Causes and Outcomes of Acute Chest Syndrome in Sickle Cell Disease

Thirty United States centers evaluated 671 episodes of acute chest syndrome (ACS) in 538 patients from 1993-1997 in this prospective study to determine the cause, outcome, and response to therapy. ACS was defined as a new pulmonary infiltrate on chest radiograph in association with chest pain, temperature elevation (>38.5°C), tachypnea, wheezing, or cough in a patient known to have hemoglobin SS, SC or SS-beta thalassemia and at least one prior episode of ACS. Patients were treated with a standardized protocol including oxygen, antibiotics, fluid management, respiratory therapy and bronchodilators, pain management, and transfusion therapy. Laboratory evaluations included blood counts, blood gases, chest radiographs, pulmonary function testing, viral cultures, bacterial cultures, serologies (for Mycoplasma pneumoniae, Epstein-Barr virus, Chlamydia, and parvovirus), and histologic examination for fat embolism (lipid laden macrophages on bronchoalveolar lavage).

The mean age at the time of the first episode of ACS was 13.8 years, and slightly over half of the patients were male (58%). Only half were admitted because of ACS, while the others developed it during hospitalization for another reason (most commonly a vaso-occlusive crisis). A specific cause for ACS was discovered in 38% of all episodes and 70% of episodes with complete data. A wide variety of causes were identified including fat embolism (8.8%), Chlamydia (7.2%), Mycoplasma (6.6%), virus (6.4%), bacteria (4.5%), Legionella (0.6%), and mixed infection (3.7%). Multi-lobe pneumonia was common in all ages. Pleural effusion was seen in 55% of patients. The mean hemoglobin on admission was 7.7 g/dL; mean white count, 23,000/mm³, and mean PaO₂, 70 torr.

Response to treatment varied among subjects. All subjects were started on antibiotics, initially erythromycin and a cephalosporin. Dexamethasone was not routinely administered. Sixty-one percent received bronchodilators, with 20% showing improvement in the FEV₁. Seventy-two percent received transfusions with an average of 1.6 transfusions and 3.2 units per patient. The mean duration of hospitalization was 10.5 days. Thirteen percent of the patients required mechanical ventilation, and the mean duration of ventilation was 4.6 days. Features associated with mechanical ventilation included a history of heart disease, multi-lobe pneumonia, and a platelet count less than 200,000/mm³. Nineteen percent of ventilated patients died. Neurologic complications occurred in 11% of patients and were also associated with a platelet count less than 200,000/mm³. Half of the patients with neurologic events suffered acute respiratory failure. Bronchoscopic complications occurred in 13% of the procedures (28 of 219 procedures), 8 of which led to intubation. Overall, 18
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patients died with the most common reasons being respiratory failure from pulmonary emboli (6 patients) and bronchopneumonia (6 patients). Infection was a contributing factor in 10 of the 18 deaths.

Based on these results the authors recommend careful vigilance for evidence of ACS in all patients admitted with a vaso-occlusive crisis. Once the ACS has been diagnosed, broad spectrum antibiotics (to include a macrolide) should be initiated. All patients should receive supplemental oxygen and inhaled bronchodilators for presumed airway hyperreactivity. Early transfusion therapy should be offered to subjects at high risk for complication. Because of the wide spectrum of infections, bronchoscopy may be helpful in patients who do not respond well to initial therapy.

**Commentary by Susan L. Bratton, MD, MPH, FAAP**

Care Critical Care Medicine, University of Michigan and Mott Children’s Hospital, Ann Arbor, MI

ACS is the second most common complication among children with sickle cell disease, with an estimated rate of 12.8 cases/100 patient years, and it is the most common complication leading to death among these patients. The risk of ACS is reduced in patients treated with hydroxyurea, perhaps due to decreased bone ischemia and fat embolization. Long-term therapy with hydroxyurea increases the proportion of fetal hemoglobin and decreases polymerization. Vichinsky et al show that almost half of the patients with ACS present with a pain crisis and that radiologic evidence of ACS may occur several days after admission. To identify patients who develop this syndrome, clinicians must be vigilant for symptoms consistent with ACS such as persistent fever, hypoxia, wheezing or cough, and repeat chest radiography when any of these symptoms develop. Intensive monitoring is required to prevent hypoxia and allow timely intervention for patients with respiratory failure and/or acute neurologic symptoms.

Seventy-two percent of patients received a red cell transfusion and in this study single transfusion was as effective as an exchange transfusion; however, transfusion therapy was not randomized. Exchange transfusion may be indicated in patients with severe disease or among children who are not anemic. The most commonly identified causes of ACS were fat embolism from infarcted bone and infection with *Chlamydia* or mycoplasmal pneumonia, but the failure to identify a specific cause in over one-third of these patients is disappointing and supports empirical use of a macrolide antibiotic. The progression of organ involvement despite treatment and the high risk of neurologic complications indicate that other therapies need to be developed. Dexamethasone has been helpful in a small group of patients, and blockage of erythrocyte adhesion to the endothelium may be a treatment of the future.

