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I don’t remember exactly my “Eureka” moment. For sure, it was not in a bathtub like Archimedes. My “a-ha” came more recently while dry behind the ears. At the time I was in a private practice doing what pediatricians do. The discovery was that most everything I was doing in my office was wrong. The problem was not treating asthma or rashes. It was how I executed the time-honored well-child care (WCC) visit.

In the fleeting moments between the exam and the shots, my conversation with the parents usually was filled with platitudes and medical jargon. Well visits were boring. The monologue was stale. I said nothing lasting.

Further, I knew zero about the mother, father, or family. I had no clue about the person in the exam room with me. What kind of parents were they? How did they handle a screaming kid? What made them tick? Did they know love? Personally, knowing anxiety and depression, I worried about the parents in my practice. Were they equally struggling with their moods? How did it affect their parenting? Because I knew what a pain in the butt these conditions were, I wanted to help anyone with the same challenges.

“When the student is ready, the teacher will appear.” Perhaps it was the glowing embers of burnout. Whatever the igniting spark, I was ready. The teacher who appeared was Dr. Richard Ferre.

Proponents of “attachment”
Richard C. Ferre, MD, is the former chairman of the Department of Child Psychiatry at the University of Utah School of Medicine and Primary Children’s Hospital in Salt Lake City. He opened my mind to real pediatrics. The converting scripture was Daniel J. Siegel’s *The Developing Mind*.

Siegel’s book, one of many he has authored, introduced me to a brand-new world. It was as if I had followed the White Rabbit down the hole falling into an amazing wonderland. From its pages, I met Dr. John M. Bowlby, the godfather of child attachment theory. His work began with the millions of orphaned and displaced children after World War II. He continued to formulate his thinking, borrowing the studies of children forced to be alone by the British “stiff upper lip” policy during prolonged stays in the hospital. Bowlby was familiar with Konrad Lorenz and his imprinted gaggle of goslings. He added to his theory the behavioristic research of Harry F. Harlow of young primates clinging to the terry cloth “mother.” From this emerged the articulation of a secure base. Mary Ainsworth, Mary Main, and a pantheon of other thinkers and doers of the child and parent relationship became my heroes.

Attachment is the keystone Archimedes by water displacement figured out the king’s crown was not pure gold. I discovered the gold. It is human attachment. The parent bonds to the child. The child attaches to the mother/father. The word “security” jumped out from the pages blinding me. It clarifies everything. The lack of security explains my own state of mind. Security and insecurity describe human behavior. Attachment’s propagation through the generations

“*My [well-child care visit] agenda is to help every parent understand his/her mental model to deal with stress; ie, the child.*”
—Joseph Grant Cramer, MD, FAAP

Attachment is the key to parent-child relationships
One physician’s personal agenda is to help parents understand how their own history of dealing with stress affects how they bond with their child.
is the essence of parenting. Its absence in the pediatric WCC-visit curriculum is the missing keystone for caring for children.

The message to every new parent is their power to influence their child’s brain development. Nurturing is essentially the positive repetitive task of managing energy—in the vernacular, stress. It follows that it is critical to uncover his or her child’s mental model to handle tension. One of Dr. Ferre’s pearls was, “The job of the brain is to process information and manage energy.”

Attachment is now my practice and personal mantra. Mindfulness follows. My WCC agenda is to help every parent understand his/her mental model to deal with stress; ie, the child. To understand the parents’ intuitive behavior, I ask them to share their most frightful memories of childhood. Their brains draw from their nonverbal hemisphere stories that reveal a hidden clue to their stress energy management. It is the internal blueprint they use to deal with their child. A non–story is a story of avoidance.

The one question “What is the scariest thing you remember in your childhood?” is the revelatory key to open the mind. Over the years it has revealed a treasure trove of tales. The most ordinary parent sometimes has the most extraordinary story. There are the recollections of nightmares soothe by the sleepy parent. Another shared narrative is being lost but when found, being softened with hugs. Tragically, quite a few stories do not have a happy beginning to the nearly 9.5 million minutes from birth to age 18 years. Sadly, there are repeated descriptions of violence or abandonment. Memories of dads pointing guns have been shared more than once. One patient told how her father put a gun to her head when she was about 6 years old. Her mother voiced her own craziness: “Go ahead and shoot. When the police come, they will know what idiot did it.”

Another patient remembered the night the mother said she was leaving, never to return. Today I learned a mother’s terrifying story recalling how at the age of 3 years she phoned the police because her parents were so violent. Imagine being 3 years old needing to know how, then calling the cops. One mother telling her personal history for a brief second transformed into her own alcoholic parent with a louder deeper voice and mean face leaned threateningly toward me. Knowing the story plus how a parent tells it gives a glimpse into what he or she does when the child comes for succor. The memory prompts rapid, nonspecific, nonspoken reaction. If the parent’s tale is without a secure person, his or her spontaneous action will be more dismissive. “You are fine” is the automatic response. Decreased empathy is the result. The child is on its own. This by itself is not bad. Talk to the self-starters. It is a problem when the emotional skills run out. Avoidance of relationships, loneliness, procrastination, freezing, and fleeing take over.

**Measuring security**

Mary Ainsworth’s contribution is the standard test to measure security. Her research has been duplicated thousands of times around the world. In this experiment, the child is stressed by the mother stepping away, leaving the toddler with a stranger. How the child and the mother react upon leaving and reuniting can reveal how the parent had or had not matched the child’s needs. Their actions often link back to the parent’s story.

In one scenario, the child cries with the mother, cries when she leaves, and cries when she returns. Obviously, the presence of the mother is not soothing. This is labeled insecure ambivalent. In another setting labeled avoidant insecure, the child shows no emotion either on separation or return. However, the hidden sympathetic tone is as high as with the child who cries continuously in the mother’s presence. This is the child with whom the parents take pride in how well adjusted he/she is. Instead, it is the opposite. The presence of the mother does not calm the internal storm.

The secure child cries but quiets with the reappearance of the mother. With the child’s secure base again in the room, the child goes off to play. Secure parenting teaches that stress has limits in time and intensity. More importantly, the baby learns for a lifetime that he or she is not alone.

**Steps to attachment**

As doctors, our first task is to **awake** our parents to the grandeur of their role as creators. They move from making a baby to creating a child. We do that with our sincere efforts to arouse them to the unbelievable...
beauty of their baby. Gazing at a baby’s face is incentivized by the large eyes and rounded red face, and by the baby’s imitating expressions back to the parent. I want the mother to gaze upon her beautiful child. I want them to at least think “Wow, wow, wow” (the last mortal words of Steve Jobs). In the world of complexity to increase probability, nature has made a baby beautiful to promote our connection. Studies show children imitate almost out of the womb. Very early on a child can tell the difference between a sad, happy, and angry face. The mother transmits emotion information to the infant, downloading lifetime files of happiness, sadness, joy, and fears.

Next, the parent must be aware of his/her own mental model of energy regulation. Self-awareness is not a gift bestowed upon everyone. Alexithymia, the inability to read internal or external emotions, can inhibit this skill. In 1 study, the capacity to recognize emotional expressions was enhanced by the mere practice. In another, maternal iron depletion contributed to poor reading of emotional signals. Unfortunately, borderline personality disorder, a form of attachment disruption, is a barrier to this reading as well.

Third, agency in a complex system permits choices. In the chaos of humans and our relationships, we are agents. We do not follow linear Newtonian courses of launched rockets. Oftentimes, after sharing a truly horrific memory, the parent, commonly the dad, says he is going to be different. In the clinic yesterday, a father and mother expressed gratitude to their absent parents. Thanks to their parents’ neglect, they know what not to do.

Fourth, without attention it is impossible to watch, listen, learn, touch, read needs, and react accordingly. Attention is the blossom and the fruit of mindfulness. Paying attention means a parent actively eliminates distractions, unplugs the screens, skips the trivial. Concentration permits seeing the previously unseen. To that end, meditation is the brain homework to increase function of the prefrontal cortex (PFC). Engage the PFC; rev up the power to discover.

Fifth, attunement is the actual emotional connection of parent brain to child brain, DNA to DNA. Here is where the epigenetics of change takes place. Opening and closing zones of the transcription, altering the histones and microRNA, all play some potential role. Simple stroking can influence methylation.

Sixth, attachment is the culmination of all the previous steps. The parents are awake, aware of their style of interaction that matches the child’s needs. They choose to follow their positive model or elect to be different. They are attentive to the child’s needs. They react brain to brain. The bond is solid; the attachment is secure.

Lastly, atonement is a word more often heard in religious corridors than in the hallways of the House of Medicine. In that setting, it is a reconciliation of humankind with God. It is becoming one with the divine. “At-one-ment” is a unity, a symbiotic fusion. In the universe of child-rearing, it is the harmony between parent and child. There is a shaping of a child in the parent’s own image.

Final thoughts
There is an Adam and Eve in every parent. The connection is manifested in the influences parents make to their children’s DNA. It is the closeness sustained by rocking a child to sleep. It is the nearness when parents read to their babes or sing them lullabies. It is hugging them when they crash or kissing their ouchie. Atonement, or this spiritual symbiosis, comes from lying on their bed to hear the details of the day or the tragedies of a teenager. It is a oneness built of sharing stories of life. It means there is more to parenting than the mechanics. There is an additional dimension that we should not ignore or pretend that it does not exist.

This is real pediatrics. It is the creation of a healthy, happy, loving, secure child.

Maybe that is what Archimedes meant when he ran naked down the street shouting “Eureka!”

Dr. Cramer is a retired pediatrician in Salt Lake City Utah. He is the father of 5 sons, grandfather to 13, and husband of an amazing wife. He has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.
Strategies for improving developmental screening

Pediatric practices could make significant improvements to their developmental surveillance and screening processes in a short time. This project team’s initiative shows just how quickly your practice can, too.

**FIGURE 1 AAP DEVELOPMENTAL SURVEILLANCE GUIDELINES**

**Components of Developmental Surveillance**

- Eliciting and attending to parents’ concerns
- Obtaining a developmental history
- Making accurate observations of the child
- Identifying risk and protective factors
- Maintaining an accurate record of the process and findings

Adapted from the American Academy of Pediatrics (AAP) Algorithm for Developmental Surveillance and Screening.

Pediatric practices could make significant improvements to their developmental surveillance and screening processes in a short time. This project team’s initiative shows just how quickly your practice can, too.

**SEND US YOUR SUCCESS STORY!** Dispatches highlight the creativity of your peers who have encountered an issue in their practice and then pilot-tested a solution. These informative “how-to’s” are tailor made for you to consider retrofitting for your own practice. Send your request for writers’ guidelines to catherine.radwan@ubm.com
We found that pediatric practices, even when already performing developmental screening, could make significant improvements in a short time period.
All teams identified referrals as an area of special focus for this project. Some reported difficulty in conducting rapid PDSA cycles around referrals because of the lengthy turnaround time involved and processes outside teams’ control.

However, teams were able to test innovative changes within their practices that improved the referral and follow-up process by refining their existing workflow, including:
- creating patient follow-up systems;
- standardizing referral orders; and
- establishing internal referral tracking systems.

Lessons learned
Despite high levels of adherence with developmental surveillance and screening recommendations, we found that use of a team approach to fine-tuning details of existing processes led to further improvements. Engagement of all clinical and support staff was critical to the success of the entire team.

“I think everyone has really started ‘waiting less’ and doing more to help and monitor developmental growth in all our patients.”

Discovering gaps in workflow, staffing, record-keeping, and referral process facilitated practicewide efforts to improve efficiency. Teams tested changes to improve multiple unique but interrelated workflows.

“I continue to be amazed by how individual contributions work together to make our overall system better. I also have been reminded about how important a positive attitude is in process change.”

Some successful changes cut across practice components. For example, one team focused on timeliness of screening completion and developed a process for screening completion prior to the clinician entering the room, with the support staff stating, “Let me know when this is completed, and I will tell the doctor you are ready.” This intervention was refined and spread to the rest of the clinic using reminders such as stickers on exam room computer screens.

Additional small tests of change established optimal screen timing and locations for the screening tools. Practice teams agreed that overall visit times did not increase or decrease significantly and communication with patients about developmental screening was somewhat easier.

Clinicians reported that discussions with families of both “passed” and “concerning” screens improved. Many found this to be an important step in providing feedback on skills and developmental anticipatory guidance. Future developmental surveillance and screening may be aided by increasing parents’ knowledge of typical developmental milestones. Teams improved documentation of discussions within their electronic health records, including provider instruction and standardized text.

Teams explored referral tracking options, including paper tracking systems (ie, spreadsheet lists or referral copies in a binder), that allowed for cross-checking for feedback from state early-intervention (EI) programs or other referral resources. (See “Strategies for improving the referral process,” left.)

---

**Strategies for Improving the Referral Process**

1. Using a standardized form (preferably a written form).
2. Seeking feedback from the EI program on patient’s evaluation and progress reports.
3. Implementing 2-way information releases between providers and EI.
4. Developing a referral flow diagram.
5. Tracking developmental referrals separately from other referrals.
6. Designating 1 central referral nurse.
7. Obtaining current family contact information.
8. Confirming specialist appointments to keep referrals from “falling through the cracks.”
9. Encouraging patients to follow up with the office after a referral was made.
10. Discussing what to expect when referred for further evaluation by specialists and EI programs and providing a typical timeline so families could better prepare to engage new, and often complex, systems.

Abbreviation: EI, early intervention.
FIGURE 3 CDC’S FREE TOOLKIT: LEARN THE SIGNS. ACT EARLY.

Provides FREE tools for monitoring the development of children in your care and making talking with parents about developmental monitoring and screening easier.

“Tall am I? 46”

“This project helped us... have documentation on when they [families] went [to a referral], if they did go, and if they had problems getting in. We’re more aware of resources, which is beneficial. We’re more efficient now in getting kids in.”

“Parents” really enjoy learning where their child should be at what point in time and kids like them [LTSAE developmental milestone books], too.”

Teams also reported feeling empowered to engage families better while referral processes were underway. Teams also used materials and resources provided in the project “change package” that included information on QI tools, surveillance and screening implementation, screening result discussion, referrals, and billing. Practice teams used and valued free CDC LTSAE family-focused patient education materials (Figure 3).

Teams found LTSAE materials helpful to engage families in developmental surveillance and anticipatory guidance and easy to incorporate into their workflow.

“We laminated the LTSAE developmental sheets and put them in the exam rooms so that sparks discussion when the provider goes in.”

“The thing I like about the milestone sheet is that it’s very literate friendly... I would say down to a 6th-grade level. It’s simple and not busy.”

“I found it very helpful to have something in writing to give to the parents in addition to what they hear me say. It augments... and reinforces what I say during the visit.”

Teams also shared favorable feedback from parents. “Parents are glad for the booklets. Parents often ask what they should be doing, and they like to know what to expect early on.”

“[Parents] really enjoy learning where their child should be at what point in time and kids like them [LTSAE developmental milestone books], too.”

Teams sought additional guidance regarding payment for screening services and resources and specialists to whom they could refer families. One team obtained a referral directory from their state AAP Chapter and additional resources to optimize...
As outcomes for developmental and autism screening, practice teams continued to make improvements in already high standarized screening processes to above 95% at project conclusion.

Teams improved, not only on quality improvement metrics, but in their awareness of the value of developmental surveillance, building relationships with families through surveillance and screening, ensuring concerning results are addressed, and the next steps to help children achieve their optimal development. The changes made by each team varied, but all were perceived to add value to children and families.

