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The Editors’ Perspectives

Safety of bumper pads

As the Back to Sleep program has effectively decreased the incidence of SIDS, the residual causes of accidental deaths in infancy become more apparent. The recent discussions about the characteristics of bedding material, bed sharing and associations with smoking are examples of the scrutiny given to accidental deaths. In this issue of The Journal, Thach et al identify bumper pads used in cribs as another source of risk for injury and accidental death for infants. Their conclusions are based on the databases of the US Consumer Product Safety Commission, which depend on what gets reported. Thus, there is neither an accurate numerator for the actual number of attributable injuries and deaths nor a denominator about frequency of use of bumper pads. Nevertheless, the probably low estimates do raise significant concerns that need to be recognized.

—Alan H. Jobe, MD, PhD
page 271 (article)
page 237 (editorial)

Treatment of childhood obesity: What works?

The epidemic of childhood obesity has left clinicians with important questions concerning effective management strategies. In this issue, van den Akker et al present the 1-year follow-up results of a multidisciplinary cognitive behavioral therapy approach to treat obese children. The program uses group therapy with a variety of behavioral therapy techniques. They found a weight loss of approximately 19% after 1 year in those who completed follow-up. Unfortunately, 33% of the patients dropped out. It is clear that behavioral therapy can be beneficial for some children who are overweight and obese. Further research is needed to determine more effective strategies for those children who drop out of therapy. In this study, the dropouts were older, had higher BMI at baseline, and were less successful in weight management at the early stages of therapy.

—Stephen R. Daniels, MD, PhD
page 280
Staphylococcal anti-adhesive antibodies fail to protect premature infants from bloodstream infection (BSI)

Very low birth weight (≤ 1500 g VLBW) infants comprise 1.4% of births in the United States, and survival rates are increasing. So too, are complications of neonatal intensive care such as late onset septicemia, which occurs in 16 to 25% of VLBW infants. DeJonge et al in this issue of The Journal report the results of a phase III, randomized, double-blind, placebo-controlled multicenter trial of prophylactic use of immunoglobulin selected for high titers of staphylococcal anti-adhesive antibodies (IHN-A21) and prepared for intravenous use (IGIV). The phase III trial was conducted on the heels of a phase II trial that showed a trend toward protection from staphylococcal and candidal bloodstream infection (BSI), with adequate sample size and power in the Phase III trial. Almost 2000 neonates in 95 centers in the United States and Canada received at least one infusion of study drug (750 mg/kg IHN-A21 or saline placebo). Although there was no safety issue, there was no effect on rate or timing of staphylococcal or other BSIs.

In the accompanying editorial, de la Morena puts this definitively negative study result in the context of other disappointments of transiently promising interventions, and speculates on what premature neonates really need.

—Sarah S. Long, MD
  page 260 (article)
  page 232 (editorial)

Vocal cord dysfunction and feeding after cardiac surgery

Pediatric patients may have feeding difficulties after cardiovascular surgery. Cardiothoracic surgery can also be associated with vocal cord dysfunction. In this issue of The Journal, Sachdeva et al evaluated the relationship of vocal cord dysfunction and feeding difficulties in a group of patients after cardiovascular surgery. Approximately 2% had vocal cord dysfunction. They found that many patients with vocal cord dysfunction had concomitant feeding difficulties, some of whom required feeding by gastrostomy tube. The authors recommend surveillance for vocal cord dysfunction in patients undergoing surgery of the aortic arch in which the recurrent laryngeal nerve can be damaged.

—Stephen R. Daniels, MD, PhD
  page 312

Kawasaki disease and subsequent risk for atherosclerosis

A major complication of Kawasaki disease is inflammation and vasculitis of the coronary arteries. This may lead to coronary artery aneurysms. An important question is whether those without aneurysms have increased long-term risk of atherosclerosis. In this issue of The Journal two studies address this question. McCrindle et al found that patients, after Kawasaki disease, have some abnormalities in cardiovascular risk factors, but have no evidence for systemic arterial endothelial dysfunction. This is reassuring. However, in a separate study, Dalla Pozza et al found that carotid artery intimal-medial thickness was greater in patients after Kawasaki disease than controls and that those with coronary artery involvement after Kawasaki disease had the largest intimal-medial thickness. These findings suggest potentially accelerated atherosclerosis in patients with Kawasaki disease.

In an editorial, Selamet Tierney and Newburger point out that we currently must rely on relatively small studies, with differing patient characteristics, different length of followup and intermediate outcomes in which interpretation of the clinical relevance of results may be difficult. They emphasize that long-term international studies with clinical outcomes will be optimum to assess the impact of Kawasaki disease on vascular health. In the meantime, appropriate management of known risk factors, such as hypertension and dyslipidemia, is important to maximize vascular health in patients who have had Kawasaki disease.

—Stephen R. Daniels, MD, PhD
  page 244 (McCrindle)
  page 239 (Dalla Pozza)
  page 225 (editorial)
Prebiotics and weight gain

There have been few studies of the impact of prebiotics on weight gain in children and adolescents. In this issue of The Journal, Abrams et al evaluated the effect of a daily prebiotic supplement which consisted of a co-spray dried 1:1 mixture of oligofructose and long chain inulin compared to a control supplement. They found that subjects randomized to the prebiotic had a smaller increase in BMI compared to controls, and maintained their BMI Z-score while controls had increased BMI Z-score. Of interest is that the prebiotic appeared to have a greater impact on BMI in subjects who had higher intake of calcium.

This study did not focus on subjects who were overweight or randomly allocate the level of calcium intake, so the results may not be applicable to treatment of overweight and could be confounded by other aspects of diet and physical activity. Further research will be needed to evaluate this product and other prebiotics in the treatment of obesity.

—Stephen R. Daniels, MD, PhD

Tonsillectomy as treatment of PFAPA syndrome

Periodic-Fever-Aphthous stomatitis-Pharyngitis and cervical Adenitis (PFAPA) syndrome is a curious, troublesome and not uncommon pediatric diagnosis. Diagnosis is entirely clinical, with the primary feature of clockwork periodicity of fever every 3-6 weeks for 3-5 days with little else. The cause is unknown, but the course is known likely to be persistent over years before spontaneous, full resolution. Case series have all reported a curious, apparent, immediate, curative effect of tonsillectomy in many affected children. In this issue of The Journal, Renko et al report results of a randomized controlled trial of tonsillectomy versus follow-up alone in 26 children with PFAPA enrolled at mean age of 4.1 years after at least 5 predictable, periodic episodes of fever. Six months after randomization, all 14 children who underwent tonsillectomy were free of symptoms, whereas 6 of 12 children randomized to follow-up alone continued to have periodic fever; 5 of these 6 children then underwent tonsillectomy and were promptly “cured.” With caveats of small sample size, inability to blind and inability to ascertain specificity of diagnosis of PFAPA (and noting that 29% had exudative tonsillitis, which is distinctly unusual in case series from the United States), these results are impressive, and “cure” is as curious as is the problem.

—Sarah S. Long, MD

In vivo magnetic resonance spectroscopy of muscle

Proton magnetic resonance spectroscopy was used in vivo to evaluate muscle metabolism in patients with neuromuscular diseases. The results show that children with Duchenne muscular dystrophy and spinal muscular atrophy have reduced tri-methyl-amid (TMA) peaks. TMA is involved in the metabolism of phospholipids and the decrease must represent a reduced rate of cell membrane synthesis, decreased cell turnover or a decreased cell number in these diseases that are characterized by fatty degeneration.

—Robert W. Wilmott, MD
American Pediatric Academia: The Looming Question
Scott A. Rivkees, MD, and Myron Genel, MD, New Haven, Connecticut

EDITORIALS

Are Patients with Kawasaki Disease at Risk for Premature Atherosclerosis?
Elif Seda Selamet Tierney, MD, and Jane W. Newburger, MD, MPH, Boston, Massachusetts

Non! to Non-Steroidal Anti-Inflammatory Therapy for Inflammatory Lung Disease in Cystic Fibrosis (at Least at the Moment)
Andrew Bush, MB, BS (Hons), MA, MD, FRCP, FRCPC, and Jane Davies, MB, ChB, MRCGP, MRCPCH, MD, London, United Kingdom

What is the Role of Cystic Fibrosis Transmembrane Conductance Regulator Dysfunction in Primary Sclerosing Cholangitis?
Dennis D. Black, Memphis, Tennessee

Specific Immune Globulin Therapy for Prevention of Nosocomial Staphylococcal Bloodstream Infection in Premature Infants: Not What We Hoped for!
M. Teresa de la Morena, MD, Dallas, Texas

Acute Viral Bronchiolitis: To Treat or Not to Treat—That Is the Question
Claudia Calogero, MD, and Peter D. Sly, MBBS, MD, DSc, FRACP, Florence, Italy, and Subiaco, Australia

“And Things that Go Bump in the Night”: Nothing to Fear?
Rachel Y. Moon, MD, Washington, DC

ORIGINAL ARTICLES

Subclinical Atherosclerosis, but Normal Autonomic Function after Kawasaki Disease
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Are Patients after Kawasaki Disease at Increased Risk for Accelerated Atherosclerosis?
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High-Dose Ibuprofen in Cystic Fibrosis: Canadian Safety and Effectiveness Trial
Larry C. Lands, MD, PhD, Ruth Milner, PhD, André M. Cantin, MD, David Manson, MD, and Mary Corey, PhD, Montreal and Sherbrooke, Quebec, Vancouver, British Columbia, and Toronto, Ontario, Canada

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Harpreet Pall, MD, Julian Zielenski, PhD, Maureen M. Jonas, MD, Deborah A. Dasilva, RN, Kimberly M. Potvin, Xiao-Wei Yuan, MSc, Qiuju Huang, MD, and Steven D. Freedman, MD, PhD, Boston, Massachusetts, and Toronto, Ontario, Canada

