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Vitamins: 1. B; 2. D; 3. B; 4. B; 5. E
Quality Improvement: 1. D; 2. A; 3. A; 4. B; 5. D
Apparent Life-Threatening Events: 1. A; 2. A; 3. B; 4. D; 5. B

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Promoting Healthy Behaviors in Pediatrics : Motivational Interviewing

Andrew J. Barnes and Melanie A. Gold

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Promoting Healthy Behaviors in Pediatrics: Motivational Interviewing

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Objectives

After completing this article, readers should be able to:

1. Describe the spirit and principles of motivational interviewing (MI).
2. Know indications for using MI in the pediatric setting.
3. Apply MI to support behavioral change in pediatric patients at all stages of development.

Case

Figure 1. Click here to see a video of a 10-minute primary care office visit, illustrating the motivational interviewing principles discussed in this article. (The full transcript of the video is available at http://pedsinreview.aappublications.org/content/33/9/e57/suppl/DC1.)

Background

Most pediatric clinicians realize that well-intentioned clinical plans can sometimes fall flat or backfire. Everyday practice is rife with times when one might wonder about which prescriptions go unfilled, whether home safety advice is being "tuned out," or whether families will return for recommended follow-up visits. In pediatrics, in which "the family is the patient," ensuring positive changes in health behaviors is daunting, especially in the face of perceived barriers such as lack of time and reimbursement for counseling.

The true obstacles to high-quality care often are interpersonal and can include how practitioners deal (or fail to deal) with their feelings of discouragement or discomfort when faced with particularly "resistant" patients. Integrating motivational interviewing (MI) into one's practice can be a very satisfying way to overcome some of these barriers. MI allows the clinician to stay more connected in a therapeutic relationship with patients by helping them identify how, when, and what behaviors they can change to improve their own health.

Abbreviations

MI: motivational interviewing
MINT: Motivational Interviewing Network Trainers

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Motivational Interviewing: What It Is, and What It Is Not

MI is a supportive counseling style that guides patients toward positive health-related behaviors by helping them resolve ambivalence toward changing. (1) MI seeks to enhance the self-efficacy of patients to facilitate these changes, helping patients move through the continuum of change proposed in the Transtheoretical Model of James Prochaska and Carlo DiClemente, progressing from not yet interested in change (*precontemplation*), to the *contemplation* of change, to making *preparations*, to taking *action*, to the *maintenance* of change, to dealing with *relapse* into old behaviors. (2) MI is not a form of psychotherapy or even a set of techniques; it is a style of communication that is patient-centered.

In MI, the clinician is a guide or coach who brings expert knowledge of healthy behaviors into a healing relationship, while patients bring their own expertise about their lives, perspectives, goals, values, and beliefs. Clinical expertise is conveyed to the patient, with permission, in an authoritative manner that is tailored to patients' individual readiness and willingness to understand how their health interacts with their attitudes, beliefs, and behaviors. When expressed with empathy, this communication conveys to patients the message that they are responsible for and capable of solving their own problems by overcoming barriers to change.

Approaches that are authoritarian ("You should…" or "You must…") or overly permissive without direction ("Whatever you feel is best…") can undermine the efficacy of communication for the clinician or patient. Generally, directing the patient in a more authoritative manner is most appropriate in times of crisis, such as when hospitalization is needed or a patient is suicidal. Permissively following along with a patient's thoughts and feelings may be needed at times when patients need to "vent" to someone who is nonjudgmental, such as during acute loss and grief. MI is the most effective approach for the gray zones that exist between these situations, in which one of many possible options would be appropriate, scenarios that are much more typical in our everyday clinical encounters when we want to guide lifestyle behavioral changes effectively.

The foundation of MI is the "spirit" in which we approach a clinical encounter. Cultivating our interpersonal styles to be more empathetic, supportive, flexible, and affirming provides the bedrock on which patients feel empowered to change. Patients often feel somewhat ambivalent about changing their behaviors as they weigh their options for leading healthier lives: wanting to do something different to change, while also wanting to stay the same, or not entirely confident in their ability to change. The clinician's task is to support and guide patients as they work to resolve their own ambivalence.

Traditional care often focuses on the clinician's impression about what the patient "should" do or needs, whereas the spirit of MI encourages collaboration. It is the patient, not the physician, who decides ultimately what health behaviors and outcomes are acceptable, given individual and cultural preferences, tolerance for risk, and knowledge base. MI sessions turn to patients to identify which health outcomes they hope for, which health goals they are aiming for, the advantages and disadvantages of obtaining these goals, the concrete actions they can take to work toward these goals, and what barriers they can imagine might prevent change.

In a typical pediatric encounter, the clinician might ask parents of a preschool-age child who has asthma to describe their understanding of how asthma causes problems for their child; how they picture poorly controlled versus well-controlled asthma would look for their child; or what they wish would be different about their child's asthma. The purpose of these open-ended questions is to continue a therapeutic conversation that engages the family's strengths and resources, helping them create change from within.

Continuing the example of asthma, the family might think that asthma medications are confusing and hard to administer to their preschool-age child, and at the same time they might have a very good understanding of asthma triggers. In this case, the clinician could collaborate with the family to identify how these triggers affect the child, and how each prescribed medication functions regarding those triggers. The family, in turn, might come up with a new plan to administer controller medications more often during certain times of the year, when seasonal allergen triggers would be more prevalent. This type of collaboration is likely to improve adherence and longitudinal follow-up.

When to Use Motivational Interviewing

MI is most useful when patients are unsure or ambivalent about change. A hallmark of readiness to change is "change talk." These communications include statements that demonstrate a patient's readiness or intentions to change and may reflect patients' desires, abilities, reasons, or needs to change, as well as their commitment to change. For example, a third-grade child who is failing at school owing to attention-deficit/hyperactivity disorder might say, "I really *want* to get my homework done, but I just can't," or the parent who refuses a vaccine for her newborn might state that she knows her child

should get vaccinated. A clinician who hears change talk can use MI to help the patient move toward commitment to change and to take steps to do so. Change talk is elicited through open-ended questions that evoke patients' values, aspirations, and goals and through reflective listening to demonstrate the clinician's understanding of the patient's perspective.

Although change talk often can be positive, and MI can proceed smoothly into helping patients formulate goals and action plans, patients often verbalize ambivalence or apparent resistance to change. This type of expression often occurs within the same sentence as a change statement, such as, "I know I should remember to check my blood sugars more often, *but* it's really hard to do it at school when everyone's looking at me." At these times, the clinician must resist the "righting reflex" that seeks to "fix" the patient's or parent's problems; instead, MI can be used to explore the patient's or parent's views of the advantages and disadvantages of working to change. MI is effective for "rolling with" resistance, by using strategies that include focusing on areas of common ground; refocusing the conversation toward patient and parent autonomy; and by using complex reflections (see the section, *Incorporating Motivational Interviewing into Pediatric Practice*).

As an example, parents in an outpatient weight-management clinic might discuss a number of nutritional factors they have tried to change for their child, and then list reasons these changes have not worked. If a clinician in such a scenario were to counter with new solutions, more dietary information, or objective data on weight gain, parents likely would express even more reasons why changes "can't" occur. During discussions in which the clinician is the only one arguing in favor of change, patients and parents easily can become even more entrenched in *not* changing, because they are literally "talking themselves into" unhealthy behavioral patterns or reasons change cannot occur. Instead, the principles of MI can be utilized to help patients and parents "argue with themselves" to resolve ambivalence. In the case of weight management, the clinician could use MI to help families recognize their own individual reasons for changing nutritional intake, clarify their goals, determine a reasonable plan that includes their own ideas for solutions to barriers, and anticipate additional barriers to changing these factors and ways to deal with these impediments if they arise.

Natural opportunities to incorporate MI into an encounter can occur when the clinician provides patients and parents with suggestions and advice, education, prescriptions, care coordination, referrals, therapies, home remedies, self-monitoring techniques, and follow-up. For example, during a typical pediatric inpatient visit for a child recovering from dehydration, a clinician may decide that the child needs to increase oral intake before discharge. Before proceeding with such advice, no matter how correct it is, the practitioner might ask an open-ended question to understand better what the caregivers or child thinks are the current criteria for the child going home or might ask the family or child permission to discuss further how they plan to ensure the child gets adequate oral intake at home. Such an approach could easily lead to the formulation of mutually acceptable goals to measure progress toward discharge.

MI has few contraindications. Absolute contraindications include immediate risk of harm to self or others, including cases of suspected child abuse and neglect, homicidality, or suicidality. MI also has no role in medical conditions that alter the patient's level of consciousness or necessitate acute hospitalization or emergency treatment (such as severe asthma in an acute exacerbation). Some conditions, including moderate-to-severe cognitive impairments, also may preclude the use of MI. Similarly, a child's developmental level always must be taken into account; most texts on MI focus on children who have achieved at least "operational" thinking (ie, age ≥7 years).

The spirit of MI exists, however, even when we engage empathetically with infant-parent dyads or use techniques of redirection and physical play with toddlers. We believe that MI principles can be used to help children at any age, through developmentally appropriate adaptations of MI, and by targeting caregivers as agents of change on behalf of the younger, pre-verbal child (see the section, *Case Studies in Motivational Interviewing: Developmental Considerations*).

The Efficacy of Motivational Interviewing in Pediatrics and Adolescent Health

Office-based "anticipatory guidance" in pediatric primary care typically has been delivered in a directive, practitioner-centered style. This model of counseling may not be particularly effective, and there is little evidence-based support for didactic counseling in this manner. For example, it remains unclear how well this traditional style works for bicycle helmet promotion, poisoning prevention, child abuse and domestic violence prevention, passive smoke exposure mitigation, sexually transmitted infection prevention, pregnancy prevention, or physical activity promotion. (3)

In contrast, several studies of pediatric populations demonstrate that MI can effectively change several health behaviors. (4) Most of the studies to date have focused on adolescents. (5)(6)(7)(8) More than 10 randomized

control trials and more than six quasi-experimental studies show that MI probably is efficacious for counseling youth about decreasing tobacco use; (6) decreasing substance abuse; (7)(8) improving glycemic control in type 1 diabetes; (9) promoting dental care; (10) and improving rates of follow-up for clinically indicated mental health referrals. (11) Other common pediatric problems, such as childhood obesity, medication adherence, sexually transmitted infections, eating disorders, and the use of alcohol and other drugs, also seem to be addressed successfully by using MI, although these studies have been smaller and less rigorous. The success of MI with youth may depend on how well the clinician incorporates the spirit and principles of MI into the encounter. (12) Few studies of MI in the pediatric setting have examined other topics of anticipatory guidance counseling, but clinical experience suggests that MI usually is more effective in these cases than routine didactic advice.

Incorporating Motivational Interviewing into Pediatric Practice

Effectively using MI involves practicing principles that foster collaborative, patient-centered problem solving. These principles include asking permission, using open-ended questions, affirming the patient, reflective listening, and summarizing (Table 1). Neutrally eliciting patients' concerns about the current state of the problem often assesses the patients' current stage of change best; for example, asking the parents of a 5-year-old with delayed toilet training, "We discussed this a few months ago, and it was something that you thought might get better when he started kindergarten. What, if anything, concerns you or bothers you about how his toilet training is going now?" The practitioner can then provide information tailored to parents' or patients' readiness to change, followed by either a reflective statement or question based on the principles of MI to elicit more responses that refine parents' or patients' goals. This model of "elicit-provide-elicit" thus informs the way that the principles of MI will be applied within that visit (Table 2).

Asking a child or parent for permission to talk about behavior change immediately helps to establish trust and conveys respect for his or her autonomy. Children's appropriate sensitivity to being talked *about*, instead of talked *to* or *with*, can be addressed well in this way. When an opportunity to use MI presents itself (eg, during a discussion of sleep hygiene in a school-age child who experiences insomnia) the clinician can ask the child, "Would it be all right if we talked more about your sleep?" or "I'd like to hear more about your sleep. Would you prefer to talk to me about it with your mom in the room or with your mom out of the room?"

If a patient or parent declines this invitation to further discussion, then he or she is likely to be in the precontemplation stage of change, and the clinician could ask if it

Table 1. Motivational Interviewing Skills

Open-ended questions	• *Tell me about how bedtime goes.* • *What does your family like to do for exercise?*
Affirmation	• *You have great ideas about how you can eat healthier.* • *You understand more about cystic fibrosis than lots of doctors do.* • *It took a lot of courage to share with me what you really have been doing, and I respect your honesty.* • *You really seem to care about your health, and it shows by how much you have read about your treatment options.*
Reflection	Example: Patient says, "I don't want to take my medicine anymore." • Simple reflection *You don't plan to keep taking it in the future.* • Reflection of emotion *It makes you angry when your mom tells you to keep taking your medicine.* • Reflection of meaning *Your medicine has too many negative adverse effects and not enough positive benefits.* • Double-sided reflection *You don't want to take your medicine anymore, and you also worry about how not taking it might affect your school performance.* • Amplified *You would rather stop taking your medicine, even if it might result in your getting sicker.*
Summary	• *So far we've talked about eating healthier and exercising more. You wish you could do both, and it's been hard to do both so far. Some of the plans you've made in the past didn't seem to work, and I'm wondering what kinds of new ideas you will come up with today to change that.*

Table 2. Using "Elicit-Provide-Elicit" to Improve the Exchange of Information or Advice

Scenario	Elicit: What Patients or Parents Understand and Their Perspectives and Concerns	Provide: Affirm Patient or Parent; With Permission, Supply New Information or Advice	Elicit: Reflect or Understand Additional Concerns
Quarterly management visit for a 13-year-old boy taking a stimulant for attention-deficit/ hyperactivity disorder	Clinician: *What are some of the good and not-so-good things about the medication?*	Clinician: *You're the expert on how the medication affects you. Some people find that the adverse effects get less noticeable over time. Others find the good parts outweigh the adverse effects. Would it be okay if I told you some additional ways we can adjust the medication to better suit you?*	Clinician: *We could either decrease the medication dose, or switch to a different medication, or maybe you have another idea. What do you think?*
	Patient: *It takes away my appetite and makes me no fun. One good thing is that I get most of my homework done at school now.*	Patient: *I guess.*	Patient: *I wish I could just stop taking it for a while and see what happens.*
Follow-up for a 5-year-old girl who has diabetes and her parent	Clinician: *Help me understand how you decide when to check your daughter's blood sugars.*	Clinician: *You've learned how to tell when your daughter's sugars might be high or low from how she acts. It's great that you've learned those signs. Would it be okay if I suggested some other ways that you could decide when to check your daughter's blood sugar?*	Clinician (after giving some suggestions): *So what do you think of those suggestions?*
	Parent: *If she seems low or high, then I'll check.*	Parent: *Sure.*	Parent: *I never thought of those before. I might try that.*
Vaccination refusal by parents of a 12-month-old boy	Clinician: *What are your thoughts on these vaccines?*	Clinician: *So you think he might be at higher risk. Some people choose to do an alternate vaccine schedule, and others prioritize which ones their child gets. I'd be happy to discuss with you what I know and understand about this issue, if you'd like.*	Clinician: *It sounds like you've done good background work on this already. How do think you'd like to proceed with future vaccinations?*
	Parent: *We think that they can trigger autism in some children, and he does have a cousin with autism.*	Parent: *That's all right. We're just going to skip these ones for now.*	Parent: *We'll have to find more about what's in those. Do you know where to find good information about them?*

would be better to discuss another topic entirely. Another strategy could include reflecting that the patient or parent is not ready yet to discuss this topic and then to reinforce that it is up to the patient or parent to decide when he or she might like help with this issue and to arrange a time in the near future to return and check in to discuss it (eg, how well he or she is sleeping).

Open-ended questions serve to elicit patients' and parents' internal motivations for behavior, whereas closed-ended questions are more useful for data gathering, hypothesis testing, and asking permission to give information or advice. Closed-ended questions are those that result in a response of "yes," "no," or a simple fact (such as timing or severity of a symptom). Clinicians often fear that open-ended questions will take too long for patients or parents to answer; however, experience with MI has shown that time usually is *saved* by asking open-ended questions, because open-ended questions elicit the core issue and agenda for the visit more quickly and fully than multiple clinician-driven, closed-ended questions. Open-ended questions also may be perceived as less threatening to children, who may otherwise feel defensive or interrogated when asked too many closed-ended questions in a row.

The simplest open-ended questions begin with "what," "how," and "when…then." Some phrases that generally are more useful with children than "why" to determine their understanding of the problem, motivational level, and readiness to change include "Tell me about…," "How come…," "Describe for me…," and "I wonder…." Another approach is to ask the child to "Walk me through…," or "Tell me the story of a time when [the specific problem behavior occurred]…and please tell me lots of details, like I'm watching a really good movie or reading a great book." The clinician can keep such fruitful conversations going by saying, "And then…?" and "Tell me more." A rich level of detail often is revealed very quickly through these conversations, which also can evoke change talk.

A specific type of closed-ended question used frequently in MI, often referred to as a "ruler," can help assess different aspects of change. After gathering data about the presenting problem and the patient's or parent's perceptions of it, the clinician can introduce the idea of a "ruler" or scale for readiness, importance, confidence, and commitment to making a specific behavior change; with children, it can be helpful to illustrate this concept (ie, as a simple number line) or to use a "prop," such as an examination room tape measure or ruler.

For preoperational children or more "active" learners, the clinician can use his or her hands to represent the scale's magnitude, and the child can "adjust" the hands up or down to self-rate his or her stage of change accordingly. After discussing this idea, the patient or parent is asked, "On a scale from 0 to 10 [or whatever he or she imagines the maximum to be on his or her own scale], where 10 is the most [ready/important or confident/committed] and 0 is the least, where would you say you are now?"

The clinician can then "probe lower," so that the patient or parent "argues for" his or her number (and thus argues *in favor of change*), by asking an open-ended question such as, "I wonder why it's an *xx* [their chosen number] instead of a *yy* [their chosen number minus 1 or 2]?" The clinician can then ask, "What else?" until the patient or parent says, for example, "That's all I can think of." (Note that it is important to *not* ask why the chosen number is low; ie, why the number is a five and not a 10, because this approach encourages the patient or parent to argue in favor of the status quo and *against* positive change.)

After summarizing all of the stated reasons for the number being as high as it is, elicit possible solutions to perceived barriers by "probing upward" and asking, "What do think it would take to *increase* the number from an *xx* to a *yy* [where *yy* is 1 or 2 points higher]?" again fully eliciting all of the patient's or parent's ideas, then summarizing these ideas to begin to develop a "menu" of self-generated solutions. Use of scales and rulers in this manner can help to operationalize the stage of readiness to change, generate solutions, and affirm change over time (eg, "When I saw you last month, you thought that you were a five in terms of how confident you were that you get your grades up, and now you're a seven. That's great; how did you do that?").

Affirmations are statements that provide positive feedback about goal-oriented behaviors or personal characteristics or strengths, reinforcing autonomy and self-efficacy. Such statements can be as simple as genuinely telling a harried parent, "I really appreciate that you came in today, and it shows how important your child's health is to you, because it probably took a lot of effort and planning to get here!"

Children are especially open to sincere affirmations, because their developmental tasks include mastering a variety of new skills. Complimenting a teenager's new shoes and asking, "Did you pick those out yourself? Wow! You have great taste in shoes," or noticing how a kindergartener proudly dresses him- or herself "just like a grown-up," are the kinds of statements that can enhance confidence and competence. Affirmations can compliment a behavior, such as taking steps toward change, or a personal characteristic, such as honesty, timeliness, resourcefulness, inquisitiveness, or openness.

Reflections are statements that demonstrate that the clinician understands the patient's or parent's thoughts and feelings. Simple reflections include repeating and rephrasing the patient's or parent's statement. Repeating what the patient or parent has said can be useful initially, but if this repetition is done too frequently, it may sound shallow or halt dialogue. It is somewhat more helpful to rephrase or restate (eg, "In other words…") what the

patient or parent has said in a manner that communicates understanding or clarifies meaning.

Complex reflections are the best way to demonstrate the clinician's understanding and can include reflections of emotion or meaning. Reflections of emotion can express empathy and understanding and may require that the clinician infer meaning. Complex reflections can include amplifying (eg, "You're really not sure what else you can do, and you're at your wit's end!"). One can employ single-sided reflections ("you wish things would change") and double-sided reflections ("On the one hand, you're feeling pretty upset about it, and on the other hand, you're uncertain about whether or not you can do anything to change it").

Reframing is a method of reflection that utilizes any implicit change talk buried within the patient's or parent's statement to create a more specific, positive, and change-oriented statement. For example, if the parent of an obese child says, "Nothing we do seems to help…and he's getting teased now, too, so then he gets depressed and just eats more," then the clinician could reframe this statement as, "His self-esteem is important for his well-being, and you're ready to go to any length to help him change things for the better." Reframing works especially well when the patient or parent makes a negative statement, because the reframing can help transform apparent "resistance," hopelessness, or helplessness into momentum toward positive change and enhance self-efficacy in the process.

Summarizing statements by clinicians are succinct and strategic integrations of the conversation between patient or parent and clinician. They serve to clarify mutual understanding, as the clinician gives and gets feedback from the patient or parent on what has been discussed. Summarizing can be a useful way to move the interview forward, transitioning from assessment to planning and closing the visit. Summarizing also can be a way for the clinician to make explicit any ambivalence and use it to develop discrepancies that make the positive value of change more concrete.

For example, the clinician could summarize the patient's or parent's goals, values, and beliefs, and the "parts" of the patient or parent that are oriented toward positive future goals and change; the clinician could then contrast these positive orientations with the current status or behaviors, helping the patient or parent to determine how his or her present behaviors are in conflict with his or her goals, values, or beliefs.

Finally, summaries can help marshal the attention of a patient or parent who tends to talk excessively or become tangential, while telling that person that the core "story" he or she is telling is being heard and comprehended. Clinicians can begin summaries with phrases such as, "I think it would be useful to summarize what we've talked about so far," or "So far, we've talked about…Next, tell me more about…," or " Let me make sure I understand what you have said so far…."

For patients or parents moving from the "planning" to the "action" stage of change, summary statements also can be used to discuss "menus" of therapeutic options, any of which could help the patient or parent reach his or her goals. For example, after having a conversation with a child that reveals that she is highly motivated and committed to stop chewing her fingernails, the clinician could summarize, "This has started to bother you, and I know that you can quit now that you're ready. There are lots of ways to do that. Some kids like to work with me on learning some new skills, like relaxation exercises; others find it helpful to talk with a counselor who helps kids get rid of bothersome habits. Maybe you've had some other ideas about what you think would help. What do you think will work the best for you?" For patients or parents who are in the "precontemplation" or "contemplation" stages of change, summary statements similarly can be useful to provide options about further education, ideas for follow-up, goals, or whatever they think is the right next step for them.

There are several developmental adaptations for using MI with latency-age children and younger adolescents. One is to use the "open-closed-open" sandwich in which an open-ended question is followed by several closed-ended questions and ends with another open-ended question. For example, rather than asking, "What do you think you want to do about your diet?" the clinician could ask, "What do you want to do about your diet? Do you want to eat more vegetables, or have fewer snacks, or change your drinks to no- or low-calorie ones? What makes the most sense to you?" It is also helpful with younger or less developmentally mature children to use fewer open-ended questions in general, as well as to use more affirmations. Children and younger adolescents may respond better to reflections of emotion than to reflections of meaning.

When starting a conversation with children and younger adolescents, it may help to begin with a limited number of choices when using open-ended questions; for example, you might ask, "Would you like to talk about how to be more physically active, ways to eat more healthily, or how to get enough calcium in your diet today?" while always ending with an open-ended question, such as "…or maybe there is something else you would rather discuss? What do you think?"

Asking permission, using open-ended questions, affirming the patient or parent, reflecting, and summarizing

are integrated easily into a typical pediatric encounter, as the preceding examples illustrate. The result is a very efficient style of communication that usually saves time during a visit. This style of interpersonal interaction uses the principles of MI: *expressing empathy* toward patients or parents and meeting them where they are; *developing discrepancies* between how patients or parents think their health is now and how they want to be in the future; *supporting self-efficacy* and the utilization of patients' or parents' own resources and solutions for self-care; and *rolling with resistance* to meet patients or parents where they are in their readiness to change. These principles are practiced with patients or parents in a *spirit* that *evokes* and makes explicit their internal motivations and commitment to behavior change, *encourages* their developmentally appropriate autonomy, and *collaborates* with them to meet mutually agreeable goals (Table 3).

Incorporating MI into pediatric practice does not present any barrier to appropriate coding and billing. Visits that include face-to-face counseling, including MI, for >50% of the total visit time can be billed as such (instead of on "elements"), and the record should state, "Greater than 50% of this xx-minute visit was spent counseling and educating about…." Common Procedural Terminology Evaluation and Management codes 99213 (15–25 minutes' total time), 99214 (25–40 minutes' total time), or 99215 (>40 minutes) usually would be most appropriate, and a prolonged visit code (99354) can be added to the latter if the visit is >70 minutes.

Codes that are or may not be reimbursed reliably by insurance companies yet, but that are applicable when MI is used, include 96150 (Initial Health & Behavior Assessment), 96151 (Health & Behavior Reassessment), 96152 (Health & Behavior Intervention– Individual), 96153 (Health & Behavior Intervention–Group), 96154 (Health & Behavior Intervention–Family with Patient), and 96155 (Health & Behavior Intervention–Family without Patient). Clinicians should check with payers to find out if these codes are reimbursable at this time.

