RNA Biosignatures and the Febrile Infant

Investigators from multiple institutions conducted a study to assess the potential of using RNA “biosignatures” (patterns of gene expression in blood leukocytes) to diagnose bacterial infections in febrile infants ≤60 days old. Infants from 22 emergency departments were enrolled in the study if they had a temperature >38°C and had a blood culture obtained; other laboratory testing was performed at the discretion of the examining physician. A random sample of patients with and without bacterial infections was selected for RNA biosignature analysis. Blood from a sample of well-afebrile infants was also collected for analysis. Microarray analysis of blood leukocytes was done to compare patterns of gene expression (RNA biosignature) in patients with culture-proven bacterial infections and those without bacterial infections, with particular focus on genes related to inflammation and interferon. Microarray samples were divided into training and test sets. Differential RNA biosignatures between infants with and without bacterial infection were identified in the training sets and the identified patterns of gene expression applied to the test set. The sensitivity and specificity of RNA biosignature in identifying children with bacterial infections was determined based on the test set results; a subgroup analysis was performed and limited to patients with bacteremia versus no bacterial infections.

Of 1,883 febrile infants with a median age of 37 days, RNA biosignatures were measured in 279 randomly selected infants (89 with bacterial infections—including 32 with bacteremia and 15 with urinary tract infections—and 190 without bacterial infections) and 19 afebrile healthy infants. Sixty-six classifier genes were identified that distinguished infants with and without bacterial infections in the test set with a sensitivity of 87% (95% CI, 73%–95%) and specificity of 89% (95% CI, 81%–93%). Ten classifier genes distinguished infants with bacteremia from those without bacterial infections in the test set (sensitivity 94%; 95% CI, 70%–100%; specificity 95%; 95% CI, 88%–98%).

Three patients had blood cultures positive for viridans streptococci; the patterns of gene expression in these children were different from those of infants with bacteremia caused by other pathogens. The authors conclude that RNA biosignatures may be clinically useful to identify young febrile infants with bacterial infections.

Commentary by
Michelle Stevenson, MD, MS, FAAP, Pediatric Emergency Medicine, University of Louisville, Louisville, KY

Dr. Stevenson 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.

The prevalence of serious bacterial infection (SBI), defined as a pathogen in the urine, blood, or cerebral spinal fluid, among infants ≤60 days old with fever is approximately 8%;1 Partially due to a lack of robust clinical scoring systems to differentiate young infants with and without SBI, the approach to their evaluation and treatment in the emergency department setting varies widely at both the patient and hospital level.2 Even among the youngest infants (≤ 28 days of age) who are at highest risk of SBI, adherence in the emergency department to recommended guidelines for management of fever varies more than twofold across hospitals (39%–88%), and hospitalization patterns are inconsistent.3 In office practice, pediatric clinicians rely on clinical judgment to evaluate and manage young febrile infants (≤90 days of age), following guidelines in only 42% of fever episodes.4

The authors of the current study have succeeded in conducting an important and rigorous multicenter preliminary study of the potential clinical utility of RNA biosignatures to aid clinicians in the prediction of SBI and guide evaluation. Inclusion of infants with known viral infections adds strength to the analysis.

Although the confidence intervals around the point estimates of sensitivity and specificity of RNA biosignatures are somewhat wide due to the relative rarity of SBI, and further validation is required, the promise of this technology is enticing to the pediatric provider who seeks to rapidly identify and treat young infants with serious illness while avoiding invasive and costly testing and treatment.

Bottom Line: Specific host responses to infection (RNA biosignatures) have the potential to accurately distinguish febrile infants ≤60 days old with and without bacterial infections.

Editors’ Note

Signs of (future) times, perhaps: the simultaneous appearance of 2 studies utilizing RNA expression profiling to evaluate young febrile children. In the second study, investigators identified a 2-transcript RNA biosignature that could differentiate bacterial from viral infection.3 The findings of both of these preliminary studies, albeit tantalizing, require confirmation.

References
Investigators from multiple institutions conducted a secondary analysis of data from 13 original studies to estimate the risk of diarrhea among beachgoers. The original studies involved participants enrolled at 13 US marine or freshwater beaches in the Great Lakes region, Southern California, the Gulf Coast, the Eastern Seaboard, and Puerto Rico. Participants filled out a short survey when leaving the beach to report demographics and swim exposure. Interviewers called participants 10–14 days later to assess timing and details of any gastrointestinal illness symptoms. Water samples were also collected at each beach and tested for *Enterococcus*. The primary exposure variable was the level of water contact (nonswimmer, body immersion, head immersion, and swallowed water); the secondary exposure variable was *Enterococcus* levels in the water samples (above or below Environmental Protection Agency [EPA] regulatory guidelines). The primary outcome was incident diarrhea among participants, defined as 3 or more loose or watery stools in 24 hours within 10 days following the beach visit. Secondary outcomes included days of missed activities (work, school, or vacation) due to any gastrointestinal illness. Investigators estimated the proportion of cases of diarrhea and missed activities that would have been prevented if water exposure was removed (ie, population-attributable risk).

Among 102,903 participants in the original studies, 84,411 completed a follow-up survey and were included in analysis. The study population included 6,580 children aged 0–4 years, 10,822 children aged 5–10 years, and 65,854 individuals older than 10 years. Compared to nonswimmers, the incidence of diarrhea was significantly higher among those with body immersion (odds ratio [OR] 1.45), head immersion (OR 1.44), and swallowed water (OR 1.74). *Enterococcus* levels above EPA regulatory guidelines were also significantly associated with increased diarrhea incidence. It was estimated that 21% of diarrhea episodes and 9% of missed activities were due to water exposure.

The authors conclude that recreational water quality guidelines help safeguard public health.

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**Commentary by**

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Dr. Rosenthal 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.

