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Incidence of Concussion Among Youth Football Players


Investigators from the University of Washington and Seattle Children’s Research Institute conducted a prospective cohort study to determine the incidence of concussion, duration of concussion symptoms, and time to return to sport and school after concussion in American youth football participants. All parents of 5-14-year-old participants in a city youth football league during two 10-week seasons were invited to participate in the study. Enrolled parent and youth participants completed a baseline demographic survey that also queried the child’s history of prior concussion and mental health history (history of diagnosed depression, anxiety, and ADHD).

The primary outcome was confirmed football-related concussion. Potential concussions were identified by study-employed athletic trainers who attended all games during the 2 football seasons. Enrolled athletes with potential concussions were subsequently interviewed by the research team to assess mechanism of injury, name of clinician seen, and any diagnosis of concussion. An independent study physician then reviewed potential concussions as confirmed or unconfirmed. Youth participants with a confirmed concussion and mental health assessment completed weekly surveys regarding concussion symptoms, return to school, and return to sport. Symptom resolution was defined as ≤3 symptoms greater than pre-injury baseline using the Sport Concussion Assessment Tool-3.

Investigators calculated the incidence of confirmed football-related concussion by player-season. Multivariable logistic regression was used to assess the association of demographics, child history of concussion, and mental health diagnoses with the primary outcome. Kaplan-Meier curves were used to assess time to symptom resolution, return to sport, and return to school.

Of 2,466 parents with child participants in the youth football league, 863 agreed to participate. Of these, 133 were followed for 2 seasons, yielding a total of 996 player-seasons. There was a history of prior concussion in 13% and a diagnosis of depression, anxiety, or ADHD in 2%, 6%, and 11%, respectively.

There were 51 confirmed football-related concussions, yielding a per-season incidence of 5.1%. Participants with (vs without) a history of concussion had significantly increased odds of an incident concussion (odds ratio [OR], 2.2; 95% CI, 1.1–4.8), as did participants with (vs without) a history of depression (OR, 5.6; 95% CI, 1.7–18.8). Most (90%) with concussions returned to school by 9 days, to sport by 1 month, and had resolution of symptoms by 2 months.

The incidence of concussion in youth football participants was higher than previously reported.

**COMMENTARY BY**

**MIKE DUBIK, MD, FAAP, PORTSMOUTH, VA**

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.

There has been little research regarding concussions among elementary and middle school-aged children, so this study is most welcome. The current researchers found a higher incidence than others, but this is likely because of greater surveillance and perhaps more general awareness.

As has been noted previously, a history of prior concussion was a risk factor for concussion. Like previous studies, most concussions occurred during games; however, that is also when the study-employed athletic trainers were present. It is interesting to note that almost half of the concussions in the current study were from head-to-head impacts.

The search for a concussion biomarker has not borne any fruit, and the best predictor of protracted recovery from a concussion is the severity of early symptoms. (See AAP Grand Rounds. 2017;37[4]:46.) The most likely symptoms (among high school athletes) are headache, dizziness, difficulty concentrating, and sensitivity to light and noise; more vague complaints, like drowsiness, insomnia, and irritability, are also common. Of course, the younger the child, the less sophisticated is the ability to conceptualize and verbalize symptoms. The authors posit the interesting observation that when managing other sports injuries, time since injury is combined with symptoms and clinical examination in deciding the return activities, suggesting a similar strategy for concussions.

But perhaps the bigger issue, the “elephant in the room,” needs to be considered. Should physicians who care for children recommend against children playing football, as others have suggested?

**Bottom Line:** Youth football concussions, although relatively uncommon, are a controversial concern, and their long-term consequences remain undefined.

**References**

Investigators from multiple institutions in the United Kingdom conducted a randomized trial to compare the efficacy and costs of using continuous subcutaneous insulin infusion (CSII) or multiple daily injection (MDI) insulin regimens for the treatment of children with newly diagnosed type 1 diabetes. Children 7 months to 15 years old seen at 1 of 15 centers in England and Wales with a new diagnosis of type 1 diabetes were eligible for the study. At enrollment, participants were randomized to CSII or MDI. Insulin treatment was started within 14 days of diagnosis and consisted of insulin aspart for children randomized to CSII, and short-acting insulin analogue insulin aspart and long-acting insulin analogue, either insulin glargine or detemir, for those randomized to MDI. At baseline, hemoglobin A1c (HbA1c) levels were measured. Patients were enrolled in the study for 12 months. During this time, insulin doses were adjusted using standard protocols.

At the 12-month study visit, HbA1c levels were measured, and patient quality of life was assessed using the PedsQL questionnaire, completed by study patients and their parents. The primary outcome was HbA1c levels at the 12-month visit. HbA1c levels were compared in participants randomized to CSII and MDI using regression analysis. Secondary outcomes, including percentage of children meeting the UK targets for HbA1c (<58 mmol/mol [7.5%] until 2015 and <48 mmol/mol [6.5%] after 2015), PedsQL scores, and costs, were compared between patients in the 2 groups.

A total of 294 children were enrolled in the study, and data on 287 (143 randomized to CSII and 144 to MDI) were analyzed. The median age of study participants at diagnosis was 9.8 years, and mean HbA1c levels were 103.6 mmol/mol (11.7%). At 12 months, mean HbA1c levels were 60.9 mmol/mol (7.7%) for those randomized to CSII and 58.5 mmol/mol (7.55%) for those randomized to MDI (P=0.09); 46.2% of those randomized to CSII and 54.9% of those in the MDI group had HbA1c levels below the <58 mmol/mol target (P=.16), and 15.4% and 20.4%, respectively, had levels <48 mmol/mol (P=.28). Quality of life was slightly, but statistically, higher, based on parental PedsQL scores, for children randomized to CSII than in those in the MDI group. However, there was no significant difference in PedsQL scores between groups among children old enough to complete the questionnaire. Calculated mean total costs were £1,863 higher in those in the CSII group (95% CI, £1,620–£2,137).

