Challenging the Adage — Growing Children Don’t Get Sprains


Investigators from multiple institutions studied the frequency of growth plate fractures in skeletally immature children who sustain lateral ankle inversion injuries. Children were eligible if they were 5-12 years old, presented to 1 of 2 participating tertiary care pediatric emergency departments (ED) with an acute lateral ankle injury, and were clinically presumed to have a Salter Harris 1 distal fibular fracture (SH1DF), defined as (1) limited weight bearing, (2) tenderness and swelling over the lateral aspect of the distal fibula at the level of the physis, and (3) 3 radiographic views of the ankle demonstrating open physes and the absence of fracture. Parents of enrolled participants completed a baseline performance Activities Scale for Kids (ASKp) to assess the child’s physical function the week prior to the injury. All participants were treated with a removable air-stirrup ankle brace and instructed to return to normal activities as tolerated.

Within 7 days of the injury, enrolled participants underwent an MRI of both the injured and uninjured ankle. Three blinded radiologists independently reviewed all images. An MRI-confirmed SH1DF was defined as fibular physis widening, displaced fibular physis, evidence of disruption of the periosteum adjacent to the fibular physis, or no associated fracture extending into the metaphysis, epiphysis, or other bony area. Avulsion fractures, bone contusions, and ligament injuries were also identified. One month after the child’s injury, parents completed a second ASKp. Patients were then examined by an orthopedist. Three months after injury, parents were queried by telephone to assess weight bearing and physical activity.

The primary outcome was the proportion of MRI-confirmed SH1DF. Secondary outcomes included the proportion of MRI-confirmed ligament injuries and avulsion fractures as well as the difference in mean ASKp scores at 1 month between those with and without MRI-evident fractures.

Of 271 children screened, 170 were eligible, 140 consented to participate, and 135 were included in the analysis. The proportion of MRI-confirmed SH1DF was 3% (n = 4; 95% CI, 0.1%-5.9%). There were 27 participants with isolated bone contusion and 108 with ligament injuries (80%), 38 of which were associated with avulsion fractures. There was no significant difference in mean ASKp scores at 1 month between participants with and without MRI-detected fibular fractures nor in functional recovery at 3 months.

The investigators conclude that SH1DF is rare in children with radiographic fracture-negative lateral ankle injuries and SH1DF has a recovery comparable to ankle sprains (ligament injuries) when treated with a removable ankle brace and self-regulated return to activity.

Commentary by
William Hennrikus, MD, FAAP, Pediatric Orthopaedics, Orthopaedics and Rehabilitation, Penn State College of Medicine, Hershey, PA

Ankle injuries are common in children, leading to more than 2 million ED visits in the United States and Canada each year. Conventional wisdom has been that a child who sustains a lateral ankle inversion injury will experience a SH1DF instead of an ankle sprain because the physeal cartilage is weaker than the surrounding ligaments. The results of the current study challenge this wisdom. In addition, the investigators of this study demonstrated that a child with a SH1DF does not require a different treatment from that of an ankle sprain: recovery at 1 and 3 months post-injury was comparable simply with a removable ankle brace.

The results of this study have the potential to simplify the treatment of lateral ankle injuries in children with negative radiographs. This could save millions of health care dollars annually. The results suggest that children with lateral ankle injuries with no radiographic evidence of fracture can be treated by pediatricians with an ankle brace, and do not require repeat radiographs, MRI, or orthopedic referral. One weakness of the study is that the investigators did not conduct long-term follow-up on the 3% of participants with SH1DF to determine whether growth arrest occurred over time. However, since the incidence of growth arrest following this injury is exceedingly rare, the clinical significance of this lack is likely minimal.

In summary, this is an elegant study that debunks an age-old adage that growing children “do not get sprains.” It appears, in fact, that most do get sprains. Perhaps it’s time to treat accordingly.

References

Key words: ankle injuries, Salter Harris 1 distal fibular growth plate fractures, ankle sprains

The AAP Policy on Disclosure of Financial Relationships and Resolution of Conflicts of Interest for AAP CME activities is designed to ensure quality, objectivity, balance, and scientific integrity of AAP CME activities by identifying and resolving conflict of interest prior to the communication of session of learners. As a precautionary measure, authors, reviewers, editorial board members, and staff are required to disclose to the AAP any and all financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial support discussed in CME activities. None of the authors, reviewers, or staff had any relevant financial relationships to disclose for this issue of AAP Grand Rounds unless noted on the article title page. The AAP has taken steps to ensure any potential conflicts of interest. JAMA Pediatrics, E1 Editorial Board Members disclosed a Speaker’s Bureau with Cephalon/Takeda, Liner Pharma; NS Editorial Board Member disclosed a Speaker’s Bureau with Pfizer; and the Editorial Board Members disclosed a Speaker’s Bureau with SanoﬁAventis. Robert H. Wilton, MD (Editorial Board Member) disclosed a Speaker’s Bureau with SanoﬁAventis, and Munir Pasmooij and Boothe, Robert H. Wilton, MD (Editorial Board Member) disclosed a Speaker’s Bureau with SanoﬁAventis.
The authors conclude that planned out-of-hospital births were associated with a higher risk of perinatal mortality, though the absolute risk increase is low.

Commentary by Benjamin Gern, MD, and Carrie Phillipi, MD, PhD, Oregon Health and Science University, Portland, OR

Ons Gern and Phillipi have disclosed no financial relationship relevant to this commentary. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

The decision to deliver at home, in a birth center, or in the hospital is a very personal choice for parents. Many factors should be considered, all of which carry risks and benefits for infants and their mothers. Though limited to the state of Oregon, the data in this study are well suited to inform providers and patients of the risks and benefits of planned out-of-hospital birth given its large size and classification by planned place of delivery. This classification system is unique for a study of this scale in the United States.