Not surprisingly, the results of this study suggest that swallowing or swimming in recreational water with *Enterococcus* levels above EPA guidelines puts children at risk for diarrhea. Younger children (aged 0–4 and 5–10 years) had the most water exposure, had stronger associations between water quality and illness, and had the largest illness burden. However, exposure to water with elevated *Enterococcus* levels was associated with increased diarrhea risk in all age groups at beaches with known point sources of human fecal pollution but not at beaches without an identified pollution source. These new findings should be utilized in designing future recreational water quality guidelines to protect public health. It will be interesting to see if utilizing this new information will dramatically alter the risks in children of acquiring gastroenteritis from contaminated beaches.

**Bottom Line:** Exposure to contaminated recreational water was associated with a higher gastroenteritis risk and associated burden in the youngest children.

**Editors’ Note**

Enterococci are indicators of human fecal contamination from sewage or other waste potentially harboring enteric pathogens. As medical consultation was not associated with recreational water-associated diarrhea episodes, the contribution of pathogens such as *Campylobacter*, *Cryptosporidia*, and *Giardia* spp could not be assessed.

Visit www.aappublications.org/blog-posts to read a post about this article appearing this month.
Researchers from multiple institutions used quantitative molecular diagnostic methods to reassess causes of diarrhea in children who had participated in the Global Enteric Multicenter Study (GEMS). GEMS was designed to investigate moderate-to-severe diarrhea in children younger than 5 years in countries in Africa and Asia. As part of GEMS, traditional microbiologic techniques were used to identify pathogens in cases (children with diarrhea) and matched controls (children without diarrhea). For the current study, quantitative real-time PCR was used to test for 32 enteropathogens in stool samples from a subset of cases and matched controls. The attributable incidence of pathogen-associated diarrhea was calculated by comparing rates found in cases and controls. The attributable incidence of enteric pathogens identified using PCR was compared to that found in GEMS. Using census data from countries in which study children resided, the overall pathogen-attributable burden of diarrhea, based on incidences determined with PCR versus in GEMS, were compared. Finally, rates of coinfection were determined.

Data were analyzed from 5,304 matched case-control pairs of stool specimens. The PCR-derived attributable incidence for most pathogens was higher than the original estimate in GEMS, particularly for adenovirus 40/41 (around 5 times higher), *Shigella* spp, enteroinvasive *Escherichia coli*, *Campylobacter jejuni* or *C. coli* (around 2 times higher), and heat-stable enterotoxin-producing *E. coli* (ST-ETEC; about 1.5 times higher). The 6 most attributable pathogens were *Shigella* spp, rotavirus, adenovirus 40/41, ST-ETEC, *Cryptosporidium* spp, and *Campylobacter* spp. These 6 pathogens accounted for 77.8% of all pathogen-attributable diarrhea. The pathogen-attributable diarrheal burden was 89.3% at the population level, compared with 51.5% in the GEMS study. Using PCR, 42.5% of 5,304 cases had one diarrhea-related pathogen detected, while 38.9% (2,063) had 2 or more. Mixed infections in children were most often associated with *Shigella* spp and rotavirus.

The authors conclude that the reanalysis of the causes of diarrhea in young children, using quantitative molecular diagnostic methods, substantially increased the attributable incidence of diarrhea and increased the estimated burden of pathogen-attributable diarrhea on a population level.

**Commentary by**

**Rebecca C. Brady, MD, FAAP**, Cincinnati Children’s Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH

Diarrheal disease is the second-leading cause of death in children under 5 years of age worldwide.1 The authors of the current study used quantitative real-time PCR to assess the incidence of diarrhea due to specific pathogens. *Shigella* spp were identified as the pathogens with the highest burden of disease. Only 10 to 100 *Shigella* organisms are required for person-to-person transmission via the fecal-oral route.2 Thus, the infectious dose is very low.

*Shigella* species are one of the most common causes of bloody diarrhea or dysentery in children.3 Often, the presence of blood in stools is used as an indication to test for *Shigella*.4 In this study with the use of quantitative molecular techniques, *Shigella* was also associated with watery diarrhea. The techniques used in this study are not currently used for clinical diagnostic testing. The results of this study suggest that many children with watery diarrhea have *Shigella* infection that cannot be detected by routine stool culture. Would there be a benefit to identifying children with watery diarrhea due to *Shigella* species and providing antibiotic treatment in order to prevent progression to more severe disease and decrease the risk of transmission to others?

Additional strategies to reduce the burden of diarrheal diseases in developing countries include advances in food and water safety, promotion of handwashing, and effective vaccines. The WHO has recommended that rotavirus vaccines be included in all national immunization programs.5 Developing an effective vaccine for *Shigella* that would cover the most commonly detected strains and be low cost is a global public health priority.6 Meanwhile, the use of cooked green bananas as a prebiotic may be a safe, simple, and low-cost adjunct to the management of childhood shigellosis. (See also AAP Grand Rounds, August 2009;22[2]:19–7.)

**Bottom Line:** *Shigella* species are an underappreciated cause of diarrhea in young children in Africa and Asia. Effective, low-cost vaccines and treatments targeted against *Shigella* and the other diarrheal pathogens would represent significant advances in decreasing deaths and disability among young children worldwide. Even a green banana may save the day!