**References**


**INFECTIONOUS DISEASES**

**Effect of a Monetary Sanction on Immunization Rates of AFDC Children**

**Source:** Kerpelman LC, Connell DB, Gunn WJ. Effect of a monetary sanction on immunization rates of recipients of Aid to Families with Dependent Children. JAMA. 2000;284:53-59.

Immunization rates for poor and minority children remain suboptimal. In a randomized, controlled trial conducted from January 1993 through December 1996 in Muscogee County, Georgia, rates of immunization with MMR, poliovirus, DTP, Hib and hepatitis B in a total of 2,500 families were examined before and after imposition of a sanction. The intervention group consisted of 2,488 children in 1,500 families whose welfare benefits were made dependent on up-to-date immunization status. The control group consisted of 1,662 children in 1,000 families that were encouraged to fully immunize their children. The groups were initially matched to average number of children per family, ethnicity, age of children in the family, number of children born during the study, and baseline immunization rates. The intervention status of each child was verified through medical records. Sanctions consisted of losing AFDC benefits for the nonimmunized child and were applied to the intervention group (after warnings had been given) if a child’s immunizations were not considered up-to-date.

At the study’s end, immunization rates were significantly higher among the intervention group for all immunizations in each year except for Hib in the second year. In the intervention group, 369 of 510 children (72.4%) who attained their second birthday during the study completed the immunization series, whereas only 206 of 340 children (60.6%) in the control group did so (*P<.001*). Out of 17 warnings given to the 1,500 families in the intervention group, 11 resulted in sanctions. The annual burden on families being required to provide documentation of immunization status to qualify for AFDC benefits amounted to 0.66 hours spent, 0.13 hours lost from work, and $0.41 for out-of-pocket transportation.
costs. The authors conclude that the threat of a penalty and regular reminders about the importance of immunization were generally successful in encouraging welfare recipients to keep their children's immunization status up-to-date.

**Editors’ Note**

In 1996 the State of Georgia began requiring all families receiving AFDC to provide proof of up-to-date immunization status for children under age 7. This study of 1,500 intervention and 1,000 control families exempted from the statewide requirement was conducted to evaluate that policy. Because the imposition of a monetary sanction was a state-level welfare innovation, the US Department of Health and Human Services waived the need for IRB review or informed consent. While immunization rates in the intervention group increased, it is important to note that 18 children in 11 families lost their AFDC benefits for periods of time ranging from 1 month to indefinitely. While the up-side of this “experiment” was significant, to judge the utility and acceptability of this sanction, we really should know whether any damage was done to those children who lost their benefits. Taking away benefits from poor children for their parent’s failure to immunize is a big step and may not be justified by an increase in immunization rates. Davis concludes that “evaluations of welfare programs are research and should be held to the same ethical standard as clinical evaluations.”

**Commentary by May Lau, MD**

The Children’s Hospital at Albany Medical Center, Albany, NY

Low parental education, large family size, low socioeconomic class, membership in an ethnic or minority group, and receipt of medical care in public health clinics have previously been identified as factors which affect immunization compliance. This study demonstrates an effective, albeit controversial, method to improve immunization rates: making welfare benefits contingent upon up-to-date immunization status. Although very few sanctions were applied, the threat of mothers losing welfare benefits appeared to improve their children’s immunization status. Threatening parents with the loss of benefits is no doubt a powerful incentive to immunize their children. Parents of these children are more likely to be concerned about providing a home and food for their children than they are about ensuring their immunizations. Visits for immunizations also provide an ideal opportunity for parental education and for establishment of office appointments as a familiar routine in family life.

Despite these favorable results, Davis et al, in a related commentary, question the ethics of the intervention and suggest that the negative impact of welfare sanctions may have been overlooked. The quandary remains: how to increase the immunization status of all children in the United States. There are two extremes—well-educated parents who refuse to immunize their children and poor and minority parents who fail to have their children fully immunized.

**Commentary by Leslie Barton, MD, FAAP**

Pediatrics and Pediatric Infectious Diseases, University of Arizona, Tucson, AZ

The presence of acquired melanocytic nevi is a strong risk factor for cutaneous malignant melanoma in white populations. These nevi begin in childhood and are mainly caused by sun exposure. Investigators from British Columbia conducted a randomized trial from 1993–1996 to determine whether use of a broad-spectrum, high-SPF sunscreen attenuates the development of nevi in white children. Children in grades 1 and 4 were randomly assigned to either a treatment group (n=222) that received SPF 30 broad-spectrum sunscreen and instructions to apply it when the child was expected to be in the sun for at least 30 minutes, or a control group (n=236) that was not provided with sunscreen or advice. The children were examined by dermatologists blinded to treatment assignment at the beginning and end of the study. Follow-up data were available on 309 children (80% of randomized white subjects) at 3 years. Children in the sunscreen group developed fewer nevi than control children (median 24 vs 28, P=0.048). Sunscreen use had a greater effect in children with freckles, who developed 30-40% fewer new nevi when assigned to the treatment group. The authors conclude that broad-spectrum sunscreens may attenuate the number of nevi in white children, especially those with freckles.