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Deaths and Injuries Attributed to Infant Crib Bumper Pads
Bradley T. Thach, MD, George W. Rutherford, Jr, MS, and Kathleen Harris, St. Louis, Missouri

Insulin Resistance in Adolescents
Ann M. Rodden, DO, Vanessa A. Diaz, MD, MS, Arch G. Mainous III, PhD, Richelle J. Koopman, MD, MS, and Mark E. Geesey, MS, Charleston, South Carolina

A Cognitive Behavioral Therapy Program for Overweight Children
Erica L. T. van den Akker, MD, Patrycja J. Puiman, MD, Mieke Groen, MSc, Reinier Timman, PhD, Mieke T. M. Jongejan, MD, PhD, and Wim Trijsburg, PhD, Rotterdam, the Netherlands

Socioeconomic Position, Maternal IQ, Home Environment, and Cognitive Development
Shilu Tong, PhD, Peter Baghurst, PhD, Graham Vimpani, PhD, and Anthony McMichael, PhD, Kelvin Grove, Adelaide, Newcastle, and Canberra, Australia

A Randomized, Controlled Trial of Tonsillectomy in Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome
M. Renko, MD, PhD, E. Salo, MD, PhD, A. Putto-Laurila, MD, PhD, H. Saxen, MD, PhD, P. S. Mattila, MD, PhD, J. Luotonen, MD, PhD, O. Ruuskanen, MD, PhD, and M. Uhari, MD, PhD, Oulu, Helsinki, and Turku, Finland

50 Years Ago in The Journal of Pediatrics—Steroid Therapy for Rheumatic Fever
Eli M. Eisenstein, MD, Mount Scopus, Jerusalem, Israel

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Long-Term Follow-Up in 12 Children with Pulmonary Arteriovenous Malformations: Confirmation of Hereditary Hemorrhagic Telangiectasia in all Cases
Aurore Curie, MD, Gaëtan Lesca, MD, Vincent Cottin, MD, PhD, Patrick Edery, MD, PhD, Gabriel Bellon, MD, PhD, Marie E. Faughnan, MD, MSc, and Henri Plauchu, MD, PhD, Lyon, France and Toronto, Canada

50 Years Ago in The Journal of Pediatrics—Niemann-Pick Disease in a Boy of 16 Months
Hans C. Andersson, MD, FACMG, New Orleans, Louisiana

Duodenogastro-Esophageal Reflux in Children with Refractory Gastro-Esophageal Reflux Disease
Ilse Hoffman, MD, Alexander Tertychnyy, MD, Nadine Ectors, PhD, Toon De Greef, Nancy Haesendonck, and Jan Tack, PhD, Leuven, Belgium, and Moscow, Russia

Vocal Cord Dysfunction and Feeding Difficulties after Pediatric Cardiovascular Surgery
Ritu Sachdeva, MD, Elora Hussain, MD, M. Michele Moss, MD, Michael L. Schmitz, MD, Richard M. Ray, MD, Michiaki Imamura, MD, PhD, and Robert D. B. Jaquiss, MD, Little Rock, Arkansas

Growing Skull Fracture after Minor Closed-Head Injury
Jean-Rodolphe Vignes, MD, PhD, N. U. Owase Jeelani, MRCS, MBA, MPhil, Ashfaq Jeelani, MD, MSc, MRCPCH, Michel Dautheribes, MD, and Dominique Liguoro, MD, PhD, Bordeaux, France, and London and Wickford, Essex, UK

In Vivo Proton Magnetic Resonance Spectroscopy Assessment for Muscle Metabolism in Neuromuscular Diseases
Tsyh-Jyi Hsieh, MD, Chien-Kuo Wang, MD, Hung-Yi Chuang, MD, ScD, Yuh-Jyh Jong, MD, MMS, Chun-Wei Li, PhD, and Gin-Chung Liu, MD, Kaohsiung, Taiwan

ABCA3 Deficiency Presenting as Persistent Pulmonary Hypertension of the Newborn
Anette M. Kunig, MD, Thomas A. Parker, MD, Lawrence M. Nogee, MD, Steven H. Abman, MD, and John P. Kinsella, MD, Denver, Colorado, and Baltimore, Maryland

Severe Cerebellar Hypoplasia Associated with Osteogenesis Imperfecta Type III
B. Tabarki, MD, S. Al-Malki, MD, and H. Al-Ghamdi, MD, Taif, Kingdom of Saudi Arabia

Clinical Research Abstracts for Pediatricians

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Transfusion Threshold in Anemic Premature Infants
Arie L. Alkalay, MD, and Charles F. Simmons, MD, Los Angeles, California

Reply
H. Kirpalani, MSc, FRCP(UK), R. Whyte, MB, FRCP(C), and R. Roberts, M.Tech, Hamilton, Ontario, Canada

The Natural History of Thyroid Autoimmunity and Thyroid Function in Children with Type 1 Diabetes
Terri H. Lipman, PhD, CRNP, Iraj Rezvani, MD, and Angelo M. DiGeorge, MD, Philadelphia, Pennsylvania

Reply
Giorgio Radetti, MD, Elena Gottardi, MD, Gianni Bona, MD, Andrea Corrias, MD, Silvana Salardi, MD, and Sandro Loche, MD, Bolzano, Novara, Torino, Bologna, and Cagliari, Italy

Extreme Obesity among Children in Mexico
Arturo Jimenez Cruz, MD, PhD, Montserrat Bacardi-Gascon, MD, EdD, and Elizabeth Jones, RD, EdD, Mexico

Information for Readers
Announcements
Guide for Authors
Available at www.jpeds.com
September 2007

Youth Mental Health: Bridging Research and Clinical Practice. September 17-18, 2007, University of Minnesota Office of Continuing Medical Education, Radisson University Hotel, Minneapolis, Minnesota. Review the most common pediatric disorders (psychosis, anxiety and depression, substance abuse, trauma) in clinical practice. Connect the science and practice of prevention and treatment. Go over current knowledge, discuss the neurobiology, and get practical advice for prevention and treatment. For more information: Office of Continuing Medical Education, University of Minnesota; phone 612-626-7600 or 800-776-8636; E-mail: cme@umn.edu; Register online: www.cmecourses.umn.edu.

October 2007

New Insights into Childhood Functional Abdominal Pain and IBS, a one-day thematic educational and research conference associated with the 2007 NASPGHAN Meeting and Postgraduate Course. October 24, 2007, Grand American Hotel, Salt Lake City, Utah. Sponsored by Columbus Children’s Hospital’s Division of Gastroenterology, Hepatology and Nutrition. More than 20 multidisciplinary health care professionals will present and serve as moderators for the day-long program, scheduled the day before the NASPGHAN event. Carlo Di Lorenzo, MD, chief of the GI Division at Columbus Children’s Hospital will be one of the lead presenters. Focusing on functional abdominal pain and IBS, the program will incorporate successive moderated discussions that include etiology and pathophysiology, lessons learned from other specialties, Rome III, treatment and research. Eight CME hours will be available. For complete registration, contact NASPGHAN National Office: phone 215-233-0808; E-mail: naspghan@naspghan.org; Website: www.naspghan.org.

The Effect of Environmental Pollutants on Foetal and Child Development: A Global Issue. October 26 and 27, 2007, Hangzhou, China. A Programme for Global Paediatric Research Symposium, presented by The Programme for Global Paediatric Research and the Chinese Pediatric Society of The Chinese Medical Association; in cooperation with The Children’s Hospital of Zhejiang University School of Medicine, Shanghai Children’s Medical Center and Xinhua Hospital, affiliated with Shanghai Jiao Tong University School of Medicine. PGPR’s sixth symposium will be held October 26 and 27, 2007 in association with the Chinese Society of Pediatrics of The Chinese Medical Association. The sessions will focus on the effects of environmental pollution on foetal and child development. Particular emphasis will be placed on child health in developing countries. The symposium will be comprised of expert presentations providing an overview of the problems, issues and instances of work that is being done; oral presentations from selected abstracts on related issues; and structured panel discussions and open forums focused on determining research that is needed. A full list of speakers and topics and details of a call for abstracts are available on the conference website: www.chinamed.com.cn/pgpr2007. For more information, contact Alvin Zipursky, MD, Chair and Scientific Director, The Programme for Global Paediatric Research, The Hospital for Sick Children, Toronto, Canada; phone (001) 416-813-8762; E-mail: Alvin.Zipursky@sickkids.ca; Website: www.globalpaediatricresearch.org.

December 2007

Hot Topics in Neonatology. December 2-4, 2007, Omni Shoreham Hotel, Washington, DC. Sponsored by Neonatal Research and Technology Assessment, Inc. (NRTA). Premier, exciting, interactive annual conference for neonatologists from around the world. Average 1400 attendees, 25+ speakers and guest discussants. Chairman, Dr. Jerold F. Lucey, Wallace Professor of Neonatology, Burlington, Vermont, Editor-in-Chief, Pediatrics. For more information, contact Gail Murphy, Neonatal Research and Technology Assessment, Inc; phone 802-865-2283; E-mail: info@hottopics.org; Website: www.hottopics.org.

May 2008

9th Congress of the European Society for Pediatric Dermatology (ESPD). May 15-17, 2008, Athens Hilton Hotel, Athens, Greece. Sponsored by The European Society for Pediatric Dermatology. For more information, contact Mrs. Penelope Mitroyianni, Erasmus Conferences Tours & Travel; phone 0030 210 7257693; E-mail: info@espd2008.com; Website: www.espd2008.com.