**Take-home message**

Our findings suggest that assessing processes around developmental and autism screening can be helpful in enhancing care for young children and their families. Practices can improve processes in a relatively short period of time, and in ways they may not perceive as needing improvement.

The comprehensive QI Project Toolkit is available on the AAP quality improvement webpage (https://www.aap.org/en-us/professional-resources/quality-improvement/Pages/Developmental-Surveillance-Screening-and-Referral.aspx). Pediatric practices also may be able to receive ABP MOC credit by implementing their own QI project (see application materials at the AAP website: https://www.aap.org/en-us/continuing-medical-education/mocportfolio/Pages/getinvolved.aspx).

**Authors' note:** The findings and conclusions in this report are those of the contributors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. This report is not intended to provide guidance to the federal government.

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**REFERENCES**


Acetaminophen prevents febrile seizure recurrence

Acetaminophen is a safe antipyretic against febrile seizures (FSs) and has the potential to prevent FS recurrence during the same fever episode, a study in Japan found.

Investigators evaluated 423 children and infants aged 6 to 60 months who visited their hospital’s emergency department (ED) because of an FS, defined in Japan as a seizure accompanied by a temperature of 100.4°F or greater without central nervous system (CNS) infection. The children were divided into 2 groups, with 1 group immediately receiving a 10 mg/kg dose of rectal acetaminophen that was repeated every 6 hours until 24 hours after the onset of the FS, as long as the child’s fever remained higher than 100.4°F. Parents of children in the no-antipyretic group were instructed not to administer any antipyretics to their child for 24 hours after the FS. No participants received diazepam suppositories during the study period.

Overall, 16% of participants experienced FS recurrence during the same fever episode, all within 24 hours of the initial FS. The recurrence rate was significantly lower in the rectal-acetaminophen group than in the no-antipyretics group: 9.1% versus 23.5%, respectively.

In children aged 6 to 21 months, recurrence rate was 13.2% in the rectal-acetaminophen group and 24.3% in the no-antipyretics group. The difference in recurrence rates between the 2 groups was even more striking among children aged 22 to 60 months: 4.1% versus 22.6% for the rectal-acetaminophen group and no-antipyretic group, respectively.

Investigators noted no serious complications related to acetaminophen, such as hypotension, hypothermia, or anaphylaxis. Although FS patients with diarrhea were excluded from randomization, investigators compared these children’s seizure recurrence rate with those of children in the trial, finding that the rate in those with diarrhea was considerably higher—35%—than the rates in both the rectal-acetaminophen group and the no-antipyretics group.

A data analysis that accounted for other clinical variables found that rectal acetaminophen was the largest contributor to prevention of FS recurrence during the same fever episode (Murata S, et al. Pediatrics. 2018;142[5]:e20181009).

**THOUGHTS FROM DR. BURKE**

At first, I thought that this study was an evaluation of prophylactic acetaminophen after a first febrile seizure. It is not. Children in the treatment group were given acetaminophen each 6 hours only if they had continued fever. Unlike in some previous studies, this approach worked in reducing subsequent seizures during the same illness. I can find no other studies that support prophylactic use of antipyretics during the duration of a febrile illness after a seizure, and a 2008 American Academy of Pediatrics (AAP) clinical practice guideline does not recommend this approach (Pediatrics. 2008;121[6]:1281-1286).

Michael G Burke, MD is Chairman, Department of Pediatrics, Saint Agnes Hospital, Baltimore, Maryland.
Teen food insecurity is associated with later accelerated BMI

A longitudinal study begun when participants were aged 15 years showed that body mass index (BMI) tends to increase more rapidly over time in individuals who experience food insecurity in their early teen-aged years than in those who don’t. Results were based on data for a 16-year period for 559 adolescents and their families from a primarily rural Midwest population that underwent an economic farm crisis.

Investigators collected participant data on food insecurity and height and weight at 10 time points beginning at age 15 years until age 31 years. Parents reported on household food insecurity, using a 2-item questionnaire, until their adolescent was aged 18 years, after which the adolescent did so along with continuing to report on height and weight, which investigators converted into BMI throughout the study period.

Overall, participants’ BMI increased over time while food insecurity decreased. However, BMI increased more rapidly in those with higher food insecurity when they were aged 15 years. A participant’s initial level of BMI was not a predictor of BMI changes.

Finally, in females, but not in males, changes in food insecurity at different time points strongly predicted changes in BMI over time, indicating that females with a faster increase in food insecurity over time also had a more rapid increase in BMI (Lohman BJ, et al. J Pediatr. 2018;202:115.e1-120.e1).

I do not understand the mechanism for this association or the finding that girls are more affected than boys, but this study supports others that show health effects of food insecurity. The AAP recommends frequent screening for food insecurity using 2 short questions (Pediatrics. 2015;136(5):e1431-e1438). For local information on food resources, call 211 in any state in the United States.

Does knowing nursing’s maternal benefits affect the decision to breastfeed?

A survey of more than 700 women who had given birth to at least 1 child found that about one-third of women who were aware that breastfeeding reduces the risk of breast cancer thought this knowledge had contributed to their decision to breastfeed. More than half the surveyed women who were not aware of this risk reduction indicated that knowing how breastfeeding benefits their own health could have influenced how they feed their infant.

The online survey had 20 questions that were designed primarily to assess mothers’ knowledge of breast cancer risk reduction from breastfeeding. About 56% said they were aware that breastfeeding reduces cancer risk, with Caucasians significantly more likely to have this knowledge than African Americans or other races. Women who knew the benefit breastfed longer than those who did not: 13.2 months versus 9.3 months, with a greater proportion of Caucasian women than African American women breastfeeding for longer than the recommended 6 months.

Interestingly, only 16.6% of women who were aware of how breastfeeding reduces the risk of breast cancer got this information from healthcare providers. Instead, they obtained it through articles, books, or the Internet (Ganju A, et al. Breastfeeding Med. October 23, 2018. Epub ahead of print).

I do not understand the association between reduced risk of breast cancer and breastfeeding first was described in 1926. The effect is particularly striking in aggressive, difficult-to-treat, triple-negative breast cancer (TNBC), a form that is more common in African American women. These authors cite other work that shows that increased breastfeeding in African American women could decrease prevalence of TNBC by two-thirds in this population. For the sake of both the women and their babies, new and prospective mothers should hear this information from obstetricians and pediatricians, not just from magazines and the Internet.
A 4-year-old girl presents to the emergency department (ED) with a 12-hour history of progressively worsening episodic left lower quadrant (LLQ) abdominal pain and nonbilious emesis. There was no history of fever, diarrhea, hematochezia, constipation, or dysuria. The child was previously healthy, did not take any medications, and had no history of prior surgery.

On initial presentation, the girl appeared mildly uncomfortable with a temperature of 98.6°F; heart rate of 102 beats/minute; respiratory rate of 18 breaths/minute; and pulse oximetry of 98% in room air. Her abdomen was soft with mild distention, and she had significant tenderness to palpation and voluntary guarding in the left lower quadrant. No masses or organomegaly were appreciated, and normal active bowel sounds were present. The remainder of her exam was unremarkable.

**Labs and imaging**
A complete blood count, basic metabolic panel, and clean catch urinalysis all were within normal limits, and fecal occult blood was negative. Abdominal radiograph revealed a lower midline, abdominal-pelvic soft tissue mass, with internal calcifications that looked like teeth (Figure 1). Bowel gas was present throughout, without obvious obstruction. Computed tomography (CT) of the abdomen and pelvis with contrast subsequently revealed a 7.0 x 6.2 x 5.4-cm unilocular, complex cystic mass within the left adnexa with internal calcifications (Figure 2).

**Differential diagnosis**
Common things being common, the differential diagnosis in the ED included constipation, gastroenteritis, viral illness, and urinary tract infection. Due to the patient’s examination findings suggestive of an acute abdomen, intestinal obstruction (to include volvulus and intussusception) was also highly considered. After review of the patient’s plain film,
the differential diagnosis was expanded to include ovarian neoplasm and torsion.

Table 1 shows the differential diagnosis for acute LLQ pain in the prepubescent pediatric age group. However, it’s important to remember that abdominal pain in young children is often poorly localized. The differential diagnosis of acute abdominal pain is guided by other key findings on review of systems (ROS) to include the presence or absence of fever, and changes in bowel or bladder habits. In the absence of diarrhea, gastroenteritis should always be a diagnosis of exclusion.

Although many cases of acute abdominal pain are benign, others require rapid diagnosis and treatment to minimize morbidity. Signs and symptoms that suggest an acute surgical abdomen include bilious vomiting, absent bowel sounds, occult blood in stool, voluntary guarding or rigidity, and rebound tenderness (Table 2).

Teratomas are neoplasms containing tissue from all 3 germ cell layers, and MCTs predominantly contain ectodermal derivatives such as hair and teeth. These MCTs are benign, with malignant transformation occurring in less than 2% of cases. Mature cystic teratomas can present with nonspecific symptoms such as abdominal pain and swelling, or may be found incidentally on imaging. Approximately 30% of MCTs in children present with acute abdominal pain, often accompanied by nausea and vomiting, subsequent to ovarian torsion. Endocrinologically functioning tumors, signs of precocious puberty, and palpable abdominal or pelvic masses are much more likely to represent malignant neoplasms. Various tumor marker assays also are helpful in detecting malignant ovarian neoplasms, to include AFP and β-hCG.

Dermoid cysts have a characteristic appearance on ultrasonography and CT (a unilocular cystic mass containing fat, with or without calcification), allowing for reasonably accurate noninvasive diagnosis.

### TABLE 1

<table>
<thead>
<tr>
<th>DIFFERENTIAL DIAGNOSIS OF ACUTE LEFT LOWER QUADRANT ABDOMINAL PAIN IN A PREPUBESCENT CHILD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GASTROINTESTINAL CAUSES</strong></td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Gastroenteritis/Viral illness</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
</tr>
<tr>
<td>Mesenteric lymphadenitis</td>
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<tr>
<td>Atypical appendicitis</td>
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Author created.
CAR T-cell therapy in pediatrics

Recent developments in chimeric antigen receptor (CAR) T-cell therapy have shown promise in treating relapsed B-cell acute lymphoblastic leukemia in children.

Leukemia is the most common malignancy in children, representing nearly 30% of pediatric cancers. B-cell acute lymphoblastic leukemia (B-ALL), which represents nearly 80% of ALL, is a disease in which most pediatric patients are cured using standard chemotherapy. However, there is a subset of these patients, approximately 20%, for whom standard chemotherapy is ineffective. Once relapsed, the survival rates have historically been poor, with long-term survival less than 20% in patients with early relapses, and 50% in those with relapses greater than 36 months from diagnosis.

Due to the high prevalence of ALL relative to other pediatric malignancies, this relapsed population is substantial. Chimeric antigen receptor T-cells (CAR-T) targeting CD19+ B-cells is an innovative new therapy that has achieved 80% to 90% complete remission rates in patients with relapsed or refractory B-ALL, with some products achieving durable remissions greater than 12 months in approximately half of pediatric patients.1

**What are CAR T-cells?**
CAR T-cells redirect a patient’s immune system toward cancer cells and, in its idealized conceptualization, the treatment is the equivalent of administering a living persisting drug. Chimeric antigen receptors are synthetically engineered receptors against a selected tumor antigen, and are incorporated into T-cells to redirect and enhance their function against the cancer cell.2

Although a CAR T-cell can be engineered to target any receptor, those targeting CD19 on B-cell malignancies have been the best-studied therapies to date, and there are now 2 CD19 CAR T-cell products available on the market (Figure). The first, Kymriah (tisagenlecleucel) by Novartis Pharmaceuticals (East Hanover, New Jersey), was approved by the US Food and Drug Administration (FDA) in August 2017.3 The second CAR T-cell product, Yescarta (axicabtagene ciloleucel) by Kite Pharma (Foster City, California), was

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**Contemporary Pediatrics** is meeting your need to stay current on pharmacologic best practices by bringing you this new recurring feature titled *The Clinical Pharmacologist’s Notebook*. Our goal is to provide pediatricians and pediatric healthcare providers with the most up-to-date information—and thinking—as provided by children’s clinical pharmacology experts.

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**Dr. Lee’s Clinical pharmacologist’s notebook**
FDA approved in October 2017. Using CAR T-cells to treat other tumor types has thus far been limited by the identification of similarly effective target antigens with limited off-target adverse effects, as well as an immunosuppressive environment that protects many solid tumors from infiltrating T-cells.

The process of manufacturing CAR T-cells begins by collecting the patient’s T-cells via apheresis, which are then genetically engineered to express the CAR gene using an inactivated viral vector. These cells are then expanded in the laboratory and undergo quality control assessments. During this time, the patient undergoes a short conditioning chemotherapy regimen to deplete remaining lymphocytes. The newly engineered T-cells are then infused into the patient, with a “vein-to-vein” time of several weeks.

Adverse effects
Like any cancer treatment, CAR T-cell therapy is not without unique adverse effects. However, unlike toxic effects associated with chemotherapies or bone marrow transplants, CAR T-cell adverse effects are reversible in nearly all cases. As these engineered T-cells become activated and release proinflammatory cytokines, up to 80% of patients experience cytokine release syndrome (CRS). This cardinal toxicity typically develops within 1 to 3 weeks after administration and is similar in presentation to sepsis, including fever, hypotension, tachycardia, and capillary leak, which can progress to hypoxia, respiratory failure, and/or shock. Approximately, 50% of patients will require a brief intensive care admission for blood pressure and respiratory support.

Treatment of CRS involves supportive care and reduction of cytokines with tocilizumab, an IL-6 antagonist, originally used for rheumatoid arthritis. Because of the lifesaving potential of tocilizumab for CRS, centers administering CAR T-cells are required by the FDA to have 2 doses of tocilizumab on hand for each patient. For CRS unresponsive to supportive care measures and tocilizumab, corticosteroids may be considered. However, due to their immunosuppressive properties, there is some concern that corticosteroids may impact the efficacy of CAR T-cells. An oncologist should always be involved when considering steroid use in patients who have recently received CAR T-cells. The presence of CRS is most prominent in patients...
with high disease burden and reflects the fact that active CAR T-cells are performing their cytotoxic function. In fact, patients who do not develop CRS are less likely to see a response to therapy.²

Additionally, 30% to 45% of patients will experience a spectrum of neurotoxicity known as CAR T-cell-related encephalopathy syndrome (CRES).¹,² that may include delirium, encephalopathy, aphasia, confusion, seizure, hallucination, and, rarely, cerebral edema. The mechanism of these neurotoxic symptoms is not yet known. Delirium screening and neurologic assessment are performed at least daily until 4 weeks after the CAR T-cell infusion. Additionally, antiseizure prophylaxis is recommended during this high-risk period, especially for patients with a history of central nervous system disease or seizures. Tocilizumab is not effective for CRES and, therefore, management is typically limited to supportive care. In severe cases, steroids may be considered but, as with their use in CRS, they may jeopardize the efficacy of the CAR T-cells and thus should never be given without the involvement of an oncologist.⁸

Most long-term effects of CAR T-cells remain unknown given the novelty of this therapy. However, by targeting CD19, patients who receive CD19 CAR T-cells will develop aplasia of their normal B-cells, and consequently the inability to produce antibodies.¹ This is not only an expected outcome, but one that renders CD19 a desirable and well-studied target because this aplasia can be easily managed with regular immunoglobulin replacement. These patients also require deferral of vaccinations for as long as the aplasia persists.⁹

**Next steps**
The future for CAR T-cell therapy is bright. There have emerged more than 100 CAR T-cell companies investigating nearly 50 tumor biomarker targets. Patients who relapse after CD19 CAR T-cells may do so because their leukemia or lymphoma cells no longer express CD19, a phenomenon called antigen loss. Thus, future targets for these disease states include other leukemia receptors, such as CD22 and CD20. Additionally, CAR T-cell therapy is being explored for other solid tumor malignancies including neuroblastoma and melanoma.⁹

Ongoing challenges involving CAR T-cells are numerous and include: feasibility across more institutions; management of relapse after CAR T-cell therapy; reversing endogenous T-cell exhaustion; and expanding the selection of patients who are most likely to derive benefit from these novel agents.⁸

Finally, the scope of CAR T-cell therapy is not limited to oncologic care but also has the potential to extend to autoimmune, infection, and degenerative conditions.¹⁰

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**CONTEMPORARY PEDIATRICS CLINICAL VIDEO EXCLUSIVE**

For *Contemporary Pediatrics*, Dr Bobby Lazzara discusses the first global trial of a CAR T-cell therapy for children with refractory acute lymphoblastic leukemia that achieved promising survival rates—even remission—in some patients.