**Commentary by Daniel R. Neuspiel, MD, MPH, FAAP**

Pediatrics, Epidemiology and Social Medicine, Albert Einstein College of Medicine and Beth Israel Medical Center, New York

Risk for cutaneous malignant melanoma increases with the presence and density of acquired melanocytic nevi in white populations. Risk factors for nevi include genetic (light skin color, freckling, propensity to burn) and environmental (unprotected sun exposure) characteristics, as well as family history of melanoma. Gallagher and colleagues have obtained important information in a randomized trial of sunscreen to prevent nevi in white children. These data suggest that pediatricians may play an important role in preventing malignant melanoma by advising appropriate sunscreen use and avoidance of unprotected sun exposure in children at risk. The authors’ findings would be strengthened by a longer period of observation, as well as by repeating a similar investigation in a population with more direct sunlight than Vancouver.

References

Sleep Disturbances and Attention Deficit Disorders


The prevalence of parent-reported and self-reported sleep disturbances in 46 unmedicated school-aged children (mean age, 7±1½ years, 74% male) with attention deficit/hyperactivity disorder (ADHD) was determined at Brown University School of Medicine, Providence, RI. The patients had been screened for marked symptoms of sleep-disordered breathing, and those diagnosed with obstructive sleep apnea were excluded. Results in the ADHD group of children were compared to those in 46 normal controls, matched for age and sex. A Children’s Sleep Habits Questionnaire (CSHQ) completed by the parents includes sub-scales referring to bedtime resistance, sleep-onset delay, sleep duration, sleep anxiety, night wakings, parasomnias (talking in sleep, restlessness, sleepwalking, teeth grinding, nightmares, bed-wetting), sleep-disordered breathing, and daytime sleepiness. A corresponding Sleep Self-Report (SSR) assessed similar sleep disturbances from the child’s perspective. Children with ADHD had significantly higher scores (and more sleep disturbances) on all sub-scales of the parent CSHQ except for sleep-disordered breathing when compared to controls. The average number of hours of sleep reported by parents on the CSHQ was significantly lower in the children with ADHD than in controls. The child’s SSR also showed a greater incidence of sleep disturbance, particularly relating to bedtime struggles and sleep resistance (P range, .05-.001). Parent and child sleep reports showed a higher correlation in ADHD children than in controls. The authors conclude that children with ADHD and comorbid sleep disorders should receive specific behavioral and pharmacological therapy.

Editors’ Note
Did you know that 80% of a person’s lifetime sun exposure occurs before age 21, that the average child receives 3 times more UVB radiation annually than the average adult, and that regular use of sunscreens with an SPF of 15 or more during the first 18 years of life can reduce an individual’s lifetime risk of skin cancer by 78%? These facts come from a very readable, useful 1997 review of photoprotection by Kim et al.

This Canadian study provides compelling additional evidence that pediatricians should routinely provide parents guidance on sun exposure.

References

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CRITICAL CARE

Attitudes Toward Life Support in the PICU


This prospective survey was conducted in a single pediatric intensive care unit (PICU) at Children’s Hospital, Seattle, WA, over a 6-month study period. All caregivers (nurses, residents, fellows and attending physicians) filled out a survey form if the caregiver thought that limitation of life-sustaining care was appropriate for a patient in the unit. Demographic and clinical information was collected along with caregiver attitudes relating to the types of care that should be limited and the reasons given by the caregiver to justify limiting life-sustaining care.

There were 503 children admitted to the PICU during the study period. Sixty-eight nurses and 45 physicians participated (10 PICU and pediatric anesthesia fellows, 24 pediatric and anesthesia residents, and 11 PICU attendings). At least 1 caregiver thought that life-sustaining care should be limited for 63 of the 503 PICU patients. Among these 63 patients, 26 (41%) had limits placed on medical support and 11 (42%) died. The remaining 37 patients did not have limits established with the family and 6 children (16%) died while receiving full medical support. No patient had care limited when only 1 team member thought it appropriate.

Among the children who died in the PICU, 53% had limits placed on their medical care prior to death. Caregivers most frequently wished to limit invasive care (eg, cardiopulmonary resuscitation [94%] and hemodialysis [83%]). Nurses were more likely to support limitation of mechanical ventilation and antibiotics than physicians. The most common reasons identified for limiting support included burden of continued medical intervention exceeding benefit (88%) and the impossibility of restoring a reasonable quality of life (83%). Inappropriate use of resources was frequently cited as a reason to limit care (72%), but was never listed as the sole reason to limit care. Preadmission quality of life was cited less frequently (50%) as a reason to limit medical intervention. Children with chronic illness were significantly less likely than previously well children to have limits placed on their care. Limitation of care was always discussed with the family. The PICU attending (58%) or the child’s primary physician (21%) usually initiated these discussions.

