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Occult Spinal Dysraphism and Cutaneous Stigmata: When to Worry

Continuous Glucose Monitoring in Type 1 Diabetes

Fluid Overload in the PICU—Can It Be Avoided?

Review of COVID-19 in Children

American Academy of Pediatrics

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Table of Contents

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Occult Spinal Dysraphism and Cutaneous Stigmata: When to Worry

Source: *Choi SJ, Yoon HM, Hwang JS, et al. Incidence of occult spinal dysraphism among infants with cutaneous stigmata and proportion managed with neurosurgery: a systematic review and meta-analysis. JAMA Netw Open. 2020;3(7):e207221; doi:10.1001/jamanetworkopen.2020.7221*

Investigators from the University of Ulsan College of Medicine, Seoul, South Korea, conducted a meta-analysis to estimate the incidence of occult spinal dysraphism (OSD) and rate of neurosurgical intervention among neonates and infants with cutaneous stigmata. They reviewed published studies in a systematic manner and had the following requirements for inclusion: studies of neonates or infants with cutaneous lesions who underwent spinal sonography, studies that included ≥ 10 participants, and studies that provided an estimate of incidence of OSD. For the included studies, the types of cutaneous stigmata were classified as low risk (simple dimple or deviated gluteal fold), intermediate risk (vascular discoloration), or high risk (atypical dimple, hypertrichosis, pedunculated skin tag, fibroma pendulum, or midline mass). Cutaneous stigmata also were categorized as single or combined and typical or atypical. The primary outcomes were any abnormalities noted on spinal sonography and neurosurgical intervention. Secondary outcomes included definite abnormalities on ultrasound after excluding patients with either borderline findings (eg, borderline conus medullaris level, prominent filum terminale) or normal variations such as filar cyst and diagnosis of OSD based on spinal sonography and/or follow-up MRI. Data from all included studies on these outcomes were combined to provide pooled estimates. Rates of OSD in those with single vs combined cutaneous stigmata, simple vs atypical dimples, and studies of low- vs intermediate-risk stigmata were compared using regression analyses.

Data on 6,558 patients from 16 studies were included in the meta-analysis. The mean age at the time of spinal sonography ranged from 1.8 to 52.8 days but was not provided in 8 studies. The pooled incidence of any spinal sonography abnormality among neonates and infants with cutaneous stigmata was 5.3% (95% CI, 2.6%, 10.5%), the rate of definite abnormalities was 3.1% (95% CI, 1.6%, 6.0%), and the rate of OSD was 2.8% (95% CI, 2.4%, 3.8%). The rate of neurosurgical intervention among children diagnosed with OSD was 16.5% (95% CI, 11.5%, 23.1%), with an overall rate of neurosurgery of 0.6% (95% CI, 0.3%, 1.3%) for patients with any cutaneous stigmata. Incidence of OSD was significantly higher in those with combined stigmata vs a single lesion (10.5% and 2.3%, respectively, $P < .001$), and among children with atypical vs typical stigmata (8.8% and 0.6%, respectively, $P = .001$). There were no studies that included only patients with high-risk stigmata. Among studies that included those with intermediate-risk lesions, the incidence of OSD was 2.8%, which was not significantly higher than studies including only patients with low-risk stigmata (0.6%, $P = .36$).

The authors conclude that rates of OSD in newborns and infants with simple and typical cutaneous stigmata were low, but further evaluation of those with combined or atypical lesions may be warranted.

COMMENTARY BY

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Dr Chung 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.

Cutaneous stigmata are found in up to 7.2% of newborns, and of these, up to 8% may have associated OSD.[1,2] Early detection of tethered cord is important to prevent progressive, neurologic deterioration and long-term sequelae of tethered cord syndrome, including leg length discrepancy, foot asymmetry, neurogenic bladder, spasticity, and pain.[3] There is substantial evidence that cutaneous stigmata, including hemangiomas, dermal sinus tracts, sacral dimples, hair patches, deviated gluteal clefts, and rudimentary tails, may herald underlying OSD.[1,4] The old adage of "If you can see the base of the dimple, then it does not need to be imaged," may hold true only for "simple dimples" of < 5 mm with a midline placement within 2.5 cm of the anus.[2]

The authors of the current study note the overall rate of neurologic surgery for infants with cutaneous stigmata to be low at 0.6%. However, tethered cord syndrome may present as late as adulthood; studies included in the current review did not follow patients long-term.[3] Some but not all of the reviewed studies included spinal MRIs; therefore, it is possible that some OSD was missed on ultrasound.[3,5] Significant differences in rates of OSD were found among those with atypical vs simple dimples, and those with combined vs single stigmata. There was not a significant difference between the incidence of OSD among intermediate-risk versus low-risk stigmata, but the rate of neurologic surgery was higher in the former group.

Bottom Line: Atypical dimples and combined cutaneous stigmata are associated with higher rates of OSD than simple dimples and single stigmata, respectively.

EDITOR'S NOTE

Although the rates of OSD were low for those with a single, simple dimple, they were not zero. Thus, the conundrum for proper management of such newborns remains unresolved.

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Continuous Glucose Monitoring in Type 1 Diabetes

***Source**: Laffel LM, L Kanapka LG, Beck RW, et al. Effect of continuous glucose monitoring on glycemic control in adolescents and young adults with type 1 diabetes: a randomized clinical trial. JAMA. 2020;323(23):2388-2396; doi: 10.1001/jama.2020.6940*

Investigators from multiple institutions conducted a randomized controlled trial assessing the effect of continuous glucose monitoring (CGM) on glycemic control in adolescents and young adults with type 1 diabetes. Participants were 14-24 years old with a duration of diabetes of at least 1 year who had baseline hemoglobin A1c (HbA1c) levels ≥ 7.5% and < 11.0%. At enrollment, study participants were randomized to use CGM or continue with their regular finger stick blood glucose monitoring (BGM). The CGM system included a disposable sensor inserted under the skin that transmitted interstitial glucose levels every 5 minutes to a receiver or smartphone app; twice-daily finger stick glucose levels were required to calibrate the system.