Case Studies in Motivational Interviewing: Developmental Considerations

Infancy and Toddler Age (Prenatal–Age 2 Years)

Emily is a 28-year-old first-time mother whose 2-month-old boy, Luis, has been breastfeeding exclusively until the past 2 weeks, when she returned to work full-time as a schoolteacher. She is now giving him 2 bottles of formula daily in addition to breastfeeding ≥6 times daily. When asked how long she would like to keep breastfeeding, she states, "I don't think I can do it much longer, but I wish I could. It seems like I'm too stressed out, and my supply is less than it used to be. I tried to pump at work, but most days I'm too busy and there's not really any place that I can do it there, anyway." Luis is growing well and is fast asleep in her arms.

Emily is ambivalent about continuing to breastfeed Luis. She has tried various strategies to continue breastfeeding and has been confronted by a number of barriers to breastfeeding that challenge her commitment to continue. To assist Emily in enhancing her commitment to breastfeeding, a clinician could ask Emily open-ended questions about what she currently knows about the advantages of continuing to breastfeed for both herself and Luis, reflecting her comments and providing, with permission, additional information if needed regarding the benefits of breastfeeding.

Then the clinician could explore the disadvantages of breastfeeding for both Emily and her son and reflect, in a double-sided reflection, the disadvantages followed by the advantages, and end with asking, "What do you think would work the best for you and Luis at this time?" During this conversation, it is important to empathize with Emily regarding the challenges of breastfeeding by using complex reflections, and to support her self-efficacy by pointing out, with an affirmation, that she is wise to be taking her own needs and stress level into account, and that it is clear, from how healthy Luis is, that she is doing a wonderful job.

A clinician also could ask Emily, "What would you need to happen for you to continue breastfeeding?" and to explore solutions to past barriers to breastfeeding. This inquiry could be followed by an autonomy statement, such as telling Emily, "You are the best judge of what is best for yourself and your baby, and I will support you in whatever choice you make regarding continuing to breastfeed or not."

Preschool-Age (2–6 Years Old)

Keisha is a 5-year-old girl whose kindergarten evaluation is unremarkable except that her parents note on the office's "safety checklist" that she refuses to wear a bicycle helmet. During the visit, while her parents describe their failed attempts to get Keisha to use her helmet by pointing out how Keisha's friends always use helmets and by disallowing her to ride her bike unless she wears a helmet, Keisha interrupts them to proclaim loudly, "I don't want to ride my bike!…but when I'm 6, I'll use my helmet 'cause then I'll be bigger."

Keisha's parents and Keisha are mismatched in their readiness for Keisha to use her helmet and ride her bicycle. Their preschool-age daughter is expressing developmentally normal statements of resistance. Keisha's parents' continued attempts at getting her to be like her friends

Table 3. **Integrating Motivational Interviewing Into Pediatric Encounters**

Guiding Principles and Spirit of Motivational Interviewing	Examples
Expressing empathy	*You've worked hard on this problem and it's frustrating you that it's not much better yet.*
Developing discrepancies	*You do not want to quit smoking yet because most of your friends smoke, and at the same time, these asthma episodes are telling you that quitting now might improve your health.*
Rolling with resistance	*You're not yet ready to talk more about your marijuana use with me, because you feel angry and believe that your parents invaded your privacy by bringing their concerns to me without telling you first.*
Supporting self-efficacy	*You've solved problems like this before, and you might already have some ideas about what might work.*
Spirit of collaboration	• Create a partnership that respects patient's or parent's unique perspective. • Focus on interpersonal interactions and rapport. • Create a mutually agreed-on agenda. • Use verbal and written summaries.
Spirit of evoking motivations and commitment to change	• Ask open-ended questions. • Use the Elicit-Provide-Elicit model of gathering and sharing information. • Explore patient's or parent's reason for and against change. • Listen for "change talk" indicative of ambivalence. • Listen reflectively. • Use readiness and confidence "rulers."
Spirit of encouraging autonomy	• Convey that responsibility for making change resides with the patient or parent, who must decide if, how, and when change will occur. • Offer affirmations and acceptance. • Encourage self-direction. • Avoid the "righting reflex," direct persuasion, and confrontation. • Check for understanding. • Present a menu of options and choices.

by wearing a helmet are unlikely to be successful because Keisha is not yet at a developmental age where peer identification is a motivator. Also typical of 5-year-olds, Keisha seems interested in "rules" but has some definite independent ideas of her own about how and when the rules should be followed.

Capitalizing on this mind-set, her parents' disciplinary strategy (no bike riding without a helmet) could be affirmed as a "good rule." The clinician also could reflect on Keisha's statements by suggesting to her parents that they roll with their child's natural resistance, pointing out that Keisha seems to be saying that she *can* ride a bike and probably *will* when she is *ready*, which certainly will be when she is a little bit *older*.

Keisha is at an age that might preclude a strict application of MI; however, she verbalizes an apparent ambivalence about helmet-wearing (ie, she says, "…but…"), and she is quite verbal; so a developmentally tailored approach to using MI with her could help her continue making small steps toward her goal of being "bigger." She has preoperational thinking: she cannot yet mentally deduce logical relationships, instead learning best through physical means and imaginary play. One approach would be to point out the discrepancy between her goal of independent bike riding and her sense that she's not yet "grown up" enough by drawing or physically demonstrating just how much she's grown in height in the past year.

The clinician could then summarize Keisha's attitudes and beliefs, utilizing her egocentric thinking and drive toward self-mastery by pointing out that she is already bigger than she used to be and wondering how proud she will feel when she starts to get on that bike and follow those big-kid rules *on her own*. Finally, the clinician could suggest a menu of options or choices for how and when to change, including waiting until she is a lot older and taller in a few

months, or a little older and taller in a few days or weeks, or whether she will be with her mom, dad, friends, or by herself when she notices that she is *big enough* to wear her helmet *and* ride her bike.

School-Age/Preadolescence (6–12 Years Old)

Bill is a 10-year-old boy with chronic constipation and encopresis. He has experienced a successful remission for the past 6 months, after monthly visits over the past year to a gastroenterology clinic, where he received education about constipation, an initial bowel clean-out regimen at home, a high-fiber diet, instruction on the importance of sitting on the toilet for 10 minutes after meals, and learning how to self-monitor his bowel movements on a chart that he keeps in his room. In the past month, he has soiled himself twice a week and was hiding dirty underwear in his closet until his parents found them. His parents have grounded him for 1 week for hiding his soiled underwear, and they explain, "He's just been lazy about this ever since school let out for the year." Bill looks ashamed while his parents speak, avoiding eye contact and seeming to be on the verge of tears.

Bill has relapsed by returning to his old patterns of behavior after some initial success in controlling his gastrointestinal function. His parents, too, have relapsed into a pattern of blame, shame, and punishment that *they* had previously successfully changed after being educated about the medical causes of soiling (as opposed to viewing encopresis as a character defect such as "laziness").

The parents' negative comments and Bill's negative affect could be reflected, reframed, and summarized with empathy; by saying to Bill's parents, "You're wondering why this has happened now, because you know that Bill can do some really effective things to solve this problem." A clinician could say to Bill, "It is frustrating to you to want to be in good control of your bowels and to feel like your parents believe you are being lazy." The clinician also might reflect the feelings of discouragement and failure that everyone in the family seems to be expressing.

The clinician also could reflect on the parents' implicit but loving wish that they could make everything better for Bill or somehow solve this problem for him, by saying, for example, "Like all parents, you love your son so much that you wish you could make his problem disappear; so, since Bill's problem came back a little bit, it's natural to feel discouraged, because you know now that this is a problem that only Bill can solve." This statement supports Bill's self-efficacy, and the clinician could further emphasize Bill's growing autonomy by giving him and his parents the option to meet with the clinician separately.

As a school-age child, Bill is in the concrete operational stage of cognitive development, so he can deduce outcomes from multiple facts and follow rules of logic. Children at this age can be become involved more actively in changing their own behavior through planning, action, and maintenance. MI can be used more directly with the child at this age. Bill should be given a measure of latitude to problem-solve with the clinician independent of his parents. Bill feels ashamed and would benefit from statements that support his self-efficacy and self-acceptance, while re-educating him about the physiology of encopresis and constipation, such as, "You've done a great job so far, and I know a lot of kids who *used to have* accidents like you did, who had the exact same thing happen to them after they started getting better, and they all got better even faster after it happened again…because they already knew so much more than they knew before. And like them, Bill, you already know a lot about your body's problem with poop and getting constipated, and how that caused these accidents, and how getting unconstipated again will prevent future accidents."

The clinician might ask Bill which parts of the plan were not working well for him, or what got in the way of doing the parts of the plan that worked for him the best in the past. Also, it would be worth readdressing Bill's treatment goals and asking him if the previous goals that he had achieved are the same goals that he would like to achieve in the future. Bill could then be asked what new ideas he has about how to reach those goals, and if he cannot come up with any, the clinician can ask, with permission, if he would like some suggestions for things to do. Finally, assessing Bill's confidence in carrying out whatever revised plan comes out of that discussion by using a confidence ruler could help him adhere better to his new plan of action.

Adolescence (12–18+ Years Old)

Clarissa is a 14-year-old girl who is being seen in an emergency department without a guardian present to receive sutures after getting into a fight with another girl after school. She has no identified primary care source, and the medical record shows that she has not been seen by a physician since a sports physical at age 12. She says, in an angry tone of voice, that this incident is the first time such a thing has happened but that she is "getting really sick of all these girls who are always talking bad about me to everyone so I have to do something to defend myself, and if they try to start something tomorrow then I'll do it again."

Establishing rapport to build a therapeutic alliance with Clarissa is critical to assess the risk she poses to

herself or others, and MI is absolutely indicated in this type of scenario. If, during the assessment, Clarissa is found to be cognitively altered by the use of alcohol or drugs, or if is she is suicidal, homicidal, or does not have a safe place to stay, MI might not be the best counseling style to use until she is stabilized.

Assuming that she poses no active risk to herself or others, Clarissa is resistant at this point to making any behavioral changes, because she does not describe ambivalence and directly states her preference to continue the same behavior. She is entering the formal operations stage of cognitive development, so she is beginning to think in the abstract and use facts to induce hypotheses, which she can then test behaviorally. Adolescent social-emotional development hinges on the formation of an identity in relation to peers, and Clarissa seems to be suffering because she perceives that her peers are rejecting or defaming her. She also seems to be a typical adolescent in that she may minimize her personal vulnerability to high-risk behaviors, seeing herself as immune to negative outcomes.

A useful way to establish rapport with her initially could be to offer a complex reflection that validates her feelings but does not endorse her behavior, such as saying, "Those girls made you feel angry and you thought fighting with them was the only way you could defend yourself. At this point, there's nothing else that you can think of to do the next time they tease you." This statement also serves to amplify her resistance to change, which might allow her to begin to express more ambivalence about her plan to fight with them again. The amplified reflection "there's nothing else you can think of to do" might elicit from her new ideas about additional ways to manage teasing from peers.

Helping Clarissa reflect on her identity, perhaps by asking about her current interests, might lead to the development of a discrepancy between her ideal self and how she is acting. The clinician might ask, "I saw that your last medical visit was for a sports physical when you were 12. Tell me more about that season…and what's life been like for you since then?" The clinician could explore hypotheses with Clarissa by helping her list the advantages and disadvantages of her current behavior, focusing on how she sees herself and how she wants others to see her, and on how she will appear if she continues to fight with her peers.

Finally, if Clarissa cannot generate her own ideas about how else she can handle conflict, with permission, a clinician can provide her with a menu of options and ask her which of these ideas might work for her in the future. Together they can come to an agreement on a reasonable short-term goal for recovery from her acute injury, such as seeing a primary care provider for a "wound check" in 1 or 2 days, or getting a follow-up telephone call from the treating physician or nurse to help ensure that she receives ongoing psychosocial support.

Next Steps in Learning Motivational Interviewing

Introductory-level training in MI frequently can be obtained in sessions at the American Academy of Pediatrics National Conference and Exhibition, or through various adolescent medicine–focused continuing medical education opportunities. Several reader-friendly and practical books on MI can be useful in continuing to expand one's communication repertoire (see Suggested Reading). The day-to-day practice of pediatrics is ripe with opportunities to use MI with patients and families, and the principles of MI can be put into action immediately without formal training.

For example, the effective use of reflective listening and summary statements to check for understanding give the tuned-in clinician cues as to how well he or she is incorporating the spirit of MI into practice (Table 3). Whenever patients or parents spontaneously use "change talk," it behooves the clinician to note silently what principles of MI were in action in that clinical encounter. When preparing to dispense educational guidance or therapeutic suggestions, using the "elicit-provide-elicit" framework helps clinicians tailor their message based on what the patient or parent already knows or has already tried.

Clinicians who are committed to refining their use of MI are encouraged to attend workshops that incorporate practice sessions and role-playing of specific skills. For example, workshops sponsored by the Motivational Interviewing Network of Trainers (MINT; http://motivationalinterviewing.org or www.motivationalinterview.net) are held around the United States and in many parts of the world. Proficiency in MI is gained through systematic feedback and skill-building with someone fully trained in MI (eg, through video or audio review of one's clinical interviews); MINT maintains one such list of qualified trainers. The MINT Web site also has practical information on MI for practitioners at all levels of proficiency.

Summary

- **Motivational Interviewing (MI) is a counseling style that guides patients and parents toward resolving their ambivalence about behavior change to enhance their self-efficacy and improve their own health.**

- The evidence base concerning MI in pediatrics is growing, with strongest support for its use in adolescents. (4)(5)(6)(7)
- Opening strategies for enhancing rapport by using MI include asking permission to provide information and advice; using open-ended questions and "rulers" for assessment; affirming autonomy and self-efficacy; testing hypotheses and actively listening with reflective statements; and using summarizing statements to integrate findings and to discuss menus of options.
- Developmentally tailoring MI in the pediatric setting includes focusing more on parents when dealing with the pre-verbal child and taking cognitive level into account when dealing with children older than preschool age.

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Promoting Healthy Behaviors in Pediatrics : Motivational Interviewing

Andrew J. Barnes and Melanie A. Gold

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Neonatal Hypoxia and Seizures

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Neonatal Hypoxia and Seizures

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Educational Gap

With 1 to 3 in 1,000 term neonates experiencing seizures, pediatricians need to know how to determine the seizure cause and manage appropriately, using brain imaging and treatments such as therapeutic hypothermia, xenon, and other pharmacologic therapies, in order to minimize long-term sequelae and leverage the infant brain's tremendous capacity for repair in the first 2 years after birth.

Objectives

After completing this article, readers should be able to:

1. **Understand the pathophysiology of neonatal seizures.**
2. **Know the many disorders associated with seizures in the newborn.**
3. **Be aware of the characteristics of different neonatal seizure syndromes.**
4. **Know how to evaluate a newborn who is having seizures.**
5. **Be aware of the treatments for neonatal seizures.**
6. **Understand the characteristics and management of hypoxic-ischemic encephalopathy.**

Introduction

Seizures occur during the newborn period at an incidence of ~1 to 3 per 1,000 infants born at term. (1)(2)(3) Numerous systemic and neurologic conditions can manifest as seizures. Cerebral hypoxia-ischemia, defined as partial lack of oxygen resulting in reduction of blood flow to the brain, is the most frequent cause of seizures in the newborn period. It is important to determine the cause of neonatal seizures and institute the appropriate therapy to minimize the long-term sequelae of both the underlying condition and the seizure.

Pathophysiology of Seizures

Seizures are paroxysmal alterations in neurologic function caused by excessive synchronous depolarization of neurons within the central nervous system. Regardless of the underlying pathology manifesting as a seizure, all seizures are due to a shift in cell energy. This shift can result from failure of the adenosine triphosphate (ATP)–dependent sodium-potassium (Na^+-K^+) pump, an imbalance of inhibitory and excitatory neurotransmitters, and both excessive synaptic release and diminished reuptake of glutamate producing increased levels in the synapses.

The neonatal brain is more susceptible to seizures than the mature brain because of a predominance of excitatory neurotransmitters and immature inhibitory systems. During the first few weeks after birth, excitatory activity via *N*-methyl-D-aspartic acid (NMDA) and α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA) receptors predominates in the hippocampus and neocortex. Not only are the inhibitory systems, such as the substantia nigra, relatively underdeveloped in the neonatal brain, but NMDA and AMPA levels in the perinatal brain actually exceed those in adult cortical neurons. (4)

Abbreviations

AED: antiepileptic drug
AMPA: α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid
ATP: adenosine triphosphate
CSF: cerebrospinal fluid
HIE: hypoxic-ischemic encephalopathy
MOCO: molybdenum cofactor
NMDA: *N*-methyl-D-aspartic acid

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Furthermore, γ-aminobutyric acid, the primary inhibitory neurotransmitter in adults, is paradoxically excitatory in the neonate, who has larger intracellular concentrations of chloride in immature neurons, further increasing the susceptibility of the neonatal brain to seizure activity. (5)

Clinical Manifestations

Newborns rarely have well-organized, generalized tonic-clonic seizures because cortical organization is needed to propagate and sustain generalized seizures. Newborns have immature synaptic connections and insufficient myelination in the cortical efferent systems to propagate seizures. In comparison with other primates, however, human newborns have more advanced limbic development and connections to the diencephalon and brainstem, commonly resulting in seizures that manifest as oral-buccal-lingual movements (sucking, chewing), oculomotor phenomena, or apnea. (4)(6)

Classification of Seizures

Neonatal seizures can be classified into four categories: subtle, clonic, tonic, or myoclonic. Subtle seizures are more common in premature infants and manifest most often as ocular phenomena (tonic horizontal eye deviation with or without eye jerking, sustained eye opening with ocular fixation), oral-buccal-lingual movements (chewing or tongue thrusting), or "bicycling" or stepping movements of the lower extremities. Subtle seizures are not consistently associated with EEG changes.

Clonic seizures tend to manifest as focal, slow, rhythmic jerks of the face, unilateral upper or lower extremities, trunk, or neck, and the infant usually remains conscious. With focal seizures, there is often a corresponding underlying focal condition, such as a cerebral infarct.

Tonic seizures can be focal or generalized. Focal tonic seizures result in sustained posturing of a limb or asymmetrical posturing of the trunk or neck, whereas generalized tonic seizures manifest as tonic extension of both upper and lower extremities. Tonic flexion of the upper extremities with extension of lower extremities actually may represent posturing, a movement frequently associated with severe intraventricular hemorrhage, but not necessarily resulting from a seizure.

Myoclonic seizures usually involve the flexor muscle groups and can be focal, multifocal, or generalized. These movements have a faster jerk speed than clonic seizures and are not commonly associated with EEG manifestations. (6)

Seizures can manifest as apnea. Apnea secondary to seizures is more common in the term than the preterm infant. Most infants who have apnea secondary to a seizure also exhibit other subtle phenomena, such as eye opening, staring, and deviation or stereotypical mouth movements during the apneic episode, which can guide the clinician to the diagnosis. In the premature infant, most apnea is not related to seizures. Bradycardia is less likely to be associated with apnea from a seizure than with nonconvulsive apnea. (6)

Differential Diagnosis of Neonatal Seizures

Hypoxic injury is by far the most common cause of seizures in the term neonate, accounting for 40% to 60% of seizures in the newborn period. (7)(8) The next three most common causes are intracranial hemorrhage, intracranial infection, and congenital brain malformations. Combined, these four causes account for 80% of all neonatal seizures.

Hypoxic–Ischemic Encephalopathy

Hypoxic-ischemic encephalopathy (HIE) is defined as brain injury caused by the combination of inadequate oxygen delivery and blood flow to the brain. (9) HIE occurs in 2.5 per 1,000 term births in developed countries, with an up-to-10 times greater incidence in developing countries. HIE can be a devastating entity, with 15% to 20% of affected neonates dying during the newborn period, leaving an additional 25% or more with permanent neurologic deficits. (6) According to the American College of Obstetrics and Gynecology and American Academy of Pediatrics, the following criteria must be present in order to diagnose HIE resulting from perinatal asphyxia (10)(11):

Metabolic acidosis with pH <7.0

- on an umbilical cord gas measurement (arterial or venous) *or*
- within 1 hour of birth on infant arterial blood gas measurement

Base deficit ≥12 mEq/L
Apgar score ≤5 at 10 minutes with continued need for resuscitation
Presence of multiple organ system dysfunction
Clinical evidence of encephalopathy (hypotonia, abnormal oculomotor or pupillary movements, weak or absent suck, apnea, hyperpnea, or clinical seizures). (9)

Determining whether perinatal HIE is attributable to antepartum, intrapartum, or early postnatal events may

be difficult. It is estimated that 20% of events occur in the antepartum period, but the majority are due to intrapartum events. (12)(13) Any event that compromises the blood or oxygen supply to the fetus contributes to hypoxia. These occurrences include maternal events (hemorrhage, amniotic fluid embolism, hemodynamic collapse); placental events (acute abruption); uterine events (rupture); umbilical cord events (tight nuchal cord, cord prolapse/avulsion); and intrapartum infection.

The pathophysiology of brain insult secondary to a hypoxic-ischemic event occurs in three stages over a 24- to 48-hour period: the immediate primary neuronal injury, a variable latent period, and finally late secondary neuronal injury. (14) Primary neuronal injury occurs with interruption of oxygen and glucose to the brain, resulting in decreased ATP and failure of the ATP-dependent Na^+-K^+ pump. Sodium enters the cell, followed by water, causing cell swelling, widespread depolarization, and cell death. Excessive stimulation by glutamate, an excitatory amino acid, results in an increase in intracellular calcium, activating a destructive cascade ultimately resulting in cell death.

If the neonate is resuscitated successfully, the period of primary neuronal injury is followed by reperfusion and a subsequent latent period, during which some neurons recover partially, only to die several hours later. The latent period lasts ~6 hours and is followed by a period of secondary neuronal injury lasting 24 to 48 hours.

As with the period of primary neuronal injury, the period of secondary neuronal injury is mediated by damage to cerebral phosphate compounds, increased intracellular calcium, and elevated extracellular glutamate. The cerebral phosphate compounds (eg, phosphocreatine, ATP) and energy state begin to deteriorate at several hours of postnatal age. This deterioration continues for several days.

Elevated intracellular calcium causes neuronal injury by several mechanisms: activation of phospholipases, proteases, and nucleases; cytoskeletal disruption; and injury to the nucleus and cell membrane. When calcium enters the mitochondria and uncouples oxidative phosphorylation, glutamate is released. Not only are increasing amounts of glutamate released abnormally, but also the mechanisms for neurotransmitter uptake are disrupted because of hypoxia-induced failure of the Na^+-dependent glutamate transmitter.

The result is excess synaptic glutamate levels and activation of NMDA and AMPA receptors. These changes cause a further influx of Na^+ and calcium, followed by water and chloride, again resulting in cell swelling and lysis. Reactive oxygen and nitrogen species are generated as well, which contribute independently to neuronal injury. (9)(10)

The signs of HIE evolve over a period of days, highlighting the importance of careful serial neurologic examinations. Encephalopathy can manifest as a depressed level of consciousness during the first hours after an insult, perhaps accompanied by periodic breathing with apnea or bradycardia. Cranial nerve function, pupillary responses, and spontaneous eye movements are spared in less severe cases. Hypotonia develops with injury to the cortex. (15) Transient improvement in the level of alertness may occur during the first week, but this finding may not necessarily be accompanied by other signs of improved neurologic function.

Seizures occur in the majority of patients who experience moderate to severe HIE. These seizures occur typically in the first 24 hours, with 60% occurring within 12 hours of birth. Seizures may become severe and frequent from 12 to 24 hours after birth. Most seizures are subtle, although focal clonic or multifocal clonic seizures do occur. Focal clonic seizures usually are associated with focal cerebral injury. Approximately 30% of term infants afflicted with HIE and seizures have a focal cerebral infarction. Often, these infants exhibit relatively few other overt signs of encephalopathy. (6)

Prognostication may be aided by the use of a classification scheme, such as the Sarnat stages of encephalopathy. By identifying the stage of encephalopathy, the practitioner can better inform an infant's family regarding morbidity and mortality resulting from the hypoxic-ischemic event (Table 1). (16)

Treatment of HIE has centered around minimizing the damage that occurs during secondary neuronal injury. Therapeutic hypothermia is now the standard of care for infants who experience HIE and is recommended by the International Liaison Committee on Resuscitation. For newly born infants ≥36 weeks' gestation requiring resuscitation at birth and having evolving moderate to severe HIE, cooling therapy to a core temperature of 33.5 to 34.5°C, accomplished either via a head-cooling cap or whole body cooling, should start within 6 hours. Moderate hypothermia should last for 72 hours and then be followed by rewarming for 4 hours. This therapy should be provided in neonatal intensive care facilities with experience in cooling. (17)(18)

Moderate hypothermia results in decreased mortality and decreased severe disability in survivors. The effectiveness of this therapy is evident in its low number-needed-to-treat of 9. Nine infants who have encephalopathy need to be treated with hypothermia for 1 to experience benefit. These results are most striking in the infants who had moderate encephalopathy. Interestingly, infants who had HIE who did not undergo therapeutic hypothermia and

Table 1. **Sarnat Stages of Acute Encephalopathy**

	Stage 1	Stage 2	Stage 3
Level of consciousness	Hyperalert	Lethargic/obtunded	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased/absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak/absent	Absent
Moro	Strong	Weak	Absent
Oculovestibular	Normal	Overactive	Weak/absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; often unequal
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial/salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal/decreased	Increased; diarrhea	Variable
Seizures	None	Common; focal or multifocal	Uncommon (excluding decerebration)
EEG findings	Normal (awake)	Early: low-voltage continuous delta and theta Later: periodic pattern (awake) Seizures: focal 1- to 1 1/2-Hz spike-and-wave	Early: periodic pattern with isopotential phases Later: totally isopotential
Duration	<24 h	2–14 days	Hours to weeks
Poor outcome (death or moderate/severe disability)	Low, similar to healthy comparisons	32%[a]	72%[a]

Adapted from Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol.* 1976;33:696–705, and Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med.* 2005;353:1574–1584.
[a]When treated with therapeutic hypothermia.

also experience elevated core body temperatures have worse outcomes, with the odds of death or disability increased fourfold for each 1°C increase for those in the highest quartile of core temperature (>38°C). (19) Even when cooling therapy is not available, it may be beneficial to withhold an exogenous heat source from the asphyxiated term infant (eg, avoid heating to temperatures >36.5°C).