Commentary by Susan L. Bratton, MD, MPH, FAAP

Pediatric Critical Care, University of Michigan, Ann Arbor, MI

The expectation of imminent death (physiologic futility) and the impossibility of restoring a reasonable quality of life (qualitative futility) were the most common reasons that were considered with respect to limiting care among children whose care was actually limited. Providers were significantly more likely to think that limitation of cardiopulmonary resuscitation (OR 17), surgery (OR 7), mechanical ventilation (OR 3) and inotropes (OR 3) were appropriate in children when limits were established than when they were not. Caregivers were more likely to cite poor quality of life as a reason to limit care among children for whom limits were not established. Children who did not have limits placed on their care were more likely to have chronic illness. Of interest, children with preexisting neurologic injury were significantly less likely to have limited care (28%) when compared to children who suffered an acute neurologic injury (81%). This study highlights the importance of parental preferences since providers cannot accurately judge quality of life issues for patients and families who are accustomed to living with a disabled child.1

Keenan et al also discuss the potential role of the primary care physician who cares for children with severe chronic illness. Anticipation of potential ICU care allows time for families and the patient (if possible) to discuss with their primary care physician or their sub-specialist any limitations of care they desire before being confronted with a moment of crisis. A recent study2 of pediatric oncology patients who died reported that almost a quarter of the children died in the PICU. Decisions to limit medical care to children require thoughtful and clear communication with the family and all caregivers, not just those who work in the PICU.

Editors' Note

Hopefully, no limits are being set on the primary care pediatrician’s participation in the ICU care team. If you are not a part of that team, show the PICU staff this study and offer your expertise and willingness to participate in decisions relating to limiting life-sustaining care.

References


DERMATOLOGY

Itraconazole for Dermatophyte Onychomycosis


In this retrospective study, the authors evaluated the therapeutic response to pulse itraconazole therapy in 17 children (age range 3-14 years, 9 boys) with onychomycosis who presented to a pediatric dermatology clinic in Chicago, IL, between January 1995 and June 1998. Dermatophyte infection was confirmed by a potassium hydroxide preparation or fungal culture. Patients with underlying skin diseases that could affect the nail (eg, psoriasis) were excluded. Itraconazole (in capsule form) was administered at a dose of...
n part one of this study performed in a pediatric neurology practice, 56 children with autism or pervasive developmental disorder (PDD) were entered into an open-label trial of the gastrointestinal hormone secretin which has been anecdotally reported1 to produce dramatic improvement in children with autistic spectrum disorders. A modification of the Childhood Autism Rating Scales (CARS) was administered by the same parent, both pre- and post-infusion. Some minimal but potentially significant changes in GI symptoms, language and social relatedness were reported for those children who were more severely involved at the start of the study and the authors hypothesized that this may represent “regression towards the mean.” In part two of this study, 23 children with autism/PDD were entered into a double-blind crossover design to assess the impact of secretin on autistic behavior. There were no statistically significant group differences between secretin and placebo.

Although this paper is in agreement with a previous report that noted no effect of secretin on autistic spectrum disorders,2 the complexity of the issue is reflected in the editorial3 that preceded and the comment4 that follows this paper which cast its negative data in a positive light. One major limitation of all studies on the effect of secretin on autism is the absence of reliable measures of short-term change in a population of autistic children. None of the secretin studies reported so far has looked at detailed measures of pragmatic language. For that matter, there is little agreement on how to best measure change in autistic children even when assessing the use of behavioral interventions extending over years. More sensitive measures of behavioral change are needed to assess secretin and, for that matter, any neuropsychopharmacological agents, intended for use in autism/PDD.

No one has been able to replicate any dramatic improvement in children with autism/PDD who are given secretin. It is possible a subpopulation of children with autism/PDD exists who may respond to secretin. However, until blinded studies can identify such a group, secretin cannot be recommended for routine clinical use. Pediatricians can be comfortable with the negative reassurance of “not proven.” (This “not proven although we’ve really tried” is much stronger than “not proven because we haven’t yet gotten

5 mg/kg daily for 7 consecutive days, once each month, for 3 to 5 months depending on clinical response. All patients had at least 1 follow-up visit within 3 months of initiating treatment and most were evaluated at 6 months. Prior to data analysis, telephone contact was made to assess long-term outcome. Clinical cure was defined as normal-appearing nails after itraconazole treatment; those with signs of onychomycosis and a positive culture following therapy were considered to have relapsed.

Nail changes were present for 2 months to 5 years (mean 10.8 months) before study entry. Eight patients had active or past tinea pedis and 10 had at least 1 first degree relative with nail changes. Prior unsuccessful treatments included oral griseofulvin (1 patient) and a topical antifungal (10 patients). Toenails only were involved in 15 patients; 2 had involvement of toenails and fingernails. Eight children received a 3-month course of itraconazole, 6 received 4 months, and 3 received 5 months. Sixteen of 17 patients experienced a clinical cure; 7 were cured after 3 pulses. No adverse effects were reported, although laboratory studies were not performed. The authors conclude that pulse itraconazole therapy is both safe and effective in the treatment of dermatophyte onychomycosis in children and is preferable to griseofulvin.

