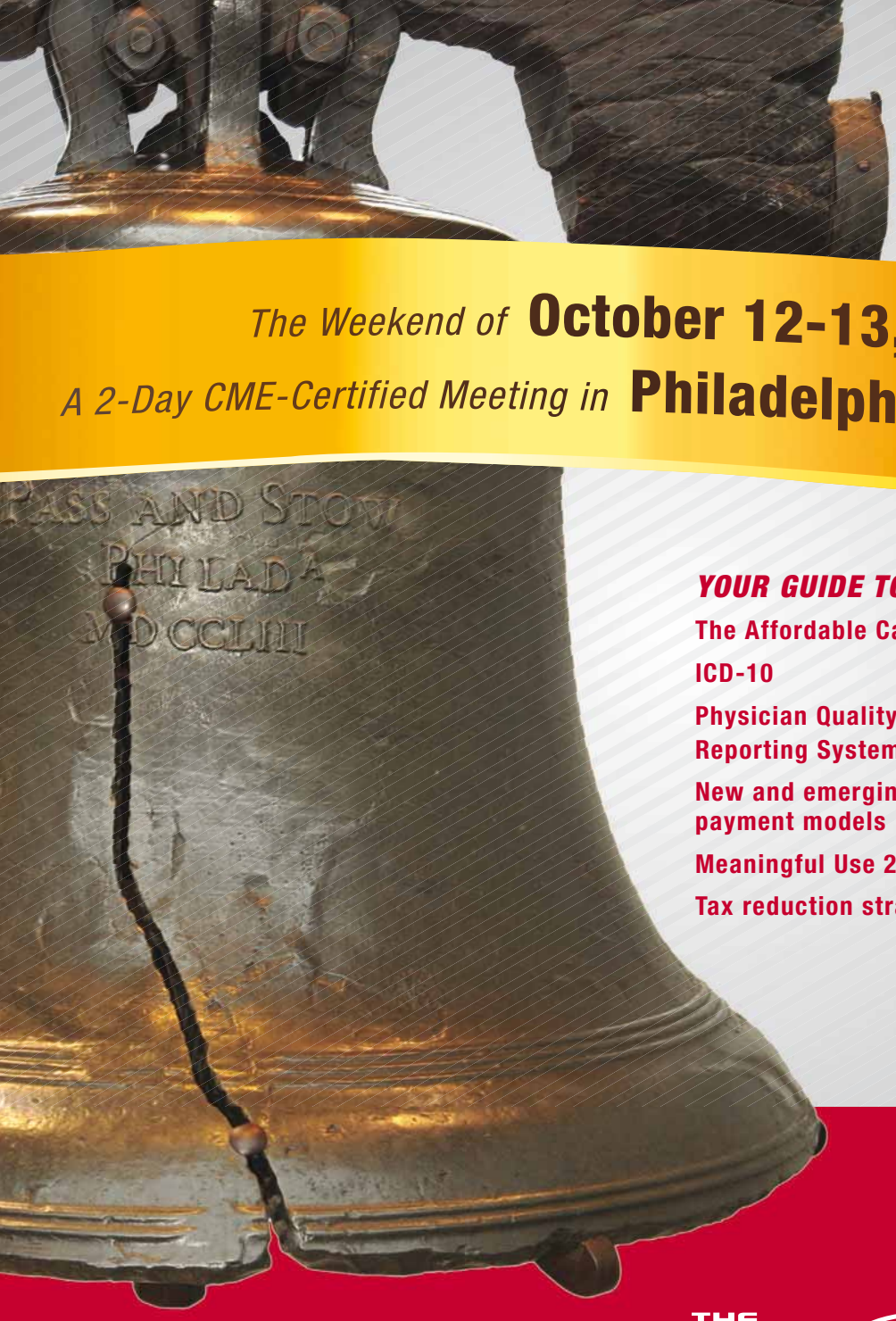
FIGURE 2
Hypopigmentation of upper extremity

Encounters with the ophthalmologist, geneticist, neurologist

During the next several months, you receive notes and letters from ophthalmologic, neurologic, and genetic consultations. The pediatric ophthalmologist found that the patient had small esotropia and mild hyperopia. The pediatric neurologist observed low muscle tone but no focal neurologic findings. He referred the patient for magnetic resonance imaging (MRI) of the brain with sedation, which was found to be within normal limits. The geneticist performed a blood chromosome analysis and the cytogenetic result was a normal male karyotype: 46,XY. She concluded that if the patient continues to attain normal developmental milestones with no seizures or other neurologic concerns, it would not be necessary to proceed with any additional cytogenetic studies on a skin fibroblast sample.