Participants were enrolled in the study for 26 weeks. The primary outcome was change in HbA1c level between baseline and week 26. Differences between groups were assessed using longitudinal linear regression. Secondary outcomes included change in HbA1c at 13 weeks and achieving a HbA1c level in the target range (< 7.5% for those < 19 years old and < 7.0% for those ≥ 19 years old) at 26 weeks. Those in the BGM group wore a CGM device during weeks 24-26 (glucose levels were not provided to the participant). Various glycemic control metrics, including mean glucose, time in the target glucose range (70-180 mg/dL), and time with glucose > 180 mg/dL and < 70 mg/dL, for those in the BGM and CGM groups were compared using regression analyses.

A total of 153 participants were included in the study, with 74 randomized to CGM and 79 to the BGM group. The mean age of study participants was 17 years, and mean duration of diabetes was 9 years. Mean baseline HbA1c values were 8.9% for both groups. However, at 26 weeks, mean HbA1c values were 8.5% for those in the CGM group and 8.9% for those randomized to BGM (adjusted difference between groups -0.37%; 95% CI, -0.66%, -0.08%; P = .01). There was also a difference in change in HbA1c levels at 13 weeks between groups (mean values 8.4% and 8.9%, respectively, for the CGM and BGM groups; difference 0.50%; 95% CI, -0.79%, -0.21%; P < .001). At week 26, there was no difference between groups in percent of participants who met target HbA1c values (13% CGM, 10% BGM, P = .42). During CGM monitoring for both groups, those in the CGM group had significantly lower mean glucose levels (P = .003), longer time in the target glucose range (P < .001), and less time with glucose > 180 mg/dL (P = .007) or < 70 mg/dL (P = .02).

The authors conclude that use of CGM led to small but statistically significant improvements in glycemic control among adolescents and young adults with type 1 diabetes.

COMMENTARY BY

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Dr Fechner 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.

Adolescents with type 1 diabetes have the worst glucose control of all pediatric age groups.[1] This may be due to responsibility of diabetes management shifting from parent to adolescent and a lifestyle that is more unpredictable and spontaneous. CGM provides the opportunity to dose insulin for glucose values and carbohydrate intake in response to a trend in glucose readings vs reacting to a high or low glucose level obtained by a finger stick at one time point. For example, a glucose of 100 mg/dL can mean: (*a*) glucose is dropping 2 mg/dl/minute; (*b*) glucose is increasing 2 mg/dL/minute; or (*c*) glucose is constant. An individual using BGM sees only the excellent value of 100 mg/dL. Thus, one might expect there to be improved diabetes control with CGM, as was found by the current investigators. However, HbA1c differences between the 2 groups could have been greater if individuals wore the CGM more consistently. Only 68% wore the CGM for more than 5 days/week at 26 weeks compared to 82% at 6 weeks. This decrease in adherence over time likely also is what happens in non-study patients. Those in the CGM group had significantly higher glucose monitoring satisfaction with the 2 finger sticks per day that were required to calibrate the CGM. The current CGM model does not require calibration, which should further improve glucose monitoring satisfaction.

The results of the current study support use of CGM in adolescents and young adults to improve glycemic control with, hopefully, fewer long-term complications. Barriers to widespread use of CGM include lack of or inadequate insurance coverage, patient needs and desires, and lack of an endocrinology workforce to implement.[2]

Bottom Line: Continuous glucose monitoring use in adolescents and young adults improves type 1 diabetes control, but the device needs to be worn consistently to be effective.

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Fluid Overload in the PICU—Can It Be Avoided?

Source: *Alobaidi R, Basu RK, DeCaen A, et al. Fluid accumulation in critically ill children. Crit Care Med. 2020;48(7):1034-1041; doi:10.1097/CCM.0000000000004376*

Investigators from the University of Alberta, Edmonton, Canada, and Children's Healthcare of Atlanta, GA, conducted a retrospective study to assess the association of fluid overload with adverse outcomes in critically ill children. Study participants were patients 1 month to 17 years old admitted to 1 of 3 pediatric ICUs (PICUs) in the province of Alberta, Canada, in 2015. Data on these children were abstracted from "eCritical Alberta," a bedside clinical information system used by the PICUs, and included age, weight, diagnoses, surgeries, laboratory data, use of mechanical ventilation, hourly fluid intake and output from all sources, and disposition (discharge from PICU or death). Severity of illness at PICU admission was classified using the pediatric index of mortality 3 (PIM3) score calculated for each participant. Fluid overload percentage (FO%) was determined daily during the first 10 days of the PICU stay for a study patient as (fluid intake – fluid output)/weight. Several measures of FO% were calculated, including daily cumulative FO% and peak FO% (maximal cumulative FO%, measured both continuously and categorically as >5%, >10%, >15%, and >20%).

The primary study outcome was PICU mortality. Secondary outcomes included major adverse kidney events (MAKE), a composite index that included death from any cause, need for renal replacement therapy or persistent serum creatinine that was >2-fold the value on admission, duration of mechanical ventilation, and length of PICU stay. Multivariate regression was used to assess the association between markers of fluid overload and these outcomes after controlling for confounders.

Data were analyzed on 1,017 children with a median age of 24 months; 42.4% were treated with mechanical ventilation, and 22.5% received vasoactive support. Peak FO% was >5% in 56.4% of study participants and >20% in 9.1%. A total of 32 children (3.1%) died during their PICU stay. After adjusting for confounders, PICU mortality was independently associated with peak FO% (P = .001); every 1% increase in FO% was associated with a 5% greater odds of death (odds ratio [OR] 1.05; 95% CI, 1.02, 1.09). The risk of PICU mortality in children with >20% peak FO% was almost 3-fold higher than in those with lower peak FO% (OR 2.97; 95% CI, 1.11, 7.97). There were 53 patients who developed MAKE. The risk of MAKE was 3-fold higher in children with peak FO% >15% than in those with less fluid overload (OR 3.11; 95% CI, 1.46, 6.65). Among survivors, peak FO% also was significantly associated with longer duration of mechanical ventilation and longer PICU stay.