Adverse effects of moderate hypothermia generally are minimal, the most common being thrombocytopenia (30%), hypoglycemia, hypotension, sinus bradycardia, prolonged QT interval, and subcutaneous fat necrosis. (20) Subcutaneous fat necrosis is an uncommon dermatologic disorder that manifests as firm, subcutaneous nodules that can occur either during or after therapeutic hypothermia. Although the nodules are benign, necrosis can trigger systemic, life-threatening hypercalcemia. (21)

Other adjunctive therapies are being studied that may augment the benefits of hypothermia or may offer a therapy in remote areas lacking ready access to controlled hypothermia. Xenon is an antagonist of the NMDA subtype of the glutamate receptor and has been shown to be neuroprotective when used in conjunction with hypothermia by reducing neuronal death in neonatal rats with HIE, even when xenon administration is delayed for several hours. Disadvantages of xenon include the high cost and the need for closed-circuit delivery via mechanical ventilation and gas-recycling systems. (22) Several phase II trials are currently underway in human neonates. Other pharmacologic therapies are being investigated, with varying neuroprotective effects, including erythropoietin, melatonin, and etanercept, a tumor necrosis factor-α inhibitor. (23)(24) These therapies are likely to be used in conjunction with therapeutic hypothermia.

Brain imaging can be helpful in confirming the diagnosis of HIE, quantifying the extent of damage, and assisting prognostication. MRI is the most accurate modality in newborns. The most common MRI findings in the first week are loss of differentiation of the cerebral cortical gray-white matter, increased signal in the basal ganglia and thalamus, and decreased signal in the posterior limb of the internal capsule.

There is controversy regarding the optimal timing of MRI, because signals are influenced by both the timing of the scan and the region being examined. It is clear that MRI on the first day likely underestimates the extent of injury. The optimal timing for diffusion-weighted MRI is at 2 to 3 days, but better predictions of future impairment based on extent of the thalamus and basal ganglia can be made from conventional MRI during the second week after birth.

Intracranial Hemorrhage

Intracranial hemorrhage accounts for ~15% of seizures occurring in the neonatal period. Subarachnoid hemorrhages, occurring most frequently in term infants, usually are of no long-term clinical significance. In an otherwise well-appearing infant who has an incidental subarachnoid hemorrhage, seizures or apnea often will occur on the second postnatal day, and the infant will appear well during interictal periods. If seizures occur on the day of birth or if the infant is not well appearing between seizures, it is important to consider HIE as an underlying cause. The seizures will subside as the hemorrhage heals.

Seizures resulting from intraventricular hemorrhage occur primarily in preterm infants and in infants who have the most severe hemorrhages with accompanying parenchymal involvement. An isolated subependymal germinal matrix hemorrhage is associated with seizures uncommonly. Seizures may occur if extension of the hemorrhage occurs into the ventricles with corresponding ventricular dilation, or when there is extension into the brain parenchyma. These seizures usually manifest with generalized tonic activity but can appear as subtle seizure activity.

Subdural hemorrhages often are traumatic and result in a cerebral contusion leading to seizures in 50% of affected infants. The seizures usually are focal and appear in the first 48 hours after an insult.

Central Nervous System Malformations

Developmental defects of the brain account for 5% to 10% of seizures in the neonatal period. Usually there is a disorder of neuronal migration resulting in cerebral cortical dysgenesis. Neuronal migration, the movement of millions of nerve cells from their sites of origin in the ventricular and subventricular zones to their ultimate location in the brain, peaks during the third to fifth months of gestation. Disorders of migration usually cause clinical deficits soon after birth. The neuronal migration disorders most commonly presenting with seizures are schizencephaly, lissencephaly, pachygyria, and polymicrogyria. (6) Newborns who have a neuronal migration disorder severe enough to cause seizures in the neonatal period will almost certainly have subsequent epilepsy.

Infection

Intracranial infections account for 5% to 10% of neonatal seizures and must always be considered as a possible cause in any infant experiencing new-onset seizures. Bacterial meningitis is due most commonly to group B *Streptococcus* or *Escherichia coli*. Gram-negative organisms are particularly notable for causing brain abscesses and cysts. Infants hospitalized for other causes may be at risk for catheter-related or hospital-acquired sepsis or meningitis. Nonbacterial causes of neonatal seizures include infection with toxoplasmosis, herpes simplex virus, group-B coxsackie virus, rubella, and cytomegalovirus.

Seizures occur in 50% of cases of bacterial meningitis. One half of the seizures are subtle and are likely the result of inflammation of the arachnoid. Focal seizures occur in the other half of cases and are due to ischemic lesions. A significant number of septic infants also develop seizures. Therefore, it is recommended that any infant who has proven bacteremia or septicemia who develops seizures undergo an evaluation for meningitis, including a cerebrospinal fluid (CSF) analysis.

Metabolic Disturbances

Numerous metabolic disturbances can cause seizures in the neonate. These conditions include electrolyte disorders, as well as amino and organic acidopathies and mitochondrial disorders. Electrolyte disorders that can cause seizures include hypoglycemia, hypocalcemia, hypomagnesemia, hyponatremia, and hypernatremia.

Hypoglycemia is a common cause of seizures in infants who are small for gestational age and in those born to diabetic mothers. Seizures due to hypoglycemia often are preceded by other neurologic signs, such as jitteriness and hypotonia. The duration of hypoglycemia is the most important factor in the subsequent development of neurologic signs. Prompt recognition and treatment of hypoglycemia is imperative to prevent permanent neurologic sequelae.

The most common area of brain injury seen on MRI in infants who sustained severe hypoglycemia is

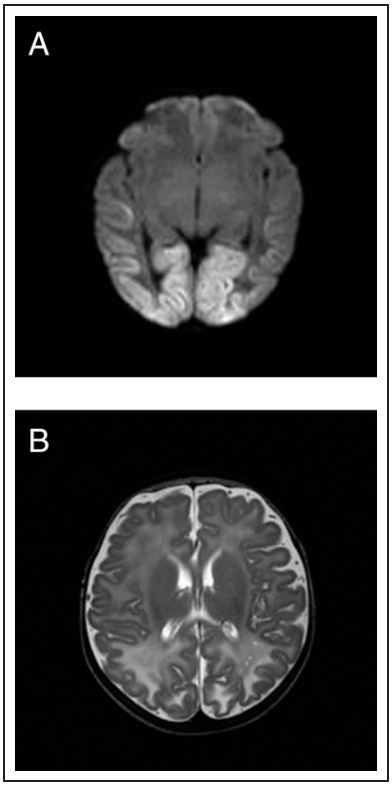

Figure. A. Brain MRI from a 4-day-old infant who experienced profound hypoglycemia. Note the restricted diffusion in the bilateral occipital and posterior parietal regions that can be seen with ischemia and severe hypoglycemia. B. Repeat MRI of same patient at age 6 weeks. Note the T2 hyperintensity in the bilateral occipital lobes consistent with gliosis from previous injury. There is also occipital lobe cystic encephalomalacia.

the occipital region (Fig). (25) This finding can differentiate brain injury caused by hypoglycemia from that caused by HIE, which often is global and affects the deep nuclei.

As with other electrolyte abnormalities associated with seizures, hypocalcemia is much more likely to coexist in an infant who has another cause of seizures (eg, HIE) rather than be the primary cause. There are two peak time periods for hypocalcemia to present in newborns. Infants who are premature, small for gestational age, or have diabetic mothers will present with seizures in the first 3 days after birth.

Hypocalcemia that appears later often is due to consumption of cow milk with high phosphorus content or to a syndromic (DiGeorge syndrome) or endocrine abnormality (hyperparathyroidism). Hypomagnesemia may accompany hypocalcemia or may exist primarily.

Both hyponatremia and hypernatremia can cause seizures. Hyponatremia in newborns commonly is iatrogenic, caused by administration of an excessive volume of hypotonic intravenous fluid or oral administration of free water. The syndrome of inappropriate antidiuretic hormone can occur with central nervous system disease (eg, meningitis, HIE, intraventricular hemorrhage, hydrocephalus) or with lung disease (eg, pneumonia). Rare causes of hyponatremia in a term infant are maternal water intoxication during labor (26) or a water birth that leads to excessive gulping of free water by the infant at time of birth. (27)

Although the metabolic disturbances due to inborn errors of metabolism are relatively rare, these disorders should be considered in infants who have seizures. Suspicion for an underlying inborn error of metabolism should be raised when there is severe and persistent hypoglycemia, metabolic acidosis or alkalosis, lack of a birth history suggesting perinatal oxygen deprivation, an elevated ammonia level, or congenital anomalies. Prompt diagnosis and treatment can, in some cases, prevent further damage to the infant's neurologic development (Table 2).

Nonketotic hyperglycinemia is a devastating progressive encephalopathy manifesting shortly after birth with lethargy, hypotonia, apnea leading to respiratory failure, and intractable seizures. This disorder is due to a defect in the glycine cleavage enzyme system. Laboratory findings are notable for a lack of metabolic acidosis, ketones, hyperammonemia, or signs of end-organ damage in an infant who appears to have been asphyxiated. The diagnosis is made by finding increased levels of CSF glycine. There is often a history of in utero and postnatal hiccups. Multiple therapies, including strychnine, tryptophan, and dextromethorphan, have been tried with limited success. Treatment with valproate paradoxically increases seizure activity by inhibiting glycine uptake in the mitochondria and increasing CSF glycine levels. (28)

Sulfite oxidase deficiency and molybdenum cofactor (MOCO) deficiency present soon after birth with feeding difficulties, vomiting, and seizures that are difficult to control. The clinical course progresses to spasticity, severe developmental delay, and microcephaly. Dislocated lenses and a seborrheic rash appear later in infancy. Sulfite oxidase deficiency can occur in isolation or as part of MOCO in 75% of cases. The diagnosis is made via mass spectrometry.

Simple screening analysis in an infant having seizures of unknown cause can include the use of a fresh urine sulfite strip test and testing for the presence of low plasma homocysteine or hypouricemia (in MOCO deficiency). There will be progressive destruction of neuronal structures and white matter on brain imaging.

Table 2. Metabolic Disturbances Presenting With Seizures in the Neonatal Period

Organic aciduria/acidemia
- Methylmalonic acidemia, propionic acidemia, isovaleric acidemia
- Severe acidosis, hyperammonemia, unusual odor, neutropenia, thrombocytopenia

Peroxisomal disorders
- Zellweger syndrome (hepatomegaly, renal and hepatic cysts)
- Neonatal adrenoleukodystrophy

Urea cycle defects
- Ornithine-transcarbamylase deficiency (OTC) (X-linked recessive)

Nonketotic hyperglycinemia (NKH)
- Severe encephalopathy, hiccups; marked lack of acidosis, hypoglycemia, or hyperammonemia

Multiple carboxylase deficiency
- Holocarboxylase synthetase deficiency (hypotonia, vomiting, tachypnea, skin rash, metabolic ketoacidosis, hypoglycemia, moderate hyperammonemia); autosomal recessive

Glutaric aciduria, type II
- Severe hypotonia and nonketotic metabolic acidosis, hypoglycemia, hepatomegaly, polycystic enlarged kidneys, facial dysmorphism, rock-bottom feet, muscular defects of anterior abdominal wall, abnormal external genitalia, odor of sweaty feet, impaired cerebral neuronal migration; autosomal recessive

Molybdenum cofactor deficiency
- Presence of sulfites in urine, low plasma levels of homocysteine and uric acid

Pyridoxine dependency
- Dramatic improvement with administration of vitamin B_6

Folinic acid–responsive seizures
- Improvement with administration of folinic acid

Treatment involves a diet low in sulfur-containing amino acids, supplementation with sulfate, and administration of a MOCO precursor. However, these measures have not yet resulted in lasting clinical benefit. (6)(29)(30)

Multiple carboxylase deficiency has two basic types, one of which (holocarboxylase synthetase deficiency) typically presents in the neonate. The underlying mechanism involves the metabolism of biotin, and the condition is inherited in an autosomal recessive pattern. This disorder presents clinically in the first days after birth with vomiting, tachypnea, hypotonia, seizures, and rash. Laboratory findings include ketoacidosis, moderate hyperammonemia, hypoglycemia, and elevation of several organic acids in the serum. Treatment is with high doses of biotin. Many state newborn screening programs include testing for this disorder.

Glutaric acidemia type II is due to a defect in the mitochondrial electron transport chain. This disorder can have a neonatal form that presents soon after birth with lethargy, tachypnea, vomiting, profound hypotonia, and seizures. These infants often are born prematurely and have congenital anomalies such as hepatomegaly, polycystic kidneys, rocker-bottom feet, anterior abdominal wall muscular defects, abnormal external genitalia, and an odor of sweaty feet. Neuronal migration defects affect the cerebral cortex. Despite a diet low in fat and protein, and supplementation with riboflavin and L-carnitine, the prognosis is poor.

The most common of the urea cycle defects, ornithine transcarbamylase deficiency is transmitted in an X-linked recessive fashion. Boys are affected most severely in the neonatal period and present often with feeding difficulties, lethargy, respiratory distress, impairment of consciousness, vomiting, seizures, and hyperammonemic encephalopathy. Plasma ammonia levels often are extremely elevated, and dialysis can be life saving during the acute presentation. Long-term treatment includes a low-protein diet, arginine supplementation, and sodium benzoate and phenylbutyrate administration to remove excess nitrogen.

Pyridoxine dependency is a rare autosomal recessive disorder of lysine degradation resulting in intractable seizures unresponsive to antiepileptic medication but responsive to treatment with vitamin B_6 (pyridoxine). The classic presentation occurs shortly after birth with refractory seizures. The infant may present with some symptoms of encephalopathy (apnea, lethargy, temperature instability), but there is no history of hypoxia. Burst suppression is a common EEG manifestation. (31) The diagnosis can be made clinically with resolution of seizures after administration of high-dose pyridoxine (100 mg IV) or by measuring increased α-aminoadipic semialdehyde in the urine. This deficiency also can be identified by a mutation in the ALDH7A1 (antiquitin) gene. Prompt diagnosis and treatment is imperative to reduce long-term cognitive impairment.

Folinic acid–responsive seizures present similarly to those of pyridoxine dependency but respond to treatment

with folinic acid. There is currently no test available, and diagnosis usually is made when seizures are controlled after empiric treatment with folinic acid. (32)

Neonatal Seizure Syndromes

Idiopathic syndromes of clinical seizures in newborns can be subdivided into the nonepileptic syndromes (benign neonatal sleep myoclonus, hyperexplexia) and the epileptic syndromes (benign familial neonatal seizures, benign idiopathic neonatal seizures, early myoclonic encephalopathy, early infantile epileptic encephalopathy). Infantile seizure syndromes, which present typically after the first month after birth, occasionally may manifest in the neonatal period.

Benign neonatal sleep myoclonus has its onset in the first week after birth and presents with clinical myoclonic seizures occurring only during non–rapid eye movement sleep. The infant manifests bilateral, synchronous, and repetitive movements of the upper or lower extremities (or both) that are provoked by gentle rocking of the crib in a head-to-toe direction and cease with the infant's arousal from sleep.

Hyperexplexia, or "startle disease," is a nonepileptic syndrome characterized by an exaggerated startle response with sustained tonic spasm to unexpected auditory, visual, or somatic stimuli. This reaction is caused by increased excitability of the reticular neurons in the brainstem. The mother may have noted sudden jerky movements of the fetus in utero, and hypertonia with an exaggerated startle response may be apparent from the first hours of postnatal age. The recurrent startle may result in increasing rigidity and jittery movements that become rhythmic and may mimic seizures. The tonic spasms can lead to apnea. Forced truncal flexion terminates the episodes. Clonazepam decreases the episodes, which ultimately disappear spontaneously by age 2 years. (33)

Benign familial neonatal seizures disorder is a rare autosomal dominant disorder that manifests with seizure onset on postnatal day 2 or 3. The infant can have 10 to 20 focal clonic or tonic seizures per day but appears well between seizures. The EEG shows brief flattening with apnea and tonic motor activity, followed by bilateral spikes and slow waves with clonic activity. The voltage-gated K^+ channel KCNQ2 encoded on chromosome 20 is implicated in 90% of affected cases. These seizures generally have a good response to antiepileptic medications, and affected newborns have normal neurologic development if their syndrome is self-limited, resolving in early infancy.

Another neonatal epileptic syndrome, termed benign idiopathic neonatal seizures, or fifth-day fits, is characterized by seizures peaking around the fifth postnatal day in otherwise apparently healthy term infants. This disorder manifests typically with multifocal clonic seizures accompanied by apnea. The seizures last <24 hours, but status epilepticus occurs during this time in a great majority of affected infants. Although the cause is not yet fully defined, both the possibility of acute zinc deficiency or mutations of KCNQ2, the K^+ channel most commonly affected in benign familial neonatal seizures, have been suggested. The outcome is favorable.

Early myoclonic encephalopathy is characterized by severe recurrent myoclonic and focal clonic seizures. The EEG shows a persistent suppression burst pattern enhanced during sleep. Multiple underlying causes have been implicated, primarily metabolic (eg, nonketotic hyperglycinemia). Seizure management is challenging, but the spells may respond to adrenocorticotropic hormone. The outcome is poor.

Early infantile epileptic encephalopathy, or Ohtahara syndrome, is a devastating disorder characterized clinically by severe recurrent "tonic spasms" and on EEG by burst suppression or markedly disorganized background rhythms. Over time, the EEG pattern evolves to hypsarrhythmia and West syndrome. The causes usually are structural (eg, neuronal migrational disorders). There have been reports of infants who have early infantile epileptic encephalopathy having CSF monoamine findings similar to aromatic acid decarboxylase deficiency who respond to treatment with pyridoxal 5-phosphate. As in early myoclonic encephalopathy, the seizures in this syndrome are difficult to control, but may respond favorably to adrenocorticotropic hormone; ultimately, these patients have a very poor outcome. (6)

Other Causes of Seizures

Drug Withdrawal

The neonate who was exposed passively to certain drugs in utero is at risk for the neonatal abstinence syndrome, a syndrome that can include seizures infrequently. Other signs and symptoms of neonatal abstinence depend on the specific maternal substance ingested, but include hyperirritability, hyperalertness, increased rooting and uncoordinated sucking, emesis, loose stools, yawning, and sneezing.

The drugs most commonly implicated are opioids (heroin, methadone, propoxyphene, codeine, oxycodone, hydrocodone, etc). Benzodiazepines, barbiturates, tricyclic antidepressants, cocaine, alcohol, pentazocine, and tripelennamine (the combination of the latter two is referred to as "Ts and Blues"), and the antidepressant class of selective serotonin reuptake inhibitors also may be associated with neonatal seizures or encephalopathy. (34)

Depending on the particular drug exposure and the extent to which the fetus was exposed (the maternal length of usage, amount of usage, and last usage before delivery), symptoms of abstinence and seizure can occur in the first 1 to 5 days after birth. Most of these passive exposures result in nonspecific withdrawal symptoms, but opioid withdrawal presents with a pathognomonic neonatal abstinence syndrome that usually is present when seizures occur. The seizures usually subside with appropriate treatment of the abstinence syndrome. Many drug withdrawal syndromes involve jitteriness that may be mistaken for seizures. Seizures resulting from use of tripelennamine may be a toxic effect of the drug because seizures are an adverse effect of this drug in adults.

Most abstinence syndromes develop within the first 24 to 48 hours after birth, although onset may be later if the mother used a long-acting drug (eg, methadone). Treatment of neonatal abstinence syndrome includes supportive measures, as well as appropriate drug therapy with tincture of opium, methadone, or morphine for opioid-exposed infants, in addition to phenobarbital or diazepam for seizures.

Local Anesthetic Infiltration

Local anesthetic infiltration is a rare cause of seizures immediately after birth. The typical scenario is an infant who develops tonic seizures in the first 6 hours after a birth in which a local anesthetic, typically for a paracervical or pudendal block, was inadvertently injected into the infant scalp. The newborn's pupils will be dilated and fixed to light, and a doll's eyes reflex may be present. The diagnosis can be made by history, measurement of anesthetic in the blood or CSF, and telltale marks on the scalp.

Electroencephalography

An important tool in the evaluation of infants who have seizures is the surface EEG. Clinical recognition of neonatal seizures is challenging because not only may neonates display behaviors concerning for seizures without an electrographic correlate, but also there may be seizure activity on EEG not clinically recognizable as a seizure. In neonates who have seizures and are monitored with continuous EEG, up to 79% of electrographic seizures are not accompanied by clinical seizure activity, and 47% of infants who have HIE and are undergoing head cooling experience electrographic seizures exclusively. (35)(36)

Despite these issues, a 1- to 2-hour EEG can confirm the clinical diagnosis of seizures, diagnose subclinical seizures, and show the level of background interictal involvement. Video-EEG for 12 to 24 hours often is useful to correlate specific physical manifestations with electrical activity. Because of immature myelination in neonates, abnormal signals from seizure activity in deeper areas of the brain may not be fully propagated to the surface for capture by the EEG.

Amplitude-integrated EEG can be a useful bedside tool for cerebral function monitoring in infants who have HIE. Its utility in the nonencephalopathic infant who has seizures is limited. This technique records a single-channel EEG that modifies the wave recording for bedside interpretation. The interpretation of the EEG is based on pattern recognition, and the study is useful for correlating the early findings of HIE with subsequent neurodevelopmental outcomes of term infants, especially those managed with normothermia. This type of EEG is not helpful in detecting subclinical seizures. (37)

Treatment

The conventional first-line treatment for neonatal seizures is phenobarbital administered intravenously (Table 3). Phenobarbital alone completely controls seizures in a little over 40% of cases. When combined with fosphenytoin, historically the second-line choice, 60% of cases are completely controlled. (38) Disadvantages of phenobarbital include sedation, which can impair clinical neurologic assessments. Like fosphenytoin, blood levels

Table 3. Antiepileptic Drug Dosing

	Loading Dose	Maintenance Dose	Mode of Administration
Phenobarbital	20 mg/kg. Refractory seizures: Additional 5 mg/kg doses up to a total of 40 mg/kg	3–4 mg/kg every 24 h IV, IM, PO, PR	IV, IM, PO, PR
Fosphenytoin	15–20 mg/kg	4–8 mg/kg every 24 h	IV, IM
Levetiracetam	10 mg/kg	Up to 30 mg/kg/dose every 12 h	IV or PO
Lorazepam	0.05–0.1 mg/kg		IV

IM=intramuscularly; IV=intravenously; PO=orally; PR=rectally.

need to be monitored. Phenobarbital induces neuronal apoptosis in many areas of the brain in rats, leading to concern for use in neonates, especially those who have HIE in whom there is already damage and death of neurons. Levetiracetam is well tolerated and, unlike phenobarbital and fosphenytoin, is not metabolized by the cytochrome P450 system, which can be altered in the face of systemic hypoxic injury. Levetiracetam's exact mechanism of action is yet to be elucidated but may involve prevention of hypersynchronization of epileptiform bursts and propagation of seizure activity. Lorazepam, a benzodiazepine, can be effective in infants who have seizures refractory to other antiepileptic medications. (39)

Duration of treatment with antiepileptic drugs (AEDs) depends upon the neurologic examination, frequency of seizures, EEG findings, and underlying etiology for seizures. On one extreme, infants who have cortical dysgenesis experiencing seizures in the neonatal period will almost assuredly have persistent seizure activity and require long-term AEDs. A neurologic examination with abnormal results is also associated with increased risk of persistent seizures. In general, consideration for trial of discontinuation of AEDs is made when infants are seizure free and have a neurologic examination with normal findings. If the results of the neurologic examination are abnormal, but the infant is clinically free of seizures and has a reassuring EEG, a trial off AEDs is appropriate.

Prognosis

The short- and long-term prognosis of neonates who develop seizures is highly variable and depends upon the cause for seizures (Table 4). An increased level of seizure complexity, persistent abnormal electrical activity, and need for multiple medications to control the seizures are all associated with worse developmental outcomes. Multiple repetitive seizures cause damage to developing cortical circuitry (40) and when superimposed on an already abnormal brain structure (such as with cortical dysgenesis), can have a devastating result. However, because there is so much brain plasticity in the first 2 years after birth, the infant brain has tremendous potential for repair, growth, and compensation after injury. It is important that a neurologist and a developmental pediatrician follow infants who have seizures with the goals of controlling seizures, minimizing medication adverse effects, and implementing early treatment of developmental disorders.

Table 4. Neonatal Seizure Prognosis, by Etiology

Neurological Disease	Abnormal Neurodevelopment, %
Bacterial meningitis	50
Hypoxic-ischemic encephalopathy	50
Hypocalcemia	
• Early-onset	50
• Late-onset	0
Hypoglycemia (profound/prolonged)[a]	50
Intraventricular hemorrhage with parenchymal damage	90
Congenital brain malformation	100
Primary subarachnoid hemorrhage	10

[a]Whole-blood glucose <40 mg/dL for >4 hours.