Predictions for cancer care

KAREN APPOLD

Ten years from now, driverless cars might be the norm. Service bots might perform jobs that humans would prefer not to do. And what about cancer care? If a cure hasn’t been found for this deadly disease by then, what type of changes will have occurred? Several positive ones, say cancer care experts. For more on the shifting cancer care landscape, and how it will impact healthcare quality and costs, we asked experts to weigh in. Here, they share their predictions.

PREDICTION 1
More precise treatments

Carlos L. Arteaga, MD, director at UT Southwestern Simmons Cancer Center in Dallas, which provides care to more than 105,000 hospitalized patients and oversees approximately 2.4 million outpatient visits annually, expects widespread use of precision cancer medicine, which is using a cancer’s molecular profile to determine the best therapy approach for individual patients, such as single-targeted therapies or a combination. The therapy will be applicable to most solid tumors, such as those in the breast, colon, lung, and ovaries. Consequently, traditional chemotherapy will be used less frequently.

Precision medicine also includes collecting big data sets on individuals and populations and integrating that data to better predict, prevent, diagnose, and treat cancer, says Jeffrey Golden, MD, chair of pathology at Brigham and Women’s Hospital in Boston, which includes 150 outpatient practices with more than 1200 physicians. Golden is also professor of pathology at Harvard Medical School, which serves as a home base for more than 10,000 physicians and scientists with faculty appointments. Information would include biologic data such as a patient’s genome and other large data sets, as well as routine chemistry, hematology, and microbiology lab test results.

PREDICTION 2
More effective approaches

Ten years from now, fundamental knowledge about using immunotherapy to treat cancer will provide scientists with a much better understanding of why some patients respond to this treatment while others don’t. “This knowledge—drawn from data from the more than 4000 immunotherapy clinical trials ongoing today as well as academic centers of excellence where in-depth laboratory analyses are carried out parallel to clinical trials—will affect how treatment decisions are made,” says Jill O’Donnell-Tormey, PhD, CEO, and director of scientific affairs at the Cancer Research Institute in New York, which supports more than 3000 scientists globally.

“These sources will also provide insight into strategies for improving immunotherapy’s effectiveness in more patients and in diverse cancers.” It may become possible, for example, to draw a patient’s blood and know precisely why their immune system is not keeping their cancer under control. “Armed with this knowledge, doctors will be able to develop personalized treatment regimens that include combinations of drugs designed to counter whatever is preventing the immune system from attacking the cancer,” O’Donnell-Tormey says.

PREDICTION 3
Broader use of T-cell–based therapies

These therapies will be more effective and more widely used across hematological cancers as well as solid tumors, says O’Donnell-Tormey. Research and engineering
technologies will allow for the creation of either autologous (coming from the patient) or off-the-shelf (mass produced) T-cells that can recognize multiple targets on cancer cells, making them more specific to cancer and thus reducing damage to normal cells, she says. Advances in genetic engineering will also enable the inclusion of “safety switches” that allow oncologists to control the rate of T-cell expansion or deactivate T-cells entirely when they have finished the job of eliminating cancer cells. This also will reduce T-cell therapy’s toxicity and adverse effects, while maintaining its ability to attack cancer cells.

**PREDICTION 4**

**Earlier detection**

Advanced single-cell (or smaller numbers of cells) and single-molecule (or smaller numbers of molecules) analytics will drive improved diagnostics, prognostics, treatment stratification, and more precise entry into clinical trials leading to novel and improved therapies, Golden says. “Recent innovations help to detect tumor cells and tumor DNA in patients’ blood, known as a ‘liquid biopsy,’ without the need for invasive procedures such as surgery,” he says. Through a simple blood draw, tumors are being detected and specific mutations identified. Today this technology is primarily assisting in monitoring therapy, essentially evaluating if treatment is reducing tumor burden, without the need for imaging or other tests. These advances will likely provide improved diagnostics as well as early detection for cancer, or possibly even new prevention strategies.

Kevin Hrusovsky, founder of Powering Precision Health and chairman and CEO of Quanterix, a company focused on advancing the science of precision health, says studies show promise for the reliability of specific biomarkers, which are found in blood—such as PSA—in determining if a patient has a recurrence of cancer at its earliest stages, while other markers show promise for detecting cancers long before any symptoms present. While blood tests for early cancer detection today are primarily used in research environments, he foresees a day when they will be offered as point-of-care tests and be available in doctors’ offices on a routine basis.

Hrusovsky expects biomarker readings to be part of routine physicals. By taking a baseline reading of a person’s biomarker levels via a blood test, doctors will be able to detect changes to these levels, indicating that diseases like cancer may be emerging, helping doctors potentially catch it before stage one. Consequently, doctors will be able to diagnose and treat cancer earlier, he says.

**PREDICTION 5**

**More artificial intelligence applications**

Digital pathology, which entails creating digital images from glass slides, will advance cancer care by developing artificial intelligence algorithms, Golden says. Recent advances, empowered by technical innovations in computer science, have permitted the analysis of data from digital images, advancing pathologists’ ability to more accurately, more safely, and with higher quality provide additional information regarding the biologic behavior of many abnormal growths.

Golden also predicts better forecasting of growth rates, metastatic potential, and even where cancer might develop. The positioning of artificial intelligence in the pathologist’s arsenal also has promise for clinical trials; improved patient selection will likely better define appropriate therapeutics and ultimately improve the approval of pharmaceuticals by identifying the patient population most likely to respond. Finally, digital images in combination with artificial intelligence will play an essential role in the research, development, and implementation of immunotherapy, he says.

**PREDICTION 6**

**Drug development changes**

Biomarkers will change the way pharmaceutical companies develop drugs, especially for oncology, says Hrusovsky. There’s already evidence of a growing openness to using biomarkers for drug development as a complement to symptomatic clinical endpoints, which are measured in clinical research to determine if a drug is working, with recent new guidance from FDA Commissioner Scott Gottlieb that...
biomarkers can be a reliable tool for advancing clinical trials, he says. By using biomarkers, researchers have the potential to see a drug’s effect on the body long before traditional symptomatic or imaging endpoints could reveal the drug’s effect.

Pharmaceutical researchers will also increasingly use biomarkers to measure certain drugs’ efficacy and toxicity on individual patients. “Precision medicine approaches can be game changers in oncology treatment because not all cancers are alike and drugs perform differently depending on the patient and prognosis,” Hrusovsky says.

**PREDICTION 7**

**Personalized cancer vaccines**

Cancer vaccines will become an integral part of patients’ treatment protocols, especially vaccines that provide the immune system with specific cancer targets that are unique to an individual patient’s tumors, O’Donnell-Tormey says. These targets, known as neoantigens, have been shown to stimulate spontaneous anti-cancer immune responses in cancer patients and hold great potential as therapeutic targets. Advances in computational prediction of neoantigen expression will enable doctors to design personalized vaccines that drive the immune system to seek out and destroy unique antigens that are likely to appear in patients’ tumors, says O’Donnell-Tormey. Vaccines will likely be given in combination with other immunotherapies designed to overcome immune suppression at the tumor site and facilitate a targeted immune response.

**PREDICTION 8**

**More reliance on nonphysicians**

Advanced practice providers, eg, nurse practitioners and physician assistants, will provide care to many more cancer patients, particularly at academic centers, says Arteaga. This will occur due to more treatment options, the significant prolongation of patient survival, and decreased treatment time due to better therapies, as well as a huge emphasis on cancer prevention.

Already, the use of advanced practice providers in oncology practices is growing—from 52% in 2014 to 81% in 2017—according to the American Society of Clinical Oncology’s annual Practice Census. Arteaga says advanced practice providers will also provide care to cancer survivors, who will require an increasing use of telemedicine because physical cancer facilities may not be able to accommodate the large number of survivors.

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**CAR T-cell immunotherapy**

A “living drug” against cancer cells

Chimeric antigen receptors (CARs) are receptor proteins that have been engineered to give T-cells the new ability to target a specific protein. The receptors are chimeric because they combine both antigen-binding and T-cell–activating functions into a single receptor.

CAR T-cell therapy uses T-cells engineered with CARs for cancer therapy. The premise of CAR T immunotherapy is to modify T-cells to recognize cancer cells in order to more effectively target and destroy them. Scientists harvest T-cells from people, genetically alter them, then infuse the resulting CAR T-cells into patients to attack their tumors.

CAR T-cells can be derived either from T-cells in a patient’s own blood (autologous) or from the T-cells of another healthy donor (allogenic). Once isolated from a person, these T-cells are genetically engineered to express a specific CAR, which programs them to target an antigen that is present on the surface of tumors. For safety, CAR T-cells are engineered to be specific to an antigen expressed on a tumor that is not expressed on healthy cells.

After CAR T-cells are infused into a patient, they act as a “living drug” against cancer cells. When they come in contact with their targeted antigen on a cell, CAR T-cells bind to it and activate, then proceed to proliferate and become cytotoxic.
Larotrectinib for pediatric cancer
New era of genomic medicine

New research is changing views about the treatment of pediatric cancer and bolsters the rationale for sequencing tumors in children.

MARY BETH NIERENGARTEN, MA

Recent approval by the US Food and Drug Administration (FDA) of larotrectinib is a sign of a new era of genomic medicine altering the way cancer typically has been talked about and treated and opening promising possibilities of safer and more efficacious treatment.

Instead of identifying and treating cancer by and at the site of tumor development, genomic medicine identifies and targets genetic mutations underlying cancer regardless of its site of tumor development.

“Larotrectinib is only the second therapy approved by the FDA for the treatment of cancer based on the presence of a genetic mutation regardless of the type of cancer in which the mutation occurs,” says Theodore W. Laetsch, MD, University of Texas Southwestern Medical Center–Children’s Medical Center of Dallas, Texas, and coauthor of several new studies of larotrectinib for TRK fusion-positive cancers.

“This is starting to change how we think about the treatment of cancer and adds to the rationale for sequenc- ing the tumors of children with difficult to treat malignancies,” he says.

Remarkable efficacy: Paradigm shift?

On November 26, 2018, the FDA granted accelerated approval of larotrectinib for treatment of solid tumors with tyrosine kinase (TRK) gene fusion in both adult and pediatric patients. Approval was based on data from multicenter, open-label, single-arm studies that showed the efficacy and safety of larotrectinib in this setting.1-3

Results from a study published in the New England Journal of Medicine that looked at the efficacy of larotrectinib in both adults and children with TRK fusion-positive cancers found an overall response rate of 75% according to an independent review. The results reflect a combined analysis of 3 protocols in which 55 adult and pediatric patients (ranging in age from 4 months to 76 years) with consecutively and prospectively identified TRK fusion-positive cancers (17 unique types) were enrolled into 1 of 3 protocols: a phase I study of adults, a phase I/II study of children, or a phase II study of adolescents and adults.1

All patients in the study had locally advanced or metastatic solid tumor, had been treated previously with standard therapy, and had adequate functioning of major organs. Along with the primary outcome (overall response rate assessed by an independent review), the study looked at secondary endpoints including overall response rate by the investigator, duration of response, progression-free survival, and safety. Overall results of the study are shown in the Table.

A combined analysis also showed the safety of larotrectinib, with grade 1 adverse events predominating (eg, low blood counts, elevations in liver function, and gastrointestinal symptoms) and only 5% of patients experiencing grade 3 or 4 adverse events by investigator assessment. None of the patients discontinued treatment because of adverse events.

“Across children and adults, responses were seen in more than a dozen different tumor types,” says Laetsch. “It didn’t seem to matter what type of cancer the patient had as long as the tumor had a TRK fusion.”

Results in children

Recently published results highlight the safety and efficacy of larotrectinib in children.2 A phase I/II study done to assess the safety of larotrectinib as well as the recommended dose in
children found that a dose of 100 mg/m² (maximum 100 mg per dose) offered significant efficacy and safety regardless of the age of the child.

The study included 24 patients, 17 with tumors harboring TRK fusions and 7 without documented TRK fusions. The patients included infants, children, and adolescents who were enrolled in 3 dose cohorts.

Most of the children enrolled in the study with TRK fusion-positive cancers had infantile fibrosarcoma (n=8, 47%), followed by other soft tissue sarcomas (n=7, 41%), and papillary thyroid cancer (n=2, 12%).

The study found that larotrectinib was well tolerated by the pediatric patients, with grade 1 or 2 comprising most of the adverse events (n=21, 88%). “[Adverse] effects of larotrectinib are generally mild, and usually much less than we see with traditional chemotherapy,” says Laetsch, who added that no long-term adverse effects so far have been seen, but the first child with a TRK fusion tumor began treatment with larotrectinib less than 3 years ago.

The study also showed that every child with a TRK fusion solid tumor treated with larotrectinib had tumor shrinkage, with 93% of these patients meeting the criteria for a centrally confirmed objective response, according to Laetsch. An objective response, he notes, was defined as at least 30% shrinkage of the largest tumor diameter measured by an independent radiologist.

In addition, Laetsch emphasizes that the responses seem durable. “Only 1 of 17 children with a TRK fusion cancer in our study developed resistance to larotrectinib,” he says.

Of note, none of the children with TRK fusion-negative cancers had an objective response to larotrectinib.

Wendy Allen-Rhoades, MD, assistant professor, Department of Pediatrics, Section of Hematology–Oncology, Baylor College of Medicine, Texas Children’s Hospital, Houston, highlighted on the remarkable efficacy shown in this study. “This trial shows phenomenal responses, and responses like this in a phase I and II trial are extremely rare,” she says. “I think we all hope in the oncology community that this is where we go as we develop more molecularly targeted therapy.”

For Allen-Rhoades, these results indicate that a paradigm shift may be close on the horizon for treating TRK fusion solid tumors in children. “I wouldn’t say that the shift has happened, but this is definitely the door for it to swing into this molecularly targeted therapy,” she says.

However, she emphasizes that questions remain, particularly the unknowns about the long-term consequences of the drug and optimal length of therapy. “While we’re really excited as these are some of the best results we’ve seen in a long time, there is always the flip side of it that this is not a magic bullet for everyone,” she says. “There are going to be people this doesn’t work for, there will be people who develop resistance to it, so using it for upfront therapy has to be done thoughtfully.”