Hypopigmentation along Blaschko lines

Hypopigmentation along Blaschko lines (HABL), previously known as hypomelanosis of Ito (HI), is a finding that results from genetic mosaicism, in which 2 or more genetically different cell populations arise within a single zygote. The manifestation of genetic mosaicism in skin can follow patterns of clinical involvement, such as the lines of Blaschko.[13] Representing the pattern of embryologic migration of skin cells, the lines of Blaschko can be present as S-shaped curves on the abdomen, V-shape distributions on the midline of the



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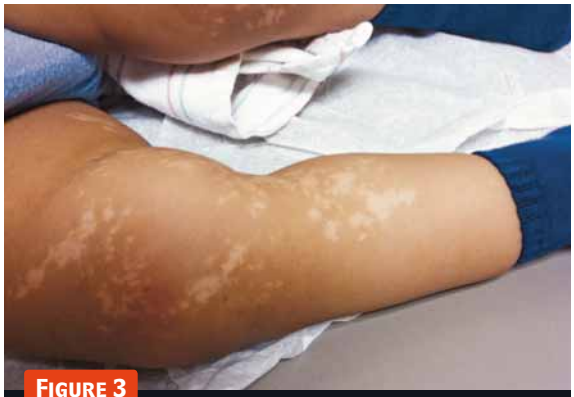

FIGURE 3
Hypopigmentation of the lower extremities

back, and a linear distribution along the extremities.[14]

Hypopigmentation along Blaschko lines is characterized by patterns of hypochromic whorls, patches, spots with irregular borders, and/or linear streaks along the lines of Blaschko.[15] The hypopigmentation may be present at birth, but it is common especially among fair-skinned individuals for the hypopigmentation to manifest during childhood, as sun exposure accentuates contrast with background skin.[9] The hypochromic lesions first appear usually within the first year of age in about 70% of patients.[7]

In the past, researchers have cited a 33% to 94% association with neurologic, musculoskeletal, and ocular abnormalities.[7] However, it has been found that pigmentary lesions along the lines of Blaschko are associated with abnormal systemic features far less often than has been reported previously. Therefore, these pigmentary anomalies are now grouped into a heterogenous collection of disorders indicative of underlying genetic mosaicism.[16] The designation "hypomelanosis of Ito" is now avoided because the term incorrectly implies a neurocutaneous syndrome and its use creates unwarranted anxiety in parents. Therefore, some researchers may reserve the designation of HI for patients with extracutaneous abnormalities.[9]

Clinical manifestations

The cutaneous findings in our patient are consistent with skin patterns reported in patients with hypomelanosis along Blaschko lines, previously known as HI. Ruggieri et al reports hypochromic, circumferential whorls, patches, zigzagging, and/or S-shaped markings around the trunk.[8] Our patient presented with hypopigmented macules coalescing into reticulated patches and whorls (Figure 1). A linear pattern of streaks going down the limbs has been reported[8] and such a pattern was observed on the upper extremities of our patient (Figure 2). Our patient's cutaneous findings are also consistent with previously observed pigmentation patterns of HI: Leukoderma of the trunk usually does not cross over the midline and linear patterns predominate on the limbs.[17] On an ultrastructural level, the regions of hypopigmentation are believed to be caused by decreased functional activity of melanocytes. These melanocytes have been shown to have poorly developed cytoplasmic projections and to contain scarce melanosomes that are reduced in size.[18] Other skin anomalies found in HI include café au lait spots, cutis marmorata and angiomatous nevi, and linear hyperkeratosis,[8] which were not reported in our patient.