**References**

Safety of MRI and Risks of Gadolinium Contrast During Pregnancy


Researchers from multiple institutions in Toronto investigated the long-term safety of fetal exposure to magnetic resonance imaging (MRI) alone and with the intravenous contrast agent gadolinium. For this population-based retrospective cohort study, the investigators reviewed health care databases to identify all births of more than 20 weeks in Ontario from 2003–2015. Women aged 16 to 50 years old were assigned to cohort 1 if they underwent MRI between the second and fourteenth weeks of pregnancy. Cohort 2 consisted of women who had MRI with gadolinium between the second week of pregnancy and 2 days before the index birth date. Outcomes for cohort 1 included stillbirth or neonatal death in the index neonate, or any diagnosis of neoplasm, vision or hearing loss, or congenital anomaly—up until age 4 years in the children. Outcomes for cohort 2 included stillbirths and neonatal deaths and nephrogenic systemic fibrosis (NSF)-like outcome, because gadolinium may potentially increase the risk of NSF. In addition, a broader outcome of any rheumatologic, inflammatory, or infiltrative skin condition was assessed in cohort 2. Data on outcomes were abstracted from multiple Canadian and Ontario-specific health databases. Data on these outcomes were also abstracted for the cohort of women unexposed to MRI during pregnancy. The risk of outcomes (relative risk [RR] or hazard ratio [HR]) for cohorts 1 and 2 were compared to that of the unexposed cohort after adjusting for confounding variables.

More than 1.4 million deliveries were included in the final analysis, with an MRI rate of 3.97 per 1,000 pregnancies. In cohort 1, the risk of stillbirth or death was not significantly higher than in the unexposed cohort (RR 1.68; 95% CI, 0.97–2.90). There were also no significant differences between cohort 1 and unexposed women for the other outcomes. For cohort 2, there was no increased risk for the NSF-like outcome, but there was a significantly increased risk for the broader category of any rheumatologic, inflammatory, or infiltrative skin condition (HR 1.36; 95% CI, 1.09–1.69). There was also a significant increase in stillbirth or neonatal death for those in cohort 2 compared to the unexposed cohort (RR 3.70; 95% CI, 1.55–8.85).

The authors conclude that MRI during the first trimester of pregnancy was not associated with increased risk of harm to the fetus or in early childhood. However, gadolinium MRI increased the risk of stillbirth, neonatal death, and adverse outcomes in childhood.

Commentary by
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Deciding on any medical intervention involves balancing risks and benefits. Pregnancy adds a level of complexity, because of risks and benefits to both mother and fetus. The benefits of detecting a variety of medically significant issues for both mother (eg, placenta previa) and fetus (eg, congenital heart disease, diaphragmatic hernia, urinary tract obstruction, spina bifida) are clear, since they directly change pregnancy and delivery management. Fetal MRI during the second and third trimesters is thought to be safe for both mother and fetus; however, data on the safety of first trimester MRI and gadolinium contrast are limited. Gadolinium has been associated with NSF almost exclusively in patients with kidney disease, but its safety during pregnancy has not been systematically evaluated. The current investigators were able to take advantage of the public health system in Ontario, Canada, to study a very large number of pregnancies and outcomes in resulting children through age 4 years. As described previously, they found that first trimester MRI was not associated with adverse outcomes, while gadolinium exposure was.

Overall, the results are sound. Surprisingly, the authors did not highlight the apparent increased risk of stillbirth in the gadolinium-exposed pregnancies, nor did they discuss potential mechanisms. Although sophisticated statistical techniques were used to minimize confounding, the potential for residual confounding (due to maternal conditions requiring contrast MRI that are also associated with adverse outcomes in children) remains. Unfortunately, the indications for MRI evaluation were not available for the analysis; therefore, the results should be interpreted with some caution.

Nonetheless, the study highlights the benefit of large, high-quality studies to determine the risk of rare adverse outcomes associated with common medical interventions. The results of the study support the current recommendation to avoid the use of gadolinium contrast during pregnancy.

Bottom Line: Exposure to MRI during the first trimester of pregnancy did not appear to harm the fetus. Gadolinium contrast at any time during pregnancy was associated with adverse outcomes.

References

Visit www.aappublications.org/blog-posts to read a post about this article appearing this month.
Liquid Medication Dosing Errors


Researchers from multiple institutions conducted a study to assess the effects of misalignment between units of measurement on drug labels and dosing tools and specific types of dosing tools, on liquid medication dosing errors. As part of the SAFE Rx for Kids study, a randomized controlled experiment was carried out at 3 urban pediatric clinics located in New York City, Atlanta, and Stanford, CA. Participants were parents of children <8 years old who were randomized to 1 of 5 study groups with different pairings of units on medication bottle labels and dosing devices. Study groups had varying levels of concordance between medication bottle dosing units (eg, mL) and dosing tool units. Using standard medication bottles filled to the same level, caregivers measured out 3 doses of medicine each at 2.5 mL, 5 mL, and 7.5 mL using, in random order, 1 cup (with incremental markings) and 2 dosing syringes (0.2 mL or 0.5 mL incremental markings). The primary outcome was dosing error, defined as >20% difference in labeled and measured dose. The association between various variables (eg, dosing tool, concordance between dosing tool and medication bottle units) and dosing errors was assessed.

A total of 2,100 parents were enrolled, and 2,099 completed the study. Overall, 84.4% of parents made at least one dosing error. Parents in group 5, in which medication bottle dosing was given in “teaspoon” units only, made significantly more dosing errors than parents in the other groups (odds ratio [OR] 1.2; 95% CI, 1.01–1.4). Dosing errors were also significantly more common when cups were used for measuring doses than when doses were measured with syringes (OR = 4.6; 95% CI, 4.2–5.1); this was particularly true when measuring the 2.5 mL dose. The rate of dosing errors using either of the 2 dosing syringes was not significantly different.

The authors conclude that recommending dosing syringes rather than cups might result in fewer dosing errors by parents of young children.

Commentary by

Mike Dubik, MD, FAAP, Sleep Medicine Associates, Manchester, CT

Dr. Dubik 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.