Summary

- Based on observational and animal studies, human newborns are more susceptible to seizures than older children. (5)(6)
- Based on observational studies and expert opinion, compared with older children, newborn infants are more likely to manifest seizures with oral-buccal-lingual movements, oculomotor phenomena, or apnea. (4)(6)
- Based on strong research evidence, the degree of severity of hypoxic-ischemic encephalopathy strongly influences the neurodevelopmental outcome of affected infants. (16)
- Based on strong research evidence, newborns who have hypoxic-ischemic encephalopathy should be treated with moderate hypothermia (head- or whole-body cooling). (17)(18)
- Based on some research evidence and consensus, newborns who have hypoxic-ischemic encephalopathy or clinical concern for seizures should undergo a bedside EEG. (35)(36)(37)
- Based on consensus, discontinuation of antiepileptic medications can be considered in infants without congenital brain malformations who are subsequently free of seizures (clinically and electrographically). (6)

Different types of neonatal seizures can be viewed as part of a recent article in NeoReviews. *All of these seizure types can result from hypoxia. To view these seizures, visit neoreviews.aappublications.org/content/13/4/e213/suppl/DC1.*

To view the references for this article, visit the September issue at http://pedsinreview.aappublications.org and click on "Neonatal Hypoxia and Seizures."

PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Since January 2012, learners can take *Pediatrics in Review* quizzes and claim credit online *only*. No paper answer form will be printed in the journal.

New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for *AMA PRA Category 1 Credit™*. To successfully complete 2012 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

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1. A neonate experiences a moderate intrapartum hypoxic-ischemic event. The first seizure occurs 20 hours after birth. In such circumstances, seizures primarily reflect
   A. Destruction of inhibitory receptors.
   B. Inadequate intrasynaptic glutamate accumulation.
   C. Increased permeability of the cell membrane to sodium.
   D. Myelin destruction.
   E. Reduced permeability of the cell membrane to potassium.
2. A neonate experiences a moderate intrapartum hypoxic-ischemic event. Among the following therapeutic options, the choice that offers the best chance of minimizing secondary neuronal injury is
   A. Erythropoietin.
   B. Hypothermia.
   C. Melatonin.
   D. Phenobarbital.
   E. Xenon.
3. A 30-hour-old appropriate-for-gestational-age term neonate experiences recurrent brief apnea associated with wide opening of the eyes. In between the spells, the infant appears normal. Gestation was unremarkable. Maternal screening for infectious disease was negative. Rupture of membranes occurred 1 hour before delivery. The fluid was clear. Delivery was vaginal, vertex with Apgar scores of 7 at 1 minute and 9 at 5 minutes. The physical examination is unrevealing. Blood glucose is 75 mg/dL. The most likely explanation for the spells is
   A. A disorder of neuronal migration.
   B. Bacterial meningitis.
   C. Hypoxic-ischemic encephalopathy.
   D. Nonketotic hyperglycinemia.
   E. Subarachnoid hemorrhage.
4. You are seeing a 10-day-old boy whose mother is concerned about the simultaneous jerks of the upper and lower extremities that occur in her son during sleep. She first noted this when he was age 5 days. He was delivered vaginally at term with normal weight for age. His Apgar scores were 8 at 1 minute and 9 at 5 minutes. He left the hospital with his mother at age 2 days. He has been breastfeeding well and makes no unusual movements other than hiccups when awake. You suspect
   A. Benign familial neonatal seizures.
   B. Benign idiopathic neonatal seizures (fifth-day fits).
   C. Benign neonatal sleep myoclonus.
   D. Hyperexplexia (startle disease).
   E. Myoclonic encephalopathy.
5. A 1-day-old boy with suspected hypoxic-ischemic encephalopathy has two episodes of tonic horizontal eye deviation associated with rapid chewing movements. You suspect subtle seizures and decide to treat them. Which of the following anticonvulsants has been used in these circumstances, is well tolerated, and is not metabolized by the cytochrome P450 system?
   A. Ethosuximide.
   B. Fosphenytoin.
   C. Levetiracetam.
   D. Phenobarbital.
   E. Valproic acid.

Neonatal Hypoxia and Seizures

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Educational Gap

Recent studies have provided updated guidelines for the diagnosis of head injury and the management of patients who experience concussions. A multidisciplinary panel has recently issued new guidelines for return to play after head injury.

Objectives

After reading this article, readers should be able to:

1. **Understand the anatomy and pathophysiology relevant to pediatric head injuries.**
2. **Take an appropriate history, perform an appropriate physical examination, and decide what imaging, if any, is warranted in the case of a child with a head injury.**
3. **Know the characteristics of the various types of intracranial injuries.**
4. **Understand the proper management of both minor and severe head injuries in children.**

Introduction

Pediatric head injury is extremely common. Although the vast majority of children with head trauma have minor injuries, a small number, even among well-appearing children, will have more serious injuries with the potential for deterioration and significant sequelae. The clinician is challenged to discern which few among the many injured are at high risk for intracranial complications. Clinical symptoms are neither completely sensitive nor specific for significant injury: vomiting may be associated with intracranial injury (ICI), but most children who experience vomiting do not have a complication. Computed tomography (CT) accurately identifies ICIs requiring intervention, but also identifies minor lesions with unclear clinical importance (ie, not requiring intervention) and exposes developing brains to ionizing radiation with the associated risks.

Although clinical decision rules determine which children are at highest risk and provide a useful clinical framework, they may not necessarily direct care. Additionally, in this era of reliance on imaging, it is important to remember what the clinical examination tells us regarding brain function, information that may or may not correlate with the structural information provided on head CT.

The purpose of this discussion is to review important aspects of pediatric head trauma. Sections on epidemiology, mechanisms of injury, and the pathophysiology of specific injuries will provide a backdrop for the discussion of clinical assessment and indications for imaging and admission. What follows is a discussion of concussion, postconcussion syndrome, and return-to-play recommendations.

Abbreviations

BSF:	basilar skull fracture
CSF:	cerebrospinal fluid
CT:	computed tomography
EDH:	epidural hemorrhage
GCS:	Glasgow Coma Scale
ICI:	intracranial injury
ICP:	intracranial pressure
PECARN:	Pediatric Emergency Care Applied Research Network
SAH:	subarachnoid hemorrhage
SDH:	subdural hemorrhage
TBI:	traumatic brain injury

Epidemiology

Childhood head injuries account for more than 600,000 emergency department (ED) visits per year and presumably a larger

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number of visits and calls to primary care providers. Most pediatric head injuries are minor, including scalp and face contusions, abrasions, and lacerations that do not raise concern for significant underlying pathology; however, trauma is the leading cause of death in children older than 1 year, and among trauma patients, head injury is the leading cause of death and disability. Pediatric head trauma–related deaths in the United States are in excess of 3,000 per year.

Although children exhibit almost limitless creativity with regard to sustaining injury, most pediatric head trauma results from falls, motor vehicle collisions, auto versus pedestrian incidents, bicycle-related injuries, and sports. Younger children suffer more falls and are more often the victims of child abuse, whereas motor vehicle crashes and sports-related mechanisms play a greater role in older children. This discussion focuses on blunt head trauma rather than penetrating trauma (eg, gunshot wound) because penetrating injury is much less common and unlikely to present to the primary care clinician.

Although the approach to head injury should consider the potential for serious injury in all cases, some mechanisms can be regarded as relatively trivial and unlikely to be associated with serious injury. These injuries include low-velocity self-propelled contact into stationary objects (eg, the toddler runs into the door frame) and falls from standing or sitting height or lower. However, the presence of any symptoms of head trauma despite the history of an apparently benign mechanism would no longer qualify the head injury as trivial.

Rarely, minor mechanisms may create more serious injury in the presence of undiagnosed intracranial pathology (eg, hemorrhage into a brain tumor). The clinician also must be alert to more dangerous mechanisms that could be concealed, either because the child chooses not to disclose or because the injury was inflicted.

General Pathophysiology

Brain injury results from the blow to the head and the interplay of brain parenchyma, the brain's coverings, the brain's housing structure (the cranial vault), and the vascular supply. It is useful to consider the relevant anatomic structures as layers from outside to inside.

The scalp consists of five layers of soft tissue that cover the skull. Common injuries to the skin and subcutaneous tissue (the outer two layers) include lacerations, abrasions, and freely mobile contusions. Beneath lies the strong galea aponeurotica that also connects muscular tissue on the front and back of the skull. Underneath are the loosely applied areoloar tissue layer and then the pericranium.

Hemorrhages may occur in the subgaleal region from direct blows or as a result of bleeding from a fracture. Cephalohematomas are hematomas caused by bleeding beneath the periosteum, a condition well known to those who care for newborn infants.

The skull can be divided into the calvarium or bony skullcap and the skull base. The skullcap is composed of the frontal, parietal, occipital, and temporal bones. The base of the skull is made up of the sphenoid, palatine, and maxillary bones and portions of the temporal and occipital bones. Injury to the calvarium results from direct forces, and fractures commonly are linear.

Less commonly, skull fractures may be depressed (intruded by more than the thickness of the bone), comminuted (consisting of multiple fragments), diastatic (widely split), or open (communicating with a laceration). Fractures involving the skull base, known as basilar skull fractures (BSFs), are more complicated because of adjacent anatomic structures (eg, cranial nerves, sinuses), their association with ICI, and the risk they pose for meningitis.

Within the skull are the intracranial contents, consisting of the brain and its covering membranes (the meninges), blood, and cerebrospinal fluid (CSF). The meninges play an important role in the genesis of serious ICI. The outermost meningeal layer, the dura mater, is attached tightly to the inner aspect of the skull. The epidural space is a potential space between the dura and the skull. Meningeal arteries course between two layers of the dura and may become more grooved into the skull as the skull matures, so that a skull fracture may injure these vessels and cause bleeding into the epidural space. Meningeal arteries are particularly vulnerable to injury because they run beneath the thinnest part of the skull. Channels exist within the dura for venous drainage and these dural sinuses also may be lacerated. Blood collecting in the epidural space is referred to as an epidural hematoma or epidural hemorrhage (EDH).

Beneath the dura lies the arachnoid mater, a thin tissue layer coursing close to the brain but not following the brain sulci. This membrane separates the CSF-containing subarachnoid space beneath it from the subdural space. Within the subdural space lie the bridging veins that return blood from the brain to the dural sinuses. These bridging veins are susceptible to shearing forces when there is rapid acceleration or deceleration that moves the brain within the skull. A hematoma in this space is termed a subdural hemorrhage (SDH).

The third, innermost meningeal layer is termed the pia mater and adheres to the underlying brain, coursing over all gyri and sulci. This layer contains many small vessels that can be injured from direct blow or shear forces, resulting in a subarachnoid hemorrhage (SAH).

Beneath the meninges lies the brain parenchyma, a semisolid tissue that is not affixed to the skull and can move freely within it. The CSF that bathes the brain and the spinal cord provides some degree of cushioning for the brain.

It is useful to discuss brain injury as having two phases. The primary injury is mechanical damage sustained immediately at the time of trauma from direct impact (eg, brain impacts the inner aspect of the skull or a skull fragment moves into the brain) or from shear forces when the gray matter and white matter move at different speeds during deceleration or acceleration.

Secondary injury refers to ongoing derangement to neuronal cells not initially injured during the traumatic event. Ongoing injury results from processes initiated by the trauma, including hypoxia, hypoperfusion (local or systemic shock), metabolic derangements (eg, hypoglycemia), expanding mass and increased pressure, and edema. Because primary injury occurs at the moment of trauma, little can be done to mitigate it other than prevention, so treatment during trauma resuscitation focuses on preventing secondary injury.

When considering secondary injury, two additional concepts warrant further discussion. The first consideration relates to pressure and volume within the cranial vault. After infancy, the cranial vault is a relatively stiff, poorly compliant structure and the intracranial volume is relatively fixed. From a simplistic standpoint, the vault contains brain, blood, and CSF, and any increase in the volume of one component necessitates a relative decrease in another.

If volume compensation does not occur, intracranial pressure (ICP) will increase. With progressive increases in ICP, the patient will experience headache, vomiting, and depressed mental status, then posturing, and ultimately vital sign deterioration. Increasing ICP may lead to global ischemia through mechanisms discussed later in this section. Ultimately, increased ICP will lead to brain herniation (abnormal movement of the brain across skull structures).

Herniation can occur at several different anatomic locations (Fig 1). When a mass lesion is one-sided and supratentorial, uncal herniation may occur. This type of herniation involves movement of the innermost part of the temporal lobe, the uncus, over the tentorium, with resultant pressure on the midbrain and pressure on the third cranial nerve, impairing its parasympathetic fibers and leading to ipsilateral pupillary dilation.

Central herniation occurs when central brain structures, including the diencephalon and temporal lobes, move caudally through the tentorium cerebelli. Cingulate or subfalcine herniation occurs when the cingulate gyrus is pushed across the midline under the falx cerebrial. Although subfalcine herniation does not affect the midbrain directly, it can affect blood flow and can progress to central herniation.

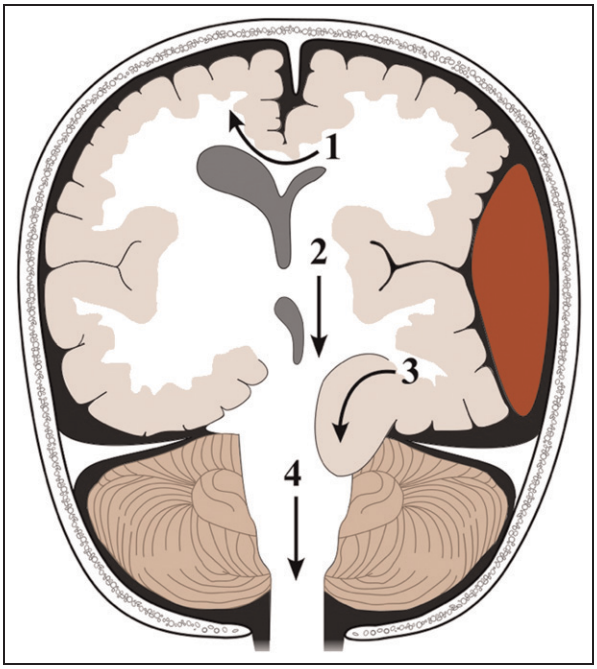

Figure 1. This figure depicts four types of brain herniation: (1) cingulated (subfalcine), (2) central, (3) uncal (transtentorial), and (4) tonsillar. (Figure is reproduced with permission from Kaye AH. Head Injuries. In: Smith JA, Tjandra JJ, Clunie GJ, Kaye AH, eds. *Textbook of Surgery*. 3rd ed. Oxford, UK: Wiley-Blackwell; 2006:445–453.)

In tonsillar herniation, the cerebellar tonsils move down through the foramen magnum with compression of the lower brainstem and upper cervical spinal cord. Compression of the brainstem may result in severe neurologic dysfunction, cardiovascular and respiratory instability, and death.

The other important concept in considering secondary injury involves cerebral perfusion. Cerebral perfusion pressure is the difference between the mean arterial blood pressure and ICP. In health, cerebral blood flow is maintained despite variable blood pressures by autoregulatory changes in cerebral vascular resistance. When severe injuries occur, this ability to autoregulate may be impaired, so that cerebral blood flow will be dependent on cerebral perfusion pressure.

In the absence of appropriate autoregulation, cerebral perfusion will diminish with elevated ICP or with systemic hypotension. In either instance, resultant ischemia, neuronal death, and subsequent edema all contribute to secondary injury.

General Management Considerations

Management focuses on prevention of secondary injury, so initial attention is directed to the ABCs of trauma resuscitation, focusing on maintaining adequate airway, breathing (ventilation and oxygenation), and circulation (blood pressure and perfusion). Cervical spine precautions are taken when head injury is present because head injury may be associated with cervical spine injury. Oxygen is applied, ventilation is supported as necessary to provide normocarbia (partial pressure of carbon dioxide at 35–45 mm Hg), and circulatory concerns are addressed.

Hyperventilation is no longer the standard of care, although there is still a limited role for acutely lowering increased ICP in the intensive care unit or operating room. Patients with Glasgow Coma Scale (GCS) <8 (see below) typically are intubated during trauma management.

The role of pharmacotherapy in head injury may include drugs for rapid sequence intubation, cardiovascular support, anticonvulsants when seizures occur, and medications to decrease ICP. In the most severely injured patients and those with herniation syndromes, mannitol (0.5–1.0 g/kg intravenously) and hypertonic (3%) saline can be used to promote osmotic withdrawal of water from the brain into the intravascular space in an effort to reduce ICP. Corticosteroid medications have no role in the treatment of acute brain injury; however, their use in treatment of spinal cord injury is controversial.

General Assessment

Assuming that concerns regarding airway, breathing, and circulation have been addressed, or arrangements for transfer or emergency care are being made, a general assessment should be performed, with specific emphasis on historical features and physical findings that might be indicators of potential complications from the trauma.

Historical elements should focus on details of the injury mechanism and timing of symptoms. Attention is placed on loss of consciousness, amnesia, confusion, seizure, vomiting, headache, and general behavior. Injury mechanism details should include height and surface for falls (eg, 2 feet or 2 stories; onto dirt, carpet, or concrete), use of restraining devices (eg, in car seat and car seat did not move), action of victim (eg, rolled up on car hood or thrown 20 feet), speed for crashes (eg, 10 mile per hour car crash, downhill on bike "really fast"), helmet use for sports, or velocity of object if child is struck (eg, golf club swung by teen versus 2-year-old). Other activities around the time of injury are important. Head injury can occur as the result of a medical condition (eg, seizure leads to fall with resultant head injury), and head injury in teens may occur in the presence of intoxication and drug use.

Physical examination includes examination of the head for evidence of abrasions, lacerations, or scalp hematomas (location, size, and character: boggy or firm); draining or bleeding from the ears or nose; blood behind the tympanic membrane (hemotympanum); apparent bruising behind the ear over the mastoid (Battle sign); blood accumulating in periorbital tissues (raccoon eyes); depression in the skull; and continuity of the skull within lacerations.

Drainage or blood from the ears and nose, hemotympanum, Battle sign, and raccoon eyes are signs of BSF, frequently associated with ICI, and they are detailed in the basilar skull fracture section. Neurologic assessment is performed and although focal findings are very uncommon, they should be sought.

Assessment of mental status is of utmost importance and serves as a common triage branch point to identify patients at risk for trauma complication. This evaluation usually is done by using the GCS, which is used in most head injury research (Table 1) and provides a starting point for following the patient's progress. For the very young child, there is a modified coma scale for infants (Table 2). It is important to judge the best response, and to follow the coma scale serially for deterioration.

Specific Injuries

Concussion

Although variably defined, in general a concussion is a head injury that results in alteration of mental status,

Table 1. Glasgow Coma Scale (Best Score Is 15)

Activity	Best Response	Score
Eye opening	Spontaneous	4
	To verbal stimuli	3
	To pain	2
	None	1
Verbal	Oriented	5
	Confused	4
	Inappropriate words	3
	Nonspecific sounds	2
	None	1
Motor	Normal spontaneous	6
	Localizes pain	5
	Withdraws to pain	4
	Abnormal flexion	3
	Abnormal extension	2
	None	1

Table 2. **Modified Coma Scale for Infants (Best Score Is 15)**

Activity	Best Response	Score
Eye opening	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Verbal	Coos, babbles	5
	Irritable, cries	4
	Cries to pain	3
	Moans to pain	2
	None	1
Motor	Normal spontaneous	6
	Withdraws to touch	5
	Withdraws to pain	4
	Abnormal flexion	3
	Abnormal extension	2
	None	1

with or without loss of consciousness. From a practical standpoint, concussion often is used to refer to more minor head injury when the GCS is 14 to 15, the patient has some symptoms (eg, headache, dizziness, vomiting, amnesia, or confusion), there is no evidence of a fracture, and there are no focal neurologic deficits. A more detailed discussion of concussion is below.

Skull Fractures

The main importance of skull fractures is that they are markers for significant impact to the head that increases the risk of ICI significantly; however, it is important to note that ICI also occurs in the absence of fractures, and many fractures are not associated with ICI. Rarely, the fracture itself may lead to a complication (more common with basilar or depressed skull fracture). Before the advent of CT, skull radiography was an important modality to identify children at risk for complications; however, because plain radiographs give no direct information about ICI, currently they are of very limited utility. Skull fractures now are diagnosed most commonly when a CT scan is obtained.

An exception to the lack of utility of skull radiographs occurs when child abuse is suspected. When child maltreatment is suspected, the presence of a skull fracture, old or new, with or without ICI, has important implications; so skull radiographs, with their higher sensitivity for fracture, are included as part of a more comprehensive skeletal survey. Skull fractures in children younger than 2 years in the absence of a history of appropriate mechanism should prompt a more thorough evaluation for inflicted trauma (including skeletal survey) and appropriate reporting and referrals.

Fracture of the calvarium is more common than fracture of the base of the skull. Most fractures are linear and, when considered in isolation (ie, not associated with ICI), of little consequence. No specific therapy need be directed to the fracture except pain management. Follow-up with primary care is appropriate to detect the exceedingly rare late complication of a growing fracture. Depressed skull fractures (those intruded more than the thickness of the bone) carry increased risk of primary injury to the brain because of intrusion of the fragment and, depending on the location, may have significant cosmetic sequelae (Fig 2). Neurosurgical consultation is necessary for all depressed skull fractures, even in the absence of more serious ICI.

Basilar Skull Fractures

BSF requires special consideration for several reasons. They can have unique clinical presentations providing clinical clues that often are readily apparent. Hemotympanum or blood draining from the ear, are the most common signs of a BSF. CSF draining from the ear or draining from the nose (attributable to a cribriform plate fracture), Battle sign, and raccoon eyes also are signs of BSF. Persistent

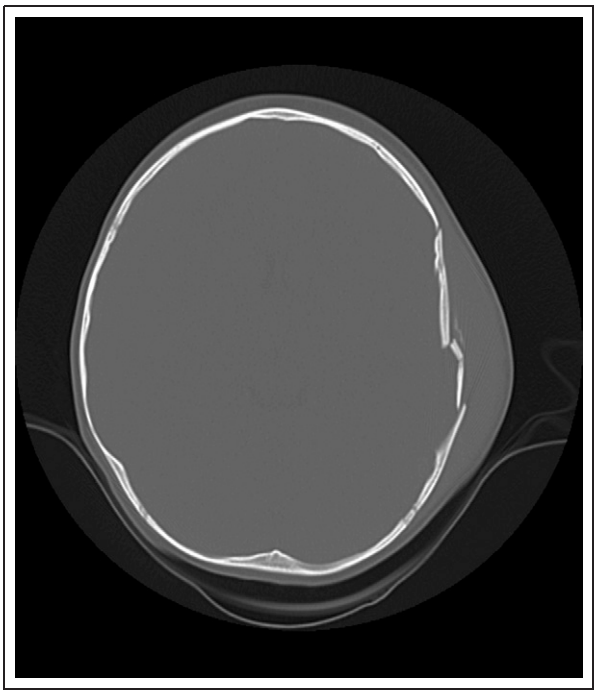

Figure 2. This toddler fell from a horse and CT scan shows depressed and comminuted parietal skull fracture.

clear drainage from the nose after head trauma should alert the clinician to the possibility of a BSF. BSF also can occur in the absence of these clinical findings and be apparent only on CT; conversely, CT scan may not detect all such fractures.

BSFs are important because they are associated with ICI and have a higher incidence of complications from the fracture itself, owing to the unique anatomic location. ICI occurs in about 20% of BSF patients who have a normal neurologic examination and GCS of 15. (1) Therefore, when signs of a BSF are noted, CT scanning is necessary.

BSF is associated also with an increased risk of meningitis. Fractures adjacent to the paranasal or sphenoid sinuses can lead to meningitis if bacteria from these areas enter the normally sterile subarachnoid space. The overall risk of developing meningitis after sustaining a BSF is probably less than a few percent, but the risk is increased if there is CSF rhinorrhea or otorrhea.

Use of prophylactic antibiotics is controversial. If there is ongoing CSF leakage, neurosurgical intervention may be needed to facilitate healing of the dural tear. Anatomic adjacency of the base of the skull to cranial nerve pathways means that BSF may cause hearing loss, facial paralysis, and a decreased sense of smell, as well as other cranial nerve dysfunction. Conductive hearing loss also may occur from blood in the middle ear.

General Intracranial Injuries

Perhaps the most important issue for the clinician evaluating a head-injured child is determining if there is an ICI. With improved CT images and current neurosurgical practice, however, detecting an ICI does not equate to a need for neurosurgery. Visible lesions on CT scan may or may not be associated with functional issues or serious morbidity. The two broad classifications of ICIs include *focal* hemorrhage (EDH, SDH, SAH, intracerebral hemorrhage, and cerebral contusion), which typically are visible on initial imaging, and *diffuse* injury (cerebral edema, diffuse axonal injury), which tends to progress and may become more visible on subsequent imaging.

Epidural Hemorrhage

When bleeding occurs between the skull and the dura mater, the patient is said to have EDH. The bleeding source is arterial in ~30%, fewer are clearly identified as venous, and in the remainder the source is unclear. EDH is caused most commonly by a blunt trauma mechanism, with falls most frequent. Often there is an overlying fracture (60% to 80%), and the EDH has a lens-shaped appearance on CT (Fig 3). Typically, the underlying brain parenchyma is not injured. Classic teaching suggested that patients with EDH had LOC, then a lucid interval, and then deteriorated. However, that clinical presentation is rare; only ~20% of children with an EDH even experience LOC. Some children may present with marked lethargy or focal neurologic findings and progress to more frank signs of herniation.