Although the results suggest that the risk of perinatal and neonatal death is increased two- to threefold for planned out-of-hospital births compared to planned in-hospital births, the increase in absolute risk is relatively small when considered on an individual level. This degree of risk is already acceptable in the obstetrics field, as vaginal birth after cesarean delivery (VBAC) carries similar increased perinatal risk versus repeat cesarean delivery. However, just as pregnant women are extensively counseled on the risks and benefits of VBAC versus repeat cesarean delivery, counseling is warranted on the risks and benefits of planned place of birth. This is nonstandardized in the United States. Counseling would ensure that pregnant women who are planning an out-of-hospital delivery are informed not only of the decreased risks of obstetrical interventions, but also the associated increased perinatal risk.

On a population level, the increased risk of planned out-of-hospital births is substantial. The author of an accompanying editorial highlighted the need for standardizing the process of transferring out-of-hospital deliveries to the hospital, as occurred in 16% of planned out-of-hospital births included in the current study, in hopes of improving outcomes in this group of mothers and babies.

Editors’ Note

In addition to implementing systems for transferring neonates to the hospital, there is obvious need to assure neonatal metabolic, bilirubin, and hearing screening for out-of-hospital births. Furthermore, recent reports suggest that delayed diagnosis of critical congenital heart disease is more frequent in infants born out-of-hospital, underscoring the importance of pulse oximetry screening in the newborn (see AAP Grand Rounds, March 2015;33[3]:29).

References


Key words: delivery, infant mortality, out-of-hospital birth

---

**NEONATAL-PERINATAL MEDICINE**

**Risks and Benefits of Out-of-Hospital Births**


Investigators from the Oregon Health and Science University conducted a retrospective cohort study to assess birth outcomes associated with planned place of birth (hospital or out-of-hospital). Singleton, cephalic-presenting, nonanomalous term infants born in Oregon between 2012 and 2013 were included in the study. Excluded were preterm births (<37 weeks’ gestation), unplanned home births, births with unknown planned place of delivery, and births that did not occur in a home, birth center, or hospital (eg, in a doctor’s office).

Data on births and deaths were obtained through review of birth, infant death, and fetal death certificates. Maternal demographics, health information, and pregnancy characteristics were also collected. Infants were grouped by planned place of birth (hospital or out-of-hospital). Planned out-of-hospital births included births at home or in birth centers. The planned out-of-hospital birth cohort also included in-hospital births to women who planned to deliver at home or at a birth center. This classification was made possible by a question added to the Oregon birth certificate in 2012 regarding the intended place of birth at the onset of labor, allowing the investigators to identify planned out-of-hospital births that were transferred to a hospital after onset of labor. Primary outcomes were fetal, neonatal (within the first 28 days), and perinatal (composite of neonatal and fetal) mortality. Secondary outcomes included frequency of maternal obstetric interventions and NICU stays. Outcomes for planned in-hospital and planned out-of-hospital births were compared; regression analyses were conducted to control for confounding variables.

Data from 79,727 deliveries were included in the analysis. Of these, 95.2% were planned hospital births, 4.0% were planned and completed out-of-hospital births (both at home and in birth centers), and 0.8% were planned out-of-hospital births delivered in-hospital after transfer. The perinatal death rate was significantly higher among planned out-of-hospital births than for planned in-hospital births (3.9 vs 1.8 per 1,000; *P* = .003). Neonatal mortality was also higher for planned out-of-hospital births (1.6 vs 0.6 per 1,000; *P* = .02); there was no significant difference in fetal mortality rates. When adjusted for maternal factors, rates of perinatal death (adjusted odds ratio [AOR] = 2.43; 95% CI, 1.37-4.30) and neonatal death (AOR = 2.87; 95% CI, 1.10-7.47) were significantly higher among newborns with planned out-of-hospital births. The rates for maternal intervention were significantly lower for births planned out-of-hospital than in planned in-hospital births (30.4% vs 4.8% for induction, 26.4% vs 7.5% for augmentation of labor, 24.7% vs 5.3% for cesarean section; *P* < .001 for all). Infants with planned out-of-hospital births had significantly higher rates of neonatal seizures and 5-minute Apgar scores <7, but lower rates of NICU admission.

In addition to implementing systems for transferring neonates to the hospital, there is obvious need to assure neonatal metabolic, bilirubin, and hearing screening for out-of-hospital births. Furthermore, recent reports suggest that delayed diagnosis of critical congenital heart disease is more frequent in infants born out-of-hospital, underscoring the importance of pulse oximetry screening in the newborn (see AAP Grand Rounds, March 2015;33[3]:29).
Hypertonic Saline for Bronchiolitis Doesn't Shorten Inpatient Stay


Investigators from multiple institutions assessed whether nebulized 3% hypertonic saline administered to infants hospitalized for bronchiolitis was associated with a shorter length of stay. Children <12 months old with bronchiolitis admitted to an urban tertiary care children’s hospital were enrolled in the study. Infants with a history of wheezing were not excluded unless they were treated for status asthmaticus. In this randomized, double-blind controlled study, participants received nebulized 3% hypertonic saline (intervention) or normal saline (control) every 4 hours while hospitalized. The primary outcome was length of hospital stay, and secondary outcomes included 7-day readmission rate and clinical worsening (defined as transfer to PICU, bronchospasm as indicated by worsening of validated respiratory distress score, or unforeseen adverse events).

Of 765 infants screened for eligibility, 227 were enrolled and randomized: 113 were assigned to the hypertonic saline group and 114 to the normal saline group. The mean age was 3.9 months in the hypertonic saline group and 4.4 months in the control group. Treatment groups did not differ in age, gender, race, viral status, history of wheeze, or history of prematurity. There was no difference in the length of stay, with both groups having a median length of stay of 2.1 days ($P = .73$). The groups also did not show significant differences in readmission rates or clinical worsening. Administration of hypertonic saline was not associated with adverse events.