The authors conclude that during the first year after diagnosis of type 1 diabetes in children, there were no differences in efficacy between receiving CSII or MDI treatment, but costs were higher with CSII.

**COMMENTARY BY**

**Patricia Y. Fechner, MD, FAAP**, Seattle Children’s Hospital, Seattle, WA

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.

The current investigators found no clinical benefit of CSII over MDI in the first year post-diagnosis of type 1 diabetes. The HbA1c differences were measured using intention to treat analysis. However, 15% of individuals assigned to CSII switched to MDI, and 20% of individuals assigned to MDI switched to CSII. When analysis was done, adjusting for randomization group, there was even less difference in HbA1c between CSII and MDI. The US target HbA1c for children and adolescents is <7.5% (58 mmol/mol)1; most children were just above the target goal. Severe hypoglycemia occurred in 4.2% of those using CSII versus 1.3% among those randomized to MDI, but the difference was not significantly different. There were 2 cases of diabetic ketoacidosis in the CSII group and none in the MDI group, also not statistically significant (P=.24).

The children in the current study did not use continuous glucose monitoring (CGM), which should be considered in all children with type 1 diabetes.1 CGM may prevent severe hypoglycemia and diabetic ketoacidosis. The current investigators looked only at the first year following diagnosis of diabetes, when many children are still able to produce some insulin during their honeymoon phase. This may also account for lack of benefit with the CSII over the MDI regimen. Thus, the results of this study can only be used in the first year following diagnosis and may not be applicable in subsequent years.

Parental PedsQL scores in the CSII group were higher, perhaps reflecting the propensity of the younger child to “graze,” requiring more frequent low doses of insulin, which are more easily given using the CSII than the MDI regimen. It is difficult to know what the cost difference in the United States would be for CSII versus MDI in view of the different prices in the 2 countries. Most likely, the insulin pump and pump supplies would be more expensive than MDI in the United States. Technology with CSII is rapidly progressing and, as it improves, the differences in benefit may increase over MDI.

**Bottom Line:** In the first year following diagnosis of type 1 diabetes, CSII does not improve HbA1c over MDI therapy but may improve parental perception of quality of life.

**EDITORS’ NOTE**

Perhaps the most striking result in the current study is that glycemic control in children is suboptimal in the first year of type 1 diabetes, regardless of mode of insulin administration.

**Reference**

Educational Objectives

1. Understand the clinical features and treatment of pediatric antibiotic-refractory Lyme arthritis (ARLA).
2. Recognize the importance of early diagnosis and treatment to prevent ARLA.
3. Discuss the role of glucocorticoids and immunosuppressive agents in the management of ARLA.

Pediatric Antibiotic-Refractory Lyme Arthritis

Investigators from multiple institutions conducted a case-control study to identify clinical and treatment features associated with antibiotic-refractory Lyme arthritis (ARLA) in children. Study participants were identified by reviewing medical records of patients <18 years old with a diagnosis of Lyme arthritis (LA) seen at 1 of 4 pediatric rheumatology clinics in a Lyme-endemic region between 2000 and 2013. Only children with a clinical diagnosis confirmed by Western blot testing and documented arthritis were eligible. Cases were patients with active LA despite ≥8 weeks of oral antibiotics (amoxicillin, doxycycline, or cefuroxime) or ≥2 weeks of IV antibiotics (ceftriaxone or cefotaxime). Controls were children with documented resolution of LA within 3 months of starting antibiotics; LA was considered resolved when there was no joint pain or stiffness and minimal or no effusion on physical examination. The medical records of study participants were reviewed, and demographic and clinical information were abstracted. Using multivariate logistic regression, independent predictors of ARLA were identified. For the primary analysis, 26 predictor variables selected before the analysis were included. A secondary analysis, including variables selected post hoc, was also conducted.

Data on 49 children meeting criteria for ARLA (cases) and 188 children whose LA resolved within 3 months (controls) were analyzed. In the primary analysis, children with ARLA were significantly more likely to have arthritis limited to one or both knees (OR, 5.1; 95% CI, 1.4–19.2) and joint symptoms for ≥6 weeks (OR, 9.4; 95% CI, 2.5–34.7) at diagnosis. Cases were also more likely than controls to have clinical worsening after initial antibiotic treatment (OR, 4.2; 95% CI, 1.4–12.6). Conversely, signs of severe inflammation (fever, severe pain, and erythrocyte sedimentation rate ≥40 mm/h) were associated with a significantly reduced risk of developing ARLA (OR, 0.4; 95% CI, 0.2–0.9). In the secondary analysis, additional independent predictors of ARLA were use of amoxicillin at doses less than those recommended by LA treatment guidelines and anti-biotic non-adherence (defined as the patient receiving <80% of prescribed doses).

The authors conclude that children with LA who present with prolonged joint symptoms, arthritis limited to the knees, and/or who fail to respond to the initial course of antibiotics are at risk for ARLA.