However, presentation with more subtle signs, such as persistent vomiting and headache, is more common, and more than 30% of patients who have EDH are alert with normal neurologic findings at the time of diagnosis. Although some small epidurals may produce minimal or no symptoms, they have the potential to expand, which can result in cerebral herniation and death. Fear of missing an expanding EDH, with its high potential for mortality, has, in part, fueled the marked increase in use of CT scanning occurring in recent decades.

Patients with EDH require emergent neurosurgical consultation and close monitoring. Patients with larger EDH, midline shift, or significant symptoms are treated with emergent craniotomy and evacuation of the hematoma. Because some small EDHs do not expand significantly, relatively asymptomatic patients who have small epidurals may be managed expectantly, at the

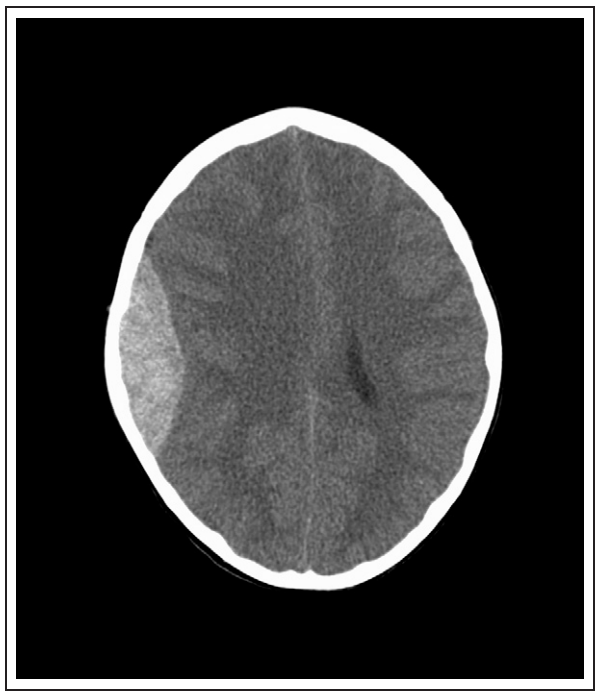

Figure 3. This CT scan demonstrates a right epidural hematoma with typical lens shape. The mass effect has caused effacement of the lateral ventricle and shift of the midline to the patient's left.

neurosurgeon's discretion, with admission and very close monitoring. Patients who have EDH successfully drained emergently have a good long-term outcome in more than 80% of cases.

Subdural Hemorrhage

When bleeding occurs between the dura and the arachnoid membrane, an SDH results. Usually, tearing of the bridging veins is the source of the bleeding and results from a direct blow, falls from significant height, or from inflicted head trauma, as seen in child abuse. SDH is not usually associated with an overlying fracture and has a crescent shape on CT (Fig 4).

Unlike the EDH, an SDH usually is associated with underlying brain injury and the hemorrhages may be bilateral. Children may present with LOC, altered mental status, seizures, irritability, vomiting, lethargy, or signs or symptoms of increased ICP (eg, bulging fontanel, decreased responsiveness). In about half the instances of SDH, the children present in coma or significantly depressed GCS.

Mortality of patients presenting with acute SDH is high and ranges from 10% to 20%. SDH in infants is associated with child abuse but is not diagnostic that abuse has occurred. Child abuse should be suspected highly when there is no explanation for the injury, when the mechanism of injury does not match the degree of injury, or in instances in which there appears to be evidence of SDH with both new and old blood.

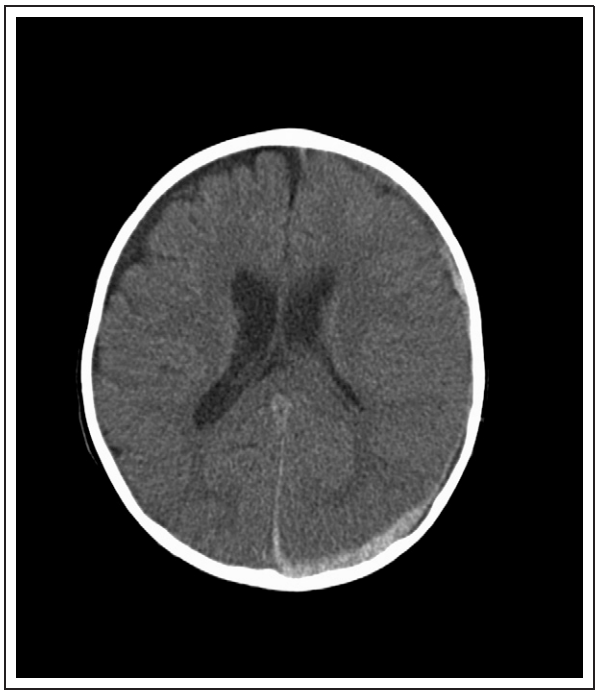

Figure 4. CT scan demonstrates subdural hemorrhage left posterior and left lateral that resulted from child abuse.

A chronic SDH may occur in children with coagulopathies, but usually results from child abuse, and may present with subtle findings, including macrocephaly, full fontanel, fussiness, seizures, and vomiting.

SDH requires emergency neurosurgical consultation. Patients who have an acute large SDH with evidence of mass effect within the cranium and altered level of consciousness are candidates for surgical drainage. Smaller SDH and more chronic forms may be managed without surgical decompression. Children with SDH often have significant long-term morbidity that may include developmental delay and seizures. These adverse, persistent neurologic sequelae are more likely to occur in patients who present with coma, or when CT scan demonstrates underlying brain injury.

Subarachnoid Hemorrhage

In more severely injured patients, SAH occurs about 25% of the time. This lesion results from tearing of the small vessels of the pia mater secondary to significant blunt trauma and associated shearing forces. Because the bleeding is in a space that communicates with other CSF-containing spaces (within the brain, around the brain and spinal cord), problems related to the mass effect that is seen with EDH and SDH rarely occur. SAH often is seen in association with other ICIs, so presentation is variable, but SAHs occurring in isolation may present with LOC, headache, or signs of meningeal irritation (eg, vomiting, photophobia, nuchal rigidity).

Cerebral Contusion

A cerebral contusion is essentially a brain bruise caused by a well-localized area of neuronal injury with bleeding (Fig 5). This injury results from movement of the brain against the skull. Blunt trauma to the head may cause a cerebral contusion near the site of impact (a "coup" lesion) or may cause a cerebral contusion opposite the site of impact (a "contrecoup" lesion). Typical signs may be subtle, and can include vomiting, headache, LOC, or, less commonly, a focal neurologic finding or a seizure. In most instances, small contusions have little acute or long-term sequelae.

Diffuse Axonal Injury

Diffuse axonal injury involves injury to the white matter tracts within the brain and is likely caused by shear forces. This type of injury is caused by severe acceleration,

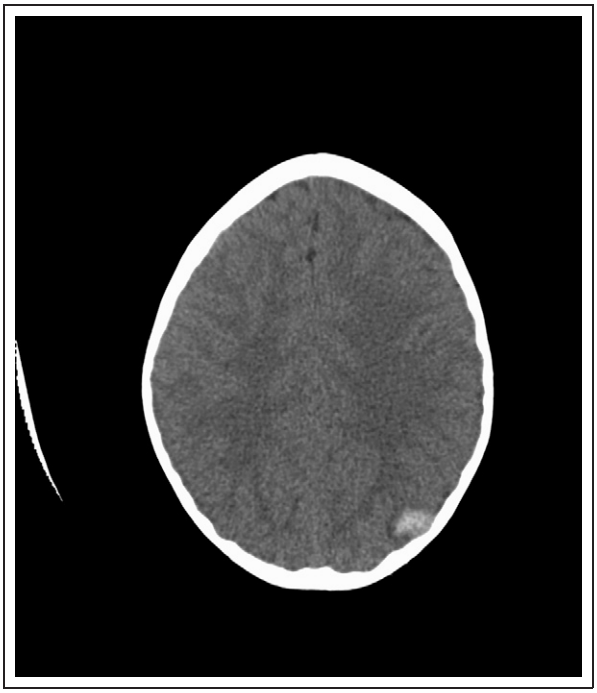

Figure 5. This 12-year-old was struck by a softball in the occiput. CT scan demonstrates cerebral contusion left posterior parietal region with small area of surrounding edema.

deceleration, or rotational forces, occurring most commonly in motor vehicle crashes. The injury often is at the gray-white matter junction but may occur deeper within the corpus collosum, brainstem, or cerebellum. These children usually are in coma at presentation, although occasionally the child will have only concussion-type symptoms. The CT scan shows small areas of hemorrhage located near the gray-white interface that do not expand. Management of diffuse axonal injury is supportive, mortality is 10% to 15%, and persistent neurologic dysfunction occurs in 30% to 40%.

Diffuse Brain Swelling

This condition is seen almost exclusively in children who experience severe head trauma and the mechanism appears to be a reaction to cellular injury. Diffuse brain swelling may not be apparent on initial imaging; subsequent CT scans demonstrate findings of progressive edema. The cellular insults may be varied, and cytotoxic edema, vasogenic edema, and autoregulatory dysfunction all may play a role. The children present with marked depression or deterioration of the GCS, and the main threat is the associated increase in ICP.

Who Needs Computed Tomography?

The clinician's goal is to identify patients who develop clinically important ICI so as to prevent deterioration and secondary brain injury (eg, from expanding EDH), while limiting unnecessary radiographic imaging. Unfortunately, defining sensitive and specific clinical predictors for identifying high-risk patients who require a head CT has been challenging.

Several issues contribute to the challenge of evaluating head-injured children:

- Although patients with ICI often have symptoms or functional derangements, many patients with these same symptoms have no ICI.
- Patients with normal neurologic examinations who exhibit symptoms as common as vomiting or headache may harbor an ICI that has the potential to become life-threatening. Repeated examination of the fundi is prudent because papilledema may not be present initially but may develop later in the course of intracranial hypertension.
- Many intracranial lesions detected by CT are only rarely associated with significant morbidity (eg, small cerebral contusion or small SAH).
- Although CT can effectively identify clinically important ICI, this imaging modality carries the risks of radiation, including the long-term sequelae of radiation-induced malignancy.

Investigators have identified several clear predictors of ICI:

- GCS ≤ 14 or altered mental status.
- Focal neurologic abnormalities.
- Skull fracture.

Patients who have any of these findings should undergo CT imaging.

However, most patients have none of these findings (ie, they have a GCS of 15, nonfocal neurologic examination, and no obvious skull fracture); yet, patients who lack these features account for a large proportion of patients who actually have ICI. Within this group, the incidence of ICI is about 5% and the need for neurosurgery <1%. Identifying reliably sensitive and specific clinical indicators has been difficult, however, because studies have found conflicting evidence regarding the significance of LOC, vomiting, seizures, and headache.

Children younger than 2 years should be considered separately. Younger children are more difficult to assess clinically, are more easily injured even from short falls, have a higher incidence of asymptomatic or occult

injuries, and more often are victims of inflicted injury. In addition to the predictors of ICI found in older children, nonfrontal scalp hematomas (surrogate markers for skull fracture) were found to be predictors of ICI, with larger hematomas in younger children of greater concern. (2)

In all age groups, because of the variability of clinical predictors in identifying ICI and concern for missing ICI, clinicians have adopted a very liberal approach to the use of CT scans. ED-based studies have shown that this group with mild head injury undergoes CT scanning from 35% to 55% of the time. Head CT for pediatric minor head injury increased in Canada from 15% in 1995 to 53% in 2005 for head-injured children. In the United States, use has increased dramatically in the face of relative stability of serious injury, implying that more and more normal CT scans are being obtained.

Risk of Head Computed Tomography Scanning

Widespread imaging has increased concerns regarding safety, specifically related to sedation and radiation risk. Concern for adverse events from sedation is justified, but with increasing speed of scanners, the need for sedation should decrease. Clinical experience and research in pediatric sedation has blossomed, and overall hospital practices in this regard have become safer, so that sedation-related adverse events are less of a concern.

The potential for ill effects from ionizing radiation cannot be overlooked. Evidence for this risk assessment comes primarily from information on radiation exposure following nuclear bomb detonation and data derived from therapeutic use of radiation. It is estimated that CT scanning will induce a new malignancy at a rate of ~1 in 5,000 CT scans. It appears that the greatest lifetime risk occurs in the youngest patients (both because of life-years remaining and susceptibility of tissues), and overall risk decreases as age increases. From the standpoint of an individual or individual clinician, this rate does not seem high, but when one considers the tens of thousands of normal head CT scans being performed each year, the public health impact may not be trivial.

Recent Investigations

Recent investigations (3)(4) have better identified more meaningful predictors by using multicenter design, including large numbers of head-injured children, focusing on groups at relatively low risk, and determining decision rules to aid clinicians determining the need for CT. Some of these large studies also altered the primary outcome measure from "presence of an ICI," as previous studies had done, to "clinically important" traumatic brain injury (TBI). In a study through the Pediatric Emergency Care Applied Research Network (PECARN) involving more than 42,000 pediatric patients at 23 centers, a clinically important TBI was defined as death, need for neurosurgery, intubation >24 hours, or hospitalization for ≥2 nights. (3)

Decision rules are developed to guide the clinicians in a more thoughtful approach to CT scanning so as to avoid overuse while still identifying clinically important ICI. No rules eliminate all risk unless all patients are scanned, but they provide a needed framework for risk assignment. The clinician who appropriately elects not to scan should understand the risk of serious ICI.

In the PECARN study, (3) when only children with GCS of 14 to 15 are considered, high-risk criteria (~4% incidence of clinically important ICI) were GCS = 14, other signs of altered mental status, and palpable skull fracture (if age <2 years) or signs of BSF (if age >2 years) for which CT was recommended.

Other risk factors (~1% incidence of clinically important ICI) for age >2 years: loss of consciousness, severe injury mechanism, vomiting, and severe headache; and for age <2 years: loss of consciousness, severe injury mechanism, nonfrontal scalp hematoma, and not acting normally per parents. Recommendations were for either CT imaging or observation. If none of these risk factors was present, the incidence of clinically important ICI was <0.05% and CT was not recommended.

In a multicentered Canadian study involving 3,866 children with GCS of 13 to 15, high-risk factors (associated with need for neurologic intervention) were GCS <15 at 2 hours after injury, suspected open or depressed skull fracture, worsening headache, and irritability. (4) Medium-risk factors (associated with presence of brain injury on CT) were signs of BSF, large boggy scalp hematoma, and dangerous mechanism.

Indications for Head Computed Tomography Scanning

Table 3 lists the situations in which head CT scanning is recommended. This list represents a compilation of the recent multicenter studies, as well as recent reviews. This table pertains to all age groups, and these clinical factors indicate a relatively high risk of detecting a clinically important TBI that would make obtaining a head CT justifiable. Table 4 (age >2 years) and Table 5 (age <2 years) outline patients who generally have a risk of ICI of ~3% to 5%, and have a risk for clinically important TBI of <1%, and assumes that findings in Table 3 are not present. These patients could be considered for imaging, but observation of

Table 3. Emergent Head Computed Tomography Scan Is Recommended

- Penetrating injury
- Glasgow Coma Scale (GCS) ≤14 or other evidence of altered mental status
- Focal neurologic abnormalities
- Signs of depressed or basilar skull fracture
- Worsening headache
- Prolonged loss of consciousness (LOC) (more than a few minutes)
- Clinical deterioration during observation or significant worsening of symptoms
- Seizure (other than impact seizure) or any prolonged seizure
- Pre-existing condition that places child at increased risk for intracranial hemorrhage (eg, bleeding disorder)
- In addition for children <2 years old:
  - Concerns for inflicted injury
  - Seizure
  - Irritability
  - Bulging fontanel
  - Persistent vomiting
  - Large, boggy, nonfrontal scalp hematomas in children <1 year old
  - Definite (more than brief) LOC

Table 4. For Age >2 Years, Moderate Risk for Intracranial Injury

The following group of patients should be considered for emergent imaging but observation for 4–6 hours can be considered as an alternative (estimated risk of clinically important traumatic brain injury ~1%). In general, if more than one of the following are present, the clinician should perform head imaging:

- Loss of consciousness
- Seizure (brief and impact)
- Severe headache
- Vomiting
- High-risk mechanism (fall greater than 5 feet in older children, struck by high-impact object, ejection from motor vehicle, motor vehicle crash with death of another or auto pedestrian, auto-bike without helmet)

Additional clinical constellations that should prompt imaging:

- Behavioral change that is both significant and prolonged (especially more than a few hours)
- Multiple episodes of vomiting or onset delayed several hours after injury

at least 4 to 6 hours from the time of injury is a reasonable alternative.

It is clear from a subanalysis of the PECARN study that clinicians sometimes use observation before deciding to obtain a CT. When observation is chosen, the appearance of additional new symptoms, evidence of worsening symptoms, or clinical deterioration should prompt imaging. In instances in which multiple risk factors are present or symptoms are more severe, imaging probably is favored. Other factors that may influence the decision to image include quality of observation (eg, caretaker reliability, time of day), the ability to return for worsening symptoms, physician experience, and parental preference. Table 6 lists criteria typical of patients for whom imaging is not necessary.

Disposition

In general, patients with depressed skull fracture or any ICI should be hospitalized with emergent neurosurgical consultation for their lesions; however, some small cerebral contusions or SAHs may have little short- or long-term clinical significance, and deterioration is rare. Patients with normal CT scans and resolution of symptoms typically do not require hospitalization. Patients with persistent symptoms (despite normal CT scans) who would not be

Table 5. For Age <2 Years, Moderate Risk for Intracranial Injury

Patients with the following signs or symptoms should be considered for emergent imaging, but observation for 4–6 hours can be considered as an alternative (estimated risk of clinically important TBI ~1%). In general, if more than one of the following are present, the clinician should perform head imaging:

- Occipital, parietal, or temporal scalp hematoma
- Behavioral change per caregiver
- Nonacute (more than 24 hours) skull fracture
- High-risk mechanism (fall greater than 3 feet, struck by high-impact object, ejection from motor vehicle, motor vehicle crash or auto pedestrian with death of another, auto-bike without helmet)

Additional clinical constellations that should prompt imaging:

- Multiple episodes of vomiting or onset delayed several hours after injury

TBI=tramautic brain injury

Table 6. Criteria for Patients Who Can Reliably Forego Computed Tomography Imaging

Normal neurologic examination
Normal mental status
Normal behavior per caregiver
No loss of consciousness
No vomiting
No severe headache
No evidence of skull fracture (for children <2 years, no nonfrontal scalp hematoma)
No signs of basilar skull fracture
No high-risk mechanism (fall greater than 3 feet in children <2, fall greater than 5 feet in older children, struck by high-impact object, ejection from motor vehicle, motor vehicle crash or auto pedestrian with death of another, auto-bike without helmet)
No concern for inflicted injury

managed easily at home (persistent vomiting, severe headache, abnormal mental status) also should be admitted. For any child deemed stable for discharge (both those with and without imaging), symptoms concerning for ICI should be reviewed with reliable caretakers who are able to return to the ED should concerns arise.

Home Management of Minor Head Injury

Calls to practitioners from caregivers regarding pediatric head injury are frequent. In many instances, ongoing observation at home without an ED or office visit is reasonable, if there is a reliable caretaker with the means to seek additional care if needed, if there is no concern for inflicted injury, and if there are no underlying conditions that would predispose the child to an ICI. In cases in which there is a low-risk mechanism (typically a ground level fall from child's own height) and there are no other injuries, no LOC or mental status changes, no vomiting (one episode shortly after injury is of less concern), no significant headache, and no nonfrontal scalp hematomas (for children <2 years), ongoing home observation can be pursued. It is not necessary to prevent a child from napping as the child would normally, but the child should be checked periodically for clinical deterioration. Indications for seeking medical care should be reviewed with the caretaker.

Concussion and Mild Traumatic Brain Injury

Traditional classification of TBI grouped patients by degree of functional impairment using the GCS. This classification scheme is independent of CT findings, but the likelihood of abnormal CT findings increase in frequency as the severity of the TBI increases (ie, as GCS decreases).

Concussion has been defined variably based on clinical findings and represents a subset of the mild TBI group (GCS 13–15). In a simple definition from the American Academy of Neurology, concussion is an alteration in neurologic function or mental status after head injury that may (or may not) involve LOC. Concussion typically has a rapid onset of impairment of neurologic function that is short-lived and resolves spontaneously. This condition represents a functional problem and, by convention, patients do not have abnormalities on CT imaging (if CT was obtained).

In addition to the common signs of headache, vomiting, or dizziness, signs in patients who experience concussion might also include a vacant stare or confused expression, difficulty focusing attention, disorientation, slurred or incoherent speech, delayed response to questions, emotional response that is out of proportion to the situation, repetitive questioning, coordination problems, or memory problems. Patients typically improve over minutes to a few hours. Failure to improve or worsening symptoms are an indication for imaging, if not performed previously. Repeated concussions probably have a cumulative effect and have been implicated in long-term cognitive impairment and neuropsychiatric problems in professional athletes.

Second-Impact Syndrome

Second-impact syndrome refers to a very rare but usually fatal diffuse cerebral edema as a consequence of mild head injury. This term is applied typically when an athlete develops diffuse cerebral edema from a second head injury while still symptomatic from a first concussion. The understanding of this condition is insufficient, based mostly on a limited number of case reports, and there is controversy surrounding this complication. Even the time period of risk is debatable, but probably is less than a couple of weeks.

Concerns for this lethal condition, however, and the concerns over cumulative adverse effects from repeated head injury, have prompted guidelines for return to play following a concussion.

Return to Play

To aid return-to-play decisions, several guidelines based on acute symptoms have been published (eg, Colorado Medical Society, the American Academy of Neurology); these guidelines are not based on detailed clinical evidence, and they have not been compared in clinical

Table 7. **Graduated Return to Play**

Stage	Activity	Stage Objective
No activity	Complete physical and cognitive rest	Recovery
Light aerobic exercise	Walking, swimming, stationary cycling, low–moderate intensity	Increase heart rate
Sport-specific exercise	Skating drills ice hockey, running drills, no impact	Add movement
Noncontact training	More complex training drills (eg, passing drills), may start progressive resistance training	Exercise, coordination, cognitive effort
Full-contact practice	Normal training activities after medical clearance	Assess skills by coaches; restore confidence
Return to play	Normal game play	

In general, the athlete who has sustained a concussion should proceed to the next level if without symptoms at the current level. Each step generally takes 24 hours. If symptoms recur, then the patient drops back to previous asymptomatic level. (Adapted from Table in Consensus statement on concussion in sport. *J Clin Neuroscience*. 2008;16:755–763, with permission.)

studies. Both sets of guidelines share some common recommendations.

Athletes suspected of having a concussion should be removed from participation immediately and they should not return while signs or symptoms are present. Athletes symptomatic for >15 minutes should not return to play until they are asymptomatic for 1 week.

Most recently, a multidisciplinary panel published a consensus guideline advocating abandoning acute grading scales in favor of clinical measures of recovery. (5) Return to play should be based on resolution of symptoms and normalization of neurocognitive function for the individual, rather than based on a predetermined amount of time. Recommendations are for physical and cognitive rest until asymptomatic, followed by a graduated, monitored return to play. This graduated return to play guideline from this consensus paper is presented in Table 7.

Postconcussion Syndrome

Postconcussive symptoms develop within a few days of the initial concussion and can last anywhere from a few days to a few months. Typical symptoms include headache, fatigue, dizziness, cognitive impairment (particularly concentration), and neuropsychiatric symptoms. Some children and teens may experience long-term behavioral and cognitive problems temporally related to experiencing a concussion.

About 80% of high school athletes who experience sports-related concussions have resolution of symptoms within 1 week, and fewer than 2% are symptomatic longer than 1 month. For patients whose symptoms persist beyond a few weeks, referral to a pediatric neurologist, neuropsychologist, sports medicine physician, or other specialist with expertise in head injury probably is indicated. Investigations into understanding postconcussion syndrome risk and effectiveness of interventions is limited.

Summary

- Pediatric head injury is very common and usually minor but can result in serious morbidity and is the most common cause of lethal trauma.
- Based on strong research evidence, a thorough history and physical examination with emphasis on neurologic status and signs of skull fracture (including size, character, and location of scalp hematomas in infants) provide the clues necessary to assess the relative risk of serious intracranial injury (ICI). (1)(3)(4)(6)
- Based on strong research evidence, computed tomography (CT) scan remains a highly useful adjunct in evaluation of the head-injured child but should be used selectively for children at higher risk for ICI. (2)(3)(4)
- Based on research evidence or consensus opinion, observation can be used selectively in lieu of CT scanning for patients who are not at higher risk for ICI, minimizing the risks of CT-associated ionizing radiation. Any concerns during the observation period should prompt CT imaging. (3)(7)(8)
- Concussion from head injury in athletics has recently received increased public attention. Based on consensus opinion, premature return to play may confer increased risk to the athlete. (9)(10)

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PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Since January 2012, learners can take *Pediatrics in Review* quizzes and claim credit online *only*. No paper answer form will be printed in the journal.