The authors conclude that treatment with 3% hypertonic saline compared to normal saline does not alter length of stay or readmission rate.

**Commentary by**

Daniel Lesser, MD, FAAP, University of California, San Diego, San Diego, CA

Dr. Lesser has disclosed no financial relationship relevant to this commentary. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Bronchiolitis is the most common reason for hospital admission of infants in the United States. Hypertonic saline may be beneficial in alleviating airway obstruction in infants with bronchiolitis by decreasing mucus viscosity and improving mucociliary clearance. Yet findings of pediatric studies investigating the use of hypertonic saline for bronchiolitis have not consistently shown benefit. Several early studies suggested clinical benefit (see AAP Grand Rounds, February 2010;23[2]:162), and a 2013 Cochrane review concluded that 3% hypertonic saline may significantly reduce length of stay and improve clinical severity score. The 2014 American Academy of Pediatrics bronchiolitis guideline suggests that clinicians may administer hypertonic saline to hospitalized pediatric patients. More recently, however, larger studies failed to identify benefit for administration of hypertonic saline to hospitalized infants. The authors of 2 meta-analyses published since the 2013 Cochrane review did not agree on the effectiveness of hypertonic saline; both agreed that the inconsistency among trials limits the quality of overall evidence. A strength of the current study lies in its prospective, randomized, double-blind controlled design and relatively large number of infants enrolled. Unique features compared to previous studies include enrollment of children with and without history of wheezing and use of hypertonic saline without bronchodilators. There are some notable limitations. Although the study was relatively large, it was from a single center, potentially limiting generalizability of results. Although the primary outcome (length of stay) is important, clinicians are also interested in therapeutic benefit with regard to easing respiratory distress and decreasing oxygen need. While use of change in respiratory scores as an outcome may have imparted this information, the limited validity of these scores can affect accuracy of conclusions.

Treatment of bronchiolitis with hypertonic saline remains controversial. While most studies agree that the therapy is safe, disagreement remains as to its overall effectiveness. Heterogeneity in patient populations, diagnostic method, timing, and type of treatment likely explain this variability. Compared to earlier reports, more recent studies with higher evidence levels fail to show benefit. Based on the findings of the present study, hypertonic saline given to infants admitted for bronchiolitis does not shorten hospital length of stay.

**References**


**Key words:** bronchiolitis, hypertonic saline, length of stay

**Visit www.GrandRoundsBlog.org to read a post about this article appearing this month.**
Azithromycin versus Doxycycline for Urogenital *Chlamydia trachomatis*


I

vestigators from multiple institutions conducted a randomized trial to assess the noninferiority of oral azithromycin (1g in a single dose) to oral doxycycline (100 mg twice a day for 7 days) for the treatment of urogenital chlamydia infection. Eligible participants included females and males 12-21 years old, residing in long-term youth correctional facilities in Los Angeles, who were found to have a positive urine nucleic acid amplification test (NAAT) for chlamydia. Eligible participants who consented to the study were randomized 1:1 to the azithromycin or doxycycline arm and received chlamydia strain genotyping. The administration of study drugs in both treatment groups was directly observed by facility staff. Follow-up NAAT testing and interviews were conducted at days 28 and 67 after enrollment. The primary outcome was treatment failure at first follow-up, defined as a positive chlamydia NAAT and concordant strain genotyping. The per-protocol population (ie, participants who completed therapy and first follow-up) was included in analysis. Prior to the analysis, noninferiority was considered to be established if the upper bound of the 1-sided 90% exact confidence interval (CI) for the calculated difference in treatment failure rates between the 2 treatment groups was <5%. (For an explanation of noninferiority trials, see *AAP Grand Rounds*, September 2011;27[3]:26.)

Among the 567 patients who were screened and randomized, 284 were assigned to the azithromycin group and 283 to the doxycycline group. The per-protocol population included 155 participants in each treatment group (65% males). No treatment failures occurred in the doxycycline group (0%; 95% CI, 0.0-2.4), while 5 occurred in the azithromycin group (3.2%; 95% CI, 0.4-7.4). The difference in failure rate was 3.2% with a 90% 1-sided CI of 0.0%-5.9%. Since the upper CI limit was over 5%, the noninferiority of azithromycin compared to doxycycline was not established. The efficacy of azithromycin treatment groups was <5%. (For an explanation of noninferiority trials, see *AAP Grand Rounds*, September 2011;27[3]:26.)

The authors conclude that in the setting of directly observed treatment of urogenital chlamydia infection, both azithromycin and doxycycline were highly effective treatment options. However, the noninferiority of azithromycin to doxycycline was not established in this study.

**Commentary by**

Charlene Wong, MD, FAAP, Adolescent Medicine, Children’s Hospital of Philadelphia, Philadelphia, PA

Dr. Wong has disclosed no financial relationship relevant to this commentary. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

**Chlamydia trachomatis** infection is the most common bacterial sexually transmitted infection in the United States.1 The Centers for Disease Control and Prevention recommend screening all sexually active women <25 years old annually for chlamydia. If positive, the recommended firstline treatment options are a single oral dose of 1 g of azithromycin or 100 mg of oral doxycycline taken twice a day for 7 days, and a test of cure is not recommended.2 The American Academy of Pediatrics recommends that all sexually active adolescents be screened annually for chlamydia and other sexually transmitted infections.3

The focus of the current study was to ensure that azithromycin is not substantially worse than doxycycline for treating urogenital chlamydia infection. While the investigators found both treatment regimens to be highly effective in directly observed therapy in youth correctional facilities, they were unable to establish that azithromycin was noninferior to doxycycline.