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Dr Higgins 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 most common late manifestation of Lyme disease (LD) is oligoarticular or monoarticular arthritis, usually involving large joints, especially the knee. In the United States, LA may occur in those who did not receive or respond to appropriate antibiotic treatment for Borrelia burgdorferi infection. Diagnosis of early LD depends on a history compatible with a tick bite followed by a typical clinical manifestation: erythema migrans. Laboratory testing is not considered necessary for primary treatment because specific antibodies are often absent in early LD. However, by the time LA appears, antibodies have typically had time to develop so that Western blotting reveals serum antibodies against specific proteins of B burgdorferi, confirming diagnosis. When LA does not respond to additional appropriate oral or IV antibiotics, it is considered to be ARLA.

The current investigators describe the largest retrospective cohort of pediatric LA patients followed long enough to assess incidence and risks for ARLA. Application of the CDC definition of positive Lyme Western blotting using patient serum minimized false positive LD diagnoses. Most of the risk factors found to be associated with ARLA may be related to mild disease, which may predispose to delay in diagnosis or underdosing of medications. Conversely, the lower incidence of ARLA found in patients with severe initial systemic manifestations may result from quicker and longer antibiotic treatment, and better adherence. Other factors postulated to contribute to ARLA include infection-induced autoimmunity or failure to appropriately downregulate inflammation.

In a companion article, Horton et al report the outcome of 18 LA patients treated with intra-articular glucocorticoids (IAGCs) following primary or secondary oral antibiotics. Arthritis resolved more quickly, and the rate of ARLA was lower in children receiving IAGCs compared to those receiving secondary oral antibiotics alone (17% vs 44%), with no difference in adverse events. Other investigators have also described a favorable outcome of ARLA to anti-inflammatory therapies, including IAGCs.

Bottom Line: Early clinical recognition and appropriate antibiotic treatment of LD appears to be important in preventing the development of ARLA. IAGCs are an additional treatment option to shorten the duration of joint inflammation in selected patients.

EDITORS’ NOTE

NSAIDs are the initial recommended therapy for ARLA. When glucocorticoids and even methotrexate are contemplated, referral to a rheumatologist is a priority.

References

Dr Horton 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.

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References
Chemically Detoxified Versus Recombinant Pertussis Toxin Vaccines


Investigators from multiple institutions conducted a randomized controlled trial to assess the immunogenicity of a recombinant acellular pertussis vaccine (r-aP) that included genetically detoxified pertussis toxin (PT) and filamentous hemagglutinin (FHA), compared to that of a licensed acellular pertussis (aP) vaccine with chemically detoxified PT (cd/Tdap) in previously immunized adolescents. Healthy adolescents, 11–15 years old, from the Geneva, Switzerland area who had received 5 previous aP immunizations were randomized to receive either r-aP and tetanus-diphtheria (Td) vaccines or cd/Tdap. Blood was obtained at baseline and at 28 and 365 days after immunization for measurement of anti-PT neutralizing antibodies, and PT, FHA, tetanus toxoid (TT), and diphtheria toxoid (DT) specific immunoglobulin (IgG) antibodies. The primary outcome was concentration of PT neutralizing antibodies at days 28 and 365. Secondary outcomes included levels of IgG antigen-specific antibodies and seroresponse to each antigen (defined as a 4-fold increase in levels of antigen-specific antibodies from baseline) at days 28 and 365. Changes from baseline for the outcomes among participants in each vaccine group were assessed with paired t-tests or signed-rank tests, and t-tests or chi-square tests were used to compare results between groups.

Data on 60 adolescents, including 31 receiving r-aP and Td and 29 randomized to cd/Tdap, were included in study analyses. The mean age of study participants was 12 years. At baseline, levels of PT neutralizing and PT IgG antibodies were low among those in each group and undetectable in most. Antibody levels increased significantly in both groups by day 28. However, levels of PT neutralizing and PT IgG antibodies were significantly higher in those receiving r-aP and Td vaccines than in those randomized to cd/Tdap (P=0.016 and P=0.0006, respectively). There were no significant differences between groups at day 28 for levels of FHA, DT, or TT antibodies. At day 28, PT neutralizing and PT IgG seroresponse rates were significantly higher in those receiving r-aP and Td than among those receiving cd/Tdap (97% and 97%, respectively, vs 79% and 93%, respectively). By day 365, FHA, TT, and DT antibodies declined to similar levels in both groups, but PT neutralizing and PT IgG seroresponse rates were 79% and 71%, respectively, in those receiving r-aP and Td compared to 39% and 39%, respectively, among those in the cd/Tdap group (P=0.006 and P=0.03, respectively).

The authors conclude that the r-aP vaccine induced higher levels of anti-PT antibodies than the licensed cd/Tdap vaccine in previously immunized adolescents.

**COMMENTARY BY**

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Dr Brady has disclosed no financial relationship relevant to this commentary. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Licensed pertussis vaccines in the United States contain PT that has been chemically detoxified (cd) with formaldehyde and/or glutaraldehyde to minimize its adverse effects but preserve immunogenicity.¹ All also contain 2 or more other pertussis antigens (eg, FHA, pertactin, or fimbriae types 2 and 3).² All pertussis vaccines are combined with TT and DT (eg, DTaP for infants and young children and Tdap for adolescents and adults). With repeated immunizations of cd PT-containing vaccines, the rise in antibodies is less and, therefore, immunity wanes more quickly. In a previous study among adolescents receiving Tdap boosters, estimated vaccine effectiveness was 68.8% (95% CI, 59.7%–75.9%) during the first year after vaccination and decreased to 8.9% (95% CI, -30.6% to 36.4%) by ≥4 years after vaccination.³ The authors hypothesize that this waning protection may derive from repeated immunizations with cd PT-containing aP vaccines inducing B cells preferentially recognizing cd PT vaccine epitopes instead of epitopes from native PT.⁴

In the current study, the immunogenicity of cd/Tdap was compared to that of an r-aP that is predicted to induce B cells that recognize epitopes similar to those from native PT.⁵ Vaccination with r-aP induced significantly higher anti-PT and PT-neutralizing responses than cd/Tdap, and these higher responses persisted for at least 1 year. The PT neutralizing and PT IgG seroresponse rates to r-aP at 1 year were only 79% and 71%, respectively, so this candidate investigational pertussis vaccine may also require earlier, repeated boosting or a stronger adjuvant.