Our patient demonstrated suspicious neurologic signs of hypotonia and poor head control. Pascual-

PROFESSIONAL MESSAGES

Castroviejo et al described 14 cases of hypotonia in patients with HI.[19] These cases were usually associated with pes valgus and genu valgus. Our patient, who presented with hypotonia that resolved upon subsequent follow-up, did not present with any knee abnormalities. Our patient also presented with a sacral dimple, which may be benign or a marker for spina bifida. Although subsequent spinal ultrasound produced normal findings, there have been cases of HI with spina bifida.[20] The principal neurologic complications of HI are epilepsy and mental retardation,[8] so it would be advisable to continue with close follow-up and see if these neurologic findings develop in this patient who has not yet had a history positive for seizure activity.

Multiple ocular findings reported in cases of HI include esotropia. Leonard and colleagues reported a 17-year-old female with HI who was found to have esotropia with hyperopia and diffuse coarse mottling of retinal pigment epithelium.[21] Our patient presented solely with mild esotropia. Other ocular findings that have been reported include nystagmus, exotropia, myopia, heterochromia of the irides, coloboma of iris, dacryostenosis, corneal asymmetry, pannus, cataract and pinpoint pupils, and microphthalmia.[8]

Treatment

Although there is no specific treatment for HI, it is recommended to treat comorbidities according to standard protocols. With regard to hypopigmentation, there is no treatment or precaution necessary in terms of sun exposure or cream applications.[8] Cutaneous involvement alone in HI is very rare.[18] Neurologic, musculoskeletal, and ocular abnormalities are the most common extracutaneous manifestations of HI.[7] Because abnormalities involving the nervous system are the most common complication of HI,[19] it is in the patient's best interest to make a neurology referral to rule out epilepsy and mental retardation.[8] An ophthalmology consultation is also beneficial because multiple ocular findings have been reported. Lastly, it is important to offer genetic counseling in the management of HI.

Our patient

The geneticist recommended that our patient be followed carefully for the development of seizures and possible developmental delays when the child grew older. At 2 years of age, the patient returned to the pediatric clinic and was found to have a mild speech delay. We sent the child for speech evaluation and no speech delay was found. There was a murmur on physical examination and we referred the patient to a cardiologist who found an innocent murmur with no associated structural heart defect. Otherwise, the child continues to return for well-child examinations and does not present with complications. CP

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IMPORTANT INFORMATION ABOUT

EPIDUO® GEL

(adapalene and benzoyl peroxide) Gel, 0.1% / 2.5%

BRIEF SUMMARY

This summary contains important information about EPIDUO (EP-E-Do-Oh) gel. It is not meant to take the place of your doctor's instructions. Read this information carefully before you start using EPIDUO gel. Ask your doctor or pharmacist if you do not understand any of this information or if you want to know more about EPIDUO gel. For full Prescribing Information and Patient Information please see the package insert.

WHAT IS EPIDUO GEL?

EPIDUO gel is a prescription medicine for skin use only (topical) used to treat acne vulgaris in people 9 years of age or older. Acne vulgaris is a condition in which the skin has blackheads, whiteheads, and pimples.

WHO IS EPIDUO GEL FOR?

EPIDUO gel is for use in people 9 years of age and older. It is not known if EPIDUO gel is safe and effective for children younger than 9 years old.

Do not use EPIDUO gel for a condition for which it was not prescribed. Do not give EPIDUO gel to other people, even if they have the same symptoms you have. It may harm them.

WHAT SHOULD I TELL MY DOCTOR BEFORE USING EPIDUO GEL?

Before you use EPIDUO gel, tell your doctor if you:

- have other skin problems, including cuts or sunburn.
- have any other medical conditions.
- are pregnant or planning to become pregnant. It is not known if EPIDUO gel can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if EPIDUO gel passes into your breast milk and if it can harm your baby. Talk to your doctor about the best way to feed your baby if you use EPIDUO gel.