However, these results should be interpreted in the context of several study limitations. Mainly, adherence to a week-long course of doxycycline is a major concern, especially among youth. In prior adherence studies, up to a quarter of participants self-reported missing at least 1 dose and only 16% in another study using medication monitoring bottles took all doses.4,5 Poor adherence has resulted in higher treatment failure rates – up to 20% in some studies, which is substantially higher than the 0% failure rate in the current study where all participants completed at least 10 of 14 doxycycline doses.4,5

An additional limitation is that the study was powered using a 90% CI for test of noninferiority because the sample size required for the more typical 95% CI would have been unattainable. Using the 90% cut-off, 2 fewer failures in the azithromycin group would have met the noninferiority criteria of azithromycin to doxycycline.

The bottom line is that both azithromycin and doxycycline are highly effective in treating urogenital chlamydia infection. However, based on the limited generalizability of the study setting and directly observed treatment procedures, it is likely not reasonable to recommend doxycycline over azithromycin as the preferred chlamydia treatment regimen.6

**References**


**Key words:** chlamydia, STD treatment, adolescents

Visit www.GrandRoundsBlog.org to read a post about this article appearing this month.
Researchers from the Harvard School of Public Health and the University of Vermont used data from the National Violent Death Reporting System (NVDRS) to review unintentional (UI) firearm deaths involving children aged 0-14 years from 2005 to 2012 to characterize the circumstances of these shootings. The NVDRS links data from all available information (police reports, medical examiner records, and sociodemographic data) to describe the circumstances of violent deaths in 16 states, representing 26% of the US population and including rural and urban areas with high and low gun ownership in all regions of the country. Rates of UI firearm deaths were extrapolated to provide a national estimate and compare this estimate to data from vital statistics databases.

The authors reviewed data on 229 UI deaths in the NVDRS states during the study period. They estimate that during these years 110 US children aged ≤14 years died of UI shootings annually, exceeding the vital statistics reported rate by 80%. Most victims (>80%) were male, and the incidence increased with age. Family members were the shooters in two thirds of UI deaths in this age group, except among children ages 2-4 years, among whom self-inflicted injuries predominated. The shooters were usually family members, 97% were male, and 65% were under age 15. Among victims >12 years old, a friend was more likely to be the shooter. Fewer than 10% of victims of UI shootings were killed by someone who was not a family member or friend. While victims <11 years old almost never died at a friend’s house, 38% of UI shootings in 11- to 14-year-olds occurred at a friend’s house. About 11% of cases involved hunting or related activities.

The authors conclude that most UI firearm deaths in children aged ≤14 years involve children shooting other children or themselves, highlighting the importance of reducing their access to guns. They also conclude that the reported incidence from vital statistics records is a substantial underestimation.

Commentary by
Eliot Nelson, MD, FAAP, University of Vermont Medical Center, Pediatrics, Burlington, VT

Dr Nelson has disclosed no financial relationship relevant to this commentary. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

While UI firearm deaths are far outnumbered by homicide- and suicide-firearm deaths over the lifespan, they are relatively more common in young children. Preventable deaths. The present report demonstrates convincingly that many UI deaths in children under age 15 years have been misclassified in vital statistics databases as homicides. The authors confirm and extend previous research showing that unintentional firearm deaths among children are even more common than has been generally perceived, especially among young children.

The most important methodologic strength of this study is its use of NVDRS data – and the authors’ thorough scrutiny of the information and reports that the NVDRS provides. The hope and promise of the NVDRS from the beginning has been that by systematically reviewing cases of violent death, we can better understand the circumstances of such deaths, and thus can find better ways to prevent them. Using the NVDRS may help us avoid the pitfalls of anecdote and emotion that too often influence discussions around violent death.

While the study relies on the advantages of the NVDRS, the authors highlight some of its shortcomings. They cite the limited coverage of the NVDRS, existing in only 16 states for the period of study (as of 2015, 32 states are covered). Moreover, their report illuminates gaps in the NVDRS data, including such basic characteristics as age and gender of some shooters (which in turn reflect gaps in the sources of NVDRS data, such as police reports).

While children <4 years of age are capable of pulling triggers on handguns, and that efforts to “teach” children not to play with guns are inadequate. Pediatricians can counsel families to store guns safely or remove them from their homes. This study reinforces the need for and importance of such counseling.

References

Key words: firearms, gun accidents, children
Vitamin D Improves Mood Disorders in D-Deficient Girls With PMS


Researchers from multiple institutions sought to determine whether supplementing vitamin D-deficient adolescent girls with vitamin D-3 would improve emotional symptoms of premenstrual syndrome (PMS). This study was carried out at 2 academic centers in Italy from 2010-2012. Females 15-21 years of age were enrolled if they met standard diagnostic criteria of PMS, as outlined by the American College of Obstetrics and Gynecology (ACOG); scored in the severe to extremely severe levels of intensity on the Daily Symptoms Rating (DSR) validated scale that lists 17 PMS symptoms; and had 25-hydroxy-vitamin D (25-OHD) levels ≤10 ng/ml. Participants were randomly assigned to 1 of 2 groups: group 1 received vitamin D-3 200,000 IU orally on day 1 followed by 25,000 IU orally every 2 weeks for 4 months, and group 2 received a placebo in a similar dosing pattern. Participants were blinded to their treatment assignment. All participants had vitamin D, calcium, and parathyroid hormone (PTH) levels measured monthly for 4 months. DSR questionnaires were also completed and adverse events assessed monthly for 4 months. The primary outcome was change from baseline scores for each of the symptoms in the DSR among participants in the 2 treatment groups.

A total of 158 patients participated in the study, 80 in group 1 and 78 in group 2. At baseline, both groups were comparable in mean age, BMI, mean menarche age, and sociodemographic/psychometric measures. Each group also had comparable 25-OHD, PTH, and calcium levels.

Participants in group 1 (vitamin D) showed improvements in emotional symptoms by the third month of intervention. At the end of the 4-month study, levels of anxiety, irritability, crying, and sadness were all significantly reduced compared to baseline (P < .001). A decrease was also noted in perceived disturbance of relationships (P < .001). In group 2 (placebo), there was a reduction in the irritability score (P < .05), but there were no significant changes in the other symptoms.