**TABLE**

**RESULTS OF COMBINED ANALYSIS OF LAROTRECTINIB FOR TREATMENT OF TRK FUSION-POSITIVE TUMORS IN ADULTS AND CHILDREN**

<table>
<thead>
<tr>
<th>PRIMARY OUTCOME</th>
<th>75% (95% CI; 61 to 85)</th>
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<tbody>
<tr>
<td>Overall response rate by independent review</td>
<td>80% (95% CI; 67 to 90)</td>
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<tr>
<td>Overall response rate by investigator assessment</td>
<td>71%</td>
</tr>
<tr>
<td>Duration of response at 1 y</td>
<td>55%</td>
</tr>
<tr>
<td>Progression-free survival at 1 y</td>
<td>30%</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval. From Drilon A, et al.1

Importance of trials that include children

Along with the strong efficacy and safety shown by the trials, both Laetsch and Allen-Rhoades point to another exciting aspect of the trials—their inclusion of children.

“Children were included very early in clinical trials of larotrectinib,” says Laetsch, pointing out that the first child with TRK fusion cancer was treated only 8 months after the first adult. “This is an example of how early inclusion of children in clinical trials of a new cancer therapy can benefit children as well as expedite approval of the therapy for both children and adults,” he says.

For Allen-Rhoades, the inclusion of children in clinical trials of larotrectinib definitely showed that not only did we not hurt the trial, but in this case including children in the trial helped get FDA approval because they comprised 25% of the patients in the trial.”

—Wendy Allen-Rhoades, MD
Australian researchers have developed a quick cancer test that can identify tumor markers in blood, but it may remain an adults-only test.

“The aim of the paper was to share the discovery of these unusual properties of the DNA that are connected with cancer, and highlight that, because these properties can be measured in a very simple and fast manner, there is the potential to convert it into a new faster way to cancer detection.”

–Laura Garcia Carrascosa, PHD

Implications for future testing

The hope is to move the research ahead to clinical trials with larger sample sizes, Garcia Carrascosa says, expanding the study into additional cancer types and disease stages to validate the team’s findings.

“If successful, the potential use of the test could be to facilitate a fast and simple preliminary screening of cancer in patients, but we still don’t know how early the cancer could be detected, or if this test could be used in combination with other tests to obtain more precise information about the tumor type and stage,” Garcia Carrascosa says. “Without that information, it’s still difficult to have a clear vision of the potential use of this discovery.”

The test is based on the discovery of cancerous DNA nanostructures and their ability to stick to plain gold surfaces—more so than normal DNA. The research team tested their theory on 200 tissue and blood samples and identified cancerous cells with 90% accuracy. Initial research focused on breast, prostate, bowel, and lymphoma cancers, and human trials have not yet been attempted.

“This fundamental discovery directed us to develop a quick and easy test to identify the cancerous DNA from any tissue types. The assay, which we termed as ‘methylscape,’ requires a tiny amount of purified genomic DNA that is adsorbed for a few minutes onto an electrode surface to measure the extent of the DNA binding to the gold surface,” she explains. “We have also developed a nanoparticle-based detection method, which allows naked-eye detection by mixing this purified DNA with a few drops of gold nanoparticle solution. By simply observing the color change, it is possible to identify the cancerous DNA by naked eye within a few minutes.”

Applicability to pediatric cancers?

Donald Small, MD, PhD, director of the Division of Pediatric Oncology at Johns Hopkins Sidney Kimmel Cancer Center, Baltimore, Maryland, says that although the research is interest-
clinical brief

ing, he isn’t sure that it will be useful in pediatric patients. The test is based on DNA methylation, and there are different levels of methylation, and higher levels of methylation typically occur in cancers that develop over a lifetime. In pediatric cancers, this change may not be as evident or as easily detected.

“There are pediatric tumors where methylation of the tumors plays an important role, but it’s not so universal across tumor types. A lot of methylation changes that play a role in cancer are accumulating over lifetime,” Small says, noting that many childhood cancers are congenital or genetic in nature rather than developed as a result of changes to the cell over a lifetime, or based on lifestyle factors. “There are global changes in methylation with certain types of tumors, but that’s not the majority of tumors in pediatrics. Many pediatric tumors don’t necessarily have those same changes or have changes involving a limited number of genes.”

Still, the research is interesting, Small says, but he would like to see more investigation into how advanced tumors must be before they are detected by the test.

“They’re able to dilute down to about 1% abnormal DNA and still see it in their test. One of the questions I have with a screening test is I’m not sure how extensive a tumor would have to be to get 1% of DNA circulating in plasma. It may be that it would just show it at the point the tumor is already there,” Small says.

“There are lots of DNA circulating in plasma, so it’s not clear to me at this point how frequently you could pick something up at an early stage.”

Small says he believes that the test would more likely be used for cases where cancer was suspected and symptoms are present, rather than as a screening tool in healthy patients. He also doubts, because of the nature of pediatric cancers and the methylation process, that this test would ever be tested for pediatric use.

“All of the data from this are on patients that are [older] than 40 or 50 years, and most of those tumors are occurring in patients that are older than that,” he says. “You would have to prove that the DNA in pediatric tumors would show the same types of differences.”

Larotrectinib continued from page 21

Ms Zimlich is a freelance writer in Cleveland, Ohio. She writes regularly for Contemporary Pediatrics and sister publications Managed Healthcare Executive and Medical Economics. She has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

REFERENCE

Baby-led weaning (BLW) is an alternative approach to the introduction of complementary foods in infancy, which is gaining in popularity. In BLW, infants are presented with table foods first, foregoing traditional pureéd foods and spoon-feeding. Proponents posit that BLW allows infants to develop better autonomy and self-regulate eating, thereby reducing the risk of obesity by developing a healthier relationship with foods. However, the risks associated with BLW can be severe (eg, choking, growth faltering, anemia) if proper education around implementation and supervision are not provided.

Pediatricians, therefore, need to be aware of the best practices for BLW. This article will discuss the phenomenon of BLW, including how it differs from traditional introduction of complementary foods; outline both the theoretical and evidence-based advantages of BLW, as well as the potential risks and strategies to minimize these risks; and provide guidance for how to best counsel families who choose BLW to do so in a safe and developmentally appropriate way.

Introduction

Over the last decade, the discussion around the introduction of complementary foods (solid foods) has centered around the timing of the introduction of solid foods. Recently, however, the practice of BLW has added the question of how to best introduce solid foods.

Baby-led weaning is an alternative approach to the introduction of complementary foods in infancy, in which infants are presented with table foods rather than pureéd foods and spoon-feeding. Baby-led weaning is actually a misnomer, as the approach does not involve weaning from breast milk or formula feeding, but rather the addition of solid foods to an infant’s diet. It is often perceived as a significant deviation from traditional methods of introducing complementary foods and is in contrast to American Academy of Pediatrics (AAP) recommendations of parent-initiated spoon-feeding of pureéd foods.

However, the practices of BLW, stemming
from the central tenant of self-feeding by the infant from the first initiation of solid foods, have theoretical benefits that often are appealing to parents. Furthermore, this practice is likely what caregivers did for thousands of years prior to the introduction of commercially available, prepared “baby foods.” Healthcare providers may be skeptical about BLW practices, but given that these practices have anecdotally been gaining popularity over the last decade in the United States, there is a need for providers to familiarize themselves with BLW practices in order to counsel their patients’ parents about best practices related to BLW.

**History of BLW**

The concept of BLW has been traced back to online parent forums from around 2001, with a large gain in momentum attributed to British author Gill Rapley, PhD, who wrote a book for parents in 2008 titled *Baby-led Weaning: Helping Your Baby Love Good Food*. Since that time, BLW has gained popularity in Australia and the United Kingdom, more recently catching on in the United States. Websites, social network groups, and numerous books for parents have grown out of this movement, championing BLW as a “more natural,” “healthier,” and “fuss-free” way to introduce complementary foods.

The central tenant of BLW is allowing an infant to self-feed from the first introduction of complementary food. This eliminates the parent’s role in spoon-feeding initial puréed foods. Instead, BLW relies on the infant’s grasping and self-feeding whole-form foods starting around age 6 months (Figure). All food ingested is therefore controlled by the infant’s own actions and feeding, as opposed to a parent placing a spoon in the infant’s mouth. Parents are encouraged to provide infants with soft foods that they can easily grasp and place in their mouth, such as sticks of steamed vegetables. Babies first starting to be fed by BLW are encouraged to explore the foods presented to them, with a lesser emphasis on ingestion as the primary goal.

A common saying in the BLW community is that “Food is for fun until age 1,” meaning that in the first few months of starting complementary foods infants should be allowed to explore the new concepts of touching, manipulating, smelling, and chewing solid foods, without a focus on consumption. This low-pressure approach is hypothesized to allow an infant to develop a “healthy” relationship with food, growing his/her autonomy, and allowing the infant to self-regulate eating. Infants are in full control of their eating and set the pace of their meal, deciding when they are “done.” This contrasts to traditional spoon-feeding of purees in which the caregiver sets the pace of spoonfuls offered, perhaps being motivated to have the infant “finish” a predetermined serving of food. Baby-led weaning highlights the importance of the infant joining the family table immediately through sharing whole-form foods and observing and learning from the family’s eating practices. infants are provided with finger-food portions of the family’s prepared meals rather than puréed foods or “baby foods,” allowing for shared meal experiences.

These BLW practices deviate from currently recommended feeding protocols in the United States. Baby-led weaning suggests delaying the initiation of complementary foods until at least age 6 months or when an infant is able to sit unsupported with good head control, grasp objects, and bring objects to his/her mouth. For some infants, this may be as late as 8 months. Through delaying, proponents of BLW suggest that the child is more developmentally prepared to feed itself and consume solid foods. Current guidelines from the AAP recommend introducing iron-fortified cereals by spoon-feeding between ages 4 and 6 months. Delaying the introduction of complementary foods in BLW extends the interval of exclusive milk feedings to 6 months or beyond with continuation of full breastfeeding or formula feeding with no additional supplemental nutrition. In addition,
this delaying of complementary foods through BLW aligns with the AAP² and World Health Organization (WHO)³ recommendations for exclusive breastfeeding for the first 6 months of life. Studies have found that mothers who initiate breastfeeding, and breastfeed for longer, are more likely to follow BLW practices.³

The infant-directed nature of BLW has been noted to complement that of breastfeeding in which the infant decides how much and how quickly they eat, with proponents lauding it as a “more natural” approach.⁵ Despite BLW pairing well with breastfeeding, it should be noted that formula-fed infants also can follow the BLW approach.

**Theoretical advantages of BLW**

There are many theoretical advantages of BLW (Table). First, it is posited that as BLW allows an infant to have autonomy over feeding, the infant will learn to attend to his or her internal cues of satiety and hunger, rather than focus on external cues (ie, taking a mouthful because the infant is hungry rather than because a spoonful is being presented).⁵,¹¹,¹³ Decreasing “obesogenic” behaviors (ie, eating in the absence of hunger, lower satiety responsiveness, greater food responsivity) are thought to be especially important in light of the current pediatric obesity epidemic. The evidence around BLW in promoting these healthier eating behaviors has been limited, with one cross-sectional study¹³ finding that BLW infants (compared with non–BLW infants) have better appetite control (satiety responsiveness), and another randomized controlled study finding poorer appetite control and greater food enjoyment in BLW infants.¹⁴

Children’s later food preferences are thought to be influenced by early food exposures.¹⁵ Qualitative studies have found that parents perceive BLW to have a positive impact on their infant’s diet.¹⁶ As BLW infants are exposed to “table foods” from the beginning, it is thought that they may have preferences for a wider variety of foods than traditionally fed infants. One cross-sectional study found no difference in picky eating among BLW and non-BLW infants;¹⁵ while another cross-sectional study,¹⁷ based on parent self-report, found BLW infants to have greater preferences for carbohydrates whereas non-BLW infants had a greater preference for sweet foods. With regard to nutrient intake, a randomized controlled trial¹⁸ found no difference in macronutrient intake between BLW and non-BLW groups. Also, BLW is thought to promote greater acceptance of food textures by skipping over puréed foods and introducing a greater variety of textures at an earlier point.

Originators and lay proponents of BLW cite that healthier eating habits and intake may have a positive influence on a child’s weight status and risk for obesity. Evidence around this has been mixed with some studies finding BLW infants to be at a greater risk of underweight and overweight¹⁷ than their traditionally fed peers. However other studies have found BLW to be protective against overweight,¹³ or found no difference in weight outcomes between groups.¹⁴

Finally, BLW is considered an easier method of introduction of solid foods for parents and families. Through sharing common whole foods, there is no additional preparation of foods for the infant, allowing for increased time together at the family table, rather than the baby being spoon-fed separately in a highchair. The benefits of family mealtimes are numerous,¹⁹ underlining the importance of starting the practice of eating together as early as possible. Baby-led weaning may allow earlier introduction of the family mealtime.

**Theoretical disadvantages of BLW**

The potential disadvantages or risks of BLW are perhaps more important to discuss than the advantages (Table). A common concern from healthcare providers about BLW is its safety,¹ specifically with regard to risks of choking, growth faltering, and anemia.

With regard to choking, it is posited that an infant may be at greater risk of choking on a firmer piece of solid food as opposed to a puréed version of the same food. Proponents of BLW suggest that by allowing an infant full control over the placement of the food in their mouth they will develop better skills in mastication and moving the food bolus safely through the oral cavity.⁶ It is also thought that spoon-feeding purées may encourage infants to “slurp” their food, creating a

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**TABLE**

**THEORETICAL ADVANTAGES & DISADVANTAGES OF BABY-LED WEANING**

<table>
<thead>
<tr>
<th>Theoretical Advantages</th>
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<tr>
<td>□ Decreased eating in the absence of hunger</td>
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<tr>
<td>□ Decreased “picky eating”</td>
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<tr>
<td>□ Healthier weight</td>
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<tr>
<td>□ Ease of food preparation</td>
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<table>
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<tr>
<th>Theoretical Disadvantages</th>
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<tbody>
<tr>
<td>□ Possible choking</td>
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<tr>
<td>□ Increased risk of growth faltering</td>
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<tr>
<td>□ Increased risk of anemia</td>
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<tr>
<td>□ Increased messiness of feeding</td>
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vacuum that propels the food rapidly into the pharynx, teaching the infant to swallow before learning to chew.

Estimating the frequency of choking in BLW is difficult as it relies on parental report of true choking events as opposed to gagging, some amount of which is thought to be developmentally normal. A randomized control trial using a modified BLW approach (versus traditional approach) found no differences in choking events or infants being offered high-choking-risk foods (eg, apple slices, sausages, whole grapes, and so on) between groups.

Growth faltering is another potential disadvantage of BLW. Because the infant is given the “responsibility” of feeding itself, there are concerns that he or she may not consume enough calories to sustain growth on a healthy trajectory. Inadequate caloric consumption from BLW may result from an infant not being developmentally ready to self-feed (fine motor, gross motor, or coordination skills), or from not having the physical stamina or attention to sustain intake.