Concern for the proper dosing of liquid medications is certainly not new. In 1878, the American Medical Association (AMA) adopted the International Metric System and in 1903 officially defined a standard teaspoon as 5 mL, yet the challenges of accurate measurement continue and are often overlooked.1–3 Many have argued for abandoning English liquid measures. However, many adults in the United States are not comfortable with the metric system.4 Even with a properly labeled syringe or cup included with the medication, giving teaspoons as an option runs the risk of using one from the home kitchen.5 Nevertheless, in 2015, the AAP recommended a move away from using the terms teaspoon and tablespoons in favor of milliliters.6 Pictograms and tool size might make the process even better. However, the results of this study make clear the overall superiority of syringes over cups and milliliters over teaspoons.

Bottom Line: Use of oral syringes, and avoidance of teaspoons, have the potential to significantly reduce errors of dosing liquid medication.

References


Visit www.aappublications.org/blog-posts to read a post about this article appearing this month.
Unintentional Marijuana Ingestions in Children


Investigators from multiple institutions determined (1) the rate of visits at a Colorado children’s hospital for unintentional pediatric marijuana exposures and (2) the number of calls received by a regional poison center (RPC) in Colorado for marijuana exposure before and after recreational marijuana was legalized in Colorado in January 2014. Hospital visits were included if they involved patients 0–9 years old who were evaluated in the hospital’s emergency department, urgent care, or inpatient units for a single-substance marijuana exposure from 2009–2015. Visits were identified using an electronic medical record search for patients with either a positive urine drug screen for tetrahydrocannabinol (THC) or ICD-9 or ICD-10 codes for cannabis abuse or poisoning. Data collected on hospital visits included demographics, source and dose of marijuana exposure, and hospital disposition. RPC calls were included if they involved marijuana exposure in a child 0–9 years old from 2009–2015. RPC data included demographics, location of call, route of exposure, and disposition. Investigators compared the average rate of hospital visits in the 2 years prior to legalization (2012–2013) to the 2 years after legalization (2014–2015). They also estimated the number of hospital visits and RPC calls over time for marijuana exposure in Colorado and the United States by using census data.

There were 62 hospital visits and 163 RPC calls included in analysis. The median age of hospital and RPC cases was 2.4 and 2 years, respectively. Among hospital visits, 36% required hospitalization. The source of the marijuana was most frequently a parent or grandparent, and the marijuana product involved was most often an infused edible product (eg, brownies). Among RPC calls, 60% originated from a health care facility. Ingestion was the most common route of exposure, and 74% had no or minor effects. There was one reported death in an 11-month-old patient who presented to the hospital unresponsive, had a urine drug screen positive for THC, and a final diagnosis after autopsy of myocarditis.

The investigators concluded that there has been an increase in unintentional pediatric exposures to marijuana after legalization of recreational marijuana in Colorado, and edible marijuana products continue to be a significant source of these exposures.

Commentary by

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Dr. Bratton 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.

Many Americans use marijuana at some point in their lives as a recreational drug, and acute toxicity is low. Some medical indications (such as anorexia from cancer and chemotherapy and treatment of agitation with dementia, Tourette’s, and post-traumatic stress disorder) have been reported, although no randomized clinical trials have confirmed efficacy of medical marijuana use.

Currently, 4 states (CO, WA, AK, and OR) and Washington, DC, have legalized marijuana for recreational use. Several states, including California, passed marijuana legalization in the November 2016 general election with regulation and taxing similar to alcohol. Increased tax revenue and decreased law enforcement and penal system costs are expected. Twenty-three states allow medical use of marijuana, and a handful have decriminalized recreational marijuana use.

The current study from Colorado (where documented sales exceeded $5.5 million the first year of legalization) demonstrated that both calls to the RPC and intoxicated children ages 0–9 years presenting for care in emergency departments or hospitals increased after legalization of recreational marijuana, despite regulations intended to prevent unintended pediatric exposures. Measures such as child-resistant packaging, warning labels, and educational efforts were not sufficient to protect young children from unintended ingestions. Of note, marijuana is available in edible packaging that resembles candy and cookies, which is attractive to young children.

The AAP opposes marijuana legalization for recreational use; however, the danger from marijuana appears relatively small compared to alcohol. The Centers for Disease Control and Prevention reports that excessive alcohol consumption is responsible for over 4,300 annual deaths among underage youth, and annual societal costs exceed $24 billion. People ages 12–20 years consume just over 10% of consumed alcohol in the United States, and over 90% is consumed in binge drinking.

Bottom Line: Edible marijuana products are a significant source of pediatric exposures. More effective methods to keep marijuana away from infants and children are needed when access is increased by legalization. (See related article AAP Grand Rounds, December 2015;34(7):72).

References
Environmental Exposures and Asthma


Investigators from multiple institutions studied the effect of the environment on asthma among 2 distinctive US farming populations—the Amish of Indiana and the Hutterites of South Dakota. These 2 populations were chosen because the prevalence of asthma in each is strikingly different (5% in Amish and 21% in Hutterites) despite having similar lifestyles with respect to most of the factors known to influence the risk of asthma (eg, large sibship size, minimal exposure to tobacco smoke and air pollution, long durations of breastfeeding) and similar genetic ancestry (both populations originated in Europe and have remained reproductively isolated since immigrating to the United States). One important difference between the 2 populations is that the Amish practice traditional farming (eg, single-family dairy farms and use of horses for fieldwork) and the Hutterites live on large, highly industrialized communal farms.