With 18,975 pertussis cases reported in the United States in 2017,⁶ there is still much work ahead to improve the effectiveness of pertussis vaccines.

**Bottom Line:** An investigational recombinant PT vaccine elicited better antibody responses in aP-primed adolescents than the currently licensed cd PT vaccine. However, antibody responses were still suboptimal.

**EDITORS’ NOTE**

Waning immunity with current aP vaccines is but one factor in the resurgence of pertussis. Increased immunization rates coupled with improved vaccines are necessary to reduce pertussis-associated morbidity and mortality. (See AAP Grand Rounds. 2018;40[6]:66.)

**References**

⁵. Ibsen PH. Vaccine. 1996;31(45):359-368
Investigators from Nationwide Children’s Hospital and Ohio State University conducted a retrospective cohort study of children with foreign-body ingestion (FBI) to describe FBI types and rates over time. Children were included if they were <6 years old and were treated for FBI between 1995–2015 at a US ED that contributes data to the National Electronic Injury Surveillance System (NEISS), which weights contributed data to derive national estimates. NEISS FBI cases were identified by diagnosis code “ingested foreign object.” Cases involving ingestion of food or liquids, location of the object in the airway or mouth, or choking were excluded.

Demographics and FBI characteristics were obtained from NEISS data, including ED disposition (hospitalized or not), location of FBI (home or other), and type of FBI (coin, toy, jewelry, battery, or other). Within coin, battery, and jewelry FBI types, the proportion due to quarters, button batteries, and earrings, respectively, was determined. Investigators assessed for associations between FBI type, location, and ED disposition. Population estimates from the US Census Bureau were used to determine FBI rates per 10,000. Regression was used to assess for trends in rates of FBI over the study period overall and by FBI type.

There were 29,893 FBI cases identified, representing a national estimate of 759,075 (95% CI, 589,323–928,825) FBI cases among children <6 years old over the study period. Among patients treated for FBI, the most common age was 1 year old (21.3%), and 52.9% were boys; 61.7% of ingestions involved coins, 97.2% occurred at home (97.2%), and 89.7% of cases of FBI did not require hospitalization. Button batteries accounted for 85.9% of battery FBI, and earrings comprised 33.7% of jewelry FBI.

The rate of FBI cases increased significantly over the study period (9.4 vs 17.9 per 10,000 in 1995 and 2015, respectively; P<.001). Rates of coin (6.3 vs 10.5 per 10,000 in 1995 and 2015, respectively; P<.001), jewelry (0.7 vs 1.5 per 10,000 in 1995 and 2015, respectively; P<.001), and battery (0.01 vs 1.5 per 10,000 in 1995 and 2015, respectively; P<.001) FBI increased significantly over the study period. Compared to cases of other FBI types, cases of coin FBI had increased risk of being hospitalized (relative risk, 2.4; 95% CI, 2.1–2.8). Compared to other types of coin FBIs, cases of quarter FBIs also had a significantly increased risk of hospitalization.

The investigators conclude that FBI ingestions have increased over time.

COMMENTARY BY
Michelle Stevenson, MD, MS, FAAP, Emergency Medicine, University of Louisville; Louisville, KY

Dr Stevenson has disclosed no financial relationship relevant to this commentary. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

The rise in the rate of FBI within the NEISS among children over time is impressive and concerning. It is important to keep in perspective that this finding may represent a true increase in the number of children who experience FBI, a change in the location of evaluation or injury coding, or more likely a combination of these factors. The NEISS only captures ED visits and therefore does not include children who experience FBI and seek care solely in a pediatric office, clinic, or urgent care setting or are managed at home. Regardless, 99 children per day were estimated to have sought care in US EDs for FBI, and the magnitude of change suggests a true increase in frequency of ingestion over time. Battery ingestions remain a potentially serious injury, with 14 fatalities from 1996–2010 and the majority of injuries caused by button batteries as reported by the CDC.

There is a paucity of literature regarding modifiable factors contributing to foreign body ingestion in children. An observational study of parent supervision on playgrounds demonstrated that over half of parents were observed to be distracted by their phone, and children of parents who used an electronic device while supervising a child in an urban playground had twice the injury risk. One hypothesis for the etiology of the increase in FBI observed in this study is a change in parental supervision practices with the increased availability of personal electronic devices over time.

Bottom Line: Young children swallow foreign objects at an alarming frequency, resulting in an increased number of ED visits and the potential for hospitalization and/or serious injury.

EDITORS’ NOTE
It is always wise to consider FBI in a child who presents with acute onset of cough or chest or abdominal pain, even in the absence of corroborating history. (See AAP Grand Rounds. 2018;40[1]:9-12)

References
Lentiviral Vector Gene Therapy for X-linked SCID


Investigators from multiple institutions conducted a phase 1–2 gene therapy trial in children with X-linked severe combined immunodeficiency (SCID-X1). Children with SCID-X1 were eligible if they were receiving care at 1 of 2 study institutions and lacked a matched sibling hematopoietic stem cell donor. Demographics and clinical status were assessed at enrollment.