The authors conclude that fluid overload in children admitted to a PICU was associated with an increased risk for mortality and morbidity.

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.

The current investigators carefully documented that virtually all pediatric patients admitted to a PICU gained fluid weight over the initial days of intensive care, and FO% >5 occurred in more than half of critically ill or injured infants and children. Additionally, the peak maximal FO% and prolonged duration of FO% were associated with longer receipt of mechanical ventilation, longer PICU stay, and greater mortality. Diagnosis of MAKE event and receipt of renal replacement therapy also were significantly associated with maximal peak FO%.

The authors assert that kidney injury and acute fluid overload are associated with increased odds of death. Fluid management in critical illness often requires resuscitation fluids due to either ongoing fluid losses (eg, gastrointestinal, bleeding) or capillary leak with fluids moving from the vascular space to the intracellular space resulting in tissue edema. Days of accumulating fluid overload increase lung interstitial fluid and impair gas exchange.[1] Management of multi-organ symptom dysfunction requires assessment of adequate cardiac output and renal perfusion to avoid development of multi-organ failure.[2]

Disease evolution and treatment timing impact risk for acute kidney injury or failure. For instance, children presenting with diarrhea and hemolysis consistent with evolving hemolytic uremic syndrome previously were routinely restricted to insensible fluid losses and urine output.[2,3] Recent studies, however, have demonstrated that more liberal fluid administration can decrease the rate of progression to renal failure and need for dialysis. (See *AAP Grand Rounds*.2016;35[5]:50.[2]) Severe fluid overload is a symptom of continuing capillary leak syndrome and a marker of continuing disease.[4] It is not clear that avoidance of severe fluid overload would improve PICU patient outcomes.

Bottom Line: Fluid overload in critically ill children is associated with considerable morbidity and mortality.

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Review of COVID-19 in Children

***Source**: Hoang A, Chorath K, Moreira A, et al. COVID-19 in 7780 pediatric patients: a systematic review [published online ahead of print June 9, 2020]. E Clinical Medicine, The Lancet. doi: 10.1016/j.eclinm.2020.100433 2589-5370*

Investigators from the University of Texas Health Sciences Center San Antonio and Texas Children's Hospital, Houston, conducted a systematic review to characterize the demographics, presenting symptoms, laboratory findings, and outcomes in children diagnosed with COVID-19 and identify specific presenting symptoms and laboratory findings in those who developed multisystem inflammatory syndrome in children (MIS-C). The authors used a systematic process to identify relevant studies for inclusion. Data from studies of children and young adults from 0 to 21 years old with COVID-19, confirmed by PCR testing, were extracted. Patients were classified as developing MIS-C based on the CDC definition. Presenting symptoms and initial laboratory results were compared in children with MIS-C to those in a group of matched controls. Differences between the group with MIS-C and controls were assessed with t-tests, rank sum, or Fisher's exact tests.

From a total of 1,142 studies reviewed, 319 articles met criteria for inclusion in the systematic review. The included studies were from 26 countries and published between January 24 and May 11, 2020. Data on 7,780 COVID-19–positive children were extracted. The mean age of study participants was 8.9 years, 55.6% were male, and 75.6% had been exposed to a family member with COVID-19. The most common symptoms reported were fever (59.1%), cough (55.9%), nasal congestion or rhinorrhea (20.0%), myalgia and/or fatigue (18.7%), sore throat (18.2%), and dyspnea (11.7%); 19.3% of COVID-19–positive children were asymptomatic. Laboratory findings were generally non-remarkable. Compared to normal ranges used by the authors, slight elevations were noted for D-dimer (mean 0.7 ± 0.1 mg/L) and C-reactive protein (mean 9.4 ± 0.5 mg/L). Patchy lesions were seen on chest x-ray (CXR) in 21.0% of patients, and 23.6% of patients had normal CXRs. Rates of complications were low, including mechanical ventilation (0.54% of patients), shock (0.24%), kidney failure (0.12%), and cardiac injury (0.10%). Seven children (0.09%) died, and 11 (0.14%) developed MIS-C. Compared to 14 control patients, those with MIS-C more often presented with dyspnea (72.7% vs 28.6%, $P = 0.04$), vomiting (45.5% vs 7.1%, $P = 0.02$), and diarrhea (45.5% vs 21.4%, $P = 0.02$). In addition, on complete blood count those with MIS-C had a lower proportion of lymphocytes (mean value 11.1% compared to 41.8% in controls, $P < 0.01$), higher mean lactate dehydrogenase (459 U/L and 217 U/L, respectively, $P < 0.01$), and higher D-dimer values (40.3 mg/L and 0.3 mg/L, $P < 0.01$) than control children.

The authors conclude that children with COVID-19 have an overall excellent prognosis.

COMMENTARY BY

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Dr Brady 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 current review adds new data on SARS-CoV-2 infection presentation, laboratory findings, and outcomes in children. Similar to the first systemic review (See *AAP Grand Rounds*. 2020;44[1]:5[1]), the major symptoms were fever and cough. Overall, children had a good prognosis. The present review included 11 children with MIS-C, a more severe manifestation.

In April 2020 the CDC initiated surveillance for severe COVID-19 disease in children and adolescents.[2] Several recent reports summarize the clinical and laboratory characteristics and management of MIS-C.[3] (See *AAP Grand Rounds*. 2020:44[3]:30.4) Almost all affected patients tested positive for SARS-CoV-2 infection by reverse transcription PCR and/or antibody testing. Most patients had involvement of at least 4 organ systems, including gastrointestinal, cardiovascular, hematologic, mucocutaneous, and respiratory. The majority received intensive care, IV immune globin, and glucocorticoids.