Infection of the nails by dermatophytes is uncommon prior to puberty but, as illustrated by the present study, the risk is increased when an adult family member has onychomycosis.1 Because topical antifungals do not penetrate the nail plate well, they generally are ineffective except in children with very mild or superficial infections.2 Although griseofulvin has been the oral agent of choice for many years, its cure rate is low, the relapse rate high, and prolonged treatment (eg, 9 to 12 months) is required. In contrast, when used daily for 3 months to treat toenail infection, newer antifungal agents such as terbinafine and itraconazole have a cure rate of approximately 80% and a relapse rate of 10% to 12%.3 Owing to its extended tissue half-life, itraconazole may be administered in a pulsed fashion. The present study confirms that this dosing schedule is effective in the treatment of children with onychomycosis caused by a dermatophyte. While experience with its use in children is limited, itraconazole appears to be well-tolerated except for diarrhea that may result from the cyclodextrin solubilizer employed in the suspension.1,2,4 Itraconazole also has important interactions with a number of drugs, including those metabolized by the cytochrome P-450 3A4 enzyme system, such as astemizole (Hismanal) and cisapride (Propulsid). In view of this, and because itraconazole is comparatively more expensive for the treatment of onychomycosis, some clinicians favor terbinafine for the treatment of onychomycosis, which requires continuous dosing for 6-12 weeks and also has interactions with a number of drugs including cimetidine and rifampin.5

References
around to trying.”) The gut and the brain may indeed be related and intriguing hypotheses on possible associations between autism and the gut continue to be formulated. However, at the present time this relationship is being advanced by additional hypotheses rather than by data.

References

NEUROLOGICAL SURGERY

Neurosurgical Treatment of Incontinence in School-age Children: Unanswered Questions


The tethered spinal cord (TSC) syndrome is characterized by variable patterns of progressive neurological signs and symptoms including pain, paresthesia, sensory loss, spasticity, weakness, bowel, bladder, and sexual dysfunction. It is assumed that the physiological disturbance is due to mechanical traction on the spinal cord occurring when normal spinal cord mobility is limited by congenital or postsurgical lesions that anchor it to adjacent structures. The most common cause of TSC is disruption of neural tube formation or a development of the caudal cell mass—the family of conditions referred to as “spina bifida.” The imaging hallmark of spinal cord tethering is a low-lying spinal cord terminating below the L1-L2 interspace. Neurosurgical treatment of tethered spinal cord syndrome is variably successful at arresting, or even reversing, the associated progressive neurological disability.

There have been attempts to define a more subtle clinical entity characterized not by structural but by functional impairment of spinal cord mobility, presumably on the basis of abnormal elasticity of the filum terminale. Affected patients are purported to have symptoms and signs of spinal cord tethering with normal spinal cord imaging. Selcuki et al from Ankara, Turkey report 2 groups of patients: a “primary” (normal imaging of the spinal cord and filum) TSC group (17 patients, average age at surgery 10.2 years) with urinary incontinence without neurological abnormalities but with normal imaging of the spinal cord and filum, and a “secondary” (abnormal imaging) group (60 patients, average age 6.3 years) with imaging signs of TSC associated with neurological deficits and developmental lesions of the skin, spinal column, lower extremities, and urogenital tract. Both groups underwent urodynamic testing before surgery and at unspecified times during the postoperative follow-up, which averaged 18 and 15 months in the primary and secondary groups, respectively. Urological results were graded by subjective patient report and by objective findings on repeat urodynamic testing. Both subjective and objective improvements were seen in 59% of the primary and 29% of the secondary group. The authors conclude that “incontinent patients with normal level conus medullaris and normal thickness filum terminale must be given a chance of untethering if urodynamic studies reveal neurogenic bladder of the hypertonic but hyperreflexic type.”

Commentary by Joseph H. Piatt, Jr., MD, FAAP

We know neither what becomes of incontinent children in the long-term, nor how to identify a neurogenic bladder disturbance in an otherwise normal child.1 Thus, the rationale for cutting the filum of incontinent children is dubious, and the population of patients who might benefit is ill-defined. So far as this reviewer knows, only 2 institutions (1 of which is represented in the above study) have reported in peer-reviewed journals on their experiences with division of normal filum for childhood incontinence.2,3 At the other center, the Hospital for Sick Children in Toronto, this procedure has fallen out of favor. Nevertheless, perhaps because the pool of potential candidates is so large, interest is growing, and the questions that have arisen deserve serious investigation. Case series, such as the current study, will not be helpful. Controlled trials featuring objective clinical, physiological, and imaging evaluations and long-term follow-up will be necessary to move this therapeutic modality beyond its present, anecdotal status.