2007-2008 Certifying Examinations of the American Board of Pediatrics

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All applicants for certifying examinations must complete applications online during the registration periods. The final month of each registration requires payment of a late fee. The requirements for online applications may be found on the ABP Website (www.abp.org) or may be obtained by contacting the ABP. Additional information including eligibility requirements and registration dates may be found on the ABP Website.
American Pediatric Academia: The Looming Question

SCOTT A. RIVKES, MD, AND MYRON GENEL, MD

Academic conferences and editorial columns have been marked in the past decade by addresses lamenting the decline of the physician-scientist, asking, “Where have all the young ones gone?”1-3 Further into the decline of the physician-scientist, coupled with progressive shortfalls of research funding and clinical revenues that have been very problematic for pediatrics, we wonder whether the next tough question will be, “Where have American academic pediatric departments gone?”

From 1998 to 2003, the National Institutes of Health (NIH) budget doubled under visionary political and research leadership. In 1997, 32 departments of pediatrics had >10 NIH grant awards.4 By 2005, >45 departments of pediatrics had >10 NIH research grants.5 Yet, as the NIH budget doubled, pediatric research growth did not keep up. The pediatric portfolio of the NIH represented 14.1% of funding in 1994.6 By 2000, this mark slipped to 12.6%.6 In 2005, the pediatric portfolio was 11.3% of NIH funding—25% less than 10 years earlier.6

Perhaps reflecting funding and faculty development issues, or perhaps not, pediatric research is shrinking on the center scientific stage. If one looks at the published reports in top-tier journals, including Science, Nature, The Proceeding of the National Academy of Sciences, The Journal of Clinical Investigation, and The New England Journal of Medicine, there has been a decline in publications from American departments of pediatrics; American pediatric departments contributed 35% fewer reports to these top journals in 2006 than in 2000.7 It is important to note that this decline is not unique to pediatrics; there has been a general decline in America’s contribution to the most meritorious literature.8

Concomitant with the decline of the physician-scientist has been large growth in the ranks of academic clinicians in pediatric departments. Financial pressures have the potential to limit the ability of this growing faculty component to contribute to scholarly activities if faculty compensation is tied to relative value unit-based clinical productivity alone.9 Proper compensation and time for education, research, publication, and non-clinical departmental activities is also needed, because these activities give a medical center enthusiasm and purpose.

The importance of the pediatric clinician-scientist is recognized at all levels of academia. Developing clinician-scientists for departments of pediatrics requires time and capital outlay that tops $1 million per junior faculty member. It costs $150,000 to $250,000, including salary, fringe benefits, and laboratory support, to train a fellow for 3 years. After completion of a fellowship, another $650,000 to $800,000 is needed to support a junior faculty member in the early years of academic growth.10 After academic independence is realized, junior and senior pediatric physician-scientists are hard-pressed to achieve sustained funding to provide substantial salary support in the current funding climate. Both junior and established senior clinician-scientists will need episodic financial support to cover funding shortfalls. Recognized for intellectual and scientific contributions, these individuals can quickly become a financial liability to departments.

In several pediatric subspecialties, including pediatric surgery, neonatology, gastroenterology, cardiology, and critical care medicine, the maximum NIH-funded salary is significantly less than the typical salaries of active practitioners.11 Although academically desirable, fully funded clinician-scientists in these subspecialties may be unaffordable, because salary supplementation needed for academic retention hurts the bottom line.
We are concerned that pediatric physician–scientists are not being trained in basic or clinical science with the same rigor and depth as PhD graduate students, with whom physician–scientists will be competing for funding. Many of us serving on grant review panels observe a “research-quality gap” between junior pediatric MD and PhD scientists. The research component of pediatric fellowship training will not succeed if viewed as a hobby or if mentors are chosen by fellows on the basis of collegiality. Reflected by the success of graduates of programs like the national Pediatric Scientist Development Program, pediatric academicians do know how to train physician–scientists—place talented individuals with great mentors and provide protected time to be creative and thrive. As is being done at a few pediatric centers, similar programs can be developed.

Pediatric departments will need to rethink their missions over the coming decade.

Serious manpower and leadership issues that limit academic growth are present in many departments of pediatrics. In pediatric endocrinology, for example, >70 positions are posted on the job-listing site of the Lawson Wilkins Pediatric Endocrinology Society, and many prestigious section-chief positions remain unfilled after lengthy searches. Perhaps we should establish distinct clinical and research training tracks in substitute of the “3-years of training for all” approach in place for 2 decades now. Shortening the duration of fellowship training to a clinical track to 2 years (or less) will speed the entry of needed clinicians to the workforce—helping one problem—and free precious departmental dollars for physician–scientist support—helping another.

Pediatric departments will need to rethink their missions in the coming decade. Biomedical research and faculty development is expensive. It may not be financially feasible to support clinical operations, medical education, the research enterprise, and faculty development and growth. Cultivating clinical faculty to develop clinical programs of excellence with sound revenue streams may be a legitimate alternative to a 4-part mission and an important form of faculty development. Such a model will be far richer if pediatric-based clinical programs are linked with institutional research programs, which can be directed toward elucidating disease mechanisms and optimizing treatment. Placing fellows and junior faculty members in non-pediatric departments during periods of training will cultivate the needed broad-based multidisciplinary ties among pediatric, basic, and other clinical departments.

Considering the current funding and medical economic climate, pediatric research may contract at many individual institutions. This change in the pediatric research base will heighten the need for federally funded center programs that can provide the needed infrastructure to maintain and enhance research in childhood diseases and disorders. In structuring such program, it will be crucial that additional funds be earmarked for pediatric research, rather than reallocating an already tight NIH pediatric research portfolio.

Failing the aforementioned, uncovering dollars to maintain academic strength and expansion may turn out to be the major challenge to academic pediatrics in the next decade. The future of academic pediatric growth in the United States may fall on the shoulders of those departments able to secure substantial philanthropic dollars, corporate investment, or medical school leaders willing to invest precious funds for the next decade. Ten years from now, we should not be surprised if pediatric academic medical prowess and leadership in the United States is concentrated in a handful of institutions that have been the beneficiaries of past and current philanthropy and commit themselves to developing the resources needed for academic achievement.

Institutions unable to make strong commitments to the years ahead with real and substantive dollars may find themselves moving from asking “Where have all our young ones gone?” to asking “Where has our once vital and thriving department gone?” And this question may arrive much sooner than we imagine.

### REFERENCES

Are Patients with Kawasaki Disease at Risk for Premature Atherosclerosis?

Kawasaki, disease (KD) is a childhood vasculitis of unknown cause characterized by fever, rash, enanthem, conjunctival injection, extremity changes, cervical adenopathy, and laboratory test results reflecting intense systemic inflammation. First described in Japan in 1967, KD has been described worldwide among children of all races and ethnicities. In the United States, more than 4000 hospitalizations associated with KD were reported in 2000, and KD has replaced rheumatic fever as the leading cause of acquired heart disease in children. Clinical and epidemiologic features suggest an infectious trigger, with expression of clinical disease likely modified by genetic susceptibility. Conventional therapy for KD includes administration of aspirin and intravenous gamma globulin (IVIG) within the first 10 days of illness, and ideally within the first week. The goal of therapy in the acute phase of KD is to reduce inflammation in the coronary artery wall and prevent coronary artery thrombosis.

The acute signs and symptoms of KD are self-limited, and the disease only rarely recurs. However, the vascular inflammation that accompanies this disease is diffuse and may have long-term sequelae. The most severely affected children have coronary artery aneurysms that can lead to myocardial infarction, ischemic cardiomyopathy, and sudden death. Coronary artery aneurysms defined by Japanese Ministry of Health criteria occur in up to 25% of untreated children; treatment with high-dose IVIG in the acute phase of the disease reduces the risk of aneurysms by approximately 5-fold. More subtle coronary artery dilation occurs among those who do not meet Japanese Ministry of Health criteria but have normal coronary arteries by Japanese Ministry of Health criteria have at least 1 coronary artery dimension more than 2 standard deviations above the expected mean. Thus coronary artery dilation in KD is even more prevalent than originally suspected. Clinical or subclinical inflammation of the coronary and systemic arteries may form the substrate for longer-term functional and structural abnormalities and increase the risk of premature atherosclerosis. A number of noninvasive methods have been developed to study endothelial function and structural changes suggestive of atherosclerosis. Brachial artery flow-mediated dilation has been studied widely and can be safely applied to large and varied groups of patients including children. The brachial artery dilation response to increased shear stress is mainly due to endothelial release of nitric oxide and correlated with coronary endothelial function. An alternative noninvasive method is measurement of arterial stiffness by pulsed-wave analysis or arterial tonometry, which is now recognized as important in predicting coronary artery disease. Structural arterial abnormalities are indicated by increased thickness of the intimal-medial portion of the carotid artery measured by B-mode ultrasonography. Increased carotid artery intima-medial thickness (IMT) has been shown to reliably indicate the presence of atherosclerosis. Tests of arterial structure and function have been applied to patients with a history of KD with and without detectable coronary artery aneurysms in the acute phase of the illness.

This issue of The Journal of Pediatrics includes 2 small studies with conflicting inferences about arterial health after KD. Dalla Pozza et al compared carotid artery IMT among 48 patients with KD and 28 control subjects of similar age and sex. Carotid artery IMT, expressed as both unadjusted dimension and z-score, was greater among patients with KD than control subjects; within the KD group, the 15 patients with a history of coronary artery aneurysms had greater carotid artery IMT than the 5 children without coronary artery lesions. Patients with KD and control subjects had similar baroreceptor sensitivity and levels of established risk factors for adult atherosclerotic heart disease, including body mass index, blood pressure, and lipid profile. These authors infer that patients with KD have subclinical atherosclerosis and may be at risk even in the absence of persistent coronary artery abnormalities.

In contrast, McCrindle et al report that 52 patients with KD, compared with 60 healthy control subjects, had similar systemic endothelial function, assessed by flow-mediated brachial artery reactivity. Furthermore, flow-mediated dilation was not significantly related to either patient or KD characteristics, similar findings to those in the authors' earlier report with fewer patients. In the past, these authors reported that patients with KD had a more adverse cardiovascular risk profile.