In addition to the direct impact of SARS-CoV-2 infection on children, the indirect impact of missed well child care visits and vaccinations has been seen.[5] Reminding parents to vaccinate their children against influenza and other vaccine-preventable diseases is especially important now. Influenza and SARS-CoV-2 likely will be co-circulating this winter. An ounce of prevention will be worth a pound of cure.

Bottom Line: Most children with COVID-19 have mild symptoms of fever and cough, but some develop MIS-C and require intensive care. Clinical and epidemiologic updates and recommendations appear frequently.

EDITOR'S NOTE

As with all new and emerging infectious diseases, the full spectrum of COVID-19–related MIS-C has yet to be revealed. The most severely affected patients have now been identified; those with less severe MIS-C await recognition and follow-up.

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Probiotics Decrease Morbidity and Mortality in Preemies

Source: *Morgan RL, Preidis GA, Kashyap PC, et al. Probiotics reduce mortality and morbidity in preterm, low birth weight infants: a systematic review and network meta-analysis of randomized trials [published online ahead of print June 24, 2020]. Gastroenterology. 2020;S0016-5085(20)34849-6. doi: 10.1053/j.gastro.2020.05.096*

Investigators from multiple institutions conducted a meta-analysis to assess the effectiveness of various single-strain and multi-strain probiotic formulations in preventing morbidity and mortality in preterm infants. Investigators used several databases (eg, Medline, Embase, Scopus) to identify randomized controlled trials through January 1, 2019 that featured single- or multiple-strain probiotics for prevention of morbidity and mortality in infants <37 weeks gestation and/or infants with a birth weight <2,500 grams. For each eligible study, reviewers extracted details of the intervention (eg, probiotics species and strains) and outcomes, particularly all-cause mortality, severe necrotizing enterocolitis (NEC, defined as stage II or greater based on Bell's criteria), number of days to reach full feeding, and duration of hospitalization. Investigators aggregated the data across included studies and assessed the effect of the intervention compared to placebo on each outcome.

There were 63 studies involving 15,712 infants included in the analysis. The median of the average birth weight was 1,204 g, and the median of the average gestational age was 30.1 weeks. The majority of studies assessed multiple-strain probiotic products.

Compared to placebo, combinations of *Lactobacillus* spp and *Bifidobacterium* spp reduced all-cause mortality (OR 0.56; 95% CI, 0.39, 0.80). Similarly, combinations of *Lactobacillus* spp and *Bifidobacterium* spp reduced severe NEC (OR 0.35; 95% CI, 0.20, 0.59); single-strain *Bifidobacterium animalis* subsp *lactis* also reduced severe NEC (OR 0.31; 95% CI, 0.13, 0.74). Combinations of *Lactobacillus* spp, *Bifidobacterium* spp, and *Saccharomyces boulardii* reduced the number of days to full feeding (mean reduction 3.30 days; 95% CI, 0.91, 5.91). Single-strain *Lactobacillus reuteri* or *Bifidobacterium animalis* subsp *lactis* reduced duration of hospitalization (mean reduction of 13 days; 95% CI, 3.29, 22.71).

The authors conclude there is high-quality evidence that several single- or multiple-strain probiotics reduce morbidity or mortality in preterm infants.

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.

The human gut is a complex ecosystem in which microbiota, nutrients, and host cells interact extensively, a process crucial for intestinal homeostasis. The various bacterial communities that make up the intestinal microbiota have many functions, including metabolic, barrier, and trophic activities. Hence, any dysbiosis could have negative consequences in terms of health; many diseases have been linked to impairment of the gut microbiota, including inflammatory bowel disease, irritable bowel syndrome, and celiac disease.[1] The close relationships between gut microbiota, health, and disease have led to great interest in using probiotics to positively modulate the gut microbiota to prevent or treat some diseases, such as NEC. Probiotic administration may have great potential in terms of health that justifies more research.

Probiotics are defined as live bacteria that, when administered in adequate numbers, confer health benefits.[2] When choosing strain(s) to give to infants, assurance of the quality of the probiotic product provided is an important issue, because variations in the manufacturing process may alter the biological activities of the probiotic strains.[3] Further, differences in quality between batches of probiotics may occur. The product formulation (dry powder, tablets, ready-to-use liquid) and storage (room temperature vs refrigerated) are also critical in maintaining viability of probiotic bacteria. Government regulation of probiotics in the United States is complex. Depending on a probiotic product's intended use, the US Food and Drug Administration (FDA) could regulate it as a dietary supplement, a food ingredient, or a drug.[4] Many probiotics are sold as dietary supplements, which do not require FDA approval before they are marketed. If a probiotic is used as a drug for treatment of a disease or disorder, such as NEC, it must be proven safe and effective for its intended use through clinical trials and be approved by the FDA before it can be sold.

The results of the current study clearly demonstrate a benefit to the use of various strains of *Lactobacillus* spp, *Bifidobacterium* spp, and *Saccharomyces boulardi* probiotics in reducing morbidity and mortality, largely due to a decrease in severe NEC, in preterm infants. A major limitation of this study is that this was a systematic review and meta-analysis. In order to determine the correct dosing, efficacy, and safety of these probiotics in infants, randomized controlled trials are necessary.

Bottom Line: Combinations of one or more *Lactobacillus* spp and one or more *Bifidobacterium* spp appear superior to single- and other multiple-strain probiotics for prevention of severe NEC and improvement of outcomes of preterm, low-birthweight neonates.

EDITOR'S NOTE

Although probiotics may be considered safe, they can translocate through the gastrointestinal tract—especially one that lacks structural or mucosal integrity—and lead to bacteremia.[5] Treatment of premature infants with probiotics should be limited to the specific strains shown to be efficacious in this study and used with caution.