The originators of BLW recommend continued volume and frequency of milk feedings “on-demand,” as well as offering a milk feeding prior to offering solid foods to ensure the infant gets adequate calories. Specifically, the originators of BLW recommend offering an infant solids when he/she is not hungry, so that milk will remain the main source of nutrition. This goes against advice from the AAP that suggests giving the infant the majority of the milk feeding after solids, so that the infant will consume more of the solid foods and not be full of milk. A randomized controlled trial of a modified version of BLW that encouraged offering high-energy foods at each meal found no cases of growth faltering in the BLW group, although some infants had nonclinical slowed growth.

Sufficient iron intake is a nutritional challenge for infants around the world. As BLW infants forego purees, including the iron-fortified cereals that are common and recommended first foods, it is thought that they could be at greater risk of anemia. Whereas a cross-sectional study found that BLW infants’ daily intake of iron was less than half that of traditionally fed infants, a randomized controlled trial investigating risk of low iron intake, markers of iron stores, and anemia found no differences between a control group and a BLW group provided with education around increased iron intake. These findings underline the important role that healthcare providers play in early nutritional counseling and the direct effect this can have on the outcomes of their patients.

The final, and least serious, potential disadvantage in a BLW approach is the mess created by allowing an infant autonomy over his/her own food and intake. Through the exploration of foods, BLW infants have free reign to mash their sweet potatoes into their hair, throw spaghetti on the floor, or cover themselves in yogurt, for example. For some families, this may represent a significant economic challenge.

**It is important for all pediatric practitioners to be familiar with BLW practices in order to effectively counsel around safest practices.**

How clinicians can support BLW

Although some pediatricians may have reservations about BLW, it is important for all pediatric practitioners to be familiar with BLW practices in or-
order to effectively counsel around safest practices. Pediatricians should not entirely dismiss or “shut down” parents who express interest in BLW, as this may lead to alienation of the caregiver, preventing an open dialogue and the ability to counsel against high-risk behaviors. The pediatrician may even open the conversation about the introduction of solid foods at the 4-month well-child visit, discussing recommendations for exclusive milk feedings until 6 months, and asking about plans for introduction of solid foods including BLW approaches.

**Summary**

Baby-led weaning is an alternative approach to the introduction of complementary foods that is rooted in a strong theoretical framework around autonomy promotion in the realm of feeding. Current evidence is equivocal with regard to the potential health benefits in terms of eating behaviors, dietary intake, and weight outcomes. There is also little-to-no current evidence to support an increased risk of choking, anemia, or growth faltering associated with BLW, especially when BLW is done in a modified way. Pediatricians should familiarize themselves with modified BLW practices to counsel their patient’s caregivers to avoid choking risks and provide sufficient energy and nutrient intake.

**BEST PRACTICES FOR BLW**

Following are best practices for baby-led weaning (BLW), which are largely derived from the modified BLW approach outlined in the Baby-led Introduction to SolidS (BLISS) study.11

| **Timing of BLW.** | Pediatricians should counsel caregivers on when the ideal time is to start BLW, specifically, when their infant is developmentally ready to ingest solids safely. This does not necessarily correspond to a chronological age, but rather developmental abilities that typically occur around or after age 6 months. Infants need to be able to sit unsupported; have good head control; have raking and grasping abilities; and show the capability to direct an object into their mouth. If an infant is not felt to be ready for BLW by age 8 months, he/she should be evaluated for developmental delays and traditional feeding approaches should be strongly considered. |
| **Minimize choking risks.** Infants being fed by BLW should always be supervised and should never be left alone when eating. Parents should be counseled to avoid high-risk choking foods that are typically firm and round (eg, coin-shaped foods such as whole cherry tomatoes or grapes, popcorn, nuts, sausages, raw apple slices). Infants should be fed in an upright supported position (eg, in a high chair), and not reclining. First foods should be soft, easily “mushed” in an infant’s mouth without teeth, and easily grasped in the infant’s hand (eg, cut in “sticks” shaped like an adult finger). Caregivers should avoid “helping” their infant by placing pieces of food in his/her mouth, which may be unexpected to the infant. Although increased choking risk has not been associated with BLW,28 as a general precaution all caregivers should be counseled on the differences between gagging and choking; what to do in the case of a choking event; and when to call for help. In addition, all parents and caregivers, regardless of weaning style, should take infant cardiopulmonary resuscitation (CPR) and first-aid courses, such as those provided by the American Red Cross or many hospitals, to learn how to intervene in case of a choking incident. |
| **Ensure adequate energy and iron intake.** Parents should be encouraged to offer a wide variety of foods to their infant at every meal, including at least 1 high-energy food and 1 high-iron food. Typically, infants should be offered 3 to 4 foods at each meal. An iron supplement may be appropriate for infants who do not eat much meat or iron-rich foods. During the first months of the introduction of complementary foods, breastmilk or formula should be offered at the same volume (if being consumed from a bottle) and frequency. Milk feedings should be offered before solid meals to ensure the infant continues to obtain adequate calories and nutrients. |
| **Encourage relaxed family mealtimes.** Caregivers should be encouraged to include their BLW infant in family mealtimes. Caregivers should talk to their infant about the food he/she is exploring but avoid pressuring the infant to “finish.” |
How to integrate oral health into pediatric primary care

Oral health screening performed at each well-child visit helps to identify oral disease or injury and promotes anticipatory guidance that can minimize caries risk and improve oral health outcomes.

PART 1

Oral health within the well-child visit

There are 5 key elements that should be integrated into the well-child visit (Table 1):

**ORAL HEALTH RISK ASSESSMENT (OHRA)**

To guide oral health discussion, an OHRA can be utilized starting at age 6 months. The American Academy of Pediatrics (AAP) OHRA is used in pediatric primary care to document a child’s risk factors, protective factors, and clinical findings, and to aid in provision of targeted anticipatory guidance. This OHRA identifies...
children who require urgent attention or more frequent dental visits.

**ORAL SCREENING EXAM**

The oral screening exam should be performed at each well-child visit and when indicated, such as following an injury or when child abuse is suspected. A systematic oral screening exam (Table 2) can identify and recognize oral disease and injury. In young children aged younger than 3 years, a knee-to-knee exam allows for a more controlled exam and improves exposure of the oral cavity (Figure 1).

During the physical exam, lifting the lip can help to visualize the teeth, gums, and teeth/gum interface (Figure 2). In general, healthy teeth appear creamy white with no changes in color, roughness, or other irregularities (Figure 3). The first stage of dental caries is white spots and lines representing de-mineralized enamel (Figure 4). In children aged younger than 6 years, these lesions are called early childhood caries, an aggressive disease that requires urgent dental referral. All white spot lesions can progress to brown cavitations as enamel loss exposes the underlying yellow dentin (hard, dense tissue forming the bulk of a tooth; Figure 5). In severe dental caries, abscesses and/or fistulae may develop (Figure 6). Abscesses are painful, and the presenting signs in young nonverbal children may be decreased appetite, inability to chew, poor sleep, or irritability.

The clinical exam is also important to assess for injury of the soft or hard oral tissues. Injured teeth may be chipped, pushed forward/back or into the gum, or avulsed (knocked out). If the root of a primary tooth is injured, the tooth may turn brown or gray, cause pain, become infected, or

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**TABLE 1**

**KEY ELEMENTS of oral health integration in primary care**

<table>
<thead>
<tr>
<th>Number</th>
<th>Key Element</th>
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<tbody>
<tr>
<td>1</td>
<td>Oral health risk assessment</td>
</tr>
<tr>
<td>2</td>
<td>Oral screening exam: “Lift the lip”</td>
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<tr>
<td>3</td>
<td>Oral health anticipatory guidance</td>
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<tr>
<td></td>
<td>▪ Teething</td>
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<td></td>
<td>▪ Oral hygiene: brushing/flossing</td>
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<td></td>
<td>▪ Diet and feeding practices</td>
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<td></td>
<td>▪ Fluoride use</td>
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<td></td>
<td>▪ Injury prevention</td>
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<td>4</td>
<td>Fluoride varnish application</td>
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<tr>
<td>5</td>
<td>Dental referral and routine future visits</td>
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require removal. Injured primary teeth can affect the development of underlying permanent teeth. In the case of a permanent tooth avulsion, the permanent tooth must be reimplanted immediately or as soon as possible for the greatest likelihood of tooth survival. Look for parallel placement, meaning that the crowns of the teeth should match to one another. Do not hold the tooth from the root surface as the periodontal ligament cells can be crushed and are needed for reattachment. If unable to insert in the socket, place tooth in milk. Water can lyse the cells and is not ideal. Primary teeth typically are not reimplanted.

Primary care clinicians also should be aware that 50% of injuries from child abuse occur in the mouth, and the oral cavity may be a focus of abuse because of its role in communication and nutrition. Craniofacial, head, face, and neck injuries are sustained in over one-half of child abuse cases, providing another impetus for a thorough oral examination.

**ORAL HEALTH ANTICIPATORY GUIDANCE**

Individualized oral health anticipatory guidance can minimize caries risk and improve health outcomes. Anticipatory guidance includes:

1. **Teething:** Discomfort associated with tooth emergence is a common concern. It is important to counsel that over-the-counter teething gels containing benzocaine are not recommended by the US Food and Drug Administration (FDA) because of potential for serious harm, including methemoglobinemia. Best practices for teething include massaging the gums with a wet washcloth or use of cool, solid (not fluid-filled) toys or teething rings that do not present a choking hazard. Oral pain medications, such as acetaminophen, should be used sparingly for severe pain.

2. **Oral hygiene:** Practices important in caries prevention include:
   - **Toothpaste use:** Fluoride toothpaste should be used for all children, starting from tooth emergence. Do not recommend fluoride-free “training toothpaste.” From tooth emergence and until age 3 years, a grain of rice-sized (or “dab”) amount of fluoride toothpaste should be used to brush teeth morning and night (Figure 7). For children aged older than 3 years, or when a child can effectively spit, a pea-sized amount of fluoride toothpaste should be applied to the toothbrush (Figure 8). Children should be encouraged to spit after brushing, but recommended amounts of toothpaste are not expected to cause fluorosis if swallowed. Like all other medications, toothpaste should be kept out of reach of small children.
   - **Toothbrushing:** Brush with proper technique (Table 3) for 2 minutes every morning and night using a soft bristled toothbrush. Children should be assisted with toothbrushing by an adult until aged 8 or 9 years. One effective AAP campaign encouraging brushing is “Brush, Book, Bed.” This campaign encourages families to have a nightly bedtime routine of brushing followed by reading a book and promoting a regular sleep time at night.
   - **Flossing:** Flossing should begin at any age that teeth touch. The American Dental Association (ADA) recommends flossing once daily between teeth with an interdental cleaner. There is a clear disadvantage to leaving food stuck in teeth for long periods of time (including visual appearance and odor). Dexterity

<table>
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<th>TABLE 2</th>
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<tr>
<td><strong>TIPS TO COMPLETING an oral screening exam</strong></td>
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<tr>
<td>1. Lift the lip to visualize the teeth, gums, and gum/teeth interface.</td>
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<tr>
<td>2. Examine the soft tissues: tongue, lips, gums, and cheeks.</td>
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<tr>
<td>3. Inspect the teeth: front, back, and sides, especially along the gum line.</td>
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<tr>
<td>4. Note plaque, white spots, cavities, abscesses, and damaged teeth.</td>
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<tr>
<td>5. Palpate the palate for submucosal clefts: These are abnormal splits between the hard and soft palate that are difficult to see because they are covered by a thin mucous membrane.</td>
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improves with maturity and flossing technique improves with practice.

Diet and feeding practices:
Dietary choices influence overall health and dental caries risk. Oral health messaging will ideally begin prenatally, continue throughout pregnancy, and be emphasized with mothers on the postpartum unit because mothers want to know about all aspects of care of their newborn. Messaging during infancy should focus on encouraging breastfeeding, early cup introduction, discontinuing bottle use by aged 12 months (especially in bed), and recommending no fruit juice consumption during the first year of life. Messaging for older children includes choosing healthy beverages, especially plain water, and limiting carbonated and sugary beverages. Children should be encouraged to choose fresh fruits, vegetables, sugar-free whole-grain snacks, and to limit soda, candy, and sweets intake. Frequent intake of carbohydrates prevents neutralization of the acid produced by the oral bacteria by saliva; therefore, eating should be limited to 3 meals per day and 1 snack between meals.

Fluoride use: Fluoride aids in caries prevention. Topical sources of fluoride including toothpaste, varnish, rinses, and fluoridated tap water provide the main effect of caries prevention by inhibiting tooth demineralization, enhancing tooth remineralization, and inhibiting local bacterial metabolism. The systemic mechanism of fluoride (through dietary supplements) has a lesser effect than the topical effect. Systemic fluoride is incorporated into the tooth matrix during tooth development to reduce enamel solubility and prevent enamel breakdown. The AAP and the US Preventive Services Task Force (USPSTF) recommend use of supplemental fluoride for children aged 6 months to 16 years if the drinking water is deficient in fluoride. Further discussion regarding fluoride modalities is forthcoming in part 2 of this article appearing in the February 2019 issue of Contemporary Pediatrics.

Injury prevention: Almost 30% of children sustain a tooth injury during childhood, with peak injuries occurring between ages 2 to 3 years in the primary dentition and 8 to 9 years in the permanent dentition. Injury prevention recommendations regarding young children include keeping one hand on infants in high places to prevent falls, avoidance of walker use, and car seats rear facing until the child is aged 2 years. Mouthguards are recommended for older children who engage in contact sports. Mouthguards decrease the risk of fractured teeth and lips, tongue, face, and jaw injuries. Three types of mouthguard protection are available including stock, boil-and-bite, and custom mouthguards, with the latter providing the best protection.

Fluoride varnish application
Fluoride varnish is a highly concentrated form of topical fluoride that is applied to teeth during the clinical visit to inhibit or reverse white spot lesions on the teeth. The USPSTF recommends that primary care clinicians “apply fluoride varnish to the primary teeth of all infants and children starting at the age of primary tooth erup-

<table>
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<tr>
<td><strong>PROPER BRUSHING TECHNIQUE for children</strong></td>
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1. Caregiver should stand or sit behind the child until age 8 or 9 years.
2. Brush all surfaces of all teeth. Lift the upper lip and focus on gum line, as dental caries often begins there in young children.
3. Brush using small backward and forward movements or small circles.
4. Encourage spitting when possible, and do not rinse the mouth, eat, or drink after brushing with fluoride toothpaste at night.

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tion” through age 5 years. The varnish dose is 0.25 ml unidose 5% NaF (2.26% F) and frequency can range from every 3 to 6 months, based on the child’s caries risk considerations. A comprehensive discussion regarding fluoride varnish is included in the upcoming part 2 of this article in Contemporary Pediatrics, February 2019.

DENTAL REFERRALS/Routine Future Dental Visits

Dental referrals are not just for urgent treatment. All children should be seen by a dentist (establish a dental home) by age 12 months or as soon as possible after age 1 year and then routinely throughout childhood and adolescence. Dental referral is required for definitive treatment once a specific need has been identified.

Over the past decade, medical and dental community collaboration has increased referral of children for dental care. Early dental visits may decrease cost, lessen need for subsequent dental procedures, and enhance future preventive dental visits. Families should be informed of what to expect at dental visits (Table 4).

Once a specific need has been identified, treatment occurs in the dental setting. Early cavities may be stabilized using fluoride-releasing restorative materials. Severe dental caries may require fillings and/or root canals, crowns, or tooth extraction with placeholders for permanent teeth eruption. The latter procedures often require use of sedation or general anesthesia with increased cost and risk of adverse events.