Amish children aged 7–14 years were eligible. Hutterite children were age- and gender-matched to the enrolled Amish children. Whole blood was collected from all participants to measure serum IgE and cytokine levels. Investigators also extracted DNA to assess ancestry by performing genotyping and comparing allele frequencies with European populations included in the Human Genome Diversity Project. Dust was collected in 10 Amish and 10 Hutterite homes and analyzed for endotoxin levels. Extract from Amish or Hutterite dust was then instilled intranasally every 2–3 days for 7 days in wild-type mice and mice deficient in proteins (MyD88 and Trif) involved in multiple innate immunity signaling pathways. Airway inflammation in mice was measured by assessing airway hyperresponsiveness and bronchoalveolar lavage (BAL) eosinophilia. The investigators compared the differences in distributions of IgE and cytokine levels between Amish and Hutterite children as well as differences in airway inflammation in mice exposed to Amish and Hutterite dust extract.

There were 30 Amish and 30 Hutterite children enrolled. None of the Amish children had asthma, and 20% of the Hutterite children did. In ancestry analysis, Amish and Hutterite children were genetically similar compared with other European populations.

Serum IgE and cytokine levels were significantly lower in Amish children compared to Hutterite children. Mean endotoxin levels were significantly higher in Amish versus Hutterite homes. When Hutterite dust extract was administered to wild-type mice, airway inflammation was observed. When Amish dust extract was administered, airway inflammation was suppressed. This protection was lost when Amish dust extract was applied to mice lacking the innate immunity proteins MyD88 and Trif.

The investigators conclude that the Amish farm dust is protective against asthma through stimulation of innate immunity.

Commentary by
Carrie Phillips, MD, FAAP, Oregon Health and Science University, Portland, OR

Asthma is increasingly common, affecting 6.3 million US children with an estimated prevalence of 8.6%.1 Reasons for the increasing prevalence of asthma are incompletely understood, but many attribute this to modern lifestyles and exposures. The hygiene hypothesis argues that a protective influence from microbial exposures early in life reduces the development of allergy and asthma. In support of this, children raised with traditional farming practices in close proximity to animals seem to be protected against asthma.2

The current investigators cleverly studied 2 genetically similar groups, the Amish and Hutterites, who differ notably in their farming practices. The authors confirmed disparate rates of asthma in the 2 populations and sought to understand if this difference could be explained by a protective effect of microbial exposures in the Amish children. They found that the Amish and Hutterite children had marked differences in the types, numbers, and function of innate immune cells, particularly when exposed to the endotoxin-rich environment of Amish dust. The authors strengthened their case by demonstrating that intranasal instillation of dust extracted from Amish, but not Hutterite, homes into mice resulted in reduced eosinophilia and airway reactivity. There are several limitations to the study. Since children <6 years old were not included, potentially critical windows of immune development were not studied. Furthermore, house dust was pooled from the homes sampled. In an accompanying editorial, the additional possibility of protection through epigenetics instead of direct, ongoing exposure to an endotoxin-rich environment was raised.3

Until very recently, we viewed humans as sterile creatures susceptible to pathogens. Microbiome studies and epigenetics, though still relatively nascent fields, have turned dogma on its ear. The expression of nature may well be dependent on nurture.

Bottom Line: Protection from asthma may be conferred by traditional farming practices and exposure to a distinct, rich microbiome that engage and shape innate immunity.

References
Assessment of Sacral Dimples in Neonates


Researchers from the University of North Carolina and North Carolina Children’s Hospital performed a retrospective chart review of infants ≤7 days old who underwent screening spinal ultrasonography (USG) because of the finding of sacral dimple on physical examination. For the study, newborns who underwent USG because of a sacral dimple over a 6-year period at North Carolina Children’s Hospital were identified, and data on physical examination findings abstracted from medical records. Sacral dimples were defined as simple if there was a single midline lesion <5 mm in diameter and <25 mm from the anus. Other classifications included deep and large (>5 mm) sacral dimples. Data on other cutaneous findings and/or congenital anomalies were also abstracted. Study outcomes included USG findings (normal vs abnormal) and further imaging with MRI and/or neurosurgical intervention.

Data were analyzed on 151 newborns; average age at the time of USG was 1.77 days. Physical examination findings that prompted a spinal ultrasound included isolated deep sacral dimple (34%); deep sacral dimple in association with other cutaneous findings, including hypertrichosis, duplicated gluteal cleft, or hemangioma (3%); a simple dimple in addition to other cutaneous findings, including hypertrichosis (13%), duplicated gluteal cleft (5%), hemangioma (1%), or skin tag (4%); multiple sacral dimples (12%); large sacral dimple (2%); dimple located >2.5 cm from the anus (1%); and “other” (9%). Forty-eight infants (32%) had a simple sacral dimple without other cutaneous findings documented. The majority (80%) of study infants had normal spinal USG. Within this group of 120 infants with normal spinal USG, 17 (11%) had an incidental finding of a filar cyst on USG. Of the 31 infants (20%) with abnormal spinal ultrasound findings, 20 went on to have a spinal MRI performed. Seven infants (5% of the total study population) had an abnormal spinal MRI. Neurosurgical consultation was documented for 13 (9%) infants who had an abnormal spinal ultrasound or MRI. Among the 151 infants who were screened, only 2 infants (1%) required surgical intervention; both of these infants had tethered cords and other congenital anomalies. None of the otherwise healthy infants in the study had spinal dysraphism related to a simple sacral dimple.

The authors conclude that nearly one-third of newborns who underwent spinal USG had simple sacral dimples with a low likelihood of spinal dysraphism.

Commentary by
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Dr. Mintzer 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.

Sacral dimple is a common finding on newborn physical examination.1 With increased availability of spinal ultrasonography, it is clear that the majority of simple sacral dimples are not associated with any underlying pathological findings.2 However, sacral dimples with additional cutaneous lesions and/or associated anomalies may portend significant underlying morbidity,3 potentially requiring neurosurgical consultation for operative correction, as in cases of tethered cord.