Marrow was harvested from enrolled children and enriched for CD34+ cells. The cells were pre-stimulated and transduced with a lentiviral vector containing a normal copy of IL2RG, the defective gene in SCID-X1. Prior to infusion of transduced CD34+ cells, children received 1–2 daily doses of busulfan intravenously. Peripheral blood and bone marrow samples were obtained at various time points after infusion of transduced CD34+ cells to assess hematopoietic recovery.

The primary outcomes included (a) safety, defined as recovery of an absolute neutrophil count to a level of >500 cells/mm³ by 42 days after busulfan infusion without any serious adverse events; (b) feasibility, defined as ≥1 million CD34+ cells/kg of body weight, with a vector copy number of ≥0.1 copies/cell; and (c) efficacy, defined as clinically significant T-cell reconstitution within 52 weeks after gene transfer. Reconstitution of natural killer (NK) and B cells was also measured. Clinical status and anthropomorphic parameters were assessed at a median follow-up time of 16 months.

Eight child patients were enrolled with a median age of 3.5 months. Five of the 8 patients had pre-existing infections, including cytomegalovirus, legionella, and coronavirus. The median dose of transduced CD34+ cells infused was 6.73 x 10⁴ cells/kg of body weight with a median graft vector copy number of 0.40 copies/CD34+ cell.

Hematopoietic recovery without severe adverse events occurred in all 8 patients by 3–4 weeks after busulfan infusion. All patients were alive and well at follow-up, had normal weight and growth parameters, and all pre-existing infections cleared. In 7 of 8 patients, normal levels of vector-marked peripheral-blood NK, T, and B cells were achieved by 4, 6, and 2 months, respectively. Vector copy numbers at 4 months ranged from 0.06–0.6 in CD34+ cells. Four patients were vaccinated against tetanus, diphtheria, pertussis (DTaP), polio, and pneumococcus 9–15 months after infusion, with 3 of the 4 demonstrating protective antibody responses to DTaP and polio, and 2 of the 4 demonstrating protective antibody responses to pneumococcus.

The investigators conclude that lentiviral gene therapy combined with busulfan conditioning is safe, feasible, and efficacious.

**COMMENTARY BY**

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

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.

SCID-X1 affects 1 in 50,000 to 100,000 US neonates,² accounting for 30%–40% of primary immunodeficiencies.² SCID-X1 results from mutations in interleukin-2 receptor gamma chain gene, IL2RG, which disrupts T and NK cell development, leading to cellular and humoral immune dysfunction.³ T-cell excision circles (TRECs) are DNA biomarkers of normal T lymphopoiesis generally measured by polymerase chain reaction on newborn dried blood spots. Universal newborn TREC screening in the United States has allowed early intervention with hematopoietic stem cell transplantation (HSCT) prior to infectious complications.¹ The average 5-year survival rate is 70%–80%, improving to 80%–90% for those who are <3.5 months of age and infection-free at time of HSCT.³ Other factors, including pre-HSCT graft manipulation, conditioning chemotherapy, and graft versus host disease prophylaxis, impact the degree and durability of T-cell reconstitution.⁴ Unfortunately, HSCT has not resulted in B-cell engraftment, placing children at risk for recurrent gastrointestinal inflammation, sinopulmonary infections, and autoimmunity.⁵

Over the past 2 decades, several gene therapy trials have been performed in approximately 30 infants without an available HSC donor and older cohorts who failed HSCT.⁵ Early gammaretroviral gene transfer into autologous HSCs yielded successful T-cell reconstitution but also leukemic transformation.⁵ The use of self-inactivating gammaretroviral vectors achieved rapid durable T-cell function without leukemia, yet also without restoration of NK- or B-cell function due to lack of conditioning chemotherapy.² A lentiviral study with conditioning chemotherapy in older children/teens who had failed prior allogeneic HSCT revealed some benefit to B-cell reconstitution.⁶

This prospective single-arm trial featured busulfan dose adjustments based on pharmacokinetics in a small SCID-X1 infant cohort, some with concurrent life-threatening infections.²,⁵ Ethical concerns about not randomizing to a placebo or HSCT were appropriate given previous viral vector therapy benefit in infants who lacked suitable HSC donors.²,⁵ Longer follow-up studies are needed to assess durability of immune function and late effects from busulfan and viral gene insertion.⁵

**Bottom Line:** When allogeneic HSCT is unavailable or risky, lentiviral vector gene therapy after nonmyeloablative busulfan is an effective alternative by achieving cellular and humoral competence in infants with SCID-X1.

**References**

Parental Smoking, E-Cigarette Use, and Smoke-Free Policies

Investigators from multiple institutions conducted a study to assess smoke- and vape-free policies in homes and cars among parents who smoke cigarettes, use e-cigarettes (vape pens, JUULs, or mods), or both. For the study, parents were approached at 5 pediatric practices in Indiana, Virginia, North Carolina, Tennessee, and Ohio and asked to participate in an interview; only parents who were current smokers (≥100 cigarettes in their lifetime and at least one cigarette in the previous 7 days) or former smokers (smoked within 2 years, but not within past 7 days) were eligible. Participants were asked about their use of e-cigarettes in the last 30 days, and their policies (rules) regarding a smoke- and vape-free home and smoke- and vape-free car. Demographic information was also obtained during the interview. Study participants were classified as cigarette users only, e-cigarette users only, or dual users (cigarettes and e-cigarettes). Differences in car and home smoke- and vape-free policies between these groups were compared with chi-square tests. Logistic regression was used to identify characteristics associated with not having a smoke- or vape-free policy for home and car.