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Early Factor VIII Prophylaxis Prevents Joint Damage in Hemophilia

Source: *Warren BB, Thornhill D, Stein J, et al. Young adult outcomes of childhood prophylaxis for severe hemophilia A: results of the joint outcome continuation study. Blood Adv. 2020;4(11):2451-2459; doi: 10.1182/bloodadvances.2019001311*

Investigators from multiple institutions conducted a longitudinal, partially retrospective, observational study to assess outcomes among boys with severe hemophilia A (HA) who started factor VIII (FVIII) prophylaxis before age 2.5 years compared to those who started prophylaxis after age 6 years. This was a continuation study of the Joint Outcome Study (JOS), a randomized control trial of 65 boys with severe HA who were <2.5 years old to receive either FVIII prophylaxis every other day or episodic FVIII only at the time of joint hemorrhage. It was found that FVIII prophylaxis resulted in significantly less joint osteochondral damage by 6 years of age.[1] As a result, all JOS participants randomized to the original episodic arm were encouraged to adopt prophylaxis and participate in the current follow-up trial to determine the impact of early FVIII prophylaxis (started before age 2.5 years) vs late prophylaxis (started after age 6 years).

The primary outcome was joint osteochondral damage, as defined by an MRI performed at study exit. Secondary outcomes included: (*a*) joint abnormality on physical exam, as performed at baseline and study exit and scored using the Colorado Pediatric Joint Assessment Scale (with higher scores indicating more joint abnormality); (*b*) annualized bleed rate (ABR), calculated as the total number of bleeds logged by participants using study treatment logs over the study time period; and (*c*) quality of life (QOL), as determined by the Haemo-QOL questionnaire administered annually. Adherence to prophylaxis was determined using chart review and pharmacy records. Investigators used logistic regression to assess the effect of early vs delayed prophylaxis on study outcomes.

Among the 65 JOS participants, 33 were included in analysis of the follow-up trial (15 in the early prophylaxis arm and 18 in the delayed prophylaxis arm). Participants were followed for a median of 3.4 years. The mean age in which prophylaxis was started was 1.3 years old in the early prophylaxis arm and 7.6 years old in the delayed prophylaxis arm. Adherence did not differ by arm.

There were significantly higher odds of joint osteochondral damage in the delayed vs early prophylaxis arm (OR 6.3; 95% CI, 1.3, 29.9). In addition, the ABR was significantly higher in the delayed vs early prophylaxis arm (10.6 ± 6.6 vs 3.5 ± 2.1; P <.001). There were no significant differences in joint abnormality exam scores or QOL between arms.

The authors conclude that early prophylaxis with FVIII in boys with severe HA continued to provide protection against joint damage compared to delayed prophylaxis.

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/device.

Severe HA is an X-linked inherited, FVIII deficiency (FVIII activity <1%), with spontaneous mutations in > 30% of cases and an incidence of 1 in 5,000 births affecting all races and ethnicities.[2] Early initiation of FVIII prophylaxis, which decreases bleeding frequency and hemarthrosis by 6 years of age, is a current World Federation of Hemophilia recommendation.[3] Compared to previous studies, this study reports the longest follow-up of the largest cohort up to 18 years of age who received randomized prophylaxis. Compared to radiography, MRI used in this study demonstrated greater sensitivity for osteochondral changes.[4] Limitations include only 57% participation from the original cohort, potentially some missed bleeding episodes or FVIII doses, and continued use of an outdated physical examination scale.

Two findings in the current study deserve attention. A subset (24 of the 33 boys) within this cohort participated in sports that were categorized as low through high bleeding risk according to the National Hemophilia Foundation.[5] In boys playing moderate- to high-risk sports, no osteochondral damage was noted in 66% receiving early prophylaxis and 37.5% receiving delayed prophylaxis. This finding supports previous research encouraging athletics with appropriate preparticipation prophylaxis.[6]

Unfortunately, the results of the current study also demonstrate that despite current prophylaxis, joint damage is evident on MRI in many adolescents. Recent advances in FVIII products with extended half-life[7] and gene therapy trials[2] hope to provide consistent FVIII levels to prevent joint damage. Emicizumab and other therapies help to bypass, eradicate, or prevent FVIII inhibitors to render FVIII products more efficacious.[7]

Bottom Line: To reduce annual bleeding episodes and joint osteochondral damage through 18 years of age, start FVIII prophylaxis before 2 years of age in boys diagnosed with severe hemophilia A.

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Fretting the Other Femur: Risk Factors for Contralateral SCFE

Source: *Swarup I, Goodbody C, Goto R, et al. Risk factors for contralateral slipped capital femoral epiphysis: a meta-analysis of cohort and case-control studies. J Pediatr Orthop. 2020;40(6):e446-e453; doi:10.1097/BPO.0000000000001482*

Investigators from multiple institutions conducted a meta-analysis to assess the risk factors for contralateral slipped capital femoral epiphysis (cSCFE) given considerable orthopedic practice variation regarding prophylactic fixation of the contralateral hip in pediatric patients with SCFE. Investigators searched all studies published before July 2017 using Medline, Embase, and Cochrane databases. Only studies that specifically investigated risk factors for cSCFE were included; case reports, cases series, and review articles were excluded. Data extracted from included studies included demographic (eg, age, gender, BMI), clinical (eg, endocrine abnormalities), and radiographic (eg, posterior sloping angle [PSA]) risk factors for cSCFE. Investigators first summarized the findings of included articles then conducted a meta-analysis that aggregated data from the included studies using random-effects modeling.

There were 20 studies included in the analysis. Demographic risk factors were assessed in several studies, with most studies reporting a younger age as a risk factor for cSCFE. Among the studies that assessed gender, none found a significant difference in development of cSCFE by gender. The mean BMI in patients with and without cSCFE was 28 and 27, respectively. Regarding clinical risk factors, 3 studies assessed endocrine abnormalities and found that among those with an endocrine abnormality, a higher proportion had cSCFE (12%) than did not (2%). Among radiographic risk factors assessed, PSA was included in 6 studies and found to be significantly different in patients with and without cSCFE.