While spinal ultrasound is a procedure associated with minimal medical risk, the potential benefit is profound when important diagnoses are uncovered. Considering that normal findings are the most common result of spinal ultrasound, widespread ultrasonography for the evaluation of simple sacral dimples is not currently recommended.4 On the other hand, further evaluation is warranted when additional cutaneous and/or other congenital abnormalities are discovered on thorough physical examination.

Bottom Line: Ultrasonography in newborns with isolated, simple sacral dimples is unlikely to reveal occult spinal dysraphism.

(See related article AAP Grand Rounds, March 2010;23[3]:25.5)

References
Functional Gastrointestinal Disorders Are Common


Investigators from the University of North Carolina conducted a study to estimate the prevalence of functional gastrointestinal disorders (FGIDs) in US children and adolescents. They collected data via a nationwide Internet survey of mothers of children aged 4–18 years who were recruited from all 50 states, Puerto Rico, and Washington, DC. The women were part of a pool of adults who had joined online panels to answer various research surveys. To avoid selection bias, respondents were invited to complete a survey on “child health.” Each mother was asked to respond about only one of her children; those with more than one child were asked to select the son or daughter whose name was first alphabetically. The women responded to the Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III Version (Rome III), a validated questionnaire for child and adolescent FGIDs, and the PedsQL4.0 Generic Core Scale, a validated scale to measure quality of life in children ages 2 years and older. Parental GI symptoms were assessed with the Functional Bowel Module of the Rome III Questionnaire for adults; data on demographics and health status were also collected. The primary outcome was the presence of FGID, and specific diagnoses, in a study child or adolescent based on the Rome III criteria. Characteristics of children with and without FGID were compared.

Data were analyzed on 949 youth whose mothers completed the survey. Based on the Rome III questionnaire results, 23.1% of youth in the study met diagnostic criteria for at least one FGID. The most common FGIDs were functional constipation and abdominal migraine. Functional constipation was more prevalent among males than females ($P = .022$), but there were no significant differences between sexes for rates of other FGIDs. There were no statistically significant associations in rates of FGID among different racial or ethnic groups. A significantly lower quality of life was reported among children who qualified for an FGID, compared with those who did not ($P < .001$), manifesting as more school absences, more illness, and less desire for social interaction with friends. Children were also more likely to meet criteria for FGID if their parent also qualified for an FGID.

The researchers conclude that FGIDs are common among US children and adolescents. Longitudinal studies may help determine if these children and adolescents with FGIDs develop into adults with FGIDs.

Commentary by

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Dr. Rosenthal 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.

Any seasoned pediatrician can vouch for the findings of this study—FGIDs are common and influence school attendance and social interactions. The investigators of the current study attempt to avoid selection bias by administering a questionnaire on “child health” via the internet throughout the United States and Puerto Rico. The results of the study demonstrated that children and adolescents with FGID frequently develop functional constipation and abdominal migraine, and that there were no differences related to sex or ethnicity, except boys more frequently developed functional constipation. Children who developed FGID had parents who also experienced FGID. What is not known is whether children with FGID will become adults with FGID. Is FGID hereditary? What genes are involved? As noted in the accompanying editorial,1 there is an association of early stress and anxiety with FGID. Are FGIDs related to epigenetic effects on genes? What we need now is a better understanding of the etiology and improved therapy of FGID.

Bottom Line: FGIDs are common in children and adolescents. We do not know if FGIDs are hereditary nor the influence of the environment on their presentation.

Reference


Continuing Thoughts — Evidence eMended*

*emend — from the Latin (c. 1400), “to free from fault”; to improve by critical editing

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Come visit our blog, Evidence eMended, hosted by Bud Wiedermann, MD, MA, FAAP. Bud is a former member of our Editorial Board who now serves as Consulting Editor for New Media.

The goal of the Blog is to add value (and fun) for our readers by creating an easy way to enter the discussion of specific studies. Discuss the perceived weight of the evidence as applied to your practice situations and the patient populations you serve, and in the process learn more about critical appraisal.

Come talk with Bud as he leads the way.
Clinical Presentation of Leukemia


Investigators from multiple institutions conducted a systematic review to describe how leukemia presents in children. They searched MEDLINE and EMBASE databases, using the search terms “leukemia” and “diagnosis” to identify studies that included infants, children, and adolescents. Studies were considered acceptable quality if they defined leukemia according to bone marrow findings, defined at least 2 baseline characteristics of participants, involved a sample that comprised all consecutive cases over the study period, and used a standardized data collection form and/or objectively measured signs. Data on presenting signs and symptoms were then extracted from all included studies that met quality criteria, and pooled proportions of children presenting with each feature were calculated.

Of the 14,963 identified in the original search, 35 studies met eligibility criteria. Of these, 33 met quality criteria and were included in analysis. All included studies were retrospective cohorts, conducted in 21 countries, and described presenting signs and symptoms in a total of 3,084 children. In pooled analysis, the 5 most common presenting signs and symptoms were hepatosplenomegaly (64%), splenomegaly (61%), pallor (54%), fever (53%), and bruising (52%). Other common presenting signs and symptoms were recurrent infections (49%), fatigue (46%), limb pain (43%), hepatosplenomegaly (42%), bruising/petechiae (42%), lymphadenopathy (41%), bleeding tendency (38%), and rash (35%). Only 6% of children were asymptomatic on diagnosis.

The investigators conclude that because >50% of children with leukemia have palpable livers or spleens, children with unexplained illness should receive a focused examination that includes abdominal palpation.

Commentary by

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Dr. Hogan 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.