Data were collected from 943 parents; 84.9% were cigarette users, 4.5% were e-cigarette users only, and 10.6% were dual users. Dual users were significantly less likely than cigarette users only to have a smoke-free car policy (25.0% vs 43.23%, P<.01), a vape-free car policy (23.9% vs 65.8%, P<.001), or a vape-free home policy (26.3% vs 72.7%, P<.001). Rates of smoke-free home policies were similar among dual users (63%), cigarette users (61.1%), and e-cigarette users (73.5%). Among parents in the dual user and e-cigarette user groups combined, rates for a smoke-free policy were significantly higher than vape-free policy for both home (66.7% vs 25.4%, P<.03) and car (35.3% vs 22.5%, P<.001). Statistically significant independent predictors for parents not having a smoke-free home and car policy included not attending college, smoking ≥10 cigarettes per day, presence of another household smoker, use of e-cigarettes, and age of youngest child ≥5 years. Predictors of a lack of a vape-free home and car policy for parents were not attending college, age between 18 and 24 years, smoking ≥10 cigarettes per day, use of e-cigarettes, and age of youngest child >10 years.

The authors conclude that parents who smoke cigarettes and/or use e-cigarettes often do not have smoke- and vape-free policies.

COMMENTARY BY

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The risks of second-hand smoke exposure from combustible cigarettes have been well-established, resulting in increased risks for cancer, chronic obstructive pulmonary disease, asthma, sudden infant death syndrome, metabolic syndrome, and worse academic performance.1 While less well-known by the public, the risk of third-hand smoke exposure—residual substances left on surfaces—results in accumulation of carcinogenic substances that increase risk of cancer, liver disorders, behavioral issues, and increased inflammation in several animal studies.2,3 The use of e-cigarettes has been rising, with the perception that this is a safer alternative to combustible cigarettes. However, even exposure to e-cigarette vapor results in accumulation of carcinogens and other toxins.4

The current investigators assessed the presence of smoke- and vape-free home and car policies among active users of cigarettes. They found that many did not have a smoke- or vape-free policy. And even when a policy was in place, many were still using cigarettes and e-cigarettes. More compelling is the issue of counseling. The authors found that only a minority of pediatricians advised smokers about the importance of a smoke-free home.

Encouragement to quit smoking by pediatricians has been found to reduce adult smoking rates, especially since parents are more likely to visit their child’s pediatrician than their own provider.5 Also, parents report improved satisfaction when the pediatrician addresses smoking cessation with them during their child’s visit.6 While smoking cessation should be addressed universally, particular attention should be paid to younger parents (18–24 years old) with higher cigarette use who are less educated. These parents are much less likely to have a strict smoke- or vape-free policy for their home or car.

Bottom Line: Many parents who use cigarettes and e-cigarettes do not have a smoke- or vape-free policy for their homes or cars. Counseling rates by pediatricians are low, revealing missed opportunities for intervention. (See AAP Grand Rounds. 2019;4(6):66–6)

References

Investigators from multiple federal health agencies conducted a study to estimate the prevalence of depression, anxiety, and behavioral/conduct problems, and treatment for these disorders, among children 3–17 years old in the United States. For the study, they reviewed data from the 2016 National Survey of Children’s Health (NSCH). NSCH is administered by the Maternal and Child Health Bureau and is designed to produce state- and national-level estimates of key indicators of the physical and emotional health of US children. Data from surveys completed by parents/caregivers in households with at least one age-eligible child were included in the analyses; in households with multiple children, one child was chosen for the survey. Respondents were asked if the child had ever been diagnosed by a health care professional (or teacher for behavioral/ conduct problems) with depression, anxiety, or behavioral/conduct problems, and if so, whether the child currently had the condition. For those currently with one of the conditions, the parent/caregiver was asked if their child had received treatment from a mental health professional. Data on child demographics (age, race/ethnicity), reported child physical and parent/caregiver mental health status, and household income were also collected. Survey responses were weighted to provide nationally representative estimates. Logistic regression was used to identify independent predictors of each of the conditions and receipt of treatment.

Data on 43,283 children were included in the analyses. The estimated prevalence of the 3 mental health conditions among US children 3–17 years old were depression 3.2% (95% CI, 2.9%–3.5%), anxiety 7.1% (95% CI, 6.6%–7.6%), and behavioral/conduct problems 7.4% (95% CI, 6.9%–7.9%). Compared to younger children, those 12–17 years old were significantly more likely to be currently diagnosed with depression and anxiety; children 6–11 years old were significantly more likely to be currently diagnosed with behavioral or conduct problems than those 12–17 years old. Overall, non-Hispanic white children were more likely to be diagnosed with one of the disorders than those of other races and ethnicities. In addition, children with worse physical health status and those whose parent/caregiver had worse mental health status were more likely to have one of the conditions. Among those with a currently diagnosed condition, 78% with depression, 59.3% of those with anxiety, and 53.5% of those with behavioral/conduct problems had received treatment. In general, children from wealthier households were more likely to have received treatment for each of the disorders than those from less advantaged households.

The authors conclude that depression, anxiety, and behavioral/conduct problems are prevalent among US children, and there are substantial gaps in treatment for children with these conditions.


**COMMENTARY BY**
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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.