No significant difference was found in the frequency of adverse events between the 2 groups. In group 1 (vitamin D), 25-OHD levels increased from <10 to 35-58 ng/ml after the first month of treatment and remained stable throughout the course of the study. Serum calcium and PTH levels also remained constant throughout the study.

The authors conclude that supplementation with vitamin D-3 is a safe and effective way to reduce the intensity of PMS emotional symptoms in adolescent females with very low vitamin D levels.

PMS is a common disorder affecting menstruating women that can cause significant disruption in their daily lives. ACOG has published diagnostic criteria for PMS that require at least 1 affective symptom (anxiety, irritation, sadness, crying easily, etc) and at least 1 somatic symptom (breast tenderness, abdominal bloating, fatigue, headache, etc) be reported 5 days before the onset of menses in the previous 3 menstrual cycles. No single cause has been identified to explain this disorder. Though serotonin reuptake inhibitors are the mainstay of treatment for PMS, other treatments include hormonal therapy with progesterone, oral contraceptives, and gonadotropin-releasing hormone agonists, none of which has had consistent results.

Vitamin D receptors are present throughout the regions of the brain implicated in the pathophysiology of depression. Vitamin D, a neurohormone, modulates serotonin synthesis, release, and function in the brain; therefore insufficient 25-OHD levels may contribute to dysfunctional serotonin activity.

The results of this well-designed study show that oral supplementation with the approximate dose of 2,000 IU of vitamin D-3 daily was sufficient to not only raise 25-OHD levels, but also reduce affective symptoms associated with PMS. Whether these same results would occur in those who have 25-OHD levels in the “sufficient” range (>20 ng/ml) remains to be seen. However, in this study, PMS symptoms improved only when 25-OHD levels were much greater than the “sufficient” level, indicating that higher levels of circulating 25-OHD may be needed for optimal functioning. The US Endocrine Society suggests that sufficient 25-OHD levels range from 30-100 ng/ml; therefore supplementation to achieve a higher 25-OHD level may be safe in order to achieve improvement in affective symptoms in those with PMS.

References

Key words: premenstrual syndrome, vitamin D, mood disorders
Heritable Mutations in Pediatric Cancer


Commentary by
Mary-Jane Staba Hogan, MD, MPH, FAAP, Pediatric Hematology Oncology, Yale School of Medicine, New Haven, CT

Prior to this study, the prevalence of children and adolescents with cancer who have a familial cancer-predisposition syndrome was difficult to determine. Recognized inherited syndromes have been associated with high-penetrance DNA mutations (eg, Li-Fraumeni syndrome with sarcomas, adrenocortical carcinoma, and others), chromosomal aneuploidy (eg, Down syndrome with leukemia), and epigenetic disorders (eg, Beckwith-Weidemann syndrome with Wilms tumor, hepatoblastoma, and others). Criteria for identifying children with cancer and their family members with inherited cancer susceptibility have included the presence of rare tumors, bilateral or multifocal tumors, cancer at a younger than expected age, multiple synchronous or metachronous tumors, other features of an underlying syndrome, consanguinity, or family history of cancer. Detecting at-risk individuals has led to improved survival from early cancer prevention, screening, and family-planning guidance.

The result of the current large study with diverse cancers and adult controls suggests that germline sequencing can incidentally uncover an inherited cancer susceptibility in 5%-10% of pediatric patients with cancer. A potential overestimation of prevalence in this study results from the inclusion of a greater proportion of high-risk childhood cancers with germline TP53 mutations compared to data from the Surveillance, Epidemiology and End Results program. Potential underestimation of prevalence arises from the limited understanding of other probable pathogenic mutations such as heterozygous mutations in autosomal recessive syndromes, or germline-truncating, mosaic germline, non-coding region, de novo, and epigenetic mutations in cancer susceptibility genes.

Comprehensive genome analyses have led to insights into tumorigenesis, potential targets for therapies, and improvement in pediatric cancer care management. Genetic testing for cancer-predisposition syndromes involves complex clinical and ethical issues related to the timing and utility of testing, interpreting results, recommending tumor screening, and providing appropriate emotional support to families.

References

Key words: cancer-predisposition syndrome, pediatric, germline mutation
Parent Questionnaire for Detection of Seizures in Children


Investigators from multiple institutions developed a questionnaire designed to accurately establish a history of seizures in children that could be used in seizure prevalence studies. For the study, parents of children 6 months to 12 years old, whose children were being seen for any reason at a pediatric neurology clinic, completed a 2-part questionnaire administered by research assistants. Part 1 was designed to be highly sensitive in detecting a history of seizures, and included 11 screening questions. Part 2 consisted of 30 questions, simulating the interview and diagnostic schema used clinically, and was designed to increase specificity by discerning seizures from nonepileptic events. An algorithm of parental responses on the questionnaire provided a 4-level ranking scale of the likelihood of seizures in their child: (1) not likely, (2) indeterminate, (3) probable, and (4) almost certain. Blinded to questionnaire results, pediatric neurologists ranked the likelihood of seizures in each child of study parents using the same 4-level scale based on the clinical history and examination; the neurologists’ rankings served as the gold standard. With both the questionnaire and neurologist assessment, a ranking of “probable” or “almost certain” for a child was classified as a seizure and lower ratings were categorized as no seizure history. The utility of the questionnaire as a test for a seizure history was determined by comparison to the gold standard classification.

The questionnaire was completed by 150 of 177 (84.7%) enrolled parents. Based on the assessments of the pediatric neurologists, seizure prevalence among participants was 38.6%. The questionnaire had a 91.4% sensitivity and an 82.6% specificity in classifying seizure history in study children. The positive predictive value of the questionnaire was 76.8% and the negative predictive value was 93.8%.

The authors conclude that the pediatric seizure questionnaire is sensitive and specific for detecting clinically confirmed seizures and may be useful as a screening tool in a large population.