Silver diamine fluoride (SDF) is a newer modality to treat primary tooth cavities. It consists of a liquid containing silver particles that is applied to a cavity and acts as a physical barrier, provides antibacterial properties, and contains fluoride to strengthen enamel. The disadvantage is permanent black discoloration of the treated tooth surface (Figures 9A and 9B); therefore, SDF is used most often to stabilize cavities in primary teeth and in children with increased risk for harm from an invasive dental procedure.

Oral health integration

Primary care office flow may require adjustment to integrate oral health into clinical practice and encourage dental referrals. A template placed in the electronic medical record (EMR) for oral health evaluation can prompt clinicians to provide appropriate guidance at the clinic while encouraging fluoride varnish application and dental referrals.

Medical-dental integration can be further fostered by primary care practices reaching out to community dental providers to collaborate on oral healthcare practices. This bidirectional relationship will lead to consistent messaging from all healthcare professionals. It may be helpful to distribute a list of local dental providers who accept specific insurances and/or create a dental referral form for use in the practice. In addition, identification of an oral health champion within a clinical care setting or the local community can further promote ongoing education and sustained advocacy to promote oral health integration into office practice.

In summary

Oral health is an important aspect of overall health. Prevention by primary care clinicians should focus on risk assessment, oral examination, provision of age-appropriate anticipatory guidance (oral hygiene, home fluoride use, fluoride varnish application, dietary counseling, injury prevention) and early dental referral while encouraging routine dental care.

For information, see modules 2 and 6 of the Smiles for Life curriculum, www.smilesforlifeoralhealth.org.

For references, go to ContemporaryPediatrics.com/pediatric-oral-health-part-1
The distribution of localized infantile hemangiomas of the face and scalp favor involvement of the midline face, scalp and ocular axis, shows a retrospective review published in the journal *Pediatric Dermatology*.

“Although previous studies have indicated that localized hemangiomas may have a predilection for sites of fusion between embryologic subunits, including the frontonasal, maxillary, and mandibular prominences, our study did not confirm this. Instead, the hemangiomas occurred most commonly along the ocular axis, which includes the region running horizontally across the eyes and the vertical midline facial axis, with higher densities on the nasal tip and perioral region of the face,” wrote the authors who were led by Anita N. Haggstrom, MD, of Indiana University. The study was published online August 31, 2018.

In an interview with *Dermatology Times*, Haggstrom said that many clinicians who see large numbers of patients with infantile hemangiomas have observed specific commonly affected sites.

“Previous studies had suggested a predilection of localized hemangiomas along the borders of facial developmental segments and it was postulated that perhaps there were local areas of tissue hypoxia at these borders that stimulated hemangioma growth,” Haggstrom said. "However, our study did not confirm these findings, which was somewhat surprising. The strong predilection for the midline for scalp hemangiomas was likewise unexpected.”

The study concluded that the regions corresponding to the boundaries between the embryonic facial segments, including the maxillary and mandibular metameres, were no more prevalent in the distribution of infantile hemangiomas.

The results also differ from a 2016 study in *Pediatric Dermatology* that evaluated the distribution of lip hemangiomas, in which upper lip infantile hemangiomas were much more common than lower lip.

“Our study demonstrated a lower lip predilection,” Haggstrom said. “Conversely, midline hemangiomas of the head and neck are not rare and in fact are a common presentation that should not prompt more extensive workup, which may be reassuring to primary caregivers.”

**The study**

Researchers evaluated 4153 local face and scalp infantile hemangiomas from 10 pediatric dermatology healthcare centers. The hemangiomas were mapped with heat-map software using standardized facial templates displaying frontal and lateral views of the
Seventy-one percent of the hemangiomas were mapped to a frontal facial template, of which 73.8% occurred along the midline axis or perpendicularly across the ocular axis in a cross-shaped area of predilection intersecting at the glabella. Scalp hemangiomas showed a predilection for the midline with 50.5% (149 of 295) observed on the top of the scalp at the midline. Localized hemangiomas did not indicate a preferential laterality.

**Significance**

“The study shows novel areas of predilection for infantile hemangiomas, which may eventually help guide our understanding of hemangioma pathogenesis,” Haggstrom said. From a developmental prospective, it is unclear why infantile hemangiomas are more frequent at some anatomic sites, despite evidence that infants with these tumors have an increased number of circulating endothelial progenitor cells. “But why these cells would gravitate to particular sites is not known,” she said. “We have also been unable to identify a mechanistic reason based on arterial or other vascular distribution.” Nonetheless, the results of the current study beg more questions, Haggstrom said. “Why do these hemangiomas occur in these locations?” she said. “Are there tissue factors specific to these areas that lend just the right environment for hemangioma growth? Ultimately, we would like the study to contribute to our understanding of hemangioma development.”

Haggstrom and her associates are now looking more closely at other types of infantile hemangiomas and the patterns in which they occur. “We are also trying to identify high-risk versus low-risk patterns to help guide physician management,” she said.

Receiving the prenatal tetanus, diphtheria toxoid, and acellular pertussis (Tdap) vaccine by the mother during pregnancy is not linked to increased autism spectrum disorder (ASD) risk in her infant, according to a large study. It is the first to evaluate the risk of ASD in children exposed prenatally to the Tdap vaccine. The results support current Centers for Disease Control and Prevention (CDC) recommendations to vaccinate all pregnant women against Tdap.2

“We provide evidence supporting the Advisory Committee on Immunization Practices (ACIP) recommendation to vaccinate pregnant women to protect vulnerable infants, who are at highest risk of hospitalization and death after pertussis infection,” wrote first author Tracy Becerra-Culqui, PHD, of Kaiser Permanente Southern California, Pasadena, California, and colleagues.

In recent years, pertussis (whooping cough) has been making a comeback in the United States, due to waning immunity and suspicions about vaccination. Young infants are at highest risk of hospitalization and death from the highly contagious infection.

To protect infants, the CDC’s ACIP recommends that all pregnant women receive the Tdap vaccine regardless of past vaccination status.2 Studies suggest that maternal antibodies are passed through the placenta and are over 90% effective in providing immunity up to age 2 years, when most children receive their first dose of the Tdap vaccine.

Research has suggested that receiving the Tdap vaccine prenatally does not increase the risk of preterm delivery or low birth weight, but longer term outcomes such as ASD in the infant have not been evaluated.

To assess the issue, researchers conducted a retrospective cohort study...
Almost bipolar
How to identify youth at risk

Researchers look at the severity of bipolar symptoms in a parent with the disorder.

CHRIS AIKEN, MD

There’s a new diagnostic concept in child psychiatry: the bipolar prodrome. It refers to children who are at risk for bipolar disorder but don’t have the full illness. Research in this area is gathering steam, and nearly all of it focuses on adolescents whose parent has bipolar disorder. This group clearly has an elevated risk, but what signs indicate that the risk is impending?

Researchers at the University of Pittsburgh arrived at an interesting conclusion. It’s not the type of symptoms but their severity that predicts conversion to bipolar in the children of parents with bipolar disorder. They followed 412 adolescents over 10 years, carefully measuring a wide array of psychiatric symptoms to see which ones predicted conversion. Surprisingly, no particular symptom cluster stood out, including mania, depression, anxiety, and mood lability. Rather, it was severity—the number of symptoms and degree of impairment—that best predicted the risk.

The study’s intention was to develop a risk calculator to estimate the chance of developing bipolar disorder.

The Bipolar Risk Calculator compared favorably with its medical cousins in terms of sensitivity and specificity. It’s easy to access, but cumbersome to perform, comprising 120 items across 5 rating scales.

The study’s take-home point, however, can be put into practice right away. Regardless of the symptoms that a child presents with, careful monitoring for hypomania is needed if the problems are significant and the parent has bipolar disorder. Most first-line psychiatric medications can hasten the onset of bipolar, and a new algorithm is available to guide the treatment of this vulnerable population.

Dr. Aiken is director of the Mood Treatment Center, editor-in-chief of The Carlat Psychiatry Report, and instructor in Clinical Psychiatry at the Wake Forest University School of Medicine, Winston-Salem, North Carolina. He does not accept honoraria from pharmaceutical companies but he receives honoraria from W.W. Norton & Co. for Bipolar, Not So Much, a book he coauthored with Jim Phelps, MD.

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Nearly one-third of patients who have psoriasis first experience the condition during childhood or adolescence. Knowing how to spot it early can help younger patients not only minimize the impact of the condition, but also reduce the emotional effect.

According to Amy Paller, MD, a dermatologist at the Feinberg School of Medicine at Northwestern University, developing psoriasis during childhood or adolescence can hurt a young person’s self-esteem and their abilities to build strong social relationships. She discussed this impact and the treatment options available during the 20th annual National Psoriasis Foundation residents meeting.

“Psoriasis can be a devastating disease for adolescents, in particular. In those formative years, they’re psychosocially developing, and we really need to treat it aggressively,” she said. “If we can’t manage it with topical corticosteroids, then we must move on to something systemic to get them the improvement they need or prevent them from developing comorbidities, including anxiety and depression.”

Like adults, children with psoriasis often struggle with obesity and metabolic syndrome, putting them at greater risk for developing cardiovascular disease. In fact, obesity frequently appears years before psoriasis, and 30% to 35% of children have a first-degree relative with psoriasis. This data raises the question of whether preventative measures are possible, Paller said.

During her presentation, she also explained to residents the various medication options, other than methotrexate, available for patients. Recently, the US Food and Drug Administration approved etanercept as the first biologic for children as young as age 4 years. Additionally, ustekinumab is approved for children as young as 12 years. Both have a faster onset than methotrexate, and they’re effective in targeting the Th17/IL23 pathway associated with psoriasis development.

In addition, there are also ongoing trials testing ixekizumab and ustekinumab in younger children. Residents should be aware of the treatment options available for children and adolescents and when to pursue new therapies, she said.

“We all hear so much about biologics, and we are using a lot of methotrexate in children. On the whole, we’ve found it to be safe,” Paller said. “But, there’s a slow onset of action with methotrexate. We see a faster onset with biologics. It’s important for residents to understand what these medications are doing for children and that we’ve got a good track record of safety with them.”

REFERENCE
1. Paller A. Psoriasis in Children and Adolescents. Presented at: 20th Annual Residents Meeting, National Psoriasis Foundation; October 21, 2018; Chicago, IL.

PLUS What’s causing streaky pigmentation in a 2-month-old boy? See Dermcase, page 52.
The term "concussion" came to fame in the past decade, as is evidenced by the increase in the number of concussion-related publications in recent years. With fame came a lot of confusion and controversy related to its definition, diagnostic criteria, management, and return to a normal lifestyle. In addition, there is a significant knowledge gap in concussion care and management among healthcare providers. Although there is no universally accepted definition for a concussion, the American Academy of Neurology describes a concussion as a trauma-induced alteration in mental status that may or may not involve loss of consciousness. Explained differently, a concussion is an abnormality in the biochemical processes leading to functional impairment without any evidence of structural findings on standard neuroimaging.

To add to the confusion, concussion has been interchangeably used with the term "mild traumatic brain injury." This equivalence is up for debate as some believe that the traumatic brain injury may have more severe implications. In this article, we provide a brief discussion on the impact of concussion on the pediatric population, the current trends in concussion care, recent advances, future implications, and the challenges faced in the management of concussion.

Concussion in pediatrics
A concussion is a complex condition that has been poorly studied in the pediatric population. The effect and outcome of concussion are far worse in the developing brains of children as compared with that of adults. Studies have shown that concussion in this age group significantly impacts school and sports-related performance, and it often leads to significant academic, social, and financial losses. Concussion may even cause permanent damage and worsening of existing neuropsychological symptoms. Most concerning, repeated head injuries, particularly recurrent and prolonged subconcussive injuries, may lead to a much more severe condition such as the chronic traumatic encephalopathy.

Issues in diagnosis
The diagnosis of concussion is mostly clinical and is based on the presence of a constellation of symptoms developed as a consequence of trauma to the head (directly or indirectly). It is suspected with the presence of any of the following symptoms: headache, loss of consciousness, confusion, dizziness, and nausea and vomiting. (See sidebar for assessment tools that aid in the diagnosis of concussion.) However, the subjective nature of these assessment tools limits their utility. Currently, there is no imaging or laboratory test to diagnose concussion. Traditional neuroimaging like computed tomography (CT) scan and magnetic resonance imaging (MRI) that are used to rule out more serious traumatic brain injury are of little value in diagnosing concussion, as they only identify structural abnormalities. Also, the possibilities of radiation with CT scan and need for sedation in MRI restricts the use of these modalities to certain conditions. While a protocol has been established for the use of the CT scan in traumatic brain injury (ie, the PECARN rule), there is no protocol for MRI. Clinician discretion determines MRI use in the pediatric population.

Since concussion is a functional disorder, attempts have been made to identify vascular and metabolic abnormalities through newer imaging modalities, laboratory tests (eg, fluid biomarkers), genetic testing, and electrophysiology. Recent advances in neuroimaging modalities like diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), functional MRI (fMRI), sus-
ceptibility-weighted imaging (SWI), and the like have shown potential use in the diagnosis of concussion.

Diffusion tensor imaging is a noninvasive method that allows estimation of the integrity of white matter tracts and has validated use in detecting axonal damage. Functional MRI shows abnormality in the blood oxygenation through BOLD (blood oxygenation dependent) signals in a concussed brain. Changes in N-acetylaspartate (NAA)/creatine and NAA/choline ratios can be detected on MRS, but the utility of these techniques only has been studied in a research environment and their routine clinical use has not been established. Transcranial-Doppler ultrasound (TCD) is an exciting modality that measures the cerebrovascular reactivity index, mean velocity of blood flow, and pulsatility index. It has already been shown that the cerebrovascular reactivity decreases post-concussion and that concussion can be effectively diagnosed through TCD—a noninvasive and low-cost option—but further research is required before routine use.

Another area of exploration is the biomarkers measured by the blood or cerebrospinal fluid (CSF) and their potential use in the diagnosis of concussion. The most extensively studied blood-based biomarker is S100β. Glial fibrillary acidic protein, Tau, neurofilament light protein, neuron-specific enolase, and amyloid protein are some commonly used blood biomarkers. The role of CSF (eg, serum albumin ratio, 1176 residue N-terminal fragment of α-spectrin, brain-derived neurotrophic factor [BDNF], ubiquitin C-terminal hydrolase L1, creatinine kinase and heart-type fatty acid binding protein) also have been studied for their possible use in concussion diagnosis.

These biomarkers are of interest since they may play a potential role in the progression and recovery of a concussion. It is hypothesized that biomarkers, in combination with neuroimaging and clinical assessment, will aid in the diagnosis of concussion. Numerous genetic biomarkers with polymorphisms concerning apolipoprotein E, glutamate ionotropic receptor N-methyl-D-aspartate -type subunit 2A, BDNF, and the like are being studied for their potential use in a concussion.

The sensitivity of these biomarkers increase significantly when used in combination. Whereas all these biomarkers are currently limited to research environments, they may be useful for clinical concussion assessment in the near future.

**Often concussion care becomes challenging for pediatric specialists, as the approach needs to be individualized for each patient.**

Management and care

Often concussion care becomes challenging for pediatric specialists, as the approach needs to be individualized for each patient. The management of concussion is crucial, since delayed management or early clearance may lead to potential complications such as second impact syndrome. Because there is limited awareness amongst teachers, trainers, athletes, and patients about the impact of a concussion, management can be challenging.