The investigators in the current study show that among children 3–17 years of age, approximately 3% had depression, 7% had anxiety, and 7% had conduct problems. Treatment was more common for depression compared to the others; one can’t help but wonder whether that is because a prescription for an antidepressant is a relatively more comfortable and efficient intervention compared to managing anxiety or conduct/behavior problems. And yet, anxiety and conduct/behavior problems are much more common.

So, what’s the answer? In the accompanying editorial, Donahue and Aalsma make essentially 3 suggestions: (1) greater integration of behavioral health services in the pediatric primary care setting, (2) revision to the AAP screening guidelines to include anxiety and (3) revamping of payment models to address the valuable time spent and to encourage primary care physician collaboration with behavioral health services. Few would argue against these efforts.

**Bottom Line:** Depression, anxiety, and behavioral/conduct problems are common among US children and adolescents.

**EDITORS’ NOTE**
Pediatricians have become adept at using developmental screening tools that assist in the identification of children at risk for delays in language, motor, and cognitive skills. The results of the current study and another recently published investigation demonstrate, however, gaps in mental health screening and treatment of children and adolescents with behavioral health problems. Their remediation is, after all, essential to the well-being of children as well as their families.

**References**

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Community Hospital Pathway for Critical Asthma Exacerbations


Investigators from Boston Children’s Hospital and South Shore Hospital in South Weymouth, MA, assessed the impact of implementation of a clinical pathway for care of children with “critical asthma” in a community hospital without a pediatric ICU. For the study, children ≥2 years old admitted with an asthma exacerbation and requiring continuous albuterol via a nebulizer (CAN) were eligible for inclusion. A clinical pathway for management of these patients was implemented at the study site community hospital in September 2016. Standardized treatments were guided by use of the Hospital Asthma Severity Score (HASS). Data on children meeting study inclusion criteria during the baseline period (September 2014 to August 2016) and those admitted during the implementation period (September 2016 through December 2017) were collected by review of medical records. The primary outcomes were time to albuterol administered every four hours (defined as “time to clinical recovery,” because children at this level of care were considered ready for discharge) and hospital length of stay (LOS). These outcomes were assessed using segmented regression analysis and analysis of variance. Other outcomes included transfer rate to a children’s hospital, percentage of patients needing ICU-level care while awaiting transfer, length of time on CAN, and readmission within 72 hours of hospital discharge.

Data on 69 patients during the baseline period and 60 during the implementation period were analyzed. There were no significant differences between children in the baseline and implementation periods in terms of age (mean ages 7.1 and 7.4 years, respectively, P=.680) or HASS scores on admission. During the implementation period, study children received CAN for a mean of 4.4 hours compared to 2.4 hours during the baseline period (P=.002). The time to albuterol administered every 4 hours was significantly shorter among those treated after implementation of the clinical pathway than in those receiving care during the baseline period (mean durations 17.4 hours vs 27.5 hours, P<.001); this difference was also significantly different in the segmented regression analysis (P<.001). Mean LOS was 31.9 hours for those treated in the implementation period compared to 40.4 hours for those in the baseline group (P=.029), but this difference was not significant within the segmented regression analysis (P=.24). There was a significant decrease in the proportion of patients transferred to another facility (11.7% vs 27.5%, P=.025). There were no significant differences between children treated during the 2 phases for the need for ICU-level care before transfer or 72-hour readmission rates.

The authors conclude that implementation of a clinical pathway for management of children with critical asthma in a community hospital was associated to a reduction in time to clinical recovery.

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.

Any hospitalization of a child is stressful and disruptive for a family.1 Admissions of critically ill patients to hospitals without an ICU have the added complication of balancing optimal patient safety with the goal of minimizing that disruption by allowing families to stay close to home. If the threshold for transfer is too high, patients may decompensate and require ICU-level care prior to transfer. If the threshold is too low, then families may have the added burden of transfer and travel to another hospital without clinical benefit. Moreover, when variation exists between providers, this variation is more likely to lead to transfer by virtue of random chance, rather than factors inherent in the patient.2

The investigators in the current study aimed to implement a standardized protocol for patients requiring CAN in a community hospital. By incorporating standardization of clinical assessment, treatment, and transfer, they succeeded in more quickly achieving discharge criteria and transferring fewer patients.

Taken at face value, this is impressive; more patients are able to stay at their initial hospital safely while being given standardized, efficient, and effective care. The investigators also provide a roadmap for developing similar clinical pathways, both for asthma at other sites and for other diseases. Any individual pathway will need to be tailored to the individual hospital’s demographics and culture. However, by partnering with the referral hospital, involving staff from the beginning, and following data, it is likely that other similar pathways can succeed.

Bottom Line: Standardizing clinical evaluation, treatment, and transfer criteria for children admitted to a community hospital with a critical asthma exacerbation is associated with decreased time to recovery, LOS, and transfer rates without increased adverse events. (See AAP Grand Rounds. 2018;39(4):42.)

EDITORS’ NOTE

Given the striking difference in length of time that CAN was used in the implementation phase compared to baseline, one wonders if this singular intervention accounted for the improved outcomes rather than the multi-pronged clinical pathway.

References
## CME QUESTIONS

The following continuing medical education questions cover the content of the July 2019 issue of AAP Grand Rounds. Please keep this issue. Each year’s material is worth up to 18 AMA PRA Category 1 Credit(s)™. Complete and claim credit online at www.aapgrandrounds.org. Need username and password? Contact customer service at 866-843-2271.