New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for *AMA PRA Category 1 Credit™*. In order to successfully complete 2012 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

Starting with the 2012 issues of *Pediatrics in Review*, *AMA PRA Category 1 Credit™* may be claimed only if 60% or more of the questions are answered correctly. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

1. A 5-year-old boy was in a motor vehicle collision as a restrained back seat passenger. He has a large laceration on his right forehead. On arrival to the emergency department, he opens his eyes with painful stimuli, but does not open his eyes when his name is called. He is mumbling, but is not using words. He withdraws to pain. His brain injury is best described as a

   A. mild traumatic brain injury
   B. moderate concussion
   C. moderate traumatic brain injury
   D. severe concussion
   E. severe traumatic brain injury

2. A 15-month-old girl is seen for fussiness, crying, and poor oral intake. On physical examination, she is fussy, but consolable. Her vital signs are stable. She is well hydrated. She has unilateral hemotympanum. The most appropriate initial intervention at this time is

   A. computed tomography (CT) scan of the brain
   B. magnetic resonance imaging of the brain
   C. prescription for antibiotics
   D. skull radiographic films
   E. skeletal survey

3. You see a 6-month-old girl with history of vomiting who presents with lethargy and irregular respirations. After intubating and stabilizing her, you obtain CT imaging of the brain that shows a parietal skull fracture and a crescent-shaped intracranial hemorrhage underlying the fracture. This radiographic finding is most consistent with a

   A. cerebral contusion
   B. diffuse axonal injury
   C. epidural hematoma
   D. subarachnoid hemorrhage
   E. subdural hemorrhage

4. A 15-year-old boy was the unrestrained passenger in a motor vehicle collision. He was ejected from the vehicle and was found unconscious 20 feet from the vehicle. A CT scan shows areas of hemorrhage at the gray-white junction. His clinical presentation and radiographic findings are most consistent with

   A. cerebral contusion
   B. diffuse axonal injury
   C. epidural hematoma
   D. subarachnoid hemorrhage
   E. subdural hemorrhage

5. You are evaluating a 6-year-old boy who sustained a head injury when he fell out of a tree. Clear fluid is noted to be draining from his nose. His parents deny any recent respiratory infection or history of nasal allergy. You order a CT scan. The most likely abnormality to show up on the scan will be

   A. basilar skull fracture
   B. cerebral contusion
   C. depressed skull fracture
   D. epidural hemorrhage
   E. subdural hemorrhage

Pediatric Head Injury

Jeff E. Schunk and Sara A. Schutzman

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Pertussis in Childhood

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Pertussis in Childhood

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Drs Snyder and Fisher have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Educational Gap

The incidence in the United States of pertussis, a potentially fatal disease, has increased during the past decade and new recommendations for vaccination have been made in recent years.

Objectives

After reading this article, readers should be able to:

1. **Understand the pathophysiology of pertussis.**
2. **Describe the clinical presentation, natural history, and potential complications of pertussis infection.**
3. **Appreciate the changing epidemiology of pertussis.**
4. **Master the laboratory diagnosis and medical management of pertussis infection.**
5. **Describe the vaccination strategies for the prevention of pertussis infection.**

Introduction

Pertussis, commonly known as "whooping cough," is a respiratory illness caused by the bacterium *Bordetella pertussis*. The classic clinical syndrome causes morbidity by affecting the upper respiratory tract in patients of all ages. The disease can be modified greatly and prevented by primary vaccination. An ongoing resurgence of clinical pertussis has been seen in the United States over the past decade, with increasing numbers of young infants affected despite the availability of effective vaccines. It is important to understand the biological properties of the bacterium, the clinical presentation, and the factors contributing to the continuing burden of this disease.

The Organism and Pathophysiology

B pertussis is a small Gram-negative coccobacillus that infects only humans. It is aerobic and grows best at 35°C to 37°C. *Bordetella* species, including *B pertussis* and *B parapertussis*, are fastidious and difficult to grow on media usually used in the laboratory to grow respiratory pathogens; *B pertussis* requires supplemental growth factors including charcoal, blood, and starch. Media such as Bordet-Gengou, which contains potato starch, and charcoal-based Regan-Lowe media typically are used in microbiology laboratories for culturing the organism.

B pertussis causes irritation and inflammation by infecting the ciliated respiratory tract epithelium. The ensuing tissue necrosis and epithelial cell damage recruits macrophages, and reactive lymphoid hyperplasia of peribronchial and tracheobronchial lymph nodes occurs.

The bacterium has several virulence factors and toxins that are important in the pathogenesis of the disease and also play a role in inducing protective immune responses. Filamentous hemagglutinin and fimbriae are adhesins required for tracheal colonization. These substances are highly immunogenic and are major components of acellular vaccines.

Abbreviations

CDC: Centers for Disease Control and Prevention
DTP: diphtheria, tetanus, and whole cell pertussis vaccine
DTaP: diphtheria, tetanus, and acellular pertussis vaccine
PCR: polymerase chain reaction
PT: pertussis toxin
RSV: respiratory syncytial virus
Tdap: diphtheria, tetanus, and acellular pertussis vaccine (reduced diphtheria component)

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Other virulence factors such as pertactin and pertussis toxin (PT) can act as adhesins as well. PT can inactivate or suppress signaling pathways of the immune system in the lung, which delays recruitment of neutrophils. The role of pertussis toxin in the pathogenesis of pertussis is not fully understood. The toxin has been shown to cause leukocytosis with lymphocytosis and possibly the rare encephalopathy seen in the clinical disease. Other direct systemic effects of PT include sensitization of the beta-islet cells of the pancreas. This effect can lead to hyperinsulinemia with a resistant hypoglycemia, and sometimes occurs in young infants who have poor feeding, which exacerbates the symptoms. Adenylate cyclase toxin inhibits migration and activation of phagocytes and T cells.

Epidemiology

Worldwide, an estimated 50 million cases and 300,000 deaths due to pertussis occur annually. (1) In the United States, pertussis is an endemic disease, with periodic epidemics every 3 to 5 years and frequent outbreaks. The last peak in the incidence of pertussis occurred in 2005, when ~25,000 cases were reported nationally. Increasing incidence has been noted in the United States and other countries despite widespread immunization. In 2009, nearly 17,000 cases of pertussis were reported in the United States, with many more going unreported. (2)

In the past year, 9,477 cases of pertussis (including 10 infant deaths) were reported in California, the highest incidence in the state since the cyclical peak in 2005. (3) According to the Centers for Disease Control and Prevention (CDC), 50% of infants under age 1 year who are infected with pertussis will require hospitalization. Of these, 50% will develop pneumonia and 1% will die of complications from their infection. Pertussis morbidity and mortality is most significant in infants younger than age 3 months. Infants in this age group have the highest incidence of hospitalization, admission to intensive care units, and death from pertussis.

In a review of a national pediatric inpatient database from 2000 to 2003, 86% of all hospitalizations for pertussis were in infants age <3 months. (4) In the United States and other industrialized countries, the resurgence of pertussis is being seen in very young infants who are not fully immunized, and in children and adolescents aged 10 years and older. Waning vaccine-induced immunity and lack of natural booster events may account for many of those cases in this older age group. Other factors that might be contributing to the increase in reported cases of pertussis are heightened awareness and reporting among health-care providers, increased use of polymerase chain reaction (PCR) testing for diagnosis, and decreased pertussis vaccination rates in some areas (Fig 1).

Pertussis in developing countries is still the source of the highest disease burdens, primarily in Asia, Africa, and South America. Pertussis worldwide remains one of the top 10 causes of mortality in infants younger than age 1 year. Varying case definitions make comparisons of incidence between countries difficult. Hospitalization rates sometimes are used to follow incidence and the severity of outbreaks.

A clinical case is defined commonly as a cough illness lasting at least 2 weeks with one of the following: paroxysms of coughing, inspiratory "whoop," or posttussive vomiting without other apparent cause (as reported by a health professional). A confirmed case is defined as any cough illness in which *B pertussis* is isolated by culture. A case that satisfies the clinical case definition and is confirmed by PCR, or that has an epidemiological link to a laboratory-confirmed case,

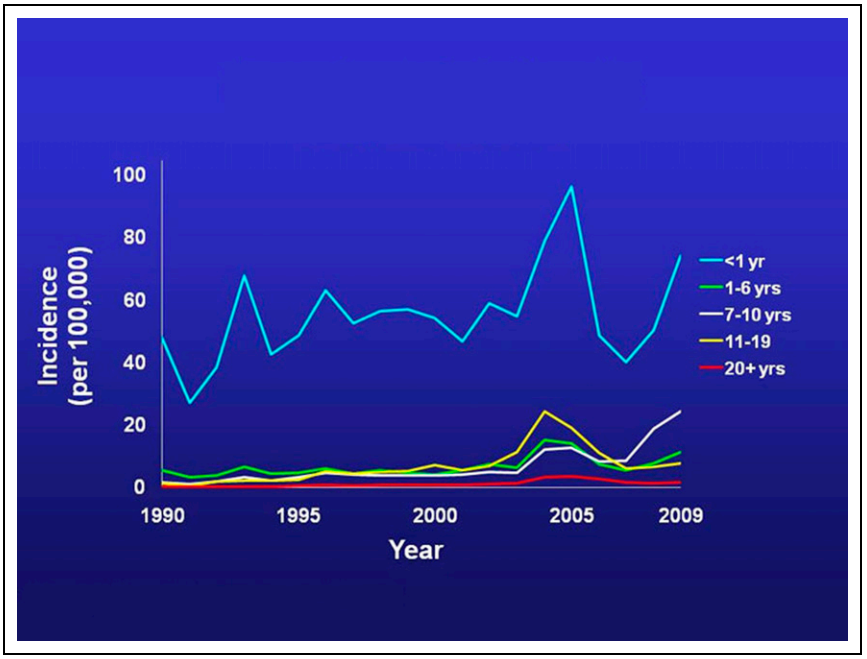

Figure 1. Reported pertussis incidence by age group 1990–2008. Source: Centers for Disease Control and Prevention, National Notifiable Diseases Surveillance System; 2009.

also may be considered a true case, particularly in outbreak situations.

Clinical Presentation and Natural History

Pertussis is spread by aerosol droplets expelled while coughing or sneezing in proximity to others. Many infants who get pertussis are infected by older siblings, parents, or caregivers who may have only mild symptoms. After an incubation period of 7 to 14 days, the natural history of pertussis tends to follow a relatively predictable clinical course, although disease severity and prognosis are quite variable. Because of this variability, a high degree of suspicion is necessary to make a timely diagnosis. A child suspected of having pertussis should be placed in appropriate isolation until the infection is confirmed or ruled out. A patient suspected of having pertussis should be masked in waiting rooms and when sent for ancillary testing.

Catarrhal Phase

The catarrhal phase of pertussis lasts from 1 to 2 weeks and includes nonspecific complaints. The mild fever, cough, and nasal signs and symptoms associated with this early phase of the illness are similar to those seen in many viral upper respiratory tract infections, which often leads to a delay in identifying suspected cases. During this phase of the illness, the cough worsens as the patient progresses to the paroxysmal phase.

Paroxysmal Phase

The paroxysmal phase of the illness lasts from weeks 2 to 6. This phase is characterized by paroxysms of cough, often described as "rapid fire" or "staccato." Classically, as many as 5 to 10 uninterrupted coughs occur in succession, followed by a "whoop" as the patient rapidly draws in a breath. An audio file of the cough and whoop can be accessed online through the following link: http://www.pkids.org/diseases/pertussis.html. This classic whooping sound is heard less commonly in adolescents and adults.

The paroxysms may occur several times per hour and can be associated with cyanosis, salivation, lacrimation, and post-tussive emesis. These paroxysms can be exhausting and often interfere with sleep and nutritional intake. Despite the severe spells, patients often appear relatively well between episodes.

Infants younger than age 6 months often have a less typical presentation. The classic "whoop" may be absent, and gasping, gagging, and apnea can occur. Sudden death has been reported. As the cough gradually improves, the patient enters the convalescent phase of the illness.

Convalescent Phase

Following the peak of the paroxysmal phase, improvement in respiratory tract integrity and function is associated with decreasing frequency and severity of the coughing episodes. The duration of this convalescent phase is highly variable, lasting from weeks to months.

Complications

Pertussis is most severe in infants under age 6 months, for whom the mortality rate is ~1%. Greater than 80% of deaths related to pertussis infection occur in infants under age 1 year, with more than half of these deaths occurring in infants age <2 months. (5) The disease tends to be milder or even subclinical in those protected by immunization.

Complications of pertussis include apnea, pneumonia, seizures, encephalopathy, and death. Pneumonia may be primary or secondary to coinfection. Concomitant infection with other organisms such as influenza or respiratory syncytial virus (RSV) can lead to a more severe clinical course.

The paroxysms themselves can result in pressure-related complications such as pneumothorax or

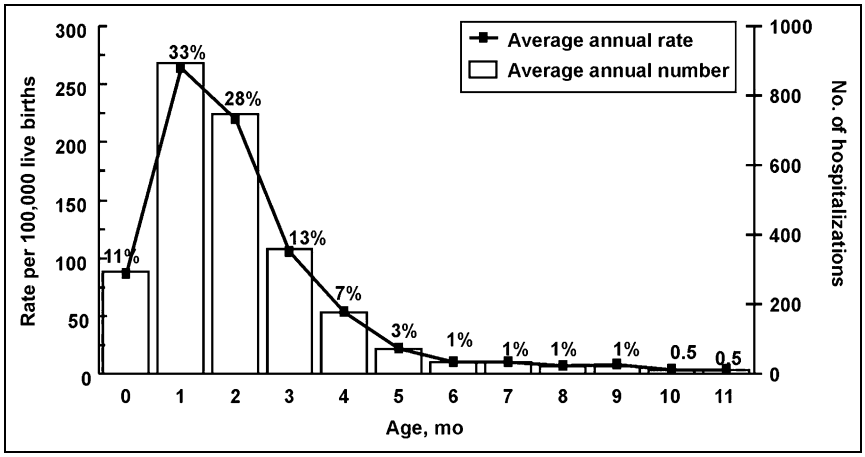

Figure 2. Average annual incidence of pertussis hospitalizations and number (percent) of hospitalizations according to age group in the KID (2000 and 2003). Reprinted, with permission, from Shinall MC et al. "Potential impact of acceleration of the pertussis vaccine primary series for infants." *Pediatrics*. 2008;121:484–492.

pneumomediastinum, subcutaneous emphysema, superficial petechial hemorrhage, rib fracture, rectal prolapse, and even intracranial hemorrhage.

Infants afflicted with pertussis often require hospitalization for fluid, nutritional, and respiratory support. During the years 1999–2003, the hospitalization rate for infants age ≤6 months was 78%. (6) In a recent review that used the Kids' Inpatient Database, 86% of children under age 1 year who were hospitalized with pertussis were age ≤3 months (Fig 2). (4)

Diagnosis by Laboratory Studies

Isolation of *B pertussis* from nasopharyngeal swab or aspirate cultured on specialized media used to be the gold standard for detecting the organism. Because the organism is variably present only in the early stage of the illness, yield from cultures done later, when clinical symptoms are more evident, is low. Specimens obtained 3 weeks after the onset of cough produces yields as low as 1% to 3%. Adolescents and adults tend to present later in the course of the illness, and the culture rate in this population is very low. Culture time generally is 2 weeks. In unimmunized infants with a high bacterial load who are cultured early in the illness, cultures may be positive in as little as 72 hours. Culture also will identify cases that are caused by *B parapertussis*.

Although culture remains the gold standard laboratory test to confirm the diagnosis of *B pertussis*, PCR is beginning to replace culture as the diagnostic test of choice for *B pertussis* in many clinical settings. PCR for *B pertussis* is a rapid, specific, and sensitive diagnostic test that will remain positive late in the course of the illness. Even in the presence of antibiotic treatment, PCR often will remain positive for as long as 7 days. Many laboratories perform only PCR and do not use culture for identifying *B pertussis*, although most state public health laboratories do maintain the ability to perform both culture and PCR testing.

The PCR test also has been adopted as an acceptable method for diagnostic case surveillance in the United States. However, because there are still no nationally standardized assays, sensitivity and specificity vary among laboratories. Since the advent of PCR testing for identifying pertussis, the number of confirmed cases has increased. Culturing for *B pertussis* still may have a role in some special circumstances, such as during an outbreak. In several instances, cases detected solely on the basis of PCR in hospital settings have proven to be "pseudo-outbreaks" due to false-positive PCR results. (7)

Table 1. Laboratory Methods for Diagnosing Pertussis Infection

Test	Sensitivity, %	Specificity, %	Optimal Timing	Advantages	Disadvantages
Culture	12–60	100	<2 wk postcough onset	Very specific (100%)	Low sensitivity; 7–10 day delay between specimen collection and diagnosis
Polymerase chain reaction	70–99	86–100	<4 wk postcough onset	Rapid test; more sensitive than culture; organisms do not need to be viable; positive postantibiotics.	No FDA approved tests or standardization; potential for false positives; DNA cross-contamination can be problematic
Paired sera	90–92	72–100	At symptom onset and 4–6 wk later	Effective indication of mounting antibody titers	Late diagnosis; no FDA-approved tests or standardization
Single sera	36–76	99	At least 2 wk postcough onset; ideally 4–8 wk postcough	Useful for late diagnosis or postantibiotics	No FDA-approved test or standardization; possibly confounded by recent vaccination; diagnostic cutoffs not validated

FDA=Food and Drug Administration.
Adapted from Centers for Disease Control and Prevention (CDC) Pertussis and Diphtheria Laboratory.

Because direct fluorescent antibody testing of nasopharyngeal secretions has been demonstrated in some studies to have low sensitivity and variable specificity, such testing should not be relied upon as a criterion for laboratory confirmation. Most laboratories therefore have discontinued use of the fluorescent antibody testing of nasal secretions for pertussis.

Serological testing for pertussis is available in some areas, but it is not standardized and, therefore, also should not be relied upon as a criterion for laboratory confirmation. Antibodies to PT are the most common serological test performed, generally utilizing an enzyme-linked immunosorbent assay. Pertussis-specific immunoglobulin M testing is not available routinely. In a nonimmune child, a single positive immunoglobulin G assay done during the second phase of the illness is considered diagnostic. In the presence of pre-existing immunity, a rise in titer using paired specimens 2 to 3 weeks after onset of clinical illness is necessary and is considered the gold standard for serologic diagnosis (Table 1).

Leukocytosis, together with an absolute lymphocytosis on a peripheral complete blood count, is another laboratory finding supportive of *B pertussis* infection. This finding often correlates with disease severity, especially in very young infants. White blood cell counts as high as 30 to 60 $\times 10^3/\mu$L can be seen. Monitoring of fluids and electrolytes is necessary in infants with severe disease. Laboratory evaluation to rule out other respiratory illness may be necessary.

Differential Diagnosis

Other respiratory pathogens causing a cough illness can mimic pertussis. Because very young infants can present only with apnea episodes without the typical whoop or spasms of cough, RSV infection should be considered. Rapid viral antigen testing by various methods, including direct fluorescent antibody panels, direct enzyme immunoassays, and multiplex PCR panels, may help differentiate among RSV, influenza, and adenoviruses. *Chlamydia trachomatis* can present as a cough illness in neonates, but usually creates an interstitial pneumonitis pattern and lower respiratory tract findings. Other causes of prolonged cough illness in older children and adolescents include *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. Specific serologies can be sent for these atypical organisms.

Management

If left untreated, most individuals will clear *B pertussis* spontaneously from the nasopharynx within 2 to 4 weeks of infection. However, nasopharyngeal carriage can persist for 6 weeks or more. During this period, individuals remain contagious and can spread the illness to others. When started early in the course of the illness, during the catarrhal stage, antibiotics can shorten the course and attenuate the severity of pertussis. Once the paroxysmal phase has started, however, antibiotics are not effective in altering the course of the disease. By this stage, clinical manifestations of the illness are due to toxin-mediated effects, and thus are not affected by antimicrobial therapy. Unfortunately, because the catarrhal phase of pertussis is nonspecific, resembling many benign upper respiratory tract infections, most cases are not yet diagnosed by this point in the illness.

Although the clinical course of pertussis is not readily affected by treatment, the use of an appropriate antibiotic is indicated, even in the catarrhal phase, because this therapy results in rapid clearance of the organism from the nasopharynx (usually within 5 days of the start of therapy) and thus can greatly shorten the period of contagiousness.

For many years, the standard regimen for the treatment of pertussis in children has been administration of oral erythromycin. Recent studies have demonstrated equal efficacy and improved tolerability of other macrolides, such as azithromycin. (8) Azithromycin is associated with fewer adverse gastrointestinal events, may be dosed once daily, and does not inhibit the cytochrome P450 system, and therefore may be preferable. In addition, erythromycin has been associated with an increased risk of pyloric stenosis when administered to infants in the first 2 weeks after birth. (9)

The use of trimethoprim-sulfamethoxazole also has been shown to be effective in eliminating the nasopharyngeal carriage of *B pertussis* and may be an appropriate alternative for individuals age >2 months who are unable to take a macrolide. A recent Cochrane review of 13 clinical trials showed that a 7-day course of therapy is equally effective as a 14-day course and is associated with fewer adverse effects (Table 2). (10)

Prophylaxis

Antibiotics may prevent infection with *B pertussis* in exposed individuals if given within 21 days of symptom onset in the index case. The CDC and the American Academy of Pediatrics currently recommend prophylaxis of high-risk close contacts, as well as close contacts who may have contact with high-risk individuals. The recommended antibiotics and dosing regimens for pertussis prophylaxis are the same as for treatment. Because an individual's previous vaccination status may not always reliably predict his susceptibility to infection, this status

Table 2. Antibiotic Regimens for Treatment and Prophylaxis of Pertussis

Agent	Dose and Regimen
Azithromycin*	• Infants age <6 mo: 10 mg/kg for 5 days • Infants and children age ≥6 mo: 10 mg/kg (maximum 500 mg) on day 1, followed by 5 mg/kg per day (maximum 250 mg) on days 2–5 • Adults: 500 mg on day 1, followed by 250 mg/day on days 2–5
Clarithromycin*	• Infants aged <1 mo: not recommended • Infants and children aged >1 mo: 15 mg/kg per day (maximum 1 g/day) in 2 divided doses each day for 7 days • Adults: 1 g/day in 2 divided doses for 7 days
Erythromycin*	• Infants aged <1 mo: Azithromycin is preferred because of risk for pyloric stenosis with erythromycin. If erythromycin is used, the dose is 40–50 mg/kg per day in 4 divided doses. These infants should be closely monitored for pyloric stenosis. • Infants aged >1 mo and older children: 40–50 mg/kg per day (maximum 2 g/day) in 4 divided doses for 14 days • Adults: 2 g/day in 4 divided doses for 14 days
TMP-SMX	• Infants aged <2 mo: contraindicated • Infants aged >2 mo and children: TMP 8 mg/kg per day, SMX 40 mg/kg per day in 2 divided doses for 14 days • Adults: TMP 320 mg/day, SMX 1,600 mg/day in 2 divided doses for 14 days

TMP=trimethoprim; SMX=sulfamethoxazole.
*Infants aged <1mo should be monitored closely for pyloric stenosis when treated with a macrolide.
Adapted from CDC. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis. *MMWR*. 2005;54(RR14):1–16.

should not be a factor when determining the need for prophylaxis (Table 3).

Individuals with confirmed or suspected pertussis should be excluded from school or child care settings pending evaluation and completion of 5 days of an appropriate antibiotic. If not appropriately treated, individuals with pertussis should be kept from school or child care settings until 21 days have elapsed from the onset of cough. (11)

Prevention

Infection with *B pertussis* can be prevented through appropriate immunization. Available vaccines are 80% to 85% effective at preventing disease after completion of the primary series. Children who do become infected with *B pertussis* after immunization are more likely to have subclinical or less severe illness. All currently available pertussis vaccines are combined with tetanus (T) and diphtheria (D) toxoids, as either DTaP or Tdap (diphtheria, tetanus, and acellular pertussis vaccine-reduced diphtheria and pertussis components) (Table 4).

The pertussis component of the vaccine designated ap or aP is acellular, containing varying amounts of PT, filamentous hemagglutinin, pertactin, and fimbriae antigens, depending on the vaccine type. The American Academy of Pediatrics and the CDC's Advisory Committee on Immunization Practices currently recommend a primary series of 3 DTaP doses to be given at age 2, 4, and 6 months, followed by boosters at age 15 to 18 months and 4 to 6 years. The fifth dose is not recommended if the fourth dose is administered at age ≥4 years. Children who have confirmed cases of pertussis also should complete the immunization series against pertussis.

Because immunity to pertussis from the DTaP series wanes over time, a booster dose is recommended at age

Table 3. Pertussis Prophylaxis: Definition of Close Contact and High Risk

Close Contact	High Risk
• Close sharing of confined space with infected individual for >1 h	• Infants age <1 y
• Direct contact with respiratory, oral, or nasal secretions from infected patient	• Pregnant women in third trimester
• Face-to-face exposure within 3 ft of infected patient	• Immunocompromised • Underlying lung disease

Adapted from CDC. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis. *MMWR*. 2005;54(RR14):1–16.

Table 4. Pertussis-Containing Vaccines

Pertussis-Containing Vaccines for Children	Brand	Licensed Date and Used For
DTaP	INFANRIX®* DAPTACEL®†	First licensed in 1991; used for all childhood doses
DTaP + IPV + HepB	PEDIARIX®*	Used for the first 3 doses
DTaP + IPV + Hib	PENTACEL™†	Approved in 2008; used for primary 4-dose series
DTaP + IPV	KINRIX™*	Approved in 2008; used for booster dose at 4–6 y
Pertussis-Containing Vaccines for Adolescents and Adults	**Brand**	**Licensed Date**
Tdap	ADACEL®† BOOSTRIX®*	First available in 2005
Other Vaccines	**Brand**	**Licensed Date**
Pertussis only		Not available in the United States
DT/Td	DECAVAC™† TENIVAC™†	Do not contain pertussis; DT used for primary series when pertussis vaccination was not desired; Td used in persons aged ≥7 y

D=diphtheria toxoid; d=diphtheria toxoid reduced dose; T=tetanus toxoid; P=pertussis vaccine; aP=acellular pertussis vaccine; ap=acellular pertussis vaccine reduced dose.
*GlaxoSmithKline, Research Triangle Park, NC.
†Sanofi Pasteur Inc., Swiftwater PA.
Adapted from CDC, Manual for the Surveillance of Vaccine-Preventable Diseases (5th Edition, 2011).