Leukemia comprises approximately 30% of childhood cancers, affecting an estimated 4,000 children annually.1 Innate risk factors for leukemia include syndromes of trisomy 21, monosomy 7, immunodeficiency, bone marrow failure, tumor suppressor gene, and DNA repair gene disorders.2–3 Associated exposure risk factors are chemotheray agents such as topoisomerase II inhibitors, anthracyclines, and alkylating agents for prior cancers.1–4

Signs and symptoms at leukemia presentation overlap with indicators of infection, allergy, autoimmune disease, or injury.1–4 Bone or joint pain, limping, adenopathy, fatigue, pallor, petechiae, excessive bruising, and hepatosplenomegaly with or without fever are common.1–4 Rarer symptoms (which include headache, nausea, vomiting, abdominal pain, weight loss, mucosal bleeding, shortness of breath, or skin lesions) need to be taken in context of symptom duration and severity in addition to a thorough physical examination.1–4 Initial investigations may include complete blood count with differential white blood cell count, comprehensive metabolic panel, sedimentation rate, lactate dehydrogenase, and uric acid.1 Although not diagnostic, a mediastinal mass detected on chest radiograph or hepatosplenomegaly on abdominal ultrasound necessitates referral to an oncologist.1–6

The authors of the current study followed a systematic, international search strategy with clear inclusion criteria of published retrospective cohort studies of presenting features of children with any type of leukemia. Their findings substantiate the importance of a careful history and examination of ill-appearing children to discover possible leukemia in a timely manner.

There are limitations of the systematic review, however, which include heterogeneity of terms used to describe signs and symptoms, sample sizes, income status of country, study periods, and leukemia subtypes. No controls were reported to determine diagnostic accuracy.1 Inherent in any systematic review is publication bias due to lack of unpublished or individual patient data, selection bias due to strict inclusion criteria, and volunteer bias due to missing information from nonparticipants who may have reported other features. Confounding factors contributing to signs and symptoms of leukemia, such as parental reporting, developmental age of child, physician records, comorbidities, and symptom duration and severity, were not addressed in the current study.1–3,6

Bottom Line: Health professionals need to consider leukemia in the differential diagnosis when an ill-appearing child presents with seemingly unrelated symptoms, such as bruising and fatigue, or pallor and limping. A thorough examination for skin lesions, adenopathy and hepatosplenomegaly is essential.

References
Outcomes of Outpatient Parenteral Antibiotic Therapy


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vestigators from The Royal Children’s Hospital Melbourne in Australia described the characteristics and outcomes of patients utilizing their outpatient parenteral antimicrobial therapy (OPAT) program. OPAT is delivered by pediatric-trained nurses through the institution’s hospital-in-the-home (HITH) program. Patients referred to HITH remain under the care of the referring team, with all decisions regarding treatment, review, and monitoring made by that team.

Investigators collected demographics, diagnosis, type of venous access (peripherally inserted central catheter [PICC], peripheral cannula, or other), and the appropriateness of antibiotic prescribing on OPAT patients over a 12-month period. Antibiotic appropriateness was assessed by a pediatric infectious disease physician and a general pediatrician, and included evaluation of antibiotic choice, dose, frequency, route, and duration (with each categorized as appropriate or inappropriate). The primary outcome measures were OPAT length of stay, adverse events (including line complications such as infections or antibiotic complications such as anaphylaxis), hospital readmissions, and the cost of OPAT per day. The estimated cost savings of OPAT compared to inpatient care was also calculated.

There were 228 patients who received OPAT during the study period. The median age of patients was 7.4 years (range 1 week to 21 years). The most common diagnoses were exacerbation of cystic fibrosis (17%), urinary tract infection (12%), and cellulitis (9%). The most frequent types of venous access were PICC (29%) and peripheral cannula (29%). Among OPAT antibiotic courses, 72% were prescribed appropriately. However, 6% of antibiotic choices were considered inappropriate (with all being considered too broad), and 26% were prescribed with an inappropriate dose, route, or duration.

The median OPAT length of stay was 7 days, corresponding to 3,084 days of OPAT treatment over the study period. The frequency of line complications was 11%, with an incidence of line infections of 0.54/1,000 line days. There were no antibiotic complications, and 4% of OPAT patients were readmitted to the hospital, with the majority due to new symptoms or inadequate clinical improvement. The cost savings of OPAT compared to inpatient care over the study period was $1.82 million.

The investigators conclude that OPAT appears to be safe, efficacious, and cost-effective.

Commentary by

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Dr. Winer 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.

The authors of the current study illustrated significant cost savings with minimal complications of a robust HITH program. This program featured daily visits to an ambulatory care center, antibiotic administration by the patient/parent, and/or daily nursing visits to provide care. This is a very different set of resources from those generally available in the United States.1 The study results provide a cogent argument for trialing similar programs here.

One potential limitation to the generalizability of the results of this study is the wide variability in the participants. The most common diagnoses seen were cystic fibrosis, urinary tract infection, and cellulitis. Among families with these 3 diagnoses, there are likely to be vastly different levels of medical knowledge and comfort with OPAT.

Almost one-fifth of participants in the study were discharged home directly from the emergency department. Interestingly, the majority of such patients had skin and soft-tissue infections. A randomized controlled trial is underway at the same medical center to determine the outcomes of this program.2 However, the protocol randomizes patients to home ceftriaxone versus inpatient flucloxacillin, which may indicate that it may not be generalizable to areas with high staphylococcal resistance to beta-lactams.

Bottom Line: Increasing resources for intravenous antibiotic treatment in the home may be a safe and effective way to both save cost and increase patient and family satisfaction.

References


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CME QUESTIONS

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CME OBJECTIVES

• Understand the utility of RNA biosignatures to distinguish febrile infants with bacterial infections.
• Describe the relationship between types of dosing tools and dosing errors.
• Understand the epidemiology of unintentional marijuana ingestions in children.