Tell your doctor about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

- Especially tell your doctor if you use any other medicine for acne. Using EPIDUO gel with topical medicines that contain sulfur, resorcinol or salicylic acid may cause skin irritation.
- Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

WHAT SHOULD I AVOID WHILE USING EPIDUO GEL?

- You should avoid spending time in sunlight or artificial sunlight, such as tanning beds or sunlamps. EPIDUO gel can make your skin sensitive to sun and the light from tanning beds and sunlamps. You should wear sunscreen and wear a hat and clothes that cover the areas treated with EPIDUO gel if you have to be in the sunlight.
- You should avoid weather extremes such as wind and cold as this may cause irritation to your skin.
- You should avoid applying EPIDUO gel to cuts, abrasions and sunburned skin.
- You should avoid skin products that may dry or irritate your skin such as harsh soaps, astringents, cosmetics that have strong skin drying effects and products containing high levels of alcohol.
- You should avoid the use of "waxing" as a hair removal method on skin treated with EPIDUO gel.
- EPIDUO gel may bleach your clothes or hair. Allow EPIDUO gel to dry completely before dressing to prevent bleaching of your clothes.

WHAT ARE THE MOST COMMON SIDE EFFECTS OF EPIDUO GEL?

The most commonly reported side effects when using EPIDUO gel include erythema, scaling, dryness, application site irritation, stinging and burning.

Depending upon the severity of these side effects, patients should be instructed to use a moisturizer, reduce the frequency of the application of EPIDUO gel, or discontinue use.

Tell your doctor right away if these side effects continue for longer than 4 weeks or get worse, you may have to stop using EPIDUO gel. Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of EPIDUO gel. For more information, ask your doctor or pharmacist.

You are encouraged to report negative side effects of prescription drugs to the FDA at *www.fda.gov/medwatch* or call 1-800-FDA-1088. You may also contact GALDERMA LABORATORIES, L.P. at 1-866-735-4137.

HOW SHOULD I USE EPIDUO GEL?

- Use EPIDUO gel exactly as your doctor tells you to use it. EPIDUO gel is for skin use only. Do not use EPIDUO gel in or on your mouth, eyes, or vagina.
- Apply EPIDUO gel 1 time a day.
- Do not use more EPIDUO gel than you need to cover the treatment area. Using too much EPIDUO gel or using it more than 1 time a day may increase your chance of skin irritation.

APPLYING EPIDUO GEL:

- Wash the area where the gel will be applied with a mild cleanser and pat dry.
- EPIDUO gel comes in a tube and a pump. If you have been prescribed the:
  - Tube: Squeeze a small amount (about the size of a pea) of EPIDUO gel onto your fingertips and spread a thin layer over the affected area.
  - Pump: Depress the pump to dispense a small amount (about the size of a pea) of EPIDUO gel and spread a thin layer over the affected area.

WHERE SHOULD I GO FOR MORE INFORMATION ABOUT EPIDUO GEL?

- Talk to your doctor or pharmacist
- Go to **www.epiduo.com** or call **1-866-735-4137**

GALDERMA LABORATORIES, L.P., Fort Worth, Texas 76177 USA
Revised: February 2013

Reference: 1. According to data from Source Healthcare Analytics, Source® Pharmaceutical Audit Suite, Retail Audit, April 2012 – March 2013.

Galderma Laboratories, L.P.
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Epiduo® Gel—the #1 branded topical acne product among dermatologists and pediatricians![1]

Important Safety Information

Indication: EPIDUO® Gel is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older. **Adverse Events:** In controlled clinical studies, the most commonly reported adverse events (≥1%) in patients treated with EPIDUO® Gel were dry skin, contact dermatitis, application site burning, application site irritation and skin irritation. **Warnings/Precautions:** Patients taking EPIDUO® Gel should avoid exposure to sunlight and sunlamps and wear sunscreen when sun exposure cannot be avoided. Erythema, scaling, dryness, stinging/burning, irritant and allergic contact dermatitis may occur with use of EPIDUO® Gel and may necessitate discontinuation.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit *www.fda.gov/medwatch* or call 1-800-FDA-1088.

Please see brief summary of full Prescribing Information on next page.

Epiduo®
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