It is universally accepted that concussion responds to adequate physical, cognitive, and psychological rest, and, in the absence of better evidence, needs to be individualized for every patient. The athlete should be removed from active sports to avoid another concussion or any form of additional injury that may exacerbate the present concussion symptoms and prolong recovery time. Proper rest also requires that the child does not attend school and avoids any mentally exhausting activities such as homework, video games, and excessive screen time. This, however, becomes challenging under numerous external pressures, especially with the failure of academic and sports personnel and family members in recognizing the effects of concussion. Similarly, patients may not be able to acknowledge concussion severity in the absence of any apparent sign and symptoms. Hence, concussion education for sports and academic professionals should emphasize the need for reasonable rest until the resolution of symptoms and the removal of stressful activity that worsens the condition.

For patients who do not respond to rest only, symptomatic pharmacological treatment may be used. Analgesics or nonsteroidal anti-inflammatory drugs may be used for headaches, but excessive use should be avoided to prevent rebound headaches. Concussion patients often complain of sleep disturbances in the form of delayed onset sleep or excessive daytime sleepiness. Sleep hygiene usually helps patients. Due to its safety profile, melatonin has been used to assist patients with sleep, but its efficacy has not been established for concussion patients. For patients experiencing nausea or vomiting, ondansetron is an optimal treatment; metoclopramide and promethazine should be avoided in
children because of adverse effects. Some patients have prolonged symptoms that may progress to post-concussive syndrome. In such cases, a multidisciplinary approach involving pediatric neurologists, neuropsychologists, physical therapists, psychiatrists, and other specialists becomes essential.

**Looking forward**

Future research is needed to address the common clinical challenges. For instance, long questionnaires are used as the gold standard in concussion clinics around the globe, but they are not always practical in the acute setting. This is especially true if patients are very symptomatic and in cases where comorbidities are present. Similarly, the severity score is important, but the long list of symptoms requires physicians to take the history of many symptoms that may not impact care management. Not only does this extend the evaluation time, but it also can make patients feel uncomfortable. A biological marker could help in the diagnosis, but numerous efforts currently underway have not been yet validated.

The current treatment philosophy also presents a dilemma. While it is agreed that patients benefit from rest, protocols often require patients to see multiple specialists. Instead of decreasing stress, this may add to it by interfering with the process of returning to school and normalcy. Finally, it is important to collaborate with primary care colleagues to ensure complex cases receive timely referrals to neurologists to avoid mismanagement and expedite coordinated efforts of recovery.


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**Young woman with difficult-to-treat chronic migraine**

**How would you advise her?**

**VERONICA HACKETHAL, MD**

**CHALLENGING CASE** Your new patient is a 16-year-old high school student who received a diagnosis of chronic migraine 2 years ago. She is currently on valproate and says she has had a significant reduction in migraine days since she started it about a year ago. Before that, she suffered from migraines 20 days per month, which caused her to miss school. During that time, her grades dropped from As and Bs to Cs and a few Ds.

She is now back to her former level of functioning at school and has just made the honor roll. Her former doctor started her on valproate after trials of onabotulinum toxin A, topiramate, amitryptiline, and propranolol were ineffective. She has a new boyfriend and has recently become sexually active. She says they always use condoms, but she is not on birth control.

**How would you counsel this patient?**

While valproate is FDA-approved for the treatment of seizures, bipolar disorder, and the prevention of migraines, the FDA has issued several warnings about its use in women of childbearing age. Valproate has been linked to severe congenital malformations, especially neural tube defects. Other possible defects include limb defects, facial and skull defects, cleft lip and palate, as well as cardiac, renal, and urogenital defects. The FDA advises that women of childbearing potential should not receive valproate unless essential for the treatment of a medical condition and states that “this is especially important when valproate use is considered for a condition not usually associated with permanent injury or death (eg,
Another professional organizations have also taken a hard line against valproate in women of childbearing potential. In 2017, the American Epilepsy Society issued a position statement endorsing the FDA’s stance about the use of valproate in women of childbearing potential.

And, in perhaps the most drastic action so far, in March 2018, the European Medical Association and European Headache Federation (EMA/EHF) introduced actions effectively banning valproate in women of childbearing age, unless they meet the conditions of a Pregnancy Prevention Program. The EMA/EHF stated that valproate is contraindicated for migraine prevention in pregnant women because of findings that suggest that the offspring might have a decreased IQ. The FDA has also advised that the benefits of valproate should be carefully weighed against the risks, and an alternative medication with lower risk to the fetus should be used if the drug is not deemed essential. The FDA further stated: “If the decision is made to use valproate in women of childbearing age, effective birth control should be used.”

The drug should not be started even in prepubescent girls, unless no other alternative is available. These restrictions are now legally binding across the European Union. The action was taken based on findings that suggest lack of awareness about the risks of valproate during pregnancy, despite 2014 recommendations intended to limit its use.

The Pregnancy Prevention Program requires an assessment of a woman’s potential for becoming pregnant and whether she will comply with contraception during treatment, pregnancy tests before starting treatment, counseling about the risks of valproate and the need for effective birth control, as well as at least one annual treatment review with a specialist using a risk acknowledgement form. Pregnancy planning should also occur before discontinuation and switching to another medication. In the case of unplanned pregnancy, the woman should seek immediate consultation about discontinuing valproate.

You discuss this information with the patient and advise her that continued use of valproate is not advisable. You inform her that in May 2018 a new drug, erenumab, was approved by the FDA for migraine prevention, based on research that suggests the drug may decrease migraine days in chronic migraine. Because the drug is new, insufficient evidence exists about its safety during pregnancy in humans, but animal data suggested no adverse effects to offspring. You further advise her to start birth control, which may also improve her migraines. If she chooses to stay on valproate, you emphasize the importance of effective contraception and taking folic acid.

**References**


How many kids are still completely unvaccinated?

Rising rate of young children who receive no vaccines at all worries CDC.

RACHAEL ZIMLICH, RN, BSN

Although rates of recommended vaccinations for children have remained stable overall, the number of children receiving no vaccines at all has quadrupled from previous years.

According to a new report from the Centers for Disease Control and Prevention (CDC), this small but increasing group of children aged younger than 2 years that have not received any immunizations is concerning officials.

“These reports show that most US parents are protecting their children from vaccine-preventable diseases by making sure they are getting recommended vaccines,” says CDC spokesperson Ian Branam, MA, “but we are seeing an increase in the number of children younger than 2 years of age who receive no vaccines. This increase means that there are about 100,000 children under 2 years old that are not protected against potentially serious vaccine-preventable diseases.”

According to the report, published in the Morbidity and Mortality Weekly Report (MMWR), 1.3% of children born in 2015 had not received any vaccines by the 2017 National Immunization Survey-Child (NIS-Child). This figure indicates an upward trend in children in the 19-month to 35-month age group going without vaccinations, up from 0.9% in 2011 and 0.3% in 2001.

The CDC’s Advisory Committee on Immunization Practices (ACIP) recommends vaccinations against 14 diseases by age 24 months, and the CDC says it is working to understand the reason for the upward tick in missed vaccinations in this group.

“Parental choice may play some role,” Branam says, “but the CDC’s data suggest that many of these parents do want to vaccinate their children, but they may not be able to get vaccines for them. They may face hurdles, like not having a healthcare professional nearby, not having time to get their children to a doctor, and/or thinking they cannot afford vaccines.”

What the data show

Coverage for most vaccines remains stable overall, according to the report, with more than 90% of children aged 19 to 35 months receiving 3 or more doses of the poliovirus vaccine; 1 or more doses of the measles/mumps/rubella vaccine (MMR); 3 or more doses of the hepatitis B vaccine (HepB); and 1 or more doses of the varicella vaccine.

Vaccine coverage was generally lower for most recommended vaccines among children who are uninsured or uninsured by Medicaid when compared with children with private health insurance. Specifically, 17.2% of unvaccinated children were uninsured compared with 2.8% of all children. Vaccination rates also were lower in rural areas. Researchers also discovered disparities for vaccines that required a booster dose in the second year of life, including diphtheria/tetanus/acellular pertussis (DTaP), Haemophilus influenzae type b (Hib), and pneumococcal conjugate vaccine (PCV).

“While the total number of uninsured children in the survey was small, they were overly represented in the unvaccinated group. Among children surveyed in 2017, 7.1% of uninsured children received no vaccines, compared with 0.8% and 1.0% of children with private insurance and Medicaid, respectively. Uninsured children are eligible to receive vaccines free of charge through the Vaccines for Children program, but there may be additional hurdles for uninsured children to access vaccines,” Branam says. “The CDC is doing research to better understand and address potential barriers for uninsured children to access vaccines.”

Branam says the report is a reminder to pediatricians to continually educate parents and share resources for vaccination with them, and the CDC offers educational materials to help.

REFERENCE

It’s often said that breakfast is the most important meal of the day, and now there is a new study to back its benefits.

New research from researchers in Brazil reveals that eating breakfast every day was associated with decreased body mass index (BMI) and body fatness in teenagers regardless of their physical activity level.1 Rômulo Fernandes, MSC, PHD, of São Paulo State University, São Paulo, Brazil, and co-author of the report, says he hopes the findings will help pediatricians spread the message to their patients about the importance of not skipping breakfast.

“I really believe that simple messages like this one—eat breakfast every day in order to control or reduce your weight—are effective because they do not require the effort of financial investment,” Fernandes says. “Moreover, simple messages are easier to spread out among the general population, even among those with lower formal education, because breakfast is already a component of our routine instead of a new one, such as physical exercise and diet control. Finally, assuming this behavior, adolescents have an opportunity to share more time with their families in a healthy and enjoyable activity.”

The role of nutrient consumption has been widely studied in regard to childhood obesity, but the impact of skipping breakfast has had less attention, Fernandes notes. The report, published in the *Journal of Pediatric Gastroenterology and Nutrition*, reveals that about 45% of teenagers skip breakfast—a choice that is linked to higher BMI, increased trunk fatness, increased dyslipidemia and fasting glucose levels, and a greater prevalence of obesity among adolescents.

Exercise and physical activity can help mitigate these problems, but researchers found that whereas physical activity has an inverse relationship with trunk fatness, regular breakfast intake can help reduce body fat independent of physical activity levels.

The study was conducted through interviews with 86 teenagers, with body weight, body fatness, and trunk fatness assessed at both the initiation and conclusion of the project. Options for breakfast consumption were daily, 3 to 5 days each week, or no days at all. Physical activity levels also were tracked using pedometers.

**Breakfast vs body fat**
Researchers found that, at baseline, adolescents who consumed breakfast daily over a period of a year had lower BMI and body fatness than their peers who skipped breakfast sometimes or altogether. After a year, the difference was even more pronounced, with teenagers who ate breakfast regularly dropping trunk fatness and body fatness at a higher rate than their peers regardless of physical activity levels. The frequency of breakfast intake was negatively correlated with body fatness, according to the report, and researchers also noted a negative relationship between changes in physical activity and trunk fatness.

The research team embarked on this investigation in an effort to inves-
tigate the impact of breakfast on childhood obesity, as well as the impact of some behaviors related to eating.

“Behaviors like parents and kids sitting around a table to eat breakfast are less common nowadays, being replaced by a frenetic morning with kids going to school and parents going to work. Even on the weekend, with no school and less or no work, the routine has been changed,” Fernandes says. “Adolescence is an important phase in human development in which many behaviors are assumed—both good ones and bad ones. In that relative phase, different actors have influence in adolescents’ decisions, such as parents, teachers, and coaches. Pediatricians need to talk with all these actors in order to create a common message that should be enhanced by these people in all domains of an adolescent’s life.”

Physiologically, Fernandes says the impact of regular breakfast consumption is more relevant than physical activity based on the chronic impact of breakfast on adiposity.

“Every single day kids sleep, and they awake the next morning and the opportunity to consume a breakfast happens, and this phenomenon happens every single day. On the other hand, physical exercise is a behavior that in the best scenario ever does not happen every day. Moreover, we have assessed physical activity measured by pedometer, which is a proxy of the amount of physical activity, and intensity was not taken into account,” Fernandes says. “In fact, activities performed at moderate-to-vigorous intensity seem more effective in combating childhood obesity because they increase the daily energy expenditure. Step counts do not discriminate the intensity in which the physical activity has been performed limiting its impact of adiposity.”

Fernandes says it’s sometimes difficult to translate study findings into data that are useful for pediatricians to share with their patients, but the simplicity of these findings can have a great impact on pediatric health.

“Many parents do not have the time to share the table with their kids every morning, and this simple act seems relevant in the combat of childhood obesity,” Fernandes says. “Pediatricians should advise parents to share this healthy behavior every single day with their kids. According to our findings, more than medicines, eating breakfast every morning seems a relevant behavior in order to prevent and treat obesity.”

Ms Zimlich is a freelance writer in Cleveland, Ohio. She writes regularly for Contemporary Pediatrics and sister publications Managed Healthcare Executive and Medical Economics. She has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

**REFERENCE**

What’s the cause of 50% of pediatric safety errors?

A new report says electronic health records may play a role in events that cause patients harm.

RACHAEL ZIMLICH, RN, BSN

Safety errors happen in medicine and, when they do, the results can be tragic. Although human error is one factor, electronic health records (EHRs) also may play a role—especially when it comes to medication errors.

A new study published in *Health Affairs* (2018) investigated what role EHRs play in safety challenges in the pediatric setting, and what might contribute to these events. Researchers investigated 9000 patient safety reports between 2012 and 2017 from 3 different healthcare institutions and found that more than half the errors recorded were related to both EHR function and medication.

“The usability of EHRs can introduce patient safety risks, and during the medication process these usability issues can result in medication errors that reach the patient,” says **Raj Ratwani, PHD**, director of the National Center for Human Factors in Healthcare and lead author of the report. “The biggest usability issues are related to system feedback and the visual display. System feedback issues are when the EHR does not provide the right feedback given the context of the patient.”

For example, Ratwani says EHRs may not provide appropriate alerts when a medication is prescribed to a patient that has a known allergy to that medication. Visual display issues occur when the EHR display is cluttered or confusing.

“These display issues can make it difficult to enter the appropriate medication information leading to errors,” Ratwani says. “Across the board, the most common type of medication errors were improper dose errors, commonly overdoses.”

**Usability issues**

Ratwani’s study found that 36% of these reports had EHR usability issues that contributed to medication errors, and 18.8% may have resulted in patient harm. Usability refers to how efficiently and effectively an EHR system can be used, and the research team found that most errors were associated with system feedback and visual displays, with medication dosing being the most common error.

Although the Office of the National Coordinator for Health Information Technology (ONC), a federal agency that oversees EHRs, has policies to promote usability including involving clinicians in the design and function of EHRs, few policies make a distinction between adult and pediatric populations. This can present particular challenges in the pediatric population when it comes to medication dosing, according to the report.

**Medication errors**

Across the study population, the research team found that 84.5% of medication errors were attributed to improper dosing, and 3.5% were related to improper timing such as missed doses, according to the researchers.

“One example of an event in this category occurred when a physician ordered 5 times the recommended dose of a medication without receiving an alert from the EHR, although the prescribed dose was outside the recommended range,” the report notes. “Both vendor design and development, as well as implementation and customization, may be contributing to the challenges associated with system feedback. To address this systemic problem, vendors and providers should consider developing more comprehensive design guidelines and use generalizable tools to assess usability and safety.”