In the meta-analysis that aggregated data across all included studies, age and PSA were the only risk factors found to be significantly different between those with and without cSCFE. Age was significantly lower among those with (vs without) cSCFE (absolute mean difference of -0.9 years; 95% CI, -1.1, -0.6). PSA was significantly higher in those with (vs without) cSCFE (absolute mean difference 4.7 degrees; 95% CI, 3.3, 6.2).

The authors conclude that younger age and higher PSA are risk factors for cSCFE.

COMMENTARY BY

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Dr Hennrikus 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.

SCFE is the most common hip disorder in adolescents, occurring in about 10 per 100,000.[1] SCFE is defined as the posterior and inferior slippage of the proximal femoral epiphysis on the metaphysis through the growth plate.[2] All patients with suspected or confirmed diagnosis of SCFE need urgent pediatric orthopedic referral to determine definitive management, which generally consists of surgical stabilization with in situ screw fixation.[3] Timely and appropriate treatment of SCFE minimizes the long-term development of hip arthritis.[4]

About 25% of patients with SCFE will develop a subsequent SCFE of the contralateral hip.[5] Because of the risk of subsequent cSCFE, prophylactic fixation of an unaffected contralateral hip may also be performed. However, this practice is controversial because prophylactic fixation of the normal hip has risks such as avascular necrosis and peri-implant fracture.[6]

The current investigators attempt to define which patients are at "highest risk" for subsequent cSCFE and would benefit from prophylactic fixation.

The authors performed a comprehensive systematic review of all observational studies focusing on risk factors for subsequent cSCFE. Demographic risk factors examined included age, sex, weight, BMI, ethnicity, and urban/rural residence. Clinical risk factors examined included endocrine disease, duration of symptoms, slip stability (independent ambulation), and slip chronicity (symptoms for <3 weeks).

Overall, the meta-analysis showed that younger age (<13 years old) and higher PSA (>12 degrees) were predictive of subsequent cSCFE. The PSA is a simple radiographic measurement made on the frog lateral image utilizing a line along the femoral shaft and neck, a line in the plane of the physis, and a perpendicular line to the first line.[7]

Bottom Line: Younger patients with a high PSA of the unaffected hip are most likely to sustain a subsequent cSCFE and likely would benefit from prophylactic fixation of the unaffected hip. (See *AAP Grand Rounds.* 2019;41[2]:20.[8])

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Biomarkers of Mortality in Patients With Sickle Cell Disease

Source: *Nouraie M, Darbari DS, Rana S, et al. Tricuspid regurgitation velocity and other biomarkers of mortality in children, adolescents and young adults with sickle cell disease in the United States: the PUSH study. Am J Hematol. 2020;95(7):766-774; doi: 10.1002/ajh.25799*

Investigators from multiple institutions conducted a prospective study to identify risk factors for early death among youths and young adults with sickle cell disease (SCD). Participants were SCD patients, 3-20 years old, seen at 1 of 4 medical centers and enrolled between 2006 and 2010. At baseline, demographic and medical history data were collected, including information regarding previous stroke, history of transfusions, severe pain episodes, and a diagnosis of asthma. Blood samples were collected for determination of multiple tests, including serum ferritin levels and neutrophil count. Pulmonary function testing was done and an echocardiogram performed. The main hypothesis was that increased tricuspid regurgitation velocity (TRV) seen on echocardiogram, as a marker for increased systolic pulmonary pressure, would be a predictor of early death in SCD patients. Values for TRV and other variables were compared in SCD patients who died or were still alive at last follow-up using Fisher exact tests or t-tests.

A total of 510 youths were enrolled in the study, and follow-up data were available for 497. The median age of participants at baseline was 12 years; 10.6% had a history of stroke, and 24.1% had asthma. Follow-up information on survival was obtained in 497 participants. The median length of follow-up was 88 months (range 1-105 months). Ten patients (2.0%) died during the follow-up period. The mean age at death was 21 years. Cause of death was known for 7 participants and included stroke in 4, multi-organ failure in 1, parvovirus B19 infection in 1, and sudden death at home in 1. An elevated baseline TRV (defined as ≥2.7 m/sec) was found in 20.0% of those who died vs 4.6% of survivors (P = .012). Pulmonary function testing results also were associated with an increased risk of death; 71.4% of those who died had a forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio of < 0.80, compared to 18.8% of survivors (P <.001). Elevated serum ferritin (>2,000 µg/L) was found in 60.0% of participants who died and 7.8% of those who survived during the follow-up period (P < .001). A baseline absolute neutrophil count (ANC) ≥ 10 x 10^9 per L also was associated with an increased risk of death (P = .018). Medical history characteristics statistically associated with an increased risk of death included history of asthma, history of stroke, treatment in a chronic transfusion program, and ≥3 severe pain episodes in the year prior to enrollment.

The authors conclude that elevated TRV, serum ferritin and neutrophil counts, and low FEV1/FVC, may be biomarkers for increased risk of early death in SCD patients.

COMMENTARY BY

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Dr Doolittle 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.

In recent years, great strides have been made to improve the longevity of patients with SCD. Newborn screening, prophylactic penicillin, hydroxyurea, and immunizations have extended the average life expectancy of those with SCD from 14.3 years in the 1970s to more than 58 years in 2014.[1,2] The current investigators address a critical question: Who is at greatest risk of death? To answer this question, the investigators conducted a multi-faceted, longitudinal study. The study had a large cohort of 510 youths who were followed for more than >7 years, with only 13 dropouts. The evaluation was thorough, with easily obtainable biomarkers such as ANC levels as a sign of underlying infection and ferritin levels as a sign of iron overload from chronic transfusions. The investigators also performed echocardiograms to determine TRV and pulmonary function testing to measure FEV1/FVC ratios.