1. According to the article by Mahajan et al, which of the following statements is most accurate regarding RNA biosignatures and febrile infants?
   a. Infants with bacteremia due to viridans streptococcus had identical RNA biosignatures to infants with other types of bacteremia.
   b. RNA biosignatures have potential clinical utility in the evaluation of febrile infants aged 60 days or younger.
   c. The sensitivity of RNA biosignatures to detect bacterial infections was 68%.
   d. One classifier gene distinguished those infants with bacteremia from those without.
   e. Although highly sensitive, the specificity of RNA biosignatures was too low (62%) to be clinically useful.

2. Which of the following is the most accurate finding of the study by Arnold et al concerning acute gastroenteritis and recreational water?
   a. Younger age was associated with a decreased risk for diarrhea from recreational water exposure.
   b. The incidence of diarrhea was significantly higher among those with recreational water exposure.
   c. Enterococcus levels in the water were not associated with risk of diarrhea.
   d. 8% of diarrhea episodes were linked to recreational water exposure.
   e. 45% of missed activities were associated with recreational water exposure.

3. A 3-year-old previously healthy boy presents to a clinic in Bangladesh with a 2-day history of nonbloody diarrhea. His parents estimate that he has had approximately 12 watery stools in the last 24 hours. On physical examination, he is tired but not toxic in appearance. His temperature is 38°C, heart rate is 120 beats/min, respiratory rate is 24 breaths/min, and blood pressure is 110/70 mm Hg. Bowel sounds are hyperactive. His abdomen is soft and mildly tender to palpation without guarding. Which of the following is the most accurate finding of the study by Liu et al regarding the causes of diarrhea in children younger than 5 years in countries in Africa and Asia?
   a. Comparing the study using PCR techniques to the original Global Enteric Multicenter Study (GEMS), the attributable incidence of Campylobacter jejuni infection was similar.
   b. Mixed infection was most often associated with Campylobacter species and adenovirus 40/41.
   c. Norovirus was 1 of the 6 most commonly detected pathogens using PCR.
   d. Over 50% of children had 2 or more diarrheal-related pathogens detected by PCR.
   e. The pathogen-attributable diarrhea burden was 89.3% at the population level in the study that used PCR detection techniques.

4. Which of the following is the most accurate statement concerning the study by Yin et al on liquid medication errors and dosing tools?
   a. Use of a teaspoon-only label was associated with fewer errors compared to milliliter-only labels.
   b. There was no difference in errors between teaspoon-only labels compared to milliliter-only labels.
   c. There was a significant difference in errors between the 2 syringe types.
   d. Significantly more dosing errors occurred with cups than syringes.
   e. There was no significant difference in errors when comparing a cup versus syringe for dosing.

6. You are advising a young mother on appropriate medication and toxic substance storage to prevent toddler ingestions. According to the report by Wang et al from Colorado, which of the following is most accurate regarding legalized marijuana and unintentional exposures?
   a. Life threatening complications are common in toddlers.
   b. Exposure from edible products (eg, brownies) containing marijuana was the most common source.
   c. Vaporizers for marijuana drug delivery are the most common route of unintentional exposure.
   d. The rate of regional poison center (RPC) marijuana exposures in Colorado showed no increase after marijuana legalization.
   e. The median age of RPC marijuana exposures was 11 years.

7. Based on the study by Stein et al concerning innate immunity and asthma risk, which of the following is the most accurate conclusion?
   a. Serum IgE levels were significantly lower in Hutterite children.
   b. Serum cytokine levels were significantly higher in Amish children.
   c. Amish house dust provided protection against asthma through stimulation of innate immunity.
   d. Significant genetic differences between Amish and Hutterite children account for the difference in asthma risk.
   e. Median endotoxin levels were significantly higher in Hutterite homes.

8. Following an uncomplicated pregnancy, a full-term boy is delivered via routine spontaneous vaginal delivery to a healthy 28-year-old mother. A shallow sacral dimple located approximately 2.0 cm from the anus without other cutaneous findings is noted on newborn examination. There were no findings on prenatal ultrasonography and no family history of any children with congenital disorders. Based on the article by Wilson et al, which of the following represents the best next step in management?
   a. Spinal ultrasound.
   b. Spinal MRI.
   c. Routine observation.
   d. Spinal plain films.
   e. Neurosurgical consultation.

9. The mother of a 9-year-old boy is in your office because the child is constipated. He has previously been diagnosed with abdominal migraines and has intermittent episodes of abdominal pain. The mother wants to know if these disorders are related. Which would be the most appropriate response based on the study by Lewis et al?
   a. FGIDs occur in less than 10% of children.
   b. Abdominal migraine and functional constipation are the most common FGIDs.
   c. A parent with FGID is not associated with their child having FGID.
   d. Functional constipation in children is equally present in boys and girls.
   e. FGIDs are more common in Caucasians.

10. A 2-year-old boy presents to the clinic with recent onset of limping, fever, and decreased appetite. Examination reveals pallor, abdominal distention, and splenomegaly. Based on the study by Clarke et al, which of the following is the most accurate statement concerning presenting features of leukemia?
    a. 85% of children with leukemia present with hepatosplenomegaly.
    b. Fever is the only common (>50%) presenting symptom or sign of leukemia.
    c. Hepatomegaly or splenomegaly occurs in >60% of patients.
    d. Fatigue is a presenting symptom in less than one quarter of patients.
    e. Lymphadenopathy is the most frequent presenting symptom or sign of leukemia.

11. Which of the following is the most accurate finding or conclusion concerning outpatient antimicrobial therapy (OPAT) from the study by Hodgson et al?
    a. OPAT was considered cost-effective.
    b. The median OPAT length was 21 days.
    c. Venous access with a portacath was more frequent than with a peripherally inserted central catheter.
    d. 28% of antibiotic choices were considered inappropriate (too broad spectrum).
    e. The frequency of line complications was less than 2%.

Answers:

6. b
7. e
8. a
9. e
10. c
11. d