### CME OBJECTIVES

1. Describe the epidemiology of concussion among youth football players.
2. Compare and contrast the efficacy and costs of insulin pump versus multiple daily insulin injections for children diagnosed with type 1 diabetes.
3. Understand the epidemiology of foreign body ingestion in children.

### 1. A 12-year-old boy is seen in the office for a sports preparticipation health exam, as he will be playing in a football league. The mother asks about the risk of concussion. Which of the following is most accurate, based on the study by Chrisman et al, concerning the epidemiology of concussions in 5- to 14-year-old American youth football players?

   a. The incidence of concussion was <2% per season.
   b. Most youths with concussion did not return to school for ≥10 days.
   c. Half of the youths who had a concussion had symptoms longer than 3 months.
   d. Youth with a history of concussion had 2-fold increased odds of concussion.
   e. Youth with a history of concussion were not at increased risk of concussion.

### 2. A 9-year-old girl is hospitalized with new onset type 1 diabetes. The parents ask the pediatric endocrinologist if the child should receive an insulin pump (continuous subcutaneous insulin infusion) versus multiple daily injections (MDI) regimens in children at diagnosis of type 1 diabetes?

   a. Children randomized to CSII versus MDI had improved HbA1c levels at 12 months.
   b. There was no cost difference between CSII and MDI during the first 12 months of therapy.
   c. Parents of children receiving CSII reported no difference in patient quality of life (PedsQL) scores compared to parents of children receiving MDI.
   d. Children receiving CSII reported higher PedsQL scores than children receiving MDI.
   e. In the first year of treatment, CSII did not improve HbA1c levels compared to MDI, but parent PedsQL scores were slightly higher.

### 3. A 9-year-old boy with a history of Lyme arthritis continues to have active arthritis after two 4-week courses of doxycycline. Which of the following factors was associated with an increased risk of pediatric antibiotic-refractory Lyme arthritis, based on the study by Horton et al?

   a. Treatment with doxycycline rather than amoxicillin
   b. Age <10 years
   c. Fever at presentation
   d. Severe pain at presentation
   e. Knee-only arthritis

### 4. An 11-year-old girl presents for a health maintenance visit and to receive a Tdap booster. The girl and her mother ask about the effectiveness of this vaccine in preventing whooping cough. Based on the article by Blanchard Rohner et al, which of the following is the most accurate statement when comparing the chemically detoxified pertussis toxin (cd/Tdap) vaccine with an investigational recombinant pertussis toxin (r-aP) vaccine?

   a. At baseline, most study participants had high levels of pertussis toxin (PT) neutralizing antibodies.
   b. By day 365, PT neutralizing antibodies were significantly higher in those receiving the r-aP vaccine compared to those receiving the cd/Tdap vaccine.
   c. Levels of FHA antibodies were significantly higher at day 28 among those receiving the r-aP vaccine compared to those receiving the cd/Tdap vaccine.
   d.Licensed acellular pertussis (aP) vaccines induce B cells to recognize epitopes identical to those from native PT.
   e. The r-aP vaccine induced high levels of anti-PT antibodies that were sustained at 5 years post-vaccination.

### 5. According to the article by Orsagh-Yentis et al, which of the following statements is most accurate concerning the prevalence and treatment of depression, anxiety, and conduct problems among US children aged 3–17 years?

   a. Depression was more common than anxiety.
   b. Depression was more common than conduct problems.
   c. Treatment for children with depression was more common than for anxiety.
   d. Greater than 70% of the children with anxiety and conduct problems received treatment.
   e. Children from wealthier households were less likely to have received treatment for depression, anxiety, or conduct problems.

### 6. A 3-month-old with SCID-X1 manifesting with lymphopenia and rhinoviral infection has received lentiviral IL2RG transduced autologous hematopoietic stem cells after busulfan conditioning. Based on the findings by Mamcarz et al, which of the following is the most accurate statement concerning infants with SCID-X1 after lentiviral gene therapy and busulfan?

   a. In 7 of 8 patients’ NK cells, T cells and B cells normalized.
   b. Growth was stunted.
   c. NK cells decreased.
   d. Neutropenia was severe and irreversible.
   e. Previous infections persisted.

### 7. You are caring for a 3-year-old boy in your practice. You learn that his parents smoke cigarettes and e-cigarettes. Which of the following most accurately represents the findings of Drehmer et al concerning parental smoking and e-cigarette use in home and cars?

   a. Parents who attended college are less likely to have a smoke- or vape-free policy.
   b. Pediatricians routinely counsel parents on the importance of smoking cessation.
   c. Among parents in the dual user and e-cigarette user groups combined, rates for a smoke-free policy were significantly higher than vape-free policy for both home and car.
   d. Parents who use e-cigarettes were more likely to have home and car smoke- or vape-free policies.
   e. Parents who smoke >10 cigarettes a day are more likely to have a smoke- or vape-free policy.

### 8. According to the article by Ghandour et al, which of the following is most accurate concerning the prevalence and treatment of depression, anxiety, and conduct problems among US children aged 3–17 years?

   a. Depression was more common than anxiety.
   b. Depression was more common than conduct problems.
   c. Treatment for children with depression was more common than for anxiety.
   d. Greater than 70% of the children with anxiety and conduct problems received treatment.
   e. Children from wealthier households were less likely to have received treatment for depression, anxiety, or conduct problems.

### 9. Which of the following was a result of the community hospital pathway for critical asthma implemented by Smith et al?

   a. Reduction in time to recovery
   b. Increased length of hospital stay
   c. No change in the transfer rate to a different facility
   d. Significant decrease in the 72-hour readmission rate
   e. Significant decrease in need for ICU care before transfer