In general, the study findings affirm clinical suspicion. Sicker patients were more likely to die. How does this help us care for our patients? Importantly, the results of the current study call attention to the importance of easily obtainable biomarkers that physicians can follow more closely and intervene before a patient's status clinically deteriorates. Potentially, certain patients at the highest risk of death could be treated with bone marrow transplant or other more aggressive treatments.

There are several study weaknesses to consider. First, among the 10 patients who died, data about the cause of death were available in only 7. Second, while the risk factors were specific, they were not very sensitive. Third, these biomarkers were objective measures that indicated significant underlying disease. Many of those risk factors, such as transfusion dependence, are not easily reversible. Physicians can be cautious and proactive in providing standard of care and close monitoring, with referral of high-risk patients for newer therapies.

Bottom Line: Children with SCD and associated comorbidities, such as a history of asthma and stroke, elevated pulmonary artery systolic pressures, increased ANC and ferritin levels, and decreased FEV1/FVC ratios, may be at increased risk for early death. (See *AAP Grand Rounds.* 2019;41[5]:53.[3])

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Identifying the Hypertensive Adolescent

Source: *Wieniawski P, Werner B. Prediction of the hypertension risk in teenagers [published online ahead of print June 9, 2020]. Cardiol J. 2020. doi: 10.5603/CJ.a2020.0079*

Investigators from the Medical University of Warsaw, Poland, conducted a cross-sectional study to create a hypertension risk stratification model and algorithm to detect hypertension in adolescents. Eligible participants were middle and high school students aged 15-17 years from schools in and around Warsaw who never had been diagnosed or suspected of having hypertension previously. Participants completed a questionnaire regarding their family history and risk factors for cardiovascular disease. Blood pressure measurements were taken 3 times on at least 2 separate visits at least a week apart. Anthropometric measurements, including weight; height; BMI; and hip, arm, and abdominal circumference, also were obtained.

The primary outcome was hypertension, defined as systolic and/or diastolic blood pressure ≥95th percentile according to norms for gender, age, and/or height. Among those with hypertension after initial blood pressure measurement, 24-hour ambulatory blood pressure monitoring was performed for confirmation. Investigators used logistic regression to identify anthropometric and family history variables associated with hypertension, then developed a model including significant variables to predict the risk of hypertension. This model was tested by administering a questionnaire that included these variables to a separate sample of students to determine its sensitivity and specificity for estimating an individual as having a > 50% or > 75% risk of hypertension.

There were 690 student participants included in the initial sample, 5.8% (*N* = 40) of whom were found to have hypertension. Variables significantly associated with hypertension included a high BMI and having at least one parent who had hypertension. In the predictive model, height, weight, waist-to-hip circumference, and family history of hypertension were included. There were 108 participants who completed the predictive model questionnaire. The sensitivity and specificity of the predictive model for estimating a > 50% risk of hypertension were 91% and 97%, respectively; for estimating a >75% risk, the sensitivity and specificity were 54% and 100%, respectively.

The authors conclude that an algorithm including height, weight, waist-to-hip circumference, and family history of hypertension can predict hypertension in adolescents.

COMMENTARY BY

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Dr Sanchez-Kazi 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.

Hypertension in children is an increasing worldwide health problem (See *AAP Grand Rounds*. 2020;43[5];59[1].) There is increased risk of chronic kidney disease and cardiovascular health problems in adults who were hypertensive as children (See *AAP Grand Rounds*. 2019;41[6];63[2,3]), so identifying children who are at risk is important. In the current study, the authors proposed a risk stratification formula to identify adolescents who are at risk of developing hypertension using anthropometric measurements and family history. Multiple worldwide investigators have demonstrated in prospective, observational, and cross-sectional studies that increased weight, high waist-to-hip ratio, and elevated BMI raise the risk of hypertension significantly.[3,4] The risk of hypertension doubles if both parents have high blood pressure.[5]

The results of the current study strongly support previous findings that increased weight, elevated waist-to-hip ratio, and familial hypertension considerably affect the risk of hypertension in adolescents. The algorithm proposed by the present investigators will be helpful in identifying adolescents who need to be followed closely and to prevent unnecessary workups in other children who may have only transient elevated blood pressures. It would be useful if the authors would translate the formula into a scoring system to predict who likely will develop complications of hypertension in adulthood. This information can be used to reinforce the counseling given to every hypertensive adolescent.

The sensitivity of 54% in estimating > 75% risk of hypertension in this study is surprising. Were there errors in obtaining blood pressures in this age group? Or would it be more useful to add BMI in the calculation? It also is unclear why birth weight was not as predictive of hypertension as has been found in other published studies.[6] Is this a regional difference since the participants were from Poland? Will this stratification risk formula stand up when applied to adolescents in other countries?

Bottom Line: Weight, height, waist-to-hip ratio, and familial hypertension can predict the risk of hypertension in adolescents.

EDITOR'S NOTE

Gone are the days when "essential" or "primary" hypertension was the provenance of adults. Essential hypertension has, in fact, become the leading cause of hypertension and its adverse cardiovascular consequences in children > 10 years of age.[7]

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CME QUESTIONS

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CME OBJECTIVES

1. Understand the relationship between occult spinal dysraphism and cutaneous stigmata.
2. Describe the effect of continuous glucose monitoring on glycemic control.
3. Understand the clinical findings of COVID-19 and multisystem inflammatory syndrome in children..

1. You examine a newborn shortly after birth and identify 2 midline lumbar and sacral dimples that are 6 mm in size. Based on the current study by Choi et al concerning occult spinal dysraphism (OSD) among infants with cutaneous stigmata, which of the following statements is most accurate?

a. Atypical dimples when compared to simple dimples were associated with an increased risk of OSD.
b. Intermediate-risk stigmata when compared to low-risk stigmata were associated with a significantly higher risk of OSD.
c. A deviated gluteal fold was considered to be an intermediate-risk stigmata.
d. There was no difference in rates of OSD for single vs combined stigmata.
e. Spinal MRI is the preferred initial imaging mode for newborns with simple dimples.