References

CARDIOLOGY

Spontaneous Closure of Atrial Septal Defects


The objective of the current study was to assess the role that certain specific variables might have on spontaneous atrial septal defects (ASD) closure. The variables included: gestational age of the infant, presence of a patent ductus arteriosus (PDA), presence of chronic lung disease, gender, and the initial size of the atrial defect (divided into 3 groups between 3 and 7 mm). This investigation was
a retrospective review of 82 newborn infants (38 premature and 44 full-term) who had echocardiographic (2-dimensional and color Doppler) examination performed before the age of 1 month. The preterm infants ranged in age from 23-36 weeks with a mean of 31 weeks. Each of the infants had follow-up echocardiographic examinations as well. None of the infants had specific interventions performed to close their ASD. Outcomes were assessed using Kaplan-Meier survival analysis and the variables were analyzed using univariate and multivariate comparisons.

Based on the data obtained in this investigation, the authors concluded that the majority of neonatal ASDs would close. Importantly, they found that gestational age (full-term infants) and the presence of a PDA at the time of the initial echocardiographic examination were significant and independent predictors for earlier spontaneous ASD closure. Chronic lung disease was associated with a delay in spontaneous closure of ASD. However, as this finding was seen only in premature infants, the independent role that chronic lung disease plays in delaying ASD closure could not be assessed in this study. Gender and the initial size of the ASD were not found to be independent predictors of ASD closure.

In summary, ASDs diagnosed in the first months of life clearly have the potential for regression in size with complete spontaneous closure whether small or large.1,4 For the primary care physician, this study means that conservative management is in order for any infant with the finding of an ASD unless there are overt signs of congestive heart failure.

Editors’ Note

While this study does bring closure concerning what to do with asymptomatic children with ASDs, it does make us ask why (if the children were asymptomatic) the echoes were done in the first place.

References

GENETICS/BIRTH DEFECTS

Gene Therapy for SCID


Severe Combined Immunodeficiency (SCID)-X1 Disease is a lethal X-linked recessive disorder in which mutations of the gene coding for a subunit of interleukin receptors result in a block in differentiation of T and natural killer (NK) lymphocytes. SCID-X1 is a reliable model for gene therapy because it is lethal and frequently can be cured by allogenic bone marrow transplantation. Two patients with SCID-X1, 11 months and 8 months old, met eligibility criteria for a gene therapy trial. Bone marrow cells from each patient were harvested, separated, and infected ex vivo by a retrovirus vector with complementary DNA, and approximately 20%-40% of the cells expressed the transgene. Each patient was infused with his infected cells without prior chemoablation. After a ten-month follow-up period, transgene-expressing T and NK cells were detected in both patients and T, B, and natural killer cell counts and function, including antigen-specific responses, were comparable to those of age-matched controls. Both patients have normal growth and psychomotor development, and no side effects have been noted.

Commentary by Lawrence R. Shapiro, MD, FAAP

Westchester County Medical Center, Valhalla, NY

This successful trial represents a milestone in the development of gene therapy. As the authors point out, the gene transfer was accomplished without myeloablative or immunosuppressive therapy; consequently, this success prepares the way for possible application of these therapeutic methods to other genetic diseases in which there is defective generation of cell subsets, such as other forms of SCID. Despite the optimistic view that gene transfer can provide a T cell pool with a functional memory for a number of years, infected cells might have reduced self-renewal ability and shortened life span resulting in deficient generation of new T and natural killer cells. As the authors conclude, long-term follow-up will be necessary to determine the long-term effects of this method of gene therapy.
Carbonated Beverages and Bone Fractures in Teenage Girls


A recent study demonstrated that teenagers have dramatically increased their consumption of soft drinks and have, concomitantly, decreased their consumption of milk. Excessive carbonated beverage consumption and low calcium intake in the adolescent population has the potential to increase obesity, tooth decay, and osteoporosis, but the risk of these potential adverse effects is poorly studied. The aim of this study was to confirm previous findings that the consumption of carbonated beverages is associated with bone fractures among adolescent females. As part of a larger Harvard School of Public Health study designed to reduce teenage pregnancy, 9th and 10th grade females attending an urban public high school completed a self-administered survey in the classroom setting. The survey included questions about intensity of physical activity, consumption of carbonated beverages and type consumed (colas versus non-colas), and medical history, including any past history of bone fractures. Of the 460 girls surveyed (mean age 15 yrs 8 months), 20% reported bone fractures and 79% reported drinking carbonated beverages, with most drinking either exclusively colas (50%) or both colas and non-colas (15%). Over half reported not participating in any organized physical activity, and 11% reported being completely inactive. After controlling for participation in organized physical activity programs and activity level by logistic regression, girls who consumed any carbonated beverages were three times more likely to report a previous bone fracture than those consuming no carbonated beverages (OR=3.14; 95% CI, 1.45-6.78), and those consuming some cola beverages reported more fractures (OR=2.01; 95% CI, 1.17-3.43). Among physically active girls the likelihood of having a fracture was almost 5 times greater than that for active girls consuming no cola beverages (OR=4.94; 95% CI, 1.79-13.62).