See related articles, p 239 and p 244

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with higher blood pressure and greater adiposity, compared with control children. In the current study, few differences in atherosclerotic risk factors were found between patients with KD and healthy control subjects, with the exception that patients with KD in this study had significantly lower apolipoprotein A1 and hemoglobin A1c levels, as well as lower blood pressure, but with less nocturnal decline. Markers of the systemic inflammatory response were not measured.

To help to interpret the importance of these contradictory manuscripts, it is useful to place them in the context of prior work in the field. We will review evidence for vascular changes according to coronary artery status, because the severity of vasculitis might be expected to affect the future risk of atherosclerotic vascular disease.

Patients with persistent coronary artery aneurysms have suffered the most severe arterial insult. In such patients, compared with control patients, the carotid arterial wall has been reported to have a higher IMT and lower distensibility, although others have not confirmed these findings. Abnormalities of arterial function have also been reported. Ikemoto et al demonstrated endothelial dysfunction, as indicated by decreased brachial artery flow–mediated dilation, in patients with persistent coronary artery lesions. Two earlier studies on endothelial function in patients with KD reported similar results. Patients with persistent aneurysms have been shown to have ongoing systemic inflammation years after disease onset, as evidenced by C-reactive protein levels that are significantly higher than those seen in normal age-matched children or among patients with KD without aneurysms or with regressed aneurysms. Inflammatory mediators, such as C-reactive protein, may themselves promote atherosclerosis.

Patients whose aneurysms have regressed to normal diameter represent an intermediate group. By 2 years after disease onset, approximately half of coronary artery aneurysms will have regressed to normal lumen diameter on angiography. Re-gressed aneurysms are characterized by fibrous intimal thickening on histopathologic examination and by marked symmetric or asymmetric myointimal thickening on intravascular ultrasonography. Indeed, initial coronary artery dimension has been shown to be highly related to coronary artery IMT by intravascular ultrasonography more than 10 years later. In addition to abnormal vascular structure, regressed coronary artery aneurysms have abnormal endothelial function, with reduced vascular reactivity to isosorbide dinitrate and constriction with acetylcholine. The proximal and peripheral arterial beds have also been reported to be stiffer among patients with KD with persistent or regressed aneurysms than in normal control subjects, with aortic pressure waveforms late after illness onset resembling those in the elderly. In the era of IVIG therapy, most children with KD do not have development of coronary artery aneurysms. With careful late clinical follow-up, such patients have morbidity and mortality rates that are similar to those in the normal population. However, data are conflicting on preclinical vascular changes in patients with KD in whom coronary abnormalities were never detected. Some studies in this subgroup have shown preclinical abnormalities in endothelial function, arterial stiffness, and myocardial flow reserve. For example, compared with normal subjects, they have been reported to have depressed endothelium–dependent brachial artery reactivity, as well as higher brachial-radial artery mean pulse wave velocity, suggesting increased arterial stiffness. Others have reported endothelial dysfunction only among patients with persistent coronary artery lesions, and that endothelial dysfunction is worst among those with coronary artery aneurysms. With respect to structural abnormalities, data are once again conflicting. Some investigators have found no difference in carotid artery IMT between patients with KD and control subjects, consistent with the hypothesis that functional abnormalities might precede those of structure. In contrast, Cheung et al found increased carotid artery IMT even among patients with KD with normal coronary arteries, compared with control subjects. Cardiac catheterization studies also have been conflicting with regard to whether endothelium–dependent relaxation is impaired in “normal” epicardial coronary artery segments of patients with KD. Of note, patients with KD without a history of coronary artery dilation appear to have lower myocardial flow reserve and higher total coronary artery resistance than control subjects. The only immunohistochemical study of the coronary arteries of a patient with KD without coronary dilation was performed in a child who died of unrelated causes, compared with control subjects, the coronary artery intima was mildly thickened, and platelet–derived growth factor–α, transforming growth factor–β1, and inducible nitric oxide synthase were expressed in the intimal smooth muscle cells.

How can we reconcile the conflicting literature on long-term vascular health among patients who have had KD, including the two most recent contributions in The Journal? Studies of arterial structure and function in KD are handicapped by small sample sizes and limited power; similar studies in adults characteristically include hundreds and even thousands of patients. Statistical significance can be reached only when differences between groups are large or sources of variance other than KD-related vascular changes are small. Unfortunately, potential sources of variation are numerous and include both technical factors associated with test performance and patient characteristics. Among patient characteristics that influence vascular health, dyslipidemia is prevalent in patients with KD with or without overt coronary artery sequelae well beyond the time that the clinical disease has resolved. Other patient factors influencing vascular health include hypertension, diabetes mellitus, smoking, obesity, systemic inflammation, age, pubertal status, and sex. It is impossible to adjust for all of these factors in a small series of patients. Furthermore, the higher prevalence of risk factors for future atherosclerotic coronary artery disease among youth in North America compared with in Japan and other Asian countries could have affected the ability of McCrindle et al to detect vascular changes related to KD.

It is unlikely that a large international study of vascular health in children with KD will be performed in the near future. Thus multiple small studies must be viewed in the aggregate to
assess the arterial health and guide management of patients with KD. Among those with persistent or regressed coronary artery aneurysms, coronary artery structure and function are well documented to be impaired; therefore the presence or absence of abnormalities in other systemic arteries does not affect their need for aggressive management of other risk factors. Further investigation is needed, however, before conclusions can be reached regarding the impact of KD on vascular health among those in whom coronary artery changes were never detected. Indeed, we will not know with certainty whether “always normal” patients with KD are at higher risk for atherosclerosis until early Japanese cohorts reach middle and older age.54 Until published data allow evidence-based practice, all patients with a history of KD should be carefully assessed for risk factors for future atherosclerotic heart disease, including dyslipidemia, hypertension, smoking, obesity, diabetes mellitus, and sedentary lifestyle. Guidance for clinicians is provided by recent American Heart Association recommendations for cardiovascular risk reduction, with thresholds for counseling and pharmacologic management in patients with KD tailored to the degree of coronary artery involvement.55

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REFERENCES

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here is generally a “love-hate” relationship between the inflammatory response and the human organism. On one hand, a major congenital or acquired defect in the recognition of, or response to, an environmental pathogen leads to recurrent severe infections and often rapid death. Conversely, failure to control the inflammatory response can lead to death and destruction from “friendly fire,” the most clear-cut examples being the formation of tissue-specific antibodies such as the anti-glomerular basement membrane antibody in Goodpasture’s syndrome.1

In the case of cystic fibrosis (CF), the relationship has been perceived as being more one of “hate–hate” rather than “love–hate.” The dogma has been that chronic airway infection has resulted in an over-exuberant inflammatory response, with the recruitment of excessive amounts of neutrophils, failure of clearance of the micro-organisms, neutrophil necrosis instead of apoptosis, and the release of tissue-damaging enzymes, with resultant tissue destruction disproportionate to the actual burden of infection.2 This idea led to the seemingly paradoxical concept that immunosuppression might be beneficial in the setting of chronic airway infection. The initial choice was prednisone, with the first study, using a huge dose (2 mg/kg on alternate days) reporting benefits, but apparently no adverse effects.3 This was not confirmed in the first of the great series of multicenter CF trials emanating from North America.4 In this study, 2 mg/kg of prednisone on alternate days was compared with 1 mg/kg on alternate days and with placebo. The well-known findings were that the benefit of prednisone was confirmed, but the adverse effects necessitated discontinuing the high- and low-dose prednisone arms after 2 and 4 years, respectively. An important clue, the significance of which has been under-appreciated, was that the benefits of prednisone were confined to those patients chronically infected with Pseudomonas aeruginosa. The subsequent history of steroids, in brief, is that after a number of contradictory studies of inhaled steroids,5 a trial of withdrawal of inhaled steroids (CF WISE study) showed that they are largely ineffective in CF.6 Furthermore, the appreciation has grown of the importance of systemic complications of CF, such as diabetes mellitus7 and bone disease,8 which may be worsened by steroids, and so enthusiasm for steroids in CF (other than when mandated by, for example, allergic bronchopulmonary aspergillosis9) has waned.

Non! to Non-Steroidal Anti-Inflammatory Therapy for Inflammatory Lung Disease in Cystic Fibrosis (At Least at the Moment)

See related article, p 249

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However, 2 important lessons can be drawn from the history of steroids in CF. The first is the credulity of physicians who treat CF in their willingness to prescribe treatments of no value; CF WISE had to study withdrawal of inhaled steroids, not prescription of them, because so few patients could be found who were not already taking these medications. Second, from the multicenter prednisone study\(^{4}\) is that the stage of the disease may determine the response to anti-inflammatory therapy. This makes biological sense; the child with CF at birth almost certainly has a sterile and normal airway and initially probably meets and repels pathogens, until eventually the defences are overwhelmed, and chronic infection supervenes. Thus it is likely, but unproven, that very early immunosuppression actually might accelerate the onset of chronic infection. The concept that immunosuppression may cause harm, not good, was further strengthened by the large multicenter study of the leukotriene (LT) B\(_4\) receptor antagonist B11L 284 BS.\(^{10}\) The trial was stopped by the data-monitoring committee because of an increase in serious adverse events (infective exacerbations) in the treatment limb.

What then are the lessons for those wishing to study anti-inflammatory medications in CF? Key (and most difficult) must be to have a focussed hypothesis about the type of patient with CF who may benefit from the intervention, rather than trying it out on all comers. This is doubly difficult; we are as yet struggling to generate these hypotheses, and, even when we do so, finding enough patients to do an adequately powered study becomes even more problematic.