2. A 17-year-old girl is seen in the office for follow-up of her type 1 diabetes. Her parents are concerned that her glycemic control has gotten worse the past 2 months. They ask if continuous glucose monitoring (CGM) would be a good option for her. Which of the following is the most accurate conclusion or finding of the study by Laffel et al concerning the effect of CGM compared to usual care using a blood glucose meter on glycemic control in adolescents and young adults with type 1 diabetes?

a. Statistically significant lower HbA1c at 26 weeks with CGM.
b. Decreased time in the target glucose range with CGM.
c. Significantly higher percentage of subjects who met target HbA1c levels with CGM.
d. No difference for time with glucose levels >180 mg/dL.
e. No difference for time with glucose levels <70 mg/dL.

3. A 6-month-old boy is admitted to the pediatric intensive care unit (PICU) with severe respiratory distress. Parents state he has had poor oral intake for the past day. He was tachycardic in the ED and received 2 normal saline fluid boluses. He is now intubated and on mechanical ventilation. Over the next 2 days he is noted to have increasing edema. Which of the following is the most accurate conclusion of the study by Alobaidi et al concerning fluid accumulation in critically ill children?

a. Duration of mechanical ventilation was not associated with peak fluid overload percentage (FO%).
b. Peak FO% was not associated with duration of PICU stay.
c. PICU mortality was independently associated with peak FO%.
d. The risk of a major adverse kidney event was no different in study subjects with peak FO% >15% compared to those with less fluid overload.
e. Peak FO% was >5% in 72% of study participants.

4. An 8-year-old boy is evaluated in the ED with fever, cough, and dyspnea. On examination, he has an oral temperature of 39°C, a respiratory rate of 28 breaths/min, and intercostal retractions. Oxygen saturation is 88% breathing room air. Scattered rhonchi are noted on examination. A chest radiograph reveals patchy infiltrates. A nasopharyngeal swab is positive for SARS-CoV-2, the virus responsible for COVID-19. His mother has been reading about potential severe manifestations of COVID-19, including multisystem inflammatory syndrome in children (MIS-C). Based on the systemic review by Hoang et al, which of the following is the most accurate statement about severe manifestations of COVID-19 in children?

a. About 5% of children died.
b. About 10% of children developed MIS-C.
c. Compared to control children, those with MIS-C had a higher proportion of lymphocytes on complete blood count.
d. Compared to control children, those with MIS-C less often presented with vomiting.
e. Compared to control children, those with MIS-C more often presented with dyspnea.

5. A 34-week premature newborn infant girl on day of life 2 is noted to have intermittent episodes of abdominal distension in the nursery. She is without fever, vomiting, or diarrhea. An abdominal x-ray is unremarkable. She is being breastfed. Based on the study by Morgan et al, which of the following actions is most appropriate?

a. Since the child is asymptomatic, no further evaluation or management is necessary.
b. Begin a probiotic containing *Lactobacillus* and *Bifidobacterium*.
c. She should be made NPO.
d. An oral antibiotic should be administered immediately.
e. A probiotic containing *Klebsiella* and *Lactobacillus* should be administered.

6. Based on the findings by Warren et al, by age 18 years boys with severe hemophilia A who received FVIII prophylaxis before 2.5 years of age compared to after 6 years of age demonstrated which of the following?

a. Greater bleeding frequency.
b. Higher quality of life scores.
c. Decreased joint osteochondral damage on MRI.
d. Lower incidence of FVIII inhibitor.
e. Reduced bleeding during sports participation.

7. An 11-year-old youth football player presents with a 3-week history of a left leg limp and radiographs demonstrating an early left SCFE and a normal right hip with a PSA (posterior sloping angle) of 16 degrees. Based on the study by Swarup et al concerning risk factors for a contralateral SCFE, which of the following is most accurate?

a. The patient could benefit from bilateral hip pinning.
b. The patient's age argues he should have only the right hip pinned.
c. The patient's right hip PSA argues he should have only the right hip pinned.
d. Only female patients need to have prophylactic pinning performed.
e. Prophylactic pinning is not indicated because the patient had symptoms for only 3 weeks.

8. The parents bring their 12-year-old boy with sickle cell disease for a routine well-child exam. The parents are concerned about the risk factors for an early death. Before responding in an empathic, thoughtful way, you recall the research by Nouraie and team concerning biomarkers of mortality in individuals with sickle cell disease. Which of the following is the most accurate finding or conclusion of the Nouraie study?

a. An elevated tricuspid regurgitation velocity was associated with increased risk of early death.
b. Participation in a chronic transfusion program was associated with a longer lifespan.
c. An absolute neutrophil count ≤1.0 x 10^9 per L was associated with increased death.
d. Ferritin levels were not associated with mortality.
e. It was impossible to draw any conclusions based on the small sample size and short duration of the study (median length of follow-up was <5 years).

9. A 15-year-old obese boy presents to clinic for his well-child check. Manual blood pressure was obtained twice, and his systolic and diastolic blood pressures were both at the 95th percentile for age, height, and gender. He is scheduled to return in 1 week to recheck his blood pressure. According to Wieniawski and colleagues, what information was included to determine the risk of hypertension in adolescents using their logistic regression model?

a. Weight, weight-to-height ratio, and body adiposity index.
b. Height, weight, weight-to-height ratio, and body mass index.
c. Weight, height, and parental history of hypertension.
d. Body mass index, body adiposity index, and weight-to-height ratio.
e. Height, weight, waist-to-hip circumference ratio, and parental history of hypertension.

Answers:
1. a 3. c 5. b 7. a 9. e
2. a 4. e 6. c 8. a