11 to 18 years, and preferably between age 11 and 12 years. This booster is administered by using the Tdap formulation of the vaccine, which contains a reduced dose of both the diphtheria and pertussis components to minimize local reactions.

Although it is not Food and Drug Administration-approved for children age 7 through 9 years, the Advisory Committee on Immunization Practices recommends a single dose of Tdap for children age 7 through 9 years who are not fully immunized against pertussis. This group includes children who have received fewer than 4 doses of DTaP, children who have received 4 doses of DTaP with the last dose given before age 4 years, and children whose immunization status is unknown. The booster is recommended also for adults aged 19 and older.

The incidence of pertussis in infants and children declined dramatically following the introduction of widespread immunization in this country. In the past decade, however, pertussis rates have been climbing. There has been a shift also in the age distribution of disease. Although infants younger than age 6 months still account for the majority of reported cases of pertussis, older children and adolescents represent an increasingly large proportion of the clinical cases.

In addition, many cases of pertussis remain undiagnosed in the United States, because illness often goes unrecognized in adolescents and adults who may not have typical symptoms. In adults, pertussis illness may not be recognized because it is a subclinical disease at least 40% of the time. (12)

Evaluation of pertussis-specific serological responses after illness indicates that prolonged cough illness in adolescents and adults often is diagnosed incorrectly as bronchitis or a viral upper respiratory tract infection.

Adults who have these clinical syndromes may be important reservoirs for spread of infection to infants. (13) Many studies have shown that the rates of interfamilial and household transmission to unimmunized infants are high. When the source can be identified in these studies of newborns with pertussis, family members are the source of transmission in up to 83% of cases. In one study, parents accounted for 55% of sources, siblings for 16%, and other family members and friends for another 18% when a source was identified. (14) Another study identified household contacts of infants younger than age 6 months age with pertussis and attributed the source to be mothers 38% of the time and siblings 41% of the time. (15)

Although the explanation for the changing epidemiology of pertussis infection is unclear, it is believed to be due both to an increased awareness and recognition of cases and to waning vaccine efficacy over time. Recent evidence suggests that at least some of this waning vaccine efficacy may be due to antigenic divergence between circulating and vaccine strains of *B pertussis*. (16)

With an adolescent Tdap vaccination rate of only 56%, and an adult rate of <6%, an increased effort at vaccinating

this older population is an important step in breaking the cycle of infection. Recent outbreaks of pertussis in infants and young children in populations with high vaccine refusal have raised the concern that pockets of underimmunization also may be contributing to the increase in pertussis cases. Recent evidence has confirmed higher rates of pertussis infection in populations of vaccine refusers. (17)

Infants, particularly those under age 3 months, are most vulnerable to the serious complications of pertussis infection. These infants typically become infected from adolescents and adults whose immunity has waned over time, making the Tdap booster an extremely important element of the overall pertussis prevention strategy. Because immunization with Tdap during pregnancy confers protection to the newborn as a result of transplacental antibodies, the CDC also recommends Tdap for pregnant women after 20 weeks' gestation who have not already received it, or whose vaccination status is unknown. If Tdap is not given during pregnancy, it should be given in the immediate postpartum period.

DTaP or Tdap (depending on age) is also recommended by the CDC for all family members and caregivers of the infant, including adults age ≥65 years, for whom Tdap is not US Food and Drug Administration-approved. This "cocooning" strategy can effectively shield the susceptible newborn from exposure to pertussis infection. Recent evidence suggests that newborns themselves may be able to mount an adequate antibody response to pertussis vaccine. Further research on infant immunization against pertussis may lead the way to improved protection for this most vulnerable population. (18)(19)

Vaccine Safety

An effective pertussis vaccine has been in use in the United States since the introduction of the original whole cell pertussis vaccine in the mid-1940s. This vaccine was combined with diphtheria and tetanus toxoids as the diphtheria, tetanus, and whole cell pertussis vaccine (DTP) vaccine in 1947. Although this vaccine was effective, it was associated with a high frequency of significant but nonlife-threatening adverse events, ranging from high fever to hypotonic-hyporesponsive episodes. These reactions were a consequence of the large number of proteins present in this whole cell preparation.

Fear of these sometimes frightening reactions led some parents and clinicians to link the vaccine to brain damage and other conditions that were seen following vaccination with DTP. Antivaccine groups and negative media coverage surrounding this alleged linkage created a backlash against the vaccine, resulting in a wave of successful litigation against the manufacturers of DTP. In the United States, pharmaceutical companies stopped producing the vaccine, requiring action from the federal government to safeguard the nation's supply by enacting the National Childhood Vaccine Injury Act of 1986. This act included the Vaccine Injury Compensation Program, which established a fund supported by an excise tax on each vaccine component to compensate parents of children who developed any condition listed on its compensable injury table.

Despite the long history of concern over the DTP vaccine, multiple well-designed studies have repeatedly failed to link the vaccine to brain injury. (20)(21)(22)(23)(24)(25) In 1990, the acellular pertussis vaccine (DTaP) was introduced, which is associated with a significantly reduced incidence of adverse events. Local reactions still are relatively common, with 20% to 40% of children experiencing some combination of local redness, swelling, and pain. Systemic reactions are uncommon, with 3% to 5% experiencing a fever (≥101°F). These reactions are seen most often following the fourth and fifth doses.

Summary

- Pertussis is a serious and potentially fatal disease caused by the bacterium *Bordetella pertussis*. In infants under age 6 months, who are too young to be adequately protected by the vaccine, pertussis is associated with a hospitalization rate of almost 80% and a mortality rate of nearly 1%.
- Complications of pertussis include encephalopathy, pneumonia, apnea, seizures, and death. The course of the illness is more severe in young children, with infants under age 6 months most at risk for hospitalization and severe complications.
- A high degree of suspicion is important. Treatment usually is initiated too late in the illness to alter the course, but can prevent transmission of the disease to others.
- An effective vaccine is available and recommended for all children. Because of waning vaccine immunity over time, an additional dose of vaccine is recommended for older children and adults.
- Women whose pregnancy has passed 20 weeks or who are in the postpartum period who were not vaccinated previously or whose vaccination status is unknown, and other individuals who may come in contact with a newborn, should be vaccinated as part of a strategy to "cocoon" the newborn from infection.
- Enlarging pockets of underimmunization may be a contributing factor to the current upswing in pertussis cases, reminding us of the importance of maintaining high vaccination rates for the prevention of disease outbreaks.

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PIR Quiz

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1. An obstetrical resident asks you when to administer the pertussis vaccine to a 25-year-old pregnant woman whose immunization status is unknown. You tell the resident that, among the following, the soonest recommended time would be after

   A. 16 weeks
   B. 20 weeks
   C. 24 weeks
   D. 28 weeks
   E. 32 weeks

2. The woman delivers before the vaccine is administered. You recommend that the following people who live in the household be vaccinated:

   A. Both parents
   B. Mother
   C. Parents and siblings over 10 years
   D. Parents, siblings over 10 years, and grandparents
   E. Parents, siblings over 10 years, grandparents, and nanny

3. A 4-month-old infant boy has had a fever (100.6˚F), a persistent cough, and nasal discharge for the past week. You are considering a diagnosis of pertussis. The most practical and rapid laboratory study to confirm the diagnosis is

   A. Complete blood count with differential
   B. Culture on Regan-Lowe medium
   C. Fluorescent antibody testing
   D. Polymerase chain reaction testing
   E. Serum antibody titer

4. The diagnosis of pertussis is confirmed. The antibiotic of choice for an infant this age is

   A. Azithromycin
   B. Erythromycin
   C. Penicillin
   D. Trimethoprim-sulfamethoxazole
   E. Vancomycin

5. The infant is begun on appropriate treatment. The parents ask when he can return to child care. You tell them that their son will no longer be contagious after receiving antibiotic therapy for

   A. 24 hours
   B. 48 hours
   C. 72 hours
   D. 5 days
   E. 10 days

Pertussis in Childhood

John Snyder and Donna Fisher

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Complementary, Holistic, and Integrative Medicine : Depression, Sleep Disorders, and Substance Abuse

Anju Sawni and Cora Collette Breuner

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Complementary, Holistic, and Integrative Medicine: Depression, Sleep Disorders, and Substance Abuse

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Author Disclosure
Drs Sawni and Breuner have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Introduction

The use of complementary and alternative medicine (CAM) has increased dramatically in the pediatric population in the United States. (1) Concerns regarding adverse effects, cultural and personal reluctance, and unknown consequences of long-term use of pharmacologic treatments for depression, sleep disorders, and substance abuse, make many parents and adolescents uncomfortable; thus, they seek treatments that are "more natural" and "safer." Medication as the first line of treatment generally is not recommended to treat mild depression. Sleep disorders in children often are related to the child's environment (chaotic home life, anxiety, poor sleep hygiene, etc). Promoting a healthy mind, body, and spirit in children is important in developing emotional stability. Achieving this goal involves good nutrition, exercise, a healthy environment, proper sleep hygiene, and supportive family, friends, and community. Integration of CAM therapies such as mind-body therapies (meditation, yoga, self-hypnosis, relaxation), herbs and supplements, and massage may be helpful as well.

Depression

Depression affects a large number of children and adolescents. Prevalence rates for depression range from 1% to 2% of prepubertal children to 3% to 8% of adolescents. (2) Despite scientific evidence supporting the effectiveness of psychopharmacologic intervention, the use of antidepressants has received negative publicity and is not easily accepted by many parents. Medication as the first line of treatment generally is not used to treat mild depression; thus, some CAM therapies may provide effective alternatives for treatment of mild depression. Children, adolescents, and young adults are using CAM to treat depression. (1)(3)(4)

Lifestyle Therapies

A child's diet is the foundation for the structure and function of the developing brain. (5) Adequate nutrients are essential for optimal production of neurotransmitters that affect mood, such as serotonin (made from tryptophan with B vitamins and zinc as cofactors). Studies in adults and children have found that folate, vitamin B_{12}, and zinc levels are lower in depressed than in nondepressed persons, and supplementing with folate, B_{12}, and zinc can lead to improvements in mood. (6)(7)(8) One study of school-age children in Guatemala at risk for zinc deficiency found that 6 months of zinc supplementation increased serum zinc concentrations and was associated with decreases in internalizing symptoms (ie, depression and anxiety). (9)

Low levels of vitamin D also are associated with depressive symptoms in adults, and treatment with vitamin D supplements is associated with improved mood. (10)(11) Iron deficiency anemia can be accompanied by depression. One study showed that severe, chronic iron deficiency in infancy and early childhood is associated with mood and learning problems years after the deficiency is corrected. (12)

Pediatricians should recommend that children at risk for mood disorders have adequate intake of folate, vitamin B, zinc, vitamin D, and iron. Children who are sedentary report higher levels of depression. (13)(14) Engaging children in vigorous physical activity instead of sedentary

Abbreviations

CAM: complementary and alternative medicine
EFAs: essential fatty acids
SJW: St John's Wort

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activities can improve mood. A meta-analysis of yoga therapy in adults found that yoga as a form of exercise has been shown to be effective in treating depression. (15)

Omega-3 Fatty Acids

Omega-3 essential fatty acids (EFAs) are a vital component of neuronal structure and function and may play a crucial role in cognitive and emotional functioning. (16) Studies done in children indicate that supplementation with omega-3 EFAs may have therapeutic benefits in childhood depression and bipolar disorder. (17)(18)(19) One study of 28 children who had major depression (age 6–12 years) and who were assigned randomly to omega-3 EFAs (1,000 mg/day, containing both eicosapentaenoic acid and docosahexaenoic acid) or placebo as pharmacologic monotherapy for at least 1 month found that children taking omega-3 EFAs had a 50% reduction in depression. (17) Daily supplementation with 1 to 3 g of EFAs (eicosapentaenoic acid/docosahexaenoic acid) can support healthy moods.

Biomechanical Modalities

Therapeutic massage can promote positive moods by decreasing the stress hormone cortisol and increasing the neurotransmitters serotonin and dopamine, which are decreased in depression. (20) Several studies and two good review articles have shown that massage as a therapeutic intervention can be effective for depression and anxiety in children. (21)(22) A study of 30 adolescents who have depression looked at the effect of a single session of massage or listening to uplifting music and found that both interventions had an immediate effect on electroencephalographic asymmetry (which may be a marker for vulnerability to depression), but direct effects on depression were not evaluated. (23)

Mind-Body Therapies

MEDITATION. Mind-body therapies enlist the mind in improving emotional well-being and physical health by "balancing" the autonomic nervous system. Approaches that calm the mind may be particularly helpful in children who have mood disorders. Meditation is a self-directed practice for relaxing the body, stilling the mind, and nurturing the development of focused attention. A study teaching a group of children Tai Chi and mindfulness resulted in improvement of general well-being, calmness, relaxation, and sleep, as well as less reactivity. (24) A small pilot study found that mindfulness meditation helped decrease depressive symptoms in minority children. (25)

Yoga is an ancient practice from India that aims to unify body and mind with "universal spirit," thereby encouraging physical and mental well-being. A preliminary study in young adults has shown Sahaj yoga to be beneficial in treating major depression. (26) Another study looked at the effects of a short-term Iyengar yoga class (emphasized yoga postures thought to alleviate depression) on mood in mildly depressed young adults (age 8–29 years) and found that the yoga decreased symptoms of depression and anxiety. (27)

Biochemical Therapies

The use of herbal remedies, such as St John's Wort (SJW), in adolescents with mood disorders is increasing. A survey of children and adolescents in the United States attending an outpatient psychiatry clinic found that 11% were using herbal medicines, and another study found that 20% of children took herbal medication for depression or attention-deficit hyperactivity disorder. (28)(29) SJW has a growing evidence base for use in depressive disorders, in particular, in adults with mild to moderate depression. The agent inhibits the reuptake of dopamine, serotonin, and norepinephrine within the brain; thus, it has the same mechanism of action as antidepressants. (30)

SJW also may be an effective treatment for adolescents who have major depressive disorder. Two open-label trials in adolescents who have major depression showed improvement within 2 weeks of starting SJW. (31)(32) Another study in children under age 12 years who had mild to moderate depressive symptoms suggested that SJW is potentially a safe and effective treatment (33) but can have adverse effects and serious interactions with commonly used medications. SJW induces the CYP450 3A4 enzyme, so its use can reduce the plasma concentrations of drugs metabolized by this pathway. SJW should not be used in conjunction with selective serotonin reuptake inhibitors, because it may increase the risk of serotonergic syndrome.

Sleep Disorders

It is estimated that as many as 30% of children and adolescents may have a sleep disorder. (34) This situation has implications for school performance, emotional adjustment, involvement in social activities, and quality of life. Many prescription medications and over-the-counter sleep aids are advertised for treating insomnia; most have adverse effects and are not always approved for children; thus, parents and pediatricians may be hesitant to use them.

The 2007 National Health Interview Survey reported that, of the children and adolescents who used CAM,

1.8% used it for insomnia or trouble sleeping. (1) Sleep hygiene remains the most important intervention for those with sleep disorders. CAM approaches that people use for sleep disorders include herbs, aromatherapy, supplements (melatonin), acupuncture, mind-body therapies (music therapy, relaxation, hypnosis), and massage.

Biomechanical Modalities

Infant massage reduces stress and promotes relaxation. A Cochrane review of infant massage found some evidence suggestive of improved mother-infant interaction, sleep, relaxation, and reduced crying. (35) A review by Beider of randomized controlled trials of pediatric massage therapies found massage to be beneficial in promoting sleep in children with autism and in psychiatric patients. (22)

Acupuncture

Acupuncture has been used in traditional Chinese medicine to treat insomnia in adults. A 2007 Cochrane review found some evidence of benefits, but many studies had design flaws. (36) To date, there are no pediatric studies looking at acupuncture to treat sleep disorder.

Mind–Body Therapies

Studies suggest that mind-body therapies and relaxation techniques may be helpful in people with sleep disorders. (37) Two studies found music therapy to be beneficial for sleep disorders in children and young adults. (38)(39) Hypnosis/self-regulation is widely, and often successfully, used in a variety of pediatric clinical settings to manage specific medical or psychological problems or to apply to various aspects of children's everyday lives (eg, stress management, sleep difficulties). (40) A retrospective chart review of 75 children and adolescents who have insomnia and who learned self-hypnosis found substantial benefits of self-hypnosis. (41)

Biochemical Therapies

Herbs and dietary supplements most commonly used to treat sleep disorders are valerian, chamomile, hops, lavender, lemon balm, passionflower, and melatonin.

VALERIAN. Valerian is one of the most popular herbal therapies for sleep disorders and insomnia. Studies in adults suggest that valerian can improve the quality of sleep and slightly reduce the time it takes to fall asleep. (42) In one study, treatment with valerian in children led to significant reduction in sleep latencies and nocturnal time awake; valerian lengthened total sleep time and improved sleep quality compared with baseline and placebo, especially in children who have hyperactivity. (43) Although research in children is very limited, valerian appears to be safe at recommended doses for short-term use for sleep disorders in some children and adolescents. Unlike benzodiazepines, valerian appears to have no residual morning drowsiness.

CHAMOMILE. Chamomile tea is used often for its sedative effects and is considered safe by the Food and Drug Administration, with no known adverse effects in pregnancy, lactation, or childhood. (44) Chamomile, hops, lavender, lemon balm, and skullcap (herbs on the "generally recognized as safe" list of the Food and Drug Administration) often are used in combination in sleep aid teas and may have sedative properties, but to date there are no studies on their effectiveness in the management of sleep disorders. Aromatherapy with the use of essential oils from herbs such as lavender or chamomile is popular as a sleep aid; preliminary research suggests some sleep-inducing effects, but studies are needed.

MELATONIN. Melatonin (*N*-acetyl-5-methoxytryptamine) is the major hormone produced by the pineal gland under the influence of the dark/light cycle. It has been used for circadian rhythm disorders, sleep disturbances, jet lag, and sleep-wake cycle disturbances. Melatonin shifts the circadian sleep-wake cycle and has mild sedating effects. (45) A very good review article and several studies in children have shown efficacy of melatonin in reducing sleep onset latency and in promoting sleep (both primary and secondary) especially in children with attention-deficit hyperactivity disorder, autism, developmental disabilities, and epilepsy. (46) Potential adverse effects of melatonin include suppression of the hypothalamic-gonadal axis and increased reactivity of the immune system in children who are taking immunosuppressants. Overall, melatonin appears to be effective and safe in treating children who have sleep disorders at doses between 0.5 and 7.5 mg before bedtime.

Substance Abuse

The 2009 Youth Risk Behavior Survey reports that ~40% of adolescents drank alcohol, 19% smoked cigarettes, 21% smoked marijuana, 3% used cocaine 30 days before the survey, and 19% had used inhalants, stimulants, or steroids at some time. (47) There is very little research on CAM therapies for treating substance abuse in adolescents. A few preliminary studies found that acupuncture and mindfulness meditation may show some promise in adults, but the data are limited and more research is needed. (48)(49)(50)(51)(52) To date, herbs and dietary supplements have little evidence

supporting their role in the treatment of substance abuse.

Summary

- A healthy lifestyle and healthy environment are the fundamental building blocks for promoting positive moods, decreasing stress, and improving sleep.
- In addition, several complementary therapies, including nutritional supplements, herbs, mind-body therapies, massage, and acupuncture may be helpful, and thus can be integrated into the treatment of depression and sleep disorders in children and adolescents.
- To date, there is very little research data on CAM for treatment of depression, sleep disorders, and especially substance abuse in children and adolescents. More research needs to be done in this area.

Note: To view the references for this article, visit the September issue at http://pedsinreview.aappublications.org and click on the "Complementary, Holistic, and Integrative Medicine" article.

Complementary, Holistic, and Integrative Medicine : Depression, Sleep Disorders, and Substance Abuse

Anju Sawni and Cora Collette Breuner

Pediatrics in Review 2012;33;422
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Index of Suspicion

Sameer Pathare, Kishore Gadikota, Charumathi Baskaran, Jonathan W. Hathaway, Jean Someshwar, Linda S. Nield, Saleem Raza, Demetrio R. Macariola and Shawn Hollinger

Pediatrics in Review 2012;33;427
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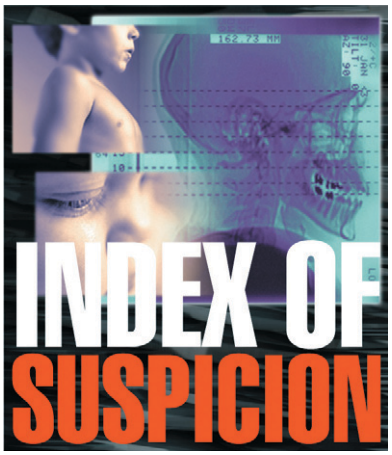

The reader is encouraged to write possible diagnoses for each case before turning to the discussion.

EDITOR'S NOTE. Case 4 was selected for publication from the 10 finalists in the 2011 Clinical Case Presentation program for residents held by the Resident Section of the American Academy of Pediatrics. Dr Hathaway, a resident from East Tennessee University Pediatrics Residency Program, wrote this case report. Choosing which case to publish involved consideration of the teaching value and excellence of writing, but also the content needs of the journal. Another case will be chosen from the finalists presented at this year's American Academy of Pediatrics National Conference and Exhibition and will be published in 2013.

Author Disclosure

Drs Pathare, Gadikota, Someshwar, Nield, Baskaran, Raza, Hathaway, Macariola, and Hollinger have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Case 1: Acute Urinary Retention in a 13-month-old Boy
Case 2: Depression in the Scalp of a 5-year-old Boy
Case 3: Acute Onset of Abnormal Behavior in a 16-year-old Boy
Case 4: Dark Urine in a 2-year-old Boy

Case 1 Presentation

A 13-month-old white boy presents to the emergency department (ED) with sudden onset of abdominal discomfort and lethargy. There is no history of fevers, vomiting, or diarrhea. He was born at 39 weeks' gestation by spontaneous vaginal delivery. He has had no surgery, and he does not take any medications. His immunizations are up to date and he is developmentally appropriate. Some older family members have had gastric, uterine, and cervical cancers.

Physical examination reveals a crying but consolable child. He is afebrile with a heart rate of 123 beats per minute, blood pressure of 107/60 mm Hg, respiratory rate of 37 breaths per minute, and oxygen saturation of 97% on room air. His abdomen is soft and nontender, with mild guarding; there are no masses or hepatosplenomegaly. Neurologic examination reveals normal strength and deep tendon reflexes. A rectal examination is deferred because of parental request.

His laboratory results reveal a serum sodium level of 134 mmol/L, potassium of 4.4 mmol/L, chloride of 105 mmol/L, bicarbonate of 13 mmol/L, blood urea nitrogen of 83 mg/dL, creatinine of 5.4 mg/dL, glucose of 98 mg/dL, calcium of 8.6 mg/dL, and lipase of 24 U/L. The complete blood count is normal for age, and urinalysis on a catheterized specimen shows moderate occult blood, but is negative for protein, leukocyte esterase, or nitrites. He receives intravenous fluids to correct his pre-renal kidney failure. Subsequently, he develops urinary retention that requires frequent urinary catheterizations. Renal ultrasonography shows bilateral hydronephrosis, and a voiding cystourethrogram shows two small bladder diverticulae and the absence of spontaneous emptying of the bladder. An advanced imaging study reveals the diagnosis.

Case 2 Presentation

A 5-year-old boy is brought to the clinic by his new foster mother for evaluation of a depression in his scalp noticed recently during bathing. The child has been living in this foster home for 2 months, but has been in multiple foster homes over the past several months because his biological mother lost custody of him because of her substance abuse and child neglect. The child's birth and past medical history are unknown except for the fact that he is 1 of 13 children born to the neglectful mother. Any history of accidental trauma or physical abuse also is unknown. The review of systems is negative except for screaming episodes during the past few weeks, which have abated.

Physical examination reveals a well-looking boy with an easily palpable skull defect, which is a 2- to 3-cm oval bony depression in the scalp at the upper left parietal bone, located ~1 cm away from the sagittal suture. The lesion is nontender and there is no bruit on auscultation. There are no other neurologic or skeletal abnormalities. Radiographs of the skull (Fig 1) reveal a well-circumscribed, lucent calvarial

defect with preserved tapered margins near the vertex adjacent to the posterior aspect of the coronal suture on the left. The lateral radiograph (Fig 2) demonstrates that the skull tapers smoothly at the margin of the lucent defect. No localized soft tissue thickening is visible. A pediatric neurosurgical consultation is obtained and magnetic resonance imaging (MRI) of the head confirms the diagnosis.

Case 3 Presentation

A 16-year-old white boy is brought to the ED by his mother for acting strangely and having hallucinations. He had a regular day at school and returned home perfectly normal. Within an hour, his mother noticed that he was not responding to her and was incoherent and confused. He was scribbling in the air and was whispering incomprehensive words. His parents claim that he does not use alcohol or illicit drugs. He has no history of trauma. He has been healthy and is not taking any medications.

On physical examination, his temperature is 97.3°F (36.3°C), pulse rate is 104 beats per minute, respiratory rate is 22 breaths per minute, and blood pressure is 127/78 mm Hg. His mucous membranes and skin are dry. His pupils are dilated to 6 to 7 mm bilaterally and react sluggishly to light. His chest is clear to auscultation and free of crackles or wheezes. His heart rate is noted at times to be in the 120 range. Abdominal examination is normal. He is disoriented with respect to time, place, and person, is agitated, and is hallucinating. He is in a state of confusion and gives incoherent responses. His muscle tone and reflexes are within normal limits.