Commentary by J. Gordon Millichap, MD, FAAP, Neurology, Ann & Robert H. Lurie Children’s Hospital of Chicago, Northwestern University, Feinberg School of Medicine, Chicago, IL

Dr Millichap has disclosed no financial relationship relevant to this commentary. This commentary does not contain a discussion of an unproven/investigative use of a commercial product/device.

In the absence of a witnessed clinical seizure or video-electroencephalographic documentation of a seizure, an evaluation by a pediatric neurologist with specialized training in pediatric epilepsy (pediatric epileptologist) provides the most reliable method of making a diagnosis of clinical seizure. The clinical manifestations of a seizure consist of sudden and transitory alterations of consciousness, motor, sensory, autonomic, or psychic events.1

A review of the recent literature documents a previous investigation of the validity and reliability of a screening questionnaire administered to parents to detect behaviors suggestive of epileptic seizures in children.2 A 10-item questionnaire was administered to 120 parents of children attending hospital-based clinics at the University of the West Indies, Kingston, Jamaica, and Dell Children’s Epilepsy Program, Austin, Texas. The validity of the questionnaire was similar to the clinical evaluation by the pediatric neurologist and pediatrician; 58% had epilepsy, and mean (SD) age was 8.1 (3.2) years. A positive response to >1 item had the highest sensitivity (89%) and specificity (91%), thus providing an accuracy similar to that of the questionnaire assessed in the current study.

In patients with an established diagnosis of epilepsy, and especially in those with a tendency to generalized tonic-clonic seizures (GTCS), it is important to detect recurrence of seizures and provide immediate therapy. Patients with GTCS have an increased risk for injuries related to seizures and for sudden unexpected death in epilepsy.3 Many nocturnal seizures remain undetected in unattended patients. A portable automatic seizure detection device would be an important help in detection and prompt control of the event. At an Epilepsy Center in Aarhus, Denmark, a wrist-worn, wireless accelerometer sensor was shown to possess high sensitivity and specificity for detection of GTCS in 73 patients at risk.3 In addition to questionnaires for diagnosis, objective devices must also be available for immediate detection and control of seizures.4

Editors’ Note

Diagnosing and identifying seizures in children is challenging for general clinicians. Since pediatric neurologists are in short supply, a screening tool such as this with high negative predictive value has the potential to direct more appropriate referrals. As investigators refine the screening tool, it will be interesting to see performance characteristics when applied to a general population with lower risk of epilepsy.

References

Key words: seizure, seizure diagnosis, epilepsy
Impact of Amblyopia on Reading Speed


Investigators from the University of Texas Southwestern Medical Center in Dallas evaluated the effect of amblyopia on reading under natural conditions of binocular reading. School-aged amblyopic children with strabismus (misaligned eyes) and/or anisometropia (refractive abnormality) were compared to nonamblyopic children successfully treated for esotropia and to normal control children. In particular, this study aimed to isolate the impact of amblyopia without strabismus on reading and associated eye movements using a habitual reading distance under binocular conditions. For the study, amblyopia was defined as an intraocular difference in visual acuity of ≥0.2 logarithmic units of the minimum angle of resolution (logMAR), best-corrected visual acuity in the nonpreferred eye of ≥0.2 logMAR (≥20/32), and best corrected visual acuity in the preferred eye of ≤0.1 logMAR (≤20/25). Participants were fitted with the ReadAlyzer, an eye movement recording system, and silently read a grade-level paragraph of text under binocular conditions. Study outcomes included reading rate, number of forward or regressive saccades (rapid movements of both eyes in the same direction) per 100 words, and fixation duration. These outcomes were compared in participants with amblyopia to those in the treated strabismus group and in control children.

Data were analyzed on 73 children including 29 children with amblyopia, 23 with treated strabismus, and 21 normal controls. The mean ages of the 3 groups were 9.4 years, 9.8 years, and 10.4 years, respectively. The 3 groups did not differ with regard to last grade completed. Mean reading speed was 148 words/minute in amblyopic children, which was significantly slower than in treated strabismic children without amblyopia (mean of 198 words/minute, \(P = .004\)) or in normal control children (mean 204 words/minute, \(P = .002\)). Treated strabismic children without amblyopia and normal control children did not differ in reading rate \((P = .76)\). Amblyopic children made significantly more forward saccades/100 words than treated strabismic children without amblyopia \((P < .001)\) and control children \((P < .001)\). Forward saccades did not differ significantly between treated strabismic children without amblyopia and normal control children \((P = .75)\). Neither the number of regressive saccades nor the mean fixation duration differed significantly among the 3 groups. In addition, amblyopic eye visual acuity was not significantly correlated with reading rate, forward saccades, regressive saccades, or fixation duration.

The authors conclude that amblyopia, not strabismus, is responsible for slower reading speed in school-aged children with amblyopia, and postulate that speed differences may result from accompanying oculomotor dysfunction (increased forward saccades in amblyopic children).

Commentary by Alexander J. Khammar, MD, FAAP, Medical College of Wisconsin, Milwaukee, WI

Dr Khammar has disclosed no financial relationship relevant to this commentary. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Amblyopia may interfere with oculomotor function, including fixation instability and abnormal saccades initiation and fixation. Previous studies of binocular reading in the presence of amblyopia have demonstrated slower reading in both adults and school-aged children; however, these studies have not been done under natural reading conditions. Also, previous studies have enrolled patients with combined strabismus and amblyopia. The authors of the current study aimed to look specifically at the effect of amblyopia alone, while comparing its effect to previously treated children with strabismus and normal controls.

The results of this study are compelling for the effects of amblyopia alone (and not strabismus) as an independent risk factor for slower binocular reading under natural conditions in children. In addition, they illustrate that the presence, and not severity, of amblyopia may cause slower reading. Finally, the study recreates natural, binocular silent reading conditions, using age-appropriate reading material. This new information emphasizes the importance of pediatric vision screening, as well as thorough treatment of amblyopia beyond the primary goals of improved visual acuity or stereopsis alone.