The findings of this study—that the intake of carbonated beverages, both colas and non-colas, is associated with a higher risk of bone fractures in adolescent females—support an earlier report by Wyshak and Frish documenting an association between cola drinks and bone fractures among physically active adolescent boys and girls. Despite its limitations—a cross-sectional design that precludes any determination of causality or temporal relationships, a reliance on self-report, a failure to quantify the amount of carbonated beverages consumed, a failure to assess the consumption of calcium-rich drinks, and the absence of any measurement of bone mineral density—this study is intriguing in light of the possible bone resorption related to high levels of phosphorus intake which may occur with high intake of carbonated beverages. Given current trends in teenagers’ diets and the substitution of phosphorus-rich carbonated beverages for calcium-rich beverages, these results warrant attention and further study. Longitudinal studies and those that include more extensive diet history and biochemical markers of bone density would go a long way in clarifying the relationships observed in this study. Because adolescence is such a critical time for bone mass formation, further studies elucidating this relationship could have significant implications for the health of women in later life and for the prevention messages that pediatricians need to communicate during the adolescent years.

References

The Ectopic Testis: Another Form of Undescended Testis


The subject of undescended testis is made up of several categories including retractile testis, undescended testis, intra-abdominal undescended testis, and ectopic testis. Ectopic testis can occur in the subcutaneous tissue above the inguinal canal (the superficial inguinal pouch), in the perineum, lateral to the scrotum, and in the femoral region. Generally, it is believed that ectopic testes are more like normal testes than undescended testes in their potential for fertility, growth, and risk of testicular cancer. Recently, there have been reports that ectopic testes in the superficial inguinal pouch have a similar histology to true undescended testes with decreased germ cell counts. Hutcheson et al studied ectopic testes that were not in the superficial inguinal pouch but had progressed further from the abdomen in order to determine if they shared the same pathological findings with undescended testes. They identified 24 boys (1.6%) out of 2,248 children who underwent orchidopexy and biopsy from 1985-1997. Seventeen of the 24 had adequate information for inclusion and the testes were located in the following sites: 7 perineal, 7 lateral to the scrotum, and 3 femoral. The age at treatment varied with each
location group and ranged from a mean of 12 months, 16 months, and 60 months respectively. The testes were localized, measured, and biopsied in order to count germ cell numbers. Germ cell counts and testicular volume were compared to established data from true undescended testes biopsied at the same institution. The study identified no significant difference between the ectopic testes and the true undescended testes in terms of germ cells per tubule and testicular size for age. Furthermore, anomalies of the processus vaginalis and epididymis were found with the same frequency in both the undescended and the ectopic testes. The authors conclude that ectopic testis is a variation of undescended testis with similar histology, developmental anomalies, and risks. They propose that ectopic testis is due to the same endocrine disturbance as undescended testis and should be considered as part of the “undescended testis sequence”.

Commentary by Anthony J. Casale, MD, FAAP

Traditional teaching has led us to believe that ectopic testis is not subject to the same risk of subfertility and cancer as the true undescended testis because it was able to descend out of the abdomen and inguinal canal. When Snyder demonstrated that high ectopic testis, in fact, appeared to be more like undescended testis than normal testis, it was not clear if all ectopic testes were uniformly dysfunctional.1 The above study demonstrates that ectopic testes, which have moved far from the inguinal canal and the abdomen, are not normal testes in an abnormal location but are, in fact, undescended testes and carry the same risks of cancer and sub-fertility.

Reference


Letter to the Editors

To the editors—

I would like to challenge the commentary on the Wong et al, NEJM piece by Drs. Gruskin and Shulman. The summary of the paper is quite good but their interpretation of the methodologic strength of this piece of research is controversial, in my view. Acceptance of this study’s conclusions verbatim could seriously impact a clinician’s approach to the febrile child with clinical signs of bacterial enteritis. Please go to the following webpage to read my interpretation of this study’s methodology http://www.pediatric-emergency.com/wong.htm With specific regards to Wong et al’s use of logistic regression analysis in this study please refer to the following piece of research: Peduzzi P, et al. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49:1373-1379.

Jay D. Fisher, MD, FAAP
Las Vegas, NV

Reply—

Thank you for your letter about the lead abstract and accompanying commentary in our July issue concerning the antibiotic treatment of E coli O157:H7 and the risk of hemolytic-uremic syndrome (HUS). Your thoughtful Web site commentary stimulated discussion of these methodologic issues among our editorial team and consultants. The finer points of regression analysis are “out of my league.” Nonetheless, based on the responses of my methodologic consultants I will attempt a brief, partial response to some of the complex issues you have raised. We agree that knowing whether a drug has a particular effect is best evaluated in a high quality randomized controlled trial. However, when the only known effect of a drug on a disease is adverse, such a randomized controlled trial may not be ethical or even possible. So far as we are aware, there are no studies suggesting that antibiotics on presentation ever prevent HUS. If it could be cogently argued that antibiotic therapy may benefit a large number of children (those with other infections), such a study might be justified; however, in the US delaying antibiotic treatment for the most common causes of bloody diarrhea—until culture results are available, ie, E coli, campylobacter, salmonella, shigella—seems unlikely to offset the potential adverse effects of antibiotic treatment on E coli suggested by this study.

We believe Wong et al attempted to deal head-on with the problem of “confounding by indication.” For example, the collection of information from clinicians occurred prior to the development of HUS and therefore should be free from recall bias that might occur if the data were collected after the onset of disease.

The number of cases of HUS relative to the number of variables remains quite small, as you point out. I believe that Wong et al’s model used three variables (antibiotics, white count, and the day of culture) and that there were in fact ten children (not five, which was the number of exposed cases) who developed HUS.

My consultants suggested that you might find of interest an article on how to assess how large an influence a hidden confounder might have: Lynn DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounder might have: Lynn DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. Biometrics. 1998;54: 948-963.

In sum, on reflection my colleagues and I continue to believe that this study represents the best data to date; that antibiotics appear to strongly increase the risk for the development of HUS; and under these circumstances an RCT is not feasible.

Thank you again for bringing your concerns to our attention. I learned a lot from the ensuing discussions with my colleagues. I hope you will continue to be a critical reader of AAP Grand Rounds.

Edgar K. Marcuse, MD, MPH, FAAP
Seattle, WA
CME Questions

The following continuing medical education questions cover the content of the September 2000 issue of AAP Grand Rounds. Please keep this issue. Each semester of material is worth 8 hours of AMA PRA Category 1 CME credit (16 hours per year).

1. According to Vichinsky et al, all of the following are appropriate early therapies for subjects with acute chest syndrome except:
   a. a macrolide antibiotic
   b. chest tube thoracostomy
   c. inhaled bronchodilators
   d. supplemental oxygen
   e. transfusion

2. What factor does not influence immunization status of children?
   a. Ethnic or minority background
   b. Large family size
   c. Low socioeconomic status
   d. Sex

3. Risk factors for malignant melanoma that may be identified in childhood include all except:
   a. light skin color
   b. overuse of sunscreens
   c. positive family history
   d. propensity to sunburn
   e. unprotected sun exposure

4. A child aged 7 years diagnosed with attention deficit hyperactivity disorder has a variety of sleep disturbances reported by the parents, and some that are also recognized by the child. Which one of the following sleep disturbances is most frequently reported by the child?
   a. Afraid of sleeping alone
   b. Fights with parents about bedtime
   c. Having nightmares
   d. Sleeps too little

5. Which of the following reasons is the least commonly reported by caregivers for considering limitation of care in a PICU?
   a. Burden vs benefit
   b. Imminent death

   c. Inability to recover to a reasonable quality of life
   d. Inappropriate use of medical resources
   e. Poor baseline neurologic function

6. A true statement about onychomycosis is:
   a. affected individuals rarely have coexisting tinea pedis
   b. infection does not occur prior to puberty
   c. intrafamilial spread of infection is uncommon
   d. oral antifungals (eg, terbinafine, itraconazole) are indicated for treatment
   e. topical antifungals (eg, clotrimazole, ketoconazole) are highly effective

7. A standard diagnostic instrument for autism is the
   a. CARS
   b. CAT/CLAMS
   c. Horvath scale
   d. Likert scale
   e. secretin test

8. What is the imaging hallmark of tethering of the spinal cord?
   a. A normal renal/bladder ultrasound
   b. Termination of the spinal cord below the L1-L2 interspace
   c. Termination of the thecal sac below the L1-L2 interspace
   d. Thickening and trabeculation of the bladder wall

9. A 3-month-old asymptomatic infant in your practice has been found to have a moderate to large ASD on a recent echocardiographic evaluation. The appropriate course of management would be:
   a. close follow-up with the anticipation of needing pharmacological management
   b. follow conservatively with follow-up echocardiography to be arranged at some future time
   c. the finding can be ignored as spontaneous ASD closure can be assumed
   d. reassess pregnancy history with special emphasis on mid-trimester problems
   e. referral to a cardiac surgical service with the intent of arranging for closure

10. A 6-month-old male with SCID-X1 Disease had a brother with this same disorder who died from an infection. The infant's parents have agreed to gene therapy utilizing gene transfer. The gene transfer involves:
    a. chemoablation of the infant's bone marrow
    b. gene transfer by ex vivo viral infection of the infant's bone marrow cells
    c. gene transfer by in vivo viral infection of progenitor cells from the infant
    d. irradiation of the infant's bone marrow
    e. proven long term clinical benefit without untoward effects

11. The study by Wyshak et al supports a relationship between consumption of carbonated beverages in the teen years and:
    a. increased bone fractures
    b. low calcium intake
    c. obesity
    d. osteoporosis
    e. tooth decay

September 2000
12. Ectopic testes make up what proportion of all undescended testes?
   a. a third of the total
   b. a very small portion of the total
   c. over one-half of all undescended testes
   d. they are unrelated to undescended testes

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CME Quiz Sheets are included in the June and December issues of AAP Grand Rounds. This is a scientific publication designed to present updates and opinions to health care professionals. It does not provide medical advice for any individual case, and is not intended for the layman.

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