The research team notes that while EHRs may have led to improvements in care delivery, it’s worth another look because one-fifth of the reported events studied reached the patients and 129 caused some type of harm.
“Whereas EHRs have improved care and safety under certain circumstances, these findings suggest that thousands of patients may be put at risk because of usability challenges that stem from the design, implementation, customization, or use of this technology,” the report points out.

What lies ahead
Moving forward, the research team suggests that healthcare facilities and EHR vendors need to put more focus on safety alerts and how dosing information is presented to clinicians. The Joint Commission also can play a role, the report suggests, adding an assessment of EHR safety to its hospital accreditation program.

On the micro level, Ratwani says clinicians should trust their EHR system, but verify that what they are seeing is what they intended to order. “Always check information being entered in and viewed in the EHR to ensure accuracy,” he says.

Clinicians also can identify any areas with potential safety problems and communicate their orders to frontline staff, or larger problems to hospital leaders.

“When placing high risk medication orders, always verbally communicate to confirm what is entered and seen in the EHR. If there are known risk areas, talk to your staff about these issues to raise awareness,” Ratwani says. “Also, report known issues. If you suspect that some aspect of the EHR may introduce safety issues, report on these items.”

Ratwani says he hopes the report will raise awareness and elicit change to EHR usability to reduce these safety events.

“Our hope is that this report will raise awareness of EHR usability and safety challenges for EHR developers, frontline clinicians, and policymakers.” —RAJ RATWANI, PHD

Random thoughts CONTINUED FROM PAGE 53

13 Having recently seen yet another child who was rushed to the ED for a fever of 104°F, despite my having educated the parents otherwise, I think families would be better served by having a thermometer that only went up to 102°F as the highest reading, and one would need a medical license to use one for recording above this cut-off.

14 Concerta capsules do not dissolve; they work on a piston-like mechanism, squeezing the medicine through a hole in the capsule. Parents will sometimes see the capsule in the stool. This is normal.

15 Unless you are sorely pressed for space, let mothers breastfeed their babies in the examining room after a visit. This will make for a happier baby, and thus mother, on the ride home.

16 Experts are vague about how long to quarantine a child with hand-foot-and-mouth syndrome, but a general rule they give is that a child can go back to daycare when afebrile and behaving well. Since the disease is generally benign, that is the guideline I follow, rather than waiting for the rash to be gone.

17 Often we “do nothing” when we see a child, in the expectation that a condition will resolve on its own. This is more palatable to a parent if we attach a plan to it. For example, if a well-looking child presents with a 5-day fever that I think is viral, besides explaining that to the family I tell them to give it 3 more days, and if not improving, they can call back and we will probably order some lab work then.

REFERENCES
How to get from 
PCP to “PGP”

Pediatricians who go above and beyond the expected in patient care can achieve the coveted status of “PGP”— pretty good pediatrician. Follow these 10 steps.

ANDREW J SCHUMAN, MD, FAAP

Being a pediatrician for more than 30 years gives one a unique perspective on pediatric practice. Over the years I’ve accumulated advice worth passing on to the next generation of pediatric providers. Whereas medical care has grown ever more complicated and impersonal over my decades of practice, it’s still fun to go to work each day. When you arrive at the office each morning, you never know what challenges lie in wait, and every day is different than the day before.

That said, in my opinion, it is our relationship with patients and parents that is the most important aspect of quality pediatric care. Although we are identified by our patients and their insurance companies as a “primary care provider” (PCP), I think every pediatrician should strive to move beyond the impersonal PCP status and endeavor to upgrade to the coveted rank of “PGP”—that is, “pretty good pediatrician.”

Qualities of a PGP

Pediatricians bond with patients and parents over time, and this is why many families are devoted to their pediatrician. It is this bond that’s associated with a high level of trust that enables one to be a better provider. All parents are different, and the PGP has learned how to deal with a wide variety of parental attitudes and demeanors. The key is not just to talk about healthcare, but to talk to mothers and fathers as real people—briefly asking where they grew up, what jobs they do, and then ask them what they enjoy about being a parent and what is most challenging for them. It is important that pediatricians adopt an appropriate demeanor as well, never paternal, never threatening, but one akin to that of a longtime trusted friend.

At follow-up visits, I usually recall the “tidbit” parts of previous conversations I’ve had with parents or patients, and I use these to quickly break the ice. It is always nice for a patient to realize that we remember he likes baseball, or she received an award at a dance competition. I ask patients to bring in school report cards at follow-up visits, or a picture they drew that I can hang up in my office or exam room. Oh, yes, and never wear a white coat, and funny ties or scarfs are always helpful.

What PGP’s can do for patients

A PGP will make the time to call or e-mail the parent of a sick child a day or 2 following the visit just to check in and answer questions. The PGP has learned to make his or her practice super-efficient so there is time in the schedule to see the few patients that must be seen ASAP. This efficiency comes from becoming proficient at using electronic health records (EHRs), scheduling the workday appropriately, and staffing to the level of need. It comes from using appropriate technologies to speed documentation (voice dictation) as well as using technologies that expedite screening for vision, hearing, and development.

Perceptive PGP’s also have a sense of when parents or patients need help getting necessary services, such as counseling for depression, or when a diagnostic study needs to be expedited. Engaging PGP’s are familiar with the many assets in their community and call in favors from colleagues to facilitate and expedite patient services. Some PGP practices employ a full- or part-time social worker to provide these services. Concerned PGP’s will call specialists to get opinions regarding assistance with diagnostic workups or expediting visits, often reducing wait time to days that would ordinarily take months.
WHEN A PGP SAYS GOODBYE

If you’re a mature pediatrician, you regularly encounter what I call the “last well visit.” This often occurs when adolescents, who became your patients as newborns, have grown to high school seniors. Graduation is the time for them to transfer their medical care to an internist or family physician.

The “last” well-child exam of these long-term patients is a special event for me. It underscores what it means to be a “pretty good pediatrician” (PGP) and brings closure to our important role in the patient’s extended family.

Our care for these long-term patients began in the nursery. We discussed feeding, burping, cord care, and jaundice with nervous parents. There was the first set of immunizations, the first ear infection, and the first case of gastroenteritis. We were there to calm and advise. We monitored growth and development, praised parents when they and their children did well, and provided a welcome ear for concerns.

A few patients had uneventful, almost boring childhoods, but for most there were lots of bumps and bruises that required pediatric intervention. If there was a speech delay, we arranged a hearing test and a consult to a speech pathologist. If severe headaches developed, we ordered magnetic resonance imaging (MRI). In the middle of the night when the patient was having abdominal pain, we met them at the emergency department to investigate the possibility of appendicitis. There were school and behavior issues, mild acne, menstrual cramps, and the occasional broken finger or arm.

When the last well visit finally comes, we talk about jobs, education, and future plans as well as future healthcare needs. At the end of the visit, thanks are exchanged between pediatrician and patient and parents. I thank them as well, for allowing me to participate in the upbringing of their child. We end the visit with a handshake, more often with a hug. The rest of the day, my pace is somewhat slowed.

After that last well visit, I may see the patient a few more times for injuries or respiratory infections before they depart from the practice. Yet there is rarely that same meaningful dialogue we shared during the last well visit. After the departure, I sometimes learn about patients through parents and younger siblings. I am always eager to hear how they are progressing through jobs, college, or life.

Sometimes, although not too often, a once-departed patient shows up at my office with a spouse—and a new baby to be seen for its first well visit.

And we start the whole process over again!

—Andrew J. Schuman, MD, FAAP
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zzures of many types, intellectual delay, behavioral disturbances, autism spectrum disorder, and cortical visual impairment.1-3

Neuroimaging can reveal hypoplastic corpus callosum, absent septum pellucidum, pachygyria, cerebral atrophy, hamartomas, gray matter heterotopias, and/or hemimegalencephaly, among other abnormalities.2,3 In terms of frequency of these associated abnormalities, a 2014 study of patients with Blaschko dyspigmentation at the Harriet Lane Pediatric Dermatology Clinic, Johns Hopkins University, Baltimore, Maryland, found that extracutaneous findings were present in only 13.9%.4

The wide range of names that are used to describe the skin findings can lead to confusion for families, and they may therefore find higher risks of extracutaneous findings when performing their own research. For this reason, it is important for providers to know that, although they certainly can be present, CNS or eye abnormalities occur in a minority of patients.4

Differential diagnosis
Various cutaneous fungal infections, such as tinea versicolor and pityriasis alba, can give the appearance of segmental differences in pigmentation.5 Wood lamp examination can be helpful to differentiate, and pigmentary mosaicism would more closely follow the lines of Blaschko and often have more jagged “coast of Maine” edges.6 These patients also are likely to have endocrine manifestations, such as vaginal bleeding and precocious puberty.

Tuberous sclerosis can, like pigmentary mosaicism, present with areas of hyperpigmentation, although not typically following lines of Blaschko, and often have more jagged “coast of Maine” edges.6 These patients also are likely to have endocrine manifestations, such as vaginal bleeding and precocious puberty.

The patient was referred to Clinical Genetics, where a diagnosis of pigmentary mosaicism was suspected, prompting a brain MRI with and without contrast and a Neurology evaluation with EEG, as well as a chromosomal microarray. The MRI was positive for mild enlargement of the subarachnoid spaces and absent right septum pellucidum. Routine EEG was unremarkable, with 24-hour EEG planned in the future.

The initial chromosome microarray also was normal. Because of the patient’s developmental delays, he

Management
In addition to a thorough skin examination including the use of a Wood lamp and a complete physical exam by system, Kromann and colleagues, in their 2018 review regarding pigmentary mosaicism, propose genetic testing to evaluate each patient in whom the diagnosis is suspected.1 This ideally entails a chromosomal microarray of uncultured cells, with consideration of exome sequencing as it becomes more available. It is important to note that both peripheral blood lymphocytes and skin fibroblasts should be used, as this increases likelihood of identifying the mosaicism.1,2,8

Neurology evaluation, electroencephalogram (EEG), and brain magnetic resonance imaging (MRI) should be considered based on neurologic and developmental findings, and focus should be on early developmental interventions with the appropriate therapeutic services.

Patient outcome
The patient was referred to Clinical Genetics, where a diagnosis of pigmentary mosaicism was suspected, prompting a brain MRI with and without contrast and a Neurology evaluation with EEG, as well as a chromosomal microarray. The MRI was positive for mild enlargement of the subarachnoid spaces and absent right septum pellucidum. Routine EEG was unremarkable, with 24-hour EEG planned in the future.

The initial chromosome microarray also was normal. Because of the patient’s developmental delays, he
Interestingly, the abdominal kidney/ureter/bladder (KUB) X-ray in this case was also strongly suggestive of the diagnosis, given the presence of calcifications that looked like teeth. Had the KUB not shown teeth, other common causes of acute abdominal pain, as well as intestinal obstruction, would have remained higher on the differential.

Ovarian cystectomy is recommended in order to make a definitive diagnosis, preserve ovarian tissue, and avoid potential complications such as ovarian torsion, cystic rupture, or malignant degeneration. Estimation of preoperative and postoperative tumor markers is essential to help assess for malignant neoplasm, although negative tumor markers do not exclude the possibility of malignancy. The long-term recurrence rate after surgical excision of MCTs is 4.2%. Given the slow growth of MCTs, the low rate of recurrence, and the rare risk of malignancy, the most appropriate postoperative method of surveillance is still up for debate.

Patient outcome
The patient’s recovery after surgical excision of her MCT was unremarkable, and she was discharged home on postoperative day 2. A CT scan of the chest and abdomen at 2 months postresection showed no evidence of recurrence or metastases. The patient was evaluated by Pediatric Hematology/Oncology 4 months postoperatively and again had a negative AFP and β-hCG. Follow-up surveillance screening with abdominal ultrasound and tumor markers was planned for every 3 months.

Conclusion
Although ovarian neoplasms are rare in the pediatric population, they are important to consider in the differential diagnosis of acute abdominal pain and vomiting, especially in the absence of fever.

For references, go to ContemporaryPediatrics.com/puzzler-0119
Streaky pigmentation suggests larger issues

AARON SAMIDE, MD; MELISSA BRINN, MD, FAAP; TARYN ANNE HILL, MD, MED, FAAP

The parents of a 2-month-old boy return to the office for a well-child visit. The infant has a history of hypotonia and poor head control but is growing normally. His parents noted streaky patterns of hypopigmentation over his trunk and extremities shortly after birth and felt they were likely just “birthmarks.”

**FIGURE 1** Streaky hypopigmentation is characteristic of pigmentary mosaicism.

**Clinical findings**

Beyond the cutaneous findings, multisystem involvement is uncommon but possible, with the central nervous system (CNS) most frequently affected. Central nervous system involvement can include epileptic sei-
Random thoughts on pediatric practices

Here are some various observations that have guided my own pediatric practice over the years. Perhaps they will help you with yours.

1. Heat can affect newborn metabolic screening tests, especially galactosemia, which would go along with my impression that false-positive tests are more common in the summer.

2. Would “head-to-head” really be the correct description of a study comparing diaper creams?

3. Parents often do not distinguish between the flu and “stomach flu.” This is not just of academic interest. For example, parents often assume that flu vaccines do not work because their child later had an intestinal virus. Please do not use the phrase “stomach flu,” and when you hear parents use it, gently educate them about it.

4. I believe the first shot hurts the most, so from a pain point of view alone, it is better to get 3 shots in 1 visit rather than spacing them out (which would mean 3 “first” shots instead of 1).

5. If I were to try to compare unpleasant sensations, I would consider nausea much worse than pain.

6. Along those lines, there have been, of course, many advances in outpatient pediatrics in my 40 years. Of these, my favorite, even more than vaccines and ceftriaxone, is perhaps ondansetron, particularly the oral-dissolving form. This works so much better, with fewer adverse effects, than the rectal phenothiazines we used to use. Besides relieving suffering, it helps keep children out of the emergency department (ED) and inpatient ward. I have a low threshold for prescribing it.

7. Physicians do not always understand how discount coupons work. For example, suppose you have to choose between a generic epinephrine with a $20 co-pay that costs the insurance company $500, and one with a coupon where the manufacturer pays the $50 co-pay but the insurer is charged $2000. The parent saves money with the coupon, but the insurance company and ultimately all the subscribers pay more. Remember this the next time you are tempted to use a coupon for what might otherwise not be your preferred medicine.

8. For many illnesses, before I examine a child, after the history, I will tell parents I have whittled the diagnosis down to 2 choices, which I will then narrow down to 1 before they leave the office. I also indicate what the treatment and expected course will be, depending on the outcome. For example, I will tell the parents that either their child has strep, or they don’t. Then, when the test is negative, they already have been informed that no antibiotic will be needed.

9. Possible thrush, which looks like a dusting of powdered sugar on the tongue, does not need to be treated. I wait until it looks more like cream cheese or spreads beyond the tongue.

10. For most diarrheal diseases, one can rehydrate with the child’s preferred beverage and not a more expensive, less tasty electrolyte solution (even apple juice).

11. Does everybody with a nonanaphylactic food allergy need to carry epinephrine around? It would be great if there were a way to determine who does and does not require one.

12. A good guideline for parents about deciding to go to the ED is the following: If they do not feel the need to call 911, they probably have time to call their pediatrician first to help decide.
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