Editors’ Note

Ophthalmologists and pediatricians stand united in their quest to promote reading as foundational to academic success. This study indicates moderate amblyopia, which may go unrecognized when tested binocular visual acuity is intact, is a risk factor for reduced reading speed and therefore reading difficulty.

References

Key words: amblyopia, reading, strabismus

AAP Journal CME
You can complete and claim credit for all of your quizzes online. Visit the AAP Grand Rounds CME Center at www.aapgrandrounds.org.
R esearchers from multiple institutions conducted a qualitative study to assess the experience of parents whose children had gone through a transition from hospital to home. Parents or caregivers of children hospitalized at Cincinnati Children’s Hospital Medical Center (CCHMC) with common, acute conditions were recruited if they had been cared for on the hospitalist, neurology, or neurosurgical service and could attend a focus group at CCHMC within 30 days of discharge. Focus groups of enrolled participants were held to characterize the experience of parents around the transition from hospital to home for their children and to identify barriers to successful transitions. During focus group sessions, the research team used an open-ended, semi-structured question guide that they had developed. Each session lasted about 90 minutes and was audiotaped and transcribed verbatim. The audiotapes and transcripts were reviewed by the research team using a standardized process to develop a set of themes and concepts describing parental experience. Results were continuously analyzed and recruitment was suspended once thematic saturation was achieved.

A total of 15 sessions were held with 61 participants. Four of these sessions yielded only 1 participant and were then conducted as personal interviews. Participants were 87% female, 46% nonwhite, and 38% were the sole adult in the household. Initial review of focus group sessions yielded 12 major themes with associated subthemes. As these were further analyzed, the team found that themes fit into 4 primary concepts: (1) “In a fog”/barriers to integrating information, (2) “What I wish I had”/suggested information or improvements, (3) “Am I ready to go home?”/discharge readiness, and (4) “I’m home, now what?”/confidence in postdischarge care. These concepts often overlapped and influenced one another.

The “In a fog” concept was focused on factors influencing a family’s ability to process and use information. Factors included mental exhaustion, handling uncertainty, information overload, and usability of information. “What I wish I had” identified themes for improvement including information desired and suggested improvements in the discharge process. “Am I ready to go home?” included concerns about both emotional and clinical discharge readiness. Finally, “I’m home, now what?” included 4 main themes: (1) knowing whom to call, (2) bridging the gap (desiring a call or nurse home visit), (3) caring for a sick child, and (4) confidence in caring for a sick child.

The authors conclude that examination of the perspectives of caregivers of children who have experienced the transition from hospital to home can be used to inform interventions to support families and facilitate an easier reentry to home.
The following medical education questions cover the content of the April 2016 issue of AAP Grand Rounds. Please keep this issue. Each year’s material is worth up to 18 AMA PRA Category 1 Credit(s)™.

Complete and claim credit online at www.aapgrandrounds.org. Need username and password? Contact customer service at 866-843-2271.

CME OBJECTIVES

- Understand the risks and benefits of out-of-hospital births
- Describe the efficacy of hypertonic saline for children hospitalized with bronchiolitis
- Describe the epidemiology of unintentional firearm deaths in children

1. A 10-year-old boy presents to the emergency department with his parents due to left ankle pain following a lateral ankle injury that occurred 2 hours ago. There was pain, tenderness, and swelling over the lateral left ankle. Ankle radiographs show no apparent fracture. Which of the following is the most accurate finding/outcome of the study by Boutis et al concerning radiograph-negative lateral ankle injuries in children?
   a. Children with a Salter-Harris I fracture have a poor outcome when treated with a removable brace and return to activities as tolerated
   b. These injuries are best treated with a removable brace and limited activity for 8 weeks
   c. These injuries are best treated with a short leg cast for 6 weeks
   d. Treatment with a removable brace and return to activities as tolerated has a good outcome
   e. Twenty percent have a Salter-Harris I fracture of the distal fibula

2. The parents of one of your patients are expecting another infant. They ask about the risks and benefits of hospital versus out-of-hospital delivery. The parents are wondering if there are increased risks for their infant if they choose to deliver in the hospital. Based on the study by Snowden et al, which of the following factors had an increased risk with in-hospital delivery when compared to planned out-of-hospital delivery?
   a. Apgar score <7
   b. Neonatal mortality
   c. Neonatal seizures
   d. NICU admission
   e. Perinatal mortality

3. Which of the following is the most accurate conclusion of the study by Silver et al concerning the use of hypertonic saline for hospitalized infants with bronchiolitis?
   a. Bronchospasm occurred more frequently in infants given hypertonic saline
   b. Hypertonic saline improved respiratory distress scores
   c. Infants given hypertonic saline had no difference in readmission rate compared to controls
   d. Infants given hypertonic saline were significantly less likely to need intensive care compared to controls
   e. The hypertonic saline group had a significantly decreased hospital length of stay compared to controls

4. A 17-year-old girl who resides in a long-term youth correctional facility presents to clinic after testing positive for Chlamydia trachomatis on a urine nucleic acid amplification test during her well adolescent check. Which of the following is the most accurate finding of the study by Skinner et al concerning treatment of urogenital chlamydia?
   a. A single dose of azithromycin is inferior to a 7-day course of oral doxycycline for the treatment of urogenital chlamydia
   b. Neither treatment regimen showed high efficacy for the treatment of urogenital chlamydia
   c. Oral azithromycin is the preferred treatment regimen for urogenital chlamydia
   d. The noninferiority of a single dose of azithromycin could not be established compared to a 7-day course of oral doxycycline for the treatment of urogenital chlamydia
   e. The treatment regimen depends on whether the patient is symptomatic