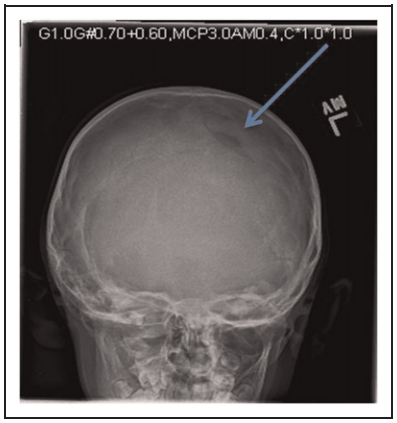

Figure 1. Radiograph revealing well-circumscribed lucent calvarial defect with preserved tapered margins near the vertex.

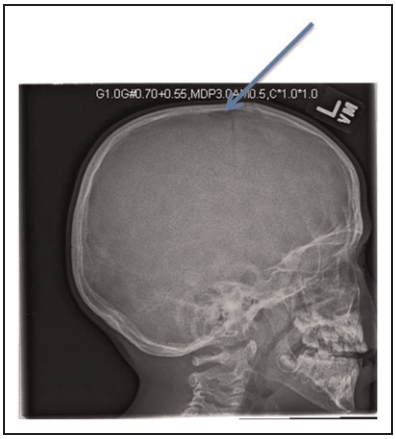

Figure 2. Lateral radiograph demonstrating that the skull tapers smoothly at the margin of the lucent defect.

Laboratory values include normal serum alcohol, salicylate, and acetaminophen levels. A urinary drug screen is negative. Serum electrolyte levels and complete blood count are within normal limits. Further inquiry into history reveals the diagnosis.

Case 4 Presentation

A 2-year-old boy presents with cough associated with fever for 6 days. He was seen initially by his pediatrician and diagnosed as having an upper respiratory illness. A few days later, he developed vomiting and diarrhea. Although his vomiting improved with ondansetron hydrochloride, he developed anorexia, and has become very irritable, with slurring of his speech. These symptoms have prompted his parents to come to the ED and seek admission. Past medical history is significant for congenital amputation of his left forearm because of an amniotic band. He has no history of excessive muscular exertion; heat stroke; or exposure to alcohol, cocaine, or methamphetamine.

His vital signs are as follows: heart rate 153 beats per minute, respiratory rate 40 breaths per minute, blood pressure 127/92 mm Hg, temperature 97.8°F (36.6°C), and oxygen saturation 96% in room air. He is irritable and his oral mucosa is dry. He has tenderness of both thighs and a pustule on his right hand. The remaining physical findings are normal.

Blood chemistry levels are as follows: sodium 122 mEq/L, potassium 4.4 mEq/L, chloride 83 mEq/L, carbon dioxide 22 mmol/L, blood urea nitrogen 15 mg/dL, creatinine 0.64 mg/dL, and calcium 9 mg/dL. His white blood cell count is 15,900/mm^3 (26% neutrophils, 11% monocytes, 37% bands), hemoglobin is 10.6 g/dL with hematocrit 31.3%, and platelet count is 136 $\times$ 10^3/μL. Urinalysis shows dark urine with two to five red blood cells per high-power field. This finding prompts the physician to test further. The child's serum creatinine phosphokinase (CPK) level is 4,922 U/L, myoglobin is 1,582 ng/mL, and lactate dehydrogenase is 481 U/L. The urine drug screen is negative. Electrocardiography shows premature ventricular contractions. Echocardiography and chest radiograph are normal. Blood culture and viral nasal swab are sent. Additional evaluation leads to the diagnosis.

Case 1 Discussion

Despite a normal neurologic examination, the voiding cystourethrogram results raised concern for a neurogenic bladder. Therefore, an MRI of the thoracic, lumbar, and sacral spine was performed and was completely normal, thus ruling out demyelinating lesions, transverse myelitis, spinal cord injury or hematoma, spinal dysraphism, spina bifida occulta, tethered cord, and epidural abscess.

Posterior urethral valves might have been considered, but the history was not suggestive. A pelvic mass obstructing the urinary tract potentially should have been seen in the imaging studies performed earlier. Urinary tract infection is a possibility, but both bacterial and viral urine cultures were negative.

The decision was made to perform cystoscopy. During cystoscopy, a firm nodular prostate gland was noted and prostatic biopsies were obtained. A pelvic MRI revealed a 5.0 × 4.2 × 3.5-cm mass involving the prostate. The mass seemed to be invading the bladder. The pelvic and inguinal lymph nodes also were prominent (Fig 3). On further review of the original spinal MRI, some images appeared to suggest an enlarged prostate.

Histopathology was positive for spindle cell neoplasm. The histologic and immunophenotypic features were consistent with embryonal rhabdomyosarcoma of the prostate. Metastatic evaluation, including bone marrow aspirate and biopsy, bone scan, and computed tomography of the chest, abdomen, and pelvis, was negative for metastases.

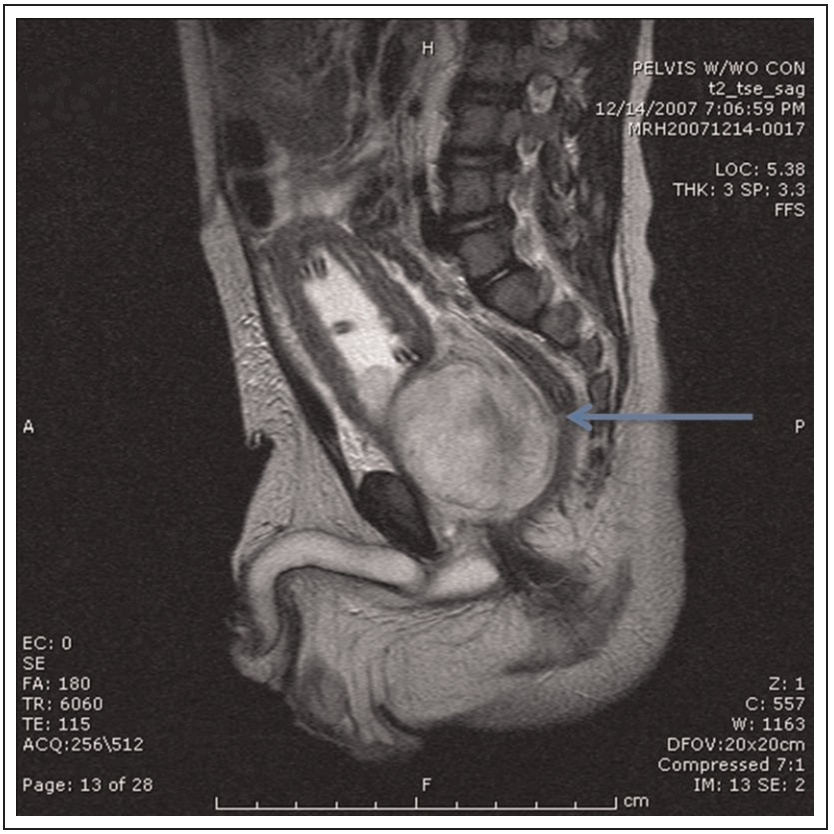

Figure 3. Pelvic MRI showing a mass involving the prostate.

The Condition

Rhabdomyosarcoma is the most common soft tissue sarcoma in children. The frequency in children <15 years is 6 cases per 1 million per year. Approximately 250 new cases of rhabdomyosarcoma are diagnosed in the United States per year. Genitourinary rhabdomyosarcomas account for 15% to 30% of all rhabdomyosarcoma cases in children. This percentage equates to an incidence of genitourinary rhabdomyosarcoma of ~1 case per million children per year. The specific incidence of isolated prostate rhabdomyosarcoma in pediatrics is even less than 1 per million per year. Rhabdomyosarcoma, in general, ranks fourth in frequency among childhood malignancies, behind central nervous system neoplasms, neuroblastoma, and Wilms tumor.

Typical presenting signs of prostatic rhabdomyosarcoma include dysuria, hematuria, and hesitancy. Progressive disease leads to symptoms of bladder outlet obstruction, abdominal pain, or rectal compression.

Prognosis

Localized genitourinary rhabdomyosarcoma has a 5-year survival rate of 65% to 80% with treatment by surgery, radiation, and chemotherapy. Metastatic disease has a 5-year survival of less than 30%.

Management

The management of genitourinary rhabdomyosarcoma requires a multidisciplinary approach involving an oncologist, radiation oncologist, and urologist. This patient underwent 1 year of chemotherapy consisting of vincristine, actinomycin D, and

cyclophosphamide. He then underwent radiation therapy and a subsequent prostate resection. It has been nearly 2.5 years since his diagnosis and he is doing well.

Lessons for the Clinician

- Imaging studies that are focused on one aspect of anatomy (in this case the spine) can be suboptimal for viewing other locations in close proximity (such as the pelvis).
- In the pediatric population, more attention should be paid to rectal examination and even prostate evaluations in children who present with signs of urinary outlet obstruction.
- Rhabdomyosarcoma is an uncommon malignancy in children and has a good prognosis when the disease is localized, before the tumor metastasizes.

(*Sameer Pathare, MD, Pediatric Hospitalist, CHOC Children's Hospital, University of California, Irvine, Orange, CA*)

Case 2 Discussion

Because of the history of neglect, which often is accompanied by nonaccidental and accidental trauma, a skull fracture or leptomeningeal cyst was considered strongly as the potential diagnosis. The MRI of the brain with and without contrast revealed the presence of a well-defined osseous defect (Fig 4) consistent with a parietal foramen. There was no intracranial mass, soft tissue mass effect, or space-occupying cutaneous or subcutaneous abnormality.

The Condition

Parietal foramina are congenital lesions and may be found as an incidental finding in routine skull examinations; usually they are located about 1 cm away from the midline of the sagittal sinus. These benign defects are smooth and have perfectly rounded edges, without new bone formation at the periphery. Parietal foramina are a consequence of defective ossification of the parietal bones. At birth, either one large midline or bilateral skull defects may be noted. The underlying brain is covered by dura and pericranium, and the overlying scalp is intact. The defects usually close during mid-childhood. Recently, a familial incidence has been identified having autosomal dominant inheritance and specific gene mutations, such as ALX4 and MSX2 involving chromosome 11.

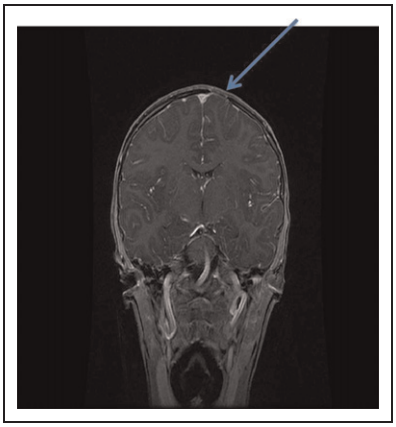

Figure 4. MRI of the brain showing the presence of a well-defined osseous defect consistent with a parietal foramina.

Differential Diagnosis

Along with parietal foramina, skull defects in children may be caused by skull fractures, leptomeningeal cysts, Langerhans cell histiocytosis, hemangiomas, epidermoid cysts, dermoid inclusion cysts, chondromas, and chondrosarcomas. Fractures will appear as lucencies on radiographs, but characteristically they are linear or depressed and appear darker than sutures. Sutures are sinusoidal and are found in their standard locations at the coronal, sagittal, and lambdoidal areas of the skull. A skull fracture also may appear sclerotic radiographically. Acutely, a history of trauma or the presence of bruising, swelling, and ear or nose drainage also would point to the diagnosis of a skull fracture.

Typically occurring in the parietal region, leptomeningeal cysts are rare complications of head trauma. The underlying dural tear is the single most important factor in the process of cyst formation. The edge of the skull is eroded gradually by the arachnoidal hernia, and a palpable scalp mass and bone erosion usually are discovered long after the initial injury. Hemiparesis, hemiatrophy, and focal cerebral seizures are common signs noted on initial presentation. Pulsations transmitted through the scalp over the lesion may be observed or palpated.

Langerhans cell histiocytosis is a proliferative disorder of histiocytes. Manifestations range from a solitary bone lesion to multisystem disease. Most cases with bony involvement are characterized by localized pain associated with a tender soft tissue swelling. Patients frequently will be symptomatic both during daily activity and at rest. Plain radiographs typically will show a single lesion or multiple lytic lesions of the bone with irregular margins.

Hemangiomas of the skull also commonly involve the parietal and the frontal bones and may cause bony erosions as they grow, typically leaving only the inner table of bone intact. Physical examination may reveal a reddish-blue, firm lesion that may or may not be tender.

Dermoid cysts are inclusion cysts and not true neoplasms. These cysts are thought to arise from sequestration of the epithelial cells during closure of the neural tube between the third and the fifth weeks of fetal life.

Skin structures, such as keratin, hair, and sebum, may be contained within dermoid cysts. Common presentations include seizures, headaches, and meningitis. Chondromas and chondrosarcomas are tumors involving the cartilaginous portion of bone.

Treatment and Prognosis

Small parietal foramina are considered benign because they do not cause any significant problems. The risk of penetrating injury to the brain through the defect is small; however, occasionally large parietal foramina may be associated with headaches, seizures, signs of elevated intracranial pressure, and hematomas. In the absence of any neurologic abnormalities, it is prudent to follow these patients with radiologic examinations in 6 months to rule out progression of the defect and to confirm the diagnosis. Parietal foramina will not change in size, but they may become smaller in relation to the growing skull. For large defects situated by a blood vessel, such as the emissary vein (Santorini vein) or a branch of the occipital artery or middle meningeal artery anastamosing with the superior sagittal sinus, a craniotomy may be needed to coagulate the vessel underneath.

For this patient, the neurosurgeon recommended no interventions except for re-examination in 6 to 12 months.

Lessons for the Clinician

- Clinicians should be aware of common pediatric skull defects and the use of appropriate radiologic studies to determine the underlying diagnosis.
- If the benign nature of parietal foramina is recognized, diagnostic procedures may be reduced to a minimum. The risk of penetrating injury to the brain is small but may cause anxiety. Education of parents, teachers, and the affected child to avoid risky behaviors is enough in most circumstances.
- Pediatric neurosurgical management may be required if the patient who has parietal foramina becomes symptomatic with intractable vascular headache, and if the defect is situated near a blood vessel requiring coagulation.

(*Kishore Gadikota, MD, Jean Someshwar, MD, Linda S. Nield, MD, West Virginia University School of Medicine, Morgantown, WV*)

Case 3 Discussion

All symptoms pointed toward the anticholinergic syndrome (ACS). Inspection of his room revealed some kind of seeds. On further inquiry with his friends, it was found that he had ingested moonflower seeds, which are used commonly for producing a "high." Thus, it is believed that the patient's symptoms were a result of ingestion of moonflower seeds (*Datura inoxia*). He developed symptoms of both central and peripheral muscarinic receptor inhibition. He continued to hallucinate for the next 48 hours. In addition, he developed urinary retention, which required intermittent catheterization.

The boy was treated symptomatically with lorazepam, haloperidol, and intravenous fluids. Poison control suggested the use of physostigmine in case he developed hallucinations severe enough to cause crawling or creeping on the floor; however, he did not require that treatment. After 48 hours, he was fully awake and oriented, he had no bowel or bladder retention, and his pupils were normal in size. He was released on day 4 after being symptom free for more than 24 hours.

The Condition

ACS is characterized by cholinergic inhibition at central and peripheral muscarinic receptors. This syndrome can be caused by an overdose of substances that produce an anticholinergic effect. Medications with anticholinergic actions include some antihistamines, antidepressants, antipsychotics, antispasmodics, and mydriatics. Hallucinogenic plants containing tropane alkaloids can result in anticholinergic syndrome as well. Tropane alkaloids contain atropine, scopolamine, and hyoscyamine, which are responsible for the symptoms.

Datura species of plants that contain scopolamine and hyoscyamine have been reported in the literature to have resulted in ACS. *Datura starmonium* (jimson weed) is the most common culprit. Some moonflowers that are used as ornamental plants in parts of the United States also belong to *Datura* species. *D inoxia* and *Ipomoea muricata* (purple moonflower) are the types of moonflowers that cause anticholinergic symptoms. The *D inoxia* plant contains the alkaloid compound scopolamine. The leaves, roots, or seeds may be ingested, smoked, or brewed for tea.

The usual clinical manifestations are a result of peripheral muscarinic blockade in the form of dry mucous membranes and skin, dilated pupils, tachycardia, hypertension, decreased bowel sounds, functional ileus, urinary retention, tremulousness, and myoclonic jerking. Central muscarinic inhibition presents as hallucinations, ataxia, disorientation, short-term memory loss, confusion, psychosis, agitated delirium, seizures (rare), coma, respiratory failure, and cardiovascular collapse. Symptoms usually begin within 30 to 60 minutes of taking the drug and last for 36 to 48 hours.

Diagnosis

There is no diagnostic test for ACS. It is of prime importance to rule out ingestion of other toxic substances.

Evaluation should include obtaining serum alcohol, acetaminophen, and salicylate levels. Urinary drug screen is helpful in identifying sympathomimetic drugs, such as methamphetamines and cocaine. A thorough history and examination of the scene often are useful in arriving at the diagnosis.

Differential Diagnosis

Although the constellation of symptoms may point toward an anticholinergic effect, sometimes findings of fever with altered mental status can be confused with meningitis, encephalitis, or neuroleptic malignant syndrome. Metabolic abnormalities, such as hypoglycemia, can produce similar effects.

However, an adolescent presenting with ACS should be suspected of intentional or accidental ingestion or overdose of substances that have an anticholinergic effect, which, as indicated, includes a large group of drugs such as anticholinergics (atropine, scopolamine, glycopyrollate), antihistamines (chlorpheniramine, diphenhydramine, cyproheptadine, doxylamine), antipsychotics (chlorpromazine, clozapine, olanzapine), antispasmodics, cyclic antidepressants, and mydriatics. Intentional abuse with hallucinogenic plants, such as *D stramonium,* and mushrooms, such as *Amanita muscaria,* can cause ACS.

Treatment

Airway, breathing, circulation, disability, and exposure (the ABCDEs of poisoning) should be addressed first, as in any poisoning. Most cases of anticholinergic intoxication can be treated symptomatically with close monitoring and observation. If seizures occur, they can be controlled with benzodiazepines. Electrocardiography may be performed; in most instances, the tracing shows sinus tachycardia. Sinus tachycardia is one of the conditions that requires the administration of activated charcoal (1–2 g/kg) orally or per nasogastric or orogastric tube for decontamination. Gastric lavage usually is not performed. Patients with hallucinations usually respond to reassurance and do not require treatment for the psychomotor agitation.

The antidote for tropane alkaloid toxicity is physostigmine salicylate. Physostigmine is a reversible cholinesterase inhibitor and is used primarily for the central nervous system symptoms. Physostigmine is known to cause cholinergic crisis, which is potentially life-threatening, so use of this drug is reserved only for severe toxicities.

Lessons for the Clinician

- Intentional use of plants and herbs by adolescents is becoming more common in the United States and can present with ACS.
- Awareness of this abuse provides an opportunity for physicians to educate their teenage patients and their parents of its potential effects as a part of regular anticipatory guidance.
- ACS is managed symptomatically, except when there are severe symptoms, when physostigmine may be used.

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Case 4 Discussion

The boy was diagnosed as having rhabdomyolysis. He was treated with intravenous fluids to correct hyponatremic dehydration as well as intravenous vancomycin and rifampin. His CPK level remained elevated and the myoglobinuria persisted for a week. Forty-eight hours after admission, methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated from his blood culture.

He remained febrile for a week, which led to the consideration of osteomyelitis. On bone scan, multiple soft tissue abscesses and osteomyelitis affecting all extremities, cervical vertebrae, and left chest wall were observed (Fig 5). All of these abscesses were drained surgically. He was improving clinically until he suddenly developed dyspnea. A chest radiograph showed cardiomegaly and an echocardiogram revealed a massive pericardial effusion. Emergency ultrasonographically guided pericardiocentesis was performed. During the procedure, he developed pulseless electrical activity because of pericardial tamponade. A pericardial window was placed, which allowed removal of 80 mL of purulent exudate. He recovered from the pulseless electrical activity and was transferred to another institution for further management. He was treated with vancomycin and rifampin for 8 weeks and had a full recovery.

The Condition

Rhabdomyolysis usually results from increased membrane permeability of muscle fibers, resulting in spillage of CPK and myoglobin into the circulation. Known causes of rhabdomyolysis in children include heat stroke, hypothermia, excessive muscular exertion, traumatic crushing soft tissue injury, infection, alcoholism, cocaine, methamphetamines, and congenital metabolic myopathies.

Environmental causes of rhabdomyolysis, such as exposure to extremes of temperature or trauma, usually are evident in the history, whereas drugs or alcohol ingestion can be ruled out easily by urine drug-screening tests. Metabolic myopathies that

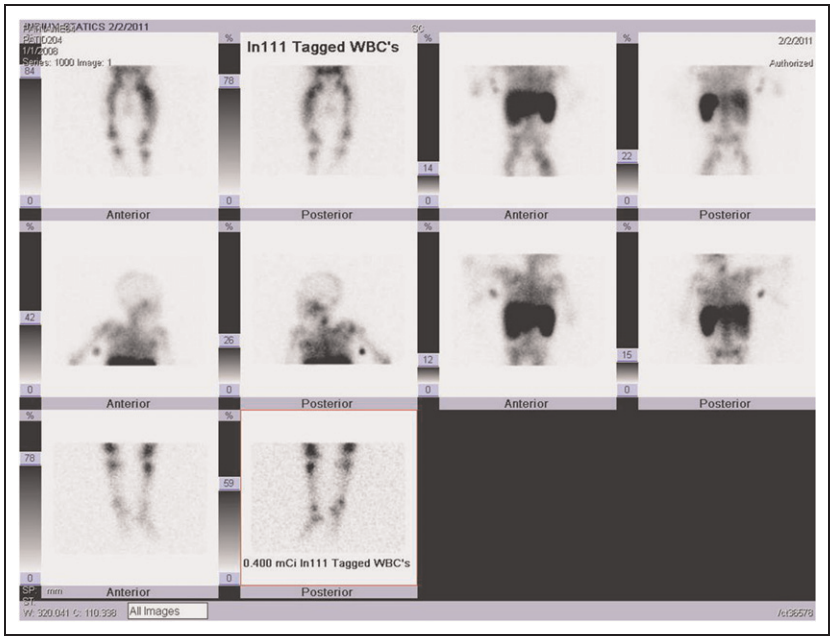

Figure 5. Bone scan shows multiple soft tissue abscesses and osteomyelitis affecting all extremities, cervical vertebrae, and left chest wall.

may cause rhabdomyolysis include muscle phosphorylase deficiency (McArdle disease) and carnitine palmitoyltransferase deficiency. Usually, children with metabolic myopathies present with recurrent myoglobinuria on muscular exertion.

Viral agents that have been described to cause myoglobinuria include influenza virus, parainfluenza virus, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, coxsackie virus, and adenovirus. Ehrlichiosis and Rocky Mountain spotted fever also can present with rhabdomyolysis. Infectious causes of myoglobinuria can be ruled out by viral or bacterial cultures or serologic studies.

The Organism

S aureus causes a variety of infections in children. It is a very resilient bacterium that develops resistance to antibiotics easily. A large percentage of *aureus* isolates have developed resistance to beta-lactam antibiotics, including resistance to methicillin. Initially, MRSA infections were present only in health-care facilities. Recently, MRSA infections also have been identified in individuals without previous exposure to health-care facilities. This type of MRSA has been designated as community-associated MRSA. MRSA may cause a variety of clinical infections, including impetigo, cellulitis, osteomyelitis, pericarditis, endocarditis, sepsis, pneumonia, and brain abscess. It is possible that when there are extensive soft tissue abscesses, as in this patient, the infection also can lead to breakdown of muscle fibers, leading to myoglobinuria.

Management

When the diagnosis of rhabdomyolysis is established, regardless of cause, hydration and urine alkalinization are crucial to prevent acute renal failure. In addition, treating the underlying cause of rhabdomyolysis is important. In the case of rhabdomyolysis caused by MRSA, as in this patient, appropriate use of antibiotics is a mainstay of treatment. This child's clinicians opted to use vancomycin in combination with rifampin. Other antibiotics used to treat MRSA infection in children include trimethoprim-sulfamethoxazole, clindamycin, doxycycline, daptomycin, and linezolid.

If clindamycin is used for treatment, it is important to make sure that the *S aureus* does not have inducible clindamycin resistance. This phenomenon can be demonstrated by the D test. (1) *S aureus* that is D test–positive has inducible clindamycin resistance and, if clindamycin is used, treatment failure will result. An abscess should be drained surgically. Likewise, if pericardial tamponade develops as a result of pericarditis, pericardiocentesis is a life-saving procedure and must be done urgently. Because this patient had osteomyelitis and pericarditis, he received 6 weeks of intravenous antibiotics until his erythrocyte sedimentation rate had normalized.

Lessons for the Clinician

- Rhabdomyolysis, although rare, can be an initial presentation of MRSA infection.
- Consider involvement of other organs, such as bone or heart, in children with documented *S aureus* bacteremia when they develop new fevers after initial recovery.
- Monitor for sudden development of cardiac tamponade in children with MRSA pericarditis.

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To view Suggested Reading lists for these cases, visit http://pedsinreview.aappublications.org and click on "Index of Suspicion."

Index of Suspicion

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