In this context, how do we interpret the results of the use of ibuprofen as an anti-inflammatory medication in CF, in particular in the light of the study by Lands et al in this issue of The Journal?\(^ {11}\) The logic for the studies is impeccable; if steroids are effective but have adverse effects, why not use non-steroidal anti-inflammatory medications? The initial carefully controlled study showed that ibuprofen slowed the rate of deterioration of first second forced expired volume (FEV\(_1\)).\(^ {12}\) The placebo group had an annual decline of \(-3.60\% \pm 0.55\%\) against \(-2.17\% \pm 0.57\%\) in the active group. The results were more dramatic in the group that was compliant with medication, and in those who were <13 years old at the start of the trial. Despite this study, ibuprofen has only enjoyed patchy use in the clinic;\(^ {13}\) whether this is because of worries of albeit rare, but not trivial, adverse effects such as gastrointestinal haemorrhage and acute renal failure,\(^ {14,15}\) the narrow therapeutic window necessitating monitoring of levels,\(^ {16}\) or more cynically, because big pharmaceutical companies were not promoting it lavishly and assiduously, is unclear. However, 12 years later, one could be forgiven for questioning the relevance of the study because the rate of decline in lung function in the placebo group is much higher than would be acceptable now,\(^ {17-19}\) and the intervention group results are inferior to those currently seen in some clinics that do not use much ibuprofen. This study\(^ {11}\) recruited more patients (\(n = 142\)), but studied them during a shorter period (2 years). Patients with relatively mild impairment of lung function (FEV\(_1\) \(>60\%\) predicted) were recruited, but children who were \(>13\)-year age cutoff of the earlier study were included. Their power calculation was based on a high expected rate of decline in the placebo group (\(\Delta FEV_1\) 4\%/year, higher than was actually seen), set the bar low at 80\% power, and concluded that substantially more patients were needed than were recruited, despite a monumental effort by the investigators. They found no change in either their primary end point (rate of change of FEV\(_1\)) or of another variable that one would expect to be affected by obstructive lung disease, mid-expiratory flow (FEF\(_{25-75}\)). However, what they did find was a beneficial effect on forced vital capacity (FVC). In the ibuprofen group, FVC actually did not change in 2 years. After a prolonged post hoc \(pas de deux\) with the data, the authors also managed to torture out a small, statistically significant benefit for the patients who were treated in days spent in hospital.

How then should ibuprofen be positioned in the therapeutic armamentarium? Lands et al\(^ {14}\) have put in a tremendous effort to make an impeccably designed study work, for which unreserved congratulations are due. However, they fail to convince us that they have shown a biologically likely benefit. Their study was under-powered and failed to show an effect in their primary end point or a biologically plausible secondary end point. Are the changes in FVC biologically plausible in an obstructive lung disease or an artefact of a relatively small study? We do not believe that the case for widespread use of ibuprofen can be made on these data alone.

What of the future? One lesson from this study is that the better we get at conventional treatment, the harder it will be to show an improvement in outcome with a novel therapy. The relative insensitivity of lung function, or rather, the huge numbers of patients needed if spirometry is to be an outcome, has been highlighted\(^ {20,21}\); reliable surrogates, changes in which truly reflect the course of the disease, need to be found. In manipulating CF inflammation, we need to know at what time in the disease we should be repressing instead of boosting the host defenses; we need to know what part of the inflammatory cascade is responsible for the host damage; and we need to be able to measure it easily, repeatedly, and non-invasively. Only at that point will we be able to design rational studies of anti-inflammatory therapies with appropriate end points; after all, the asthma doctors have eventually realized that anti-inflammatory therapy is most effective when the therapeutic target, inflammation, is measured.\(^ {22-26}\) Until that time, trials are likely to include patients who have no chance of benefiting from the proffered treatment, thus diluting any effect, and continue to be under-powered anyway, because lung function and inflammation may be only very loosely related. The concept of treating a genetic defect (premature stop codon) rather than a disease has recently gained practical currency;\(^ {27}\) we need almost certainly to move to treating specific pathways, not a global mish-mash of "inflammation."

However, it must be stressed that the absence of evidence of benefit is not the same as evidence of non-benefit. It may be that ibuprofen is the answer for some patients with CF, but we do not yet have the data. Although we disagree with their conclusions, we most readily acknowledge that Lands et al\(^ {11}\) have done a signal service by keeping ibuprofen at the forefront of the debate about optimal treatment in CF, by conducting an impressively designed study, and above all, by reminding us of
the importance of clinical trial work in children, who may gain from therapies that are useless in adults. If pediatric trial work like this is not done, then substantial therapeutic benefits in the fight against CF may be frustrated away.

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REFERENCES


What is the Role of Cystic Fibrosis Transmembrane Conductance Regulator Dysfunction in Primary Sclerosing Cholangitis?

Primary sclerosing cholangitis (PSC) is a devastating and insidiously progressive cholestatic liver disease resulting from progressive inflammation, fibrosis, and obliteration of the intrahepatic and extrahepatic bile ducts. It is a relatively uncommon disorder, with an approximate annual incidence of 1 per 100,000. Most adult patients (>70%) have or will develop inflammatory bowel disease (IBD), usually ulcerative colitis, and approximately 5% of patients with IBD may develop PSC. Ultimately, PSC leads to cirrhosis and end-stage liver disease necessitating transplantation. Cholangiocarcinoma is a dreaded and often fatal complication.

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Although predominantly an adult disease, PSC affects children as well. The prognosis may be somewhat better in children than in adults, because dominant strictures, recurrent cholangitis, and cholangiocarcinoma are uncommon in children. However, approximately 1/3 of pediatric patients require transplantation by adulthood.

There is no satisfactory treatment for PSC. Although high-dose oral ursodeoxycholic acid therapy improves biochemical measures, it does not appear to alter clinical outcome. PSC is associated with autoantibodies, occurs in the setting of IBD, and may occasionally present as an overlap syndrome with autoimmune hepatitis. However, PSC does not behave as a typical autoimmune disease and generally responds poorly to immunosuppressive therapy, although a subset of pediatric patients may demonstrate a response.

The etiology of PSC remains a mystery but is probably multifactorial. Several lines of evidence from animal models and in vitro studies suggest a process of immune dysregulation in the setting of genetic predisposition. The process is initiated by an acute or chronic insult (eg, portal bacteremia in IBD), which triggers an immune response within the liver targeting the cholangiocytes, with resultant chronic inflammation. Although hepatic immune cells, such as Kupffer cells, may be major players in this process, it is now clear that the cholangiocyte itself is susceptible to activation. This “reactive” cholangiocyte phenotype acquires the ability to secrete proinflammatory cytokines and chemotactic molecules and is an active participant in the inflammatory process. Cholangiocytes generate nitric oxide in response to proinflammatory cytokines, which in turn inhibits cAMP-dependent secretion, including that mediated by cysitic fibrosis (CF) transmembrane conductance regulator (CFTR), further contributing to decreased bile flow.

Of recent interest are genes that may predispose to PSC, participate in the disease process, modulate disease severity, and/or influence the response to therapy and prognosis. Candidate genes include HLA haplotypes, biliary transporter genes (eg, mdr-3), genes that modulate host–bacteria interactions (eg, nod2), liver disease-modifying genes (eg, alpha-1-antitrypsin), and inflammatory mediator genes (eg, tumor necrosis factor-α gene–promoter polymorphisms). However, the association of CFTR dysfunction and mutations in the CFTR gene with PSC is of particular interest. The CFTR gene product is a cAMP-regulated chloride channel expressed in diverse tissues, including respiratory tract, intestine, pancreas, sweat glands, male reproductive tract, and the hepatic canalicular and cholangiocyte membranes. Depending on their location and zygosity, CFTR gene mutations may have a clinical spectrum ranging from asymptomatic to severe illness, as well as a differing predilection for specific organs.

There is compelling clinical and experimental evidence linking CFTR dysfunction to PSC. There are similarities between liver disease seen in patients with CF and PSC, including chronic inflammation, bile duct injury, and progressive fibrosis. Presumably, thickened, in ispissated bile in CF causes obstruction and inflammation, with resultant injury of bile duct epithelium. In gfrt−/− mice with experimentally induced acute colitis, elevated serum alkaline phosphatase levels and histological bile duct injury developed. Interestingly, although both gfrt−/− and wild-type mice exhibited suppressed peroxisome proliferator-activated receptor-α (PPAR-α) expression in liver with colitis induction, mRNA levels later increased in the wild-type but not in the gfrt−/− animals, concomitant with development of bile duct injury. PPAR-α recently has been recognized as an important anti-inflammatory immunomodulator. Treatment with the long-chain polyunsaturated fatty acid docosahexaenoic acid (DHA) restored PPAR-α expression in the gfrt−/− mice and prevented bile duct injury. The protective effects of DHA may be related to its role as a PPAR-α agonist, as well as to other anti-inflammatory properties. In a study of a gfrt−/− mouse model that develops CF-like disease of all organs, including liver, DHA treatment specifically and significantly reduced hepatic periportal inflammation without effect on other organs. A human pilot study to assess the impact of DHA treatment in adults with CFTR mutations and PSC is currently underway.

The association of CFTR mutations and PSC has been studied in adults with conflicting results. However, the negative studies tended to use a small sample size or to screen for only a limited number of mutations. The article by Pall et al in this issue of The Journal is the first report in a pediatric population of patients with PSC. Their data demonstrate that CFTR function in these patients with PSC, as assessed by sweat chloride analysis and nasal transmembrane potential difference (NTPD), is intermediate between non-PSC IBD disease control and classic CF values.

A major strength of this study is the evaluation of CFTR function by 2 methods, the classic sweat chloride test and the more sensitive (and technically challenging) NTPD measurement. Few gene products are this accessible in living humans for in vivo functional analysis, but NTPD testing cannot be performed easily in young children. The comprehensive genetic analysis is another strength, although the results were not conclusive despite identification of various mutations (CF-causing), variants (associated with decreased CFTR function and/or non-CF CFTR-defective diseases), and polymorphisms (not linked to specific diseases) in a high percentage of both PSC and disease control patients. This finding differs from that of an adult study by this same group showing significantly higher frequencies of mutations and variants in PSC patients. There are several possible explanations for the discrepancy. First, it is possible that some of the IBD controls may have early, clinically silent PSC or may be predisposed to develop PSC later. Hopefully, this cohort will be followed into adulthood. Second, other genes undoubtedly contribute to the CFTR-deficient PSC phenotype, including those that modulate the inflammatory response as well as liver disease modifiers. Expanded genetic analysis to include these genes in the future may help clarify this issue. Finally, the present study involves a relatively small sample; a much larger number of subjects is needed to provide a more definitive answer.

Another intriguing relationship is that between CFTR function and IBD, given the strong association of IBD with PSC. Such factors as mucosal permeability and bacterial flora are thought to be important for the portal access of bacteria and their products, such as LPS and CpG DNA, to possibly...
Advances in medical knowledge coupled with the proliferation of capable neonatal intensive care units have been instrumental in the survival of infants born prematurely. Yet, premature birth remains an important contributor to overall infant death (>30% of all infant deaths). In this issue of *The Journal of Pediatrics*, DeJonge et al. describe the important negative findings of a study that attempted to use a pathogen-specific antibody for prevention of nosocomial infections in very low birth weight infants (VLBW; <1500 g; <32 weeks gestation).

**COINS** Coagulase-negative staphylococci  
**IVIG** Intravenous immune globulin  
**LOS** Late-onset sepsis  
**MRSA** Methicillin-resistant *Staphylococcus aureus*  
**NPRN** Neonatal Research Network  
**VLBW** Very low birth weight

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In 1986, in response to the growing population of preterm infants, the National Institutes of Child Health and Human Development created the Neonatal Research Network (NRN), a group of academic centers working in collaboration, with the goal of reducing neonatal morbidity and mortality rates and improving outcomes. Spurred on by this initiative, a series of carefully conducted observational studies and randomized clinical trials have been performed in the past decade that have not only allowed the recognition of risk factors but also provided an infrastructure to systematically analyze potential therapeutic interventions with adequate numbers of subjects. Consequently, as expected, infections are recognized as an important problem for VLBW infants. Since the early 1990s the NRN has been monitoring both early-onset sepsis (occurring before 72 hours of life) and late-onset sepsis (LOS; positive blood culture after 72 hours of life) in VLBW infants and its impact on comorbidities, survival, and long-term outcomes. The incidence of sepsis occurring early is 2% versus 25% if the child survives past 72 hours of life. The most common organisms causing LOS are Gram-positive pathogens (70%), and coagulase-negative staphylococci (CoNS) represented 48% of all infections.4,5 Taken together, VLBW infants with LOS have longer hospitalizations, high morbidity and mortality rates, and care costs resulting in a societal economic burden that reached $26.2 billion in 2005.6 Addressing prevention and treatment of LOS in these infants is imperative.

Antibodies are the effector molecules of the adaptive humoral immune response. Their physiological function is defense against extracellular microbes and microbial toxins through mechanisms of opsonization, neutralization, complement activation, and antibody-dependent cellular toxicity. Recognizing that transplacental transfer of maternal antibodies occurs after 32 to 35 weeks gestation, it was reasonable to hypothesize a benefit for intravenous administration of immune globulin (IVIG) to VLBW infants to prevent or treat infection. Since the late 1980s, more than a dozen studies and meta-analyses on the benefits of administration of immune globulin (IVIG) to VLBW infants to prevent or treat infection have been published. These studies varied in IVIG product, age, birth weight, and sample size. When death was reported as an outcome, borderline statistical significance was noted in groups treated with IVIG compared with placebo (RR 0.63; 95% CI; 0.40, 1.00).10

In spite of the lack of clear benefit of IVIG, previous successful experience with pathogen-specific immune globulin for respiratory syncytial virus prophylaxis11 suggested a potential role for the development of pathogen-specific IVIG preparations. Because CoNS is the most common organism causing LOS, staphylococcal binding proteins CIFA and SdrG were selected as possible targets. These proteins are surface adhesins, present on >98% of Staphylococcus aureus and most strains of Staphylococcus epidermidis and play a critical role in the attachment of bacteria to host tissue, an important pathogenic step for entry. In 2005, Bloom et al12 published a phase II, multicenter, double-blind clinical trial of INH-A21, a plasma-derived, donor-selected polyclonal anti-staphylococcal human immune globulin. The study was sponsored by the manufacturer and the Office of Orphan Product Development of the US Food and Drug Administration. Plasma concentrations of the staphylococcal-specific antibody necessary to achieve protection were unknown, so the trial was designed to identify a dose for future analysis. A total of 512 infants (500-1250 grams; >72 hours to 7 days of age) were randomized to 250, 500, and 750 mg/kg/dose of INH-A21. No differences in incidence of any staphylococcal (CoNS or S. aureus) infections was identified.

The study by DeJonge et al12 is the subsequent phase III analysis: A multicenter (95 different centers within the United States and Canada), randomized double-blind, placebo-controlled clinical trial. A total of 1983 neonates (500-1250 g) received either placebo or study drug INH-A21. Because the phase II study only demonstrated possible activity of INH-A21 against S. aureus LOS, this study’s primary outcome was LOS caused by S. aureus, with CoNS infections as a secondary outcome. Sepsis was clearly defined by the authors. Incidence of LOS due to S. aureus was no different between the groups (5% in the placebo vs 6% in the INH-A21 group). No association was found between the number of infusions and infections. The lack of clinical benefit is disappointing, particularly as an increase in methicillin-resistant S. aureus (MRSA) strains emerged within the study neonatal intensive care units (23% of S. aureus were MRSA)13.

For the past decades, knowledge of the neonatal human immune response has derived from analyses of the immunologic status of the mother, the role of the placenta in the transfer of antibodies, the in vitro analysis of cord and newborn peripheral blood cell, from study of patients and inferred from studies using mouse models.13 This knowledge underestimates the complexity of the immune response. For example, the B-lymphocyte system is fully developed at birth; fetal bone marrow B lymphocyte pools are similar in size to those of adults and preterm infants are capable of forming specific antibodies with comparable
isotype diversity as adults.\textsuperscript{14} Control of staphylococcal infections requires not only humoral, but cellular and phagocytic responses for effective killing. The lack of efficacy of antibody therapies may relate to confounding mechanisms necessary for clearance of pathogens by the host. The extent to which neonatal deficiencies of neutrophil function, complement, or antibody contribute to the increased risk of infection remains unknown, even though these factors are important in vitro for opsonophagocytic killing of \textit{Escherichia coli}, group B \textit{Streptococcus}, and \textit{Candida} species.

Answers may lie in expanding our knowledge and therapeutic approaches to stimulate/enhance innate components of the immune response. Antimicrobial products, receptors capable of recognizing pathogen-associated molecular patterns, phagocytic cells, complement proteins, dendritic and natural killer cells are all essential components of the innate immune response and constitute the first line of defense against invading pathogens. The skin is the most important barrier against pathogens invasion. Epithelial cells are capable of secreting 2 classes of antimicrobial peptides: defensins and cathelicidins.\textsuperscript{15} Interestingly, during the third trimester of pregnancy, the fetus becomes covered by the vernix caseosa that contains antimicrobial peptides including \textalpha-defensins and LL-37, a human cathelicidin. Vernix extracts exhibited both antibacterial activity against gram-negative bacteria, and antifungal properties against \textit{Candida albicans}.\textsuperscript{16} Intriguingly, psoriasis and atopic dermatitis, are 2 inflammatory skin conditions associated with skin breakdown. However, although infection is rarely associated with psoriasis, patients with atopic dermatitis are commonly infected with \textit{S. aureus}. Human \textbeta-defensin 2 and the cathelicidin LL-37 appear to be strongly expressed in psoriasis and not in eczematous skin. Interleukin 13, produced under atopic conditions, suppresses the induction of these antimicrobial peptides.\textsuperscript{17} Furthermore, LL-37 has also been identified in the ductal epithelium of salivary and sweat glands, suggesting a role in the protection of the gland itself from microbial invasion.\textsuperscript{18}

Finally, the molecular biology of staphylococcal infections provides hints for the interactions of innate and adaptive immune responses. In vitro and in vivo experiments demonstrate that exposure of \textit{S. aureus} to host cells induces the antimicrobial products \textbeta-defensins and LL-37/CAP-18 but vary among stains of \textit{S. aureus}, with MRSA exhibiting lower susceptibility.\textsuperscript{19}

The publication by \textit{The Journal} of this well-conducted study with negative results is essential as the accumulation of new findings that do support perceived knowledge advance the field.
Acute Viral Bronchiolitis: To Treat or Not to Treat—That Is the Question

Acute viral bronchiolitis is one of the most common conditions caused by respiratory viruses in infants and young children. For decades, controversy has surrounded both the treatment of bronchiolitis in early life and its sequelae. Part of the confusion in the literature comes from there being no common definition of acute viral bronchiolitis that is used internationally. In the United Kingdom, Australia, and New Zealand, acute viral bronchiolitis is a term used for a condition characterized by the presence of tachypnea, in-hyper-inflation of the chest, and widespread fine end-inspiratory crackles (also called crepitations) heard on auscultation. Wheeze on expiration may or may not be present. This typical clinical pattern is generally seen in the first year of life, with most children requiring admission to hospital in the first 6 months of life. It is largely caused by obstruction of respiratory and terminal bronchioles by mucosal edema and mucus production caused by the viral infection with formation of fluid menisci in the bronchioles. The fine crackles are caused by the “popping open” of these small airways in late inspiration. The developmental stage of the lung in the first year of life, with poorly developed collateral ventilation between adjacent lung units, facilitates the development of widespread airway obstruction. In North America and parts of Europe, however, the term bronchiolitis is commonly used to describe any lower respiratory viral infection occurring in the first 2 years of life. In these older children, wheeze and bronchospasm may play a greater role in the disease pathogenesis.

Traditionally, most studies of infants with acute viral bronchiolitis have involved infants requiring hospitalization, and the virus responsible for most cases has been the respiratory syncytial virus (RSV). Studies following populations of such infants have shown a substantial rate of respiratory problems up to the age of 5 to 6 years, but longer term follow-up suggests that these children do not have an increased rate of atopy or of persistent asthma in later life.1

The situation appears to be somewhat different when community-based cohorts are studied. Two recent studies have shown the major contribution of rhinoviruses (RV) to lower respiratory infection associated with wheeze (wLRI) in the first year of life. In both of these studies, RV was responsible for approximately 3-times as many wLRI as was RSV in the first year of life. The children in both of these studies have been observed to the age of 5 years, and wLRI associated with RV in the first year of life was a major risk factor for asthma at the age of 5 years. These recent reports raise significant doubts about RSV having a “special” role in inducing asthma and favor the “susceptible host” theory.

Despite decades of study, the mechanisms underlying viral-induced airway obstruction are not clear. Some authors have suggested that RSV picks out susceptible hosts. Two cohort studies that measured lung function in early life before any significant viral infections had occurred reported that low pre-morbid lung function was a major risk factor for wheezing during a lower respiratory tract infection in early life. A genetic predisposition or environmental exposures, such as maternal smoking during pregnancy, that result in sluggish maturation of the fetal and neonatal immune systems may increase the risk of contracting infection with RSV and other viruses in early life. Although there is no doubt that admission to hospital with acute viral bronchiolitis is associated with recurrent respiratory problems during early childhood and is a major risk factor for asthma at 5 to 6 years of age, the association with long-term persistent asthma is much less clear.

Acute viral bronchiolitis is associated with considerable morbidity and mortality, with associated economic and social impose on the community. The cost of hospitalization for acute viral bronchiolitis in children <1 year of age was estimated to exceed $700 million per year in the United States in 2001. Although mortality has been falling in the past decades, young children still die from acute viral bronchiolitis. The aim of treatment should therefore be to reduce mortality, to reduce the economic and social burden (decrease the length of stay in hospital and associated costs), and to reduce the long-term sequelae (recurrent respiratory problems and maybe persistent asthma).

Part of the problem in designing and implementing effective treatments is a lack of understanding of the underlying disease pathogenesis. Treatment with β-adrenergic agents, including albuterol and epinephrine, anti-cholinergic agents, corticosteroids, and, more recently, leukotriene receptor antagonists during the acute or recovery phase, have been tried with varying success. Acute viral bronchiolitis is characterized by acute inflammation of the respiratory and terminal bronchioles; the process includes edema, necrosis of epithelial cells, production of mucus, and...
and possibly some degree of bronchospasm. A variety of treatments designed to overcome the acute airway obstruction have been championed throughout the years. In the 1980s, bronchodilators, in particular β-agonists, were championed. Numerous articles debated their benefits and adverse effects. Studies measuring lung function during the acute disease phase claimed improvements or deterioration in lung function, referred to as a “paradoxical effect.” Other studies showed no effect on lung function either way. The potential for a decrease in arterial oxygen saturation relating to a worsening of the already disturbed ventilation-perfusion balance in the lungs was recognized. Despite these physiological disturbances, bronchodilators were reported to result in an acute improvement in clinical score. The use of nebulized epinephrine has also been controversial. A multicenter randomized double-blind controlled trial conducted in Australia that included 194 children reported that the length of stay in the hospital was not reduced in the group treated with epinephrine. A recent meta-analysis published by the Cochrane Collaboration concluded that bronchodilators improved clinical scores in the short term, but at a penalty of increased costs and increased adverse effects. This analysis included studies using albuterol, ipratropium bromide, and epinephrine. The rate and duration of hospitalization was not significantly reduced in the group treated with bronchodilators versus the control group. The American Academy of Pediatrics (AAP) recommends that “bronchodilators should not be used routinely in the management of bronchiolitis.”

Corticosteroids have also been favored as an acute treatment for infants hospitalized with acute viral bronchiolitis. This practice is more common in some parts of the world than others; it is uncommon in Australia, but common in many parts of the world. Despite an earlier review of 6 trials of steroid therapy supporting a small reduction (mean, 0.43 days) in hospital length of stay compared with placebo, a more recent and larger review supporting a small reduction (mean, 0.43 days) in hospital length of stay conclude that steroids, epinephrine, and antibiotics be considered in ambulatory patients with bronchiolitis when added to inhaled terbutaline. Kuzik et al randomized 47 infants to receive nebulized 3% hypertonic saline and 49 infants to receive nebulized normal saline in addition to “regular therapy” prescribed by the infant’s attending physician. A major strength of this study was that although the age range included children as old as 12 months, most children (38/47 and 35/49) were aged 0 to 6 months. This makes the data presented by Kuzik et al directly relevant to those treating acute viral bronchiolitis in other parts of the world. Unfortunately, the study did not have sufficient power to demonstrate conclusively a treatment effect in this younger age group alone. The major weakness of this study was that most infants also received other, discredited treatments, including albuterol (37%), racemic epinephrine (23%), or inhaled steroids (3%). Despite the clear recommendations from the AAP on the basis of solid evidence from Cochrane reviews that these treatments should not be used routinely in the management of acute viral bronchiolitis, they clearly are still being used.

The authors do discuss the potential for adverse effects from treatment with nebulized 3% hypertonic saline and correctly state that this is not likely to be a major problem in infants with acute viral bronchiolitis. The other issue they raise—whether there is additional benefit to combining a bronchodilator with 3% hypertonic saline—cannot be addressed by their study. The authors have, correctly, not reported the length of hospitalization separately in those children who received the study solution alone or in combination with other treatments; they would not have had sufficient power to make any valid comparisons. The authors highlight the need for further definitive studies. The results of this study, with the background literature, provide sufficient rationale for a study of nebulized 3% saline versus normal (0.9%) saline, excluding other treatments. However, the question of a synergistic interaction between 3% hypertonic saline and albuterol is worth considering. To this end, a study design with a double randomization (3% versus 0.9% saline and albuterol versus placebo-0.9% saline) would be feasible. We urge that such a study be restricted to children aged ≤6 months and that steroids, epinephrine, and antibiotics be “banned” during the study period. The question is worth pursuing because, if treatment with nebulized 3% saline does reduce the length of hospitalization in infants with acute viral bronchiolitis, the economic and social benefits gained from an inexpensive therapy would be worthwhile.

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“And Things that Go Bump in the Night”: Nothing to Fear?

E ver since the first crib bumper pads were sold, they have held a seemingly irresistible appeal to new parents. All parents, after all, are protective of their children and do their best to keep them from harm. This includes lumps, bumps, and other injuries. Childhood rhymes, such as “he went to bed and bumped his head, and couldn’t get up in the morning,” and traditional prayers equating “things that go bump in the night” with “ghoulies and ghosts” provide reinforcement that bumps are dangerous and to be avoided at all cost. Protection from these injuries is often provided in the form of a soft surface that can cushion a fall or bump. Thus, it is no surprise that parents are often resistant to providing a soft envi

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AAP American Academy of Pediatrics
CPSC Consumer Product Safety Commission
SIDS Sudden Infant Death Syndrome
environment that will protect their vulnerable infant’s head and body from bumping up against the hard dangers of the wooden crib slats. And in fact, crib bumper pads initially became popular as a means to protect infants from injury at a time when crib slats were spaced to permit wedging of the head between the slats. However, since 1986, crib safety requirements have mandated that crib slats be no more than 2-3/8 inches apart, to prevent a head from slipping between the slats.

Nonetheless, 20 years after crib bumper pads were made obsolete by crib safety standards, they continue to be extremely popular. Anecdotal reports from my practice and from my perusal of parenting websites suggest that parents buy and continue to use crib bumper pads for 1 of 3 main reasons: (1) The infant likes to sleep with his or her head in the corner of the crib, and the bumper pads provide a soft surface; (2) the infant’s extremities might become wedged between the slats or the infant will be bruised by bumping up against the crib; and (3) bumper pads look adorable and make the crib a “cozy” environment for the infant.

The use of crib bumper pads has recently become more controversial. The American Academy of Pediatrics (AAP) Task Force on Sudden Infant Death Syndrome (SIDS) has not made a recommendation about bumper pad use, except to recommend that bumper pads be “thin, firm, well-secured, and not pillow-like.”1 In contrast, the Canadian Paediatric Society and Health Canada issued recommendations in 2004 against using bumper pads, because of the concern that the softness could create a potential SIDS or suffocation risk for the infant.2

Now a study reported by Thach, Rutherford, and Harris3 in this issue of The Journal confirms these concerns. Using Consumer Product Safety Commission (CPSC) data, the authors describe 3 distinct mechanisms by which bumper pads can contribute to sudden infant death: strangulation by ties, suffocation against the bumper pad, and entrapment between the bumper pads and another object. In addition, resourceful children can use the bumper pads to step on and raise themselves up in an effort to reach outside of or climb out of the crib.

Thach et al provide data that can be used to make a stronger case against bumper pads to families reluctant to give them up. For those parents who use bumper pads to provide a soft surface because their infants like to wedge themselves in the crib corner, the descriptions and photographs clearly demonstrate the risk of wedging between the bumper pad and the mattress. In fact, the authors consider the “firm” bumper pads deemed acceptable by the AAP Task Force on SIDS to have the highest potential for wedging accidents.

Parents are very concerned about the potential for injury from the infant bumping up against the crib or getting an extremity wedged between crib slats. They should be reassured by the CPSC data that clearly show that infants suffer essentially no long-term injuries from contact with the crib slats themselves, making bumper pads unnecessary for infant safety.

Another argument against crib bumper pads not mentioned by Thach et al is that they obscure visibility. Particularly now with the new emphasis on room-sharing without bed-sharing as the preferred sleeping arrangement for parents and their infants, improved visibility of the infant in the crib may provide an additional impetus to avoid bumper pads.

Perhaps those parents who find crib bumper pads adorable can be convinced of the risks of maintaining such a “cute” or “cozy” crib environment. This is clearly more difficult than it may sound, however. Many parents ask me why stores that carry baby merchandise are selling so-called “dangerous” blankets and comforters, with the implied assumption that if an item were truly dangerous, then stores would stop selling it. However, if “truly dangerous” were actually a criterion for determining whether or not an item should be sold, then many items no longer would be on the shelves. We cannot necessarily expect merchants to stop selling an item as long as there is consumer demand for it. Instead, we as a medical community need to be more proactive in alerting parents to the dangers of soft bedding in the infant sleep environment. Parents often confuse safety for their child with objects that are soft. Although it is true that a soft surface can help cushion a fall, we must continue to remind parents that when it comes to sleep time for their infants, soft and cozy do not equal safe.

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REFERENCES
Subclinical Atherosclerosis, but Normal Autonomic Function after Kawasaki Disease

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Objective To compare the carotid artery intima-media-thickness (IMT) of children with Kawasaki disease with normative data for Western children.

Study design Forty-eight children (20 patients after Kawasaki disease, mean age 12.1 ± 4.7 years; 28 age- and sex-matched healthy controls, mean age 12.0 ± 3.1 years) were studied.

Results Mean (IMT differed significantly (0.449 ± 0.02 vs 0.424 ± 0.01, P < .001) as well as IMT standard deviation score (1.2 ± 0.6 vs 0.3 ± 0.1, P < .001). Patients with coronary arterial involvement (n = 15) showed a further increase of the IMT (0.459 ± 0.01 vs 0.436 ± 0.01, P < .05). There was no difference regarding short-term blood pressure regulation.

Conclusions In this small patient group, signs of subclinical atherosclerosis after Kawasaki disease have been detected. These preliminary data indicate that these patients may be at risk for cardiovascular disease even in the absence of permanent alterations of the coronary arteries. (J Pediatr 2007;151:239-43)
in children after Kawasaki disease has been detected. Data from animal experiments indicate that reduced compliance of the carotid arteries may lead to decreased short-term blood pressure regulation (baroreceptor sensitivity, BRS). Patients with reduced BRS in turn are at increased risk for the development of systemic hypertension. Investigating the IMT and BRS of children after Kawasaki disease may be helpful to identify those patients with an elevated risk for atherosclerosis and for systemic hypertension.

METHODS

Twenty children and adolescents who had previous Kawasaki disease were enrolled (Table I). All patients were recruited consecutively during their regular visits as outpatients at a tertiary healthcare center. Subjects were excluded if they had evidence or history of clinically relevant systemic disease (ie, malignancies, hypertension) other than Kawasaki disease. Medical records were available for all patients for the entire follow-up period. The diagnosis of Kawasaki disease was based on the current classification. All patients fulfilled the diagnostic criteria for Kawasaki disease: fever persisting for at least 5 days and the presence of at least four of the five principal features. The treatment of the acute phase of the disease included the administration of intravenous immunoglobulines (IVIG) in all patients at a dose of 400 mg/kg/day for five consecutive days in those patients who presented before 1998 and at a dose of 2 g/kg in those patients presenting after 1998. Aspirin was administrated in all patients at a dose of 80 to 95 mg/kg/day (mean dose 89.2 mg/kg/day). The control group consisted of 28 children, in part friends of the patients and in part children presenting for cardiac evaluation at our institution. After exclusion of an underlying chronic or cardiovascular disease by medical history, clinical assessment, electrocardiography, and echocardiography, the measurements were performed.

Family history of coronary artery disease and stroke was determined by questionnaire. Written informed consent was obtained for all participants from their legal guardians. The study was performed according to the Declaration of Helsinki; the study protocol was approved by the local ethics committee.

The ultrasonographic study was performed with the patients supine for at least 10 minutes in a quiet room at 22°C. For data acquisition, a Philips IE33 was used, equipped with a linear 11.0 MHz transducer (Philips, Germany). All studies were done according to a standardized scanning protocol for the right and left common carotid arteries. The common carotid artery bulb was identified, and many). All studies were done according to a standardized scanning protocol for the right and left common carotid arteries. The common carotid artery bulb was identified, and

<table>
<thead>
<tr>
<th>Table I. Patients and controls characteristics</th>
<th>Study group (n = 20)</th>
<th>Control group (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>12 m, 8 f</td>
<td>10 m, 18 f</td>
</tr>
<tr>
<td>Age (y)</td>
<td>12.1 ± 4.7 (range 6–23)</td>
<td>12.0 ± 3.1 (range 8.5–22.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>42.2 ± 18.0 (20.4–83)</td>
<td>51.7 ± 14.6 (29.8–83)*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>146 ± 17.5 (120–178)</td>
<td>160 ± 15.1 (125–185)</td>
</tr>
<tr>
<td>Body mass index (BMI) (kg/m²)</td>
<td>17.9 ± 5.5 (14.1–28.2)</td>
<td>19.8 ± 3.5 (14.5–30.0)</td>
</tr>
<tr>
<td>BMI-SDS</td>
<td>1.0 ± 1.1 (0.5–1.8)</td>
<td>1.3 ± 0.8 (0.9–1.6)</td>
</tr>
<tr>
<td>Mean follow-up interval (y)</td>
<td>4.1 ± 3.6 (0.3–9.6)</td>
<td>—</td>
</tr>
<tr>
<td>Heart rate at rest (beats/min)</td>
<td>77.9 ± 11.0 (56.9–104.7)</td>
<td>74.5 ± 11.6 (55.0–101.6)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>108 ± 13.9 (92.4–134.5)</td>
<td>110.8 ± 8.6 (94.4–137.4)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>66.1 ± 11.9 (53.9–92)</td>
<td>65.7 ± 7.5 (54.0–82.0)</td>
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<td>Total cholesterol (mg/dL)</td>
<td>169.4 ± 16.7 (140–182)</td>
<td>167.3 ± 18.4 (145–190)</td>
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<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>94.3 ± 22.4 (65–117)</td>
<td>92.5 ± 16.4 (63–121)</td>
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<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>48.5 ± 11.2 (28–62)</td>
<td>47.7 ± 17.9 (27–67)</td>
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<tr>
<td>Triglycerides (mg/dL)</td>
<td>123.6 ± 55.6 (67–189)</td>
<td>130.5 ± 65.3 (62–198)</td>
</tr>
<tr>
<td>Intima-media thickness (IMT) (mm)</td>
<td>0.449 ± 0.023 (0.417–0.495)</td>
<td>0.424 ± 0.010 (0.400–0.445)**</td>
</tr>
<tr>
<td>IMT-SDS</td>
<td>1.2 ± 0.6 (0.1–3.4)</td>
<td>0.3 ± 0.1 (0.1–0.4)**</td>
</tr>
<tr>
<td>BRS (msec/mm Hg)</td>
<td>20.5 ± 9.5 (5.84–47.49)</td>
<td>24.4 ± 8.3 (7.86–43.72)</td>
</tr>
</tbody>
</table>

IMT-SDS, standard deviation score of the intima-media thickness.

**P < .05.

**P < .001.
The baroreceptor sensitivity (BRS) was calculated as the distance between the corresponding QRS complexes: RR-interval in milliseconds) were used according to the sequence method with a cutoff point of 1 mm Hg and the heart rate (expressed in mm Hg) and of the heart rate (expressed in mm Hg). The entire measurement was conducted over a time interval of 10 minutes. When premature beats were noted, the test was stopped and started again. For the calculation of the BRS, the relative changes of blood pressure (expressed in mm Hg) and of the heart rate (expressed as the distance between the corresponding QRS complexes: RR-interval in milliseconds) were used according to the sequence method with a cutoff point of 1 mm Hg and 3 milliseconds.

Blood samples were taken during the patient’s follow-up visit, when the above-mentioned measurements were performed. HbA1c, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol were obtained by standard laboratory methods.

Calculations were performed using the Statistical Package for the Social Sciences for Windows (version 14.0, SPSS, Chicago, Ill). Differences within the patient group and between the patients and the control group were tested using the independent sample t test and the nonparametric Mann-Whitney test. Correlations were analysed using Pearson’s correlation coefficient. All significance testing was fixed at P < .05 (two-sided).

RESULTS

The anthropometric characteristics of the groups are reported in Table I. Controls showed significantly increased weight, but not body mass index (BMI) or BMI-SDS compared with the patient group. There was no family history of coronary artery disease. The mean time interval between the onset of the disease and the time of testing was 4.1 ± 3.6 years (range 0.3 ± 9.6 years). Absolute IMT and IMT-SDS were significantly different between the groups. Compared with normal values, the controls were within the normal range. In both groups, atherogenic measures such as the BMI, systolic blood pressure, and total and LDL cholesterol did not exceed normal limits enough to influence the IMT. In the patient group, a direct correlation of the IMT to factors characterizing the severity of the Kawasaki disease (i.e., the C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], duration of illness before therapy, white blood cell count [WBC]) was not found. However, the IMT was significantly increased in those patients with involvement of the coronary arteries at the time of illness (Table II). Patients with coronary arterial involvement showed increased CRP and ESR at the time of presentation of the illness (Table III) indicating more pronounced inflammatory activity. There was no direct correlation between the time course after Kawasaki disease and the IMT-SDS. However, a slightly, but not significantly, increased