5. You learn that a 14-year-old boy who was a patient in your practice was unintentionally killed by a gunshot wound from a friend at the friend’s home. Based on the study by Hemenway and Solnick, which of the following is the most accurate statement concerning children and unintentional firearm death?
   a. Among victims <11 years old, the majority occur at a friend’s house
   b. The incidence of unintentional firearm deaths decreased with age
   c. The majority involve hunting or related activities

6. A 16-year-old girl returns to the clinic with symptoms of premenstrual syndrome (PMS). Based on her Daily Symptoms Rating (DSR) scale her symptoms are severe. Her serum 25-hydroxycholecalciferol (25-OH-D) drawn last week is 8 ng/ml. Her mother stated she saw an article on the internet advocating vitamin D supplementation for PMS. Which of the following is the most appropriate response based on the placebo-controlled study by Tartagni et al of vitamin D supplementation for PMS?
   a. Adverse event rates were significantly greater in the vitamin D group compared to the placebo group
   b. Improvements were seen in levels of anxiety and irritability but not in crying or perception of disturbed relationships at the end of the treatment with vitamin D supplementation
   c. Improvements were seen in levels of anxiety, irritability, crying, and perception of disturbed relationships at the end of the treatment with vitamin D supplementation
   d. Sufficient levels of 25-OH-D were attained during the study for the group receiving vitamin D supplementation but they also developed significantly more frequent abnormal levels of calcium and PTH by the end of the study
   e. The placebo group was significantly younger and had a greater mean BMI compared to the vitamin D supplementation group, so the results of the study are not valid

7. A 13-year-old boy with high-risk leukemia has a germline mutation in APC, a cancer susceptibility gene. Based on the study by Zhang et al, which of the following is the most accurate statement concerning germline mutations in cancer-predisposition genes in pediatric cancer subjects?
   a. A family history of cancer was found in 95% of subjects with germline mutations
   b. Germline mutations were discovered in 8.5% of children and adolescents with cancer
   c. Germline mutations were discovered in a greater proportion of adults without cancer than children with cancer
   d. Germline mutations were more prevalent in children and adolescents with leukemia compared to those with central nervous system tumors
   e. Less than 10% of subjects with germline mutations had a family history of cancer

8. An 8-year-old girl has episodes of altered awareness, sometimes complicated by vomiting. The mother is administered the parent questionnaire as detailed in the study by Douglass et al. Which of the following is the most accurate statement concerning the parent questionnaire for the detection of seizures based on the study by Douglass et al?
   a. Based on the population studied the negative predictive value was greater than 90%
   b. Based on the population studied the positive predictive value was greater than 90%
   c. Positive predictive value for the population studied was 52%
   d. Specificity was greater than sensitivity
   e. When applied to a population with a lower prevalence of seizures than was noted in the study population the negative predictive value will be significantly lower

9. Which of the following school-aged children would be at highest risk of experiencing reading difficulty based on the study by Kelly et al?
   a. A 6-year-old girl with a microesotropia after strabismus surgery and visual acuity of 20/25 in the right eye and 20/20 in the left eye
   b. A 7-year-old boy with best corrected visual acuity of 20/20 in each eye and history of successfully treated esotropia
   c. A 9-year-old girl with visual acuity of 20/50 in the right eye, 20/25 in the left eye, and no history of strabismus
   d. A 9-year-old boy with visual acuity of 20/25 in the right eye and 20/20 in the left eye, with no history of strabismus
   e. A 10-year-old boy with visual acuity of 20/25 in each eye with no history of strabismus

10. Which of the following was a major factor noted to contribute to families feeling they were “in a fog” about their child’s transition from hospital to home, based on the study by Solan et al?
    a. Family stress
    b. Information overload
    c. Multiple caregivers
    d. Patient length of stay
    e. Type of medications at time of discharge

Answers:
1. d
2. c
3. e
4. a
5. b
6. a
7. e
8. d
9. b
10. a
In October 2015, 22 scientists from 10 countries evaluated the results from about 800 studies on the relationship between cancer and processed and unprocessed meat. The meeting was held in Lyon, France as part of the International Agency for Research on Cancer (IARC), the cancer agency of the World Health Organization (WHO). Although the working group’s conclusions have been summarized, the full report is in press. In 2014, a similar group had recommended that red meat and processed meat be evaluated as possible causes of cancer based on the increasing consumption of these foods worldwide, especially in low- and middle-income countries.

Red meat was classified as “probably carcinogenic to humans” based on limited evidence from epidemiological studies linking its consumption to developing colorectal cancer. Processed meat was classified as “carcinogenic to humans,” based on evidence from epidemiological studies. Tobacco smoking and asbestos are similarly classified but they are not equally dangerous. The IARC assessment does not assess level of risk, just that an association is or is not established.

The WHO, referencing the Global Burden of Disease Project, estimates that about 34,000 cancer deaths per year worldwide can be attributed to diets high in processed meat. They also estimated that smoking causes 1,000,000 deaths, alcohol 600,000 deaths, and air pollution about 200,000 deaths worldwide annually.

The IARC group acknowledged nutritional benefits from red meat. With regard to vegetarian diets, advantages and disadvantages were noted. Because there may be many other variables involved, no substantive comment was offered regarding the health benefits/risks of switching to a vegetarian diet. Common examples of processed meats include frankfurters, sausage, ham, smoked and canned meat preparations, and commercially prepared meat sauces.

No data were available on the relative risks for different groups or ages of people. Nor were there adequate data regarding cooking methods or temperatures (including consumption of raw meat.) The risk of colorectal cancer associated with consumption of processed meat was estimated (based on 10 studies) as increasing by 18% for every 50 gram portion eaten daily.

We are constantly provided with “information” about what constitutes the best (or worst) diets. It now seems prudent to strongly advise the elimination or at least moderation of the ingestion of processed meats for our patients.

References
3. Farvid MS, et al. BMJ. 2014;348:g3437; doi:10.1136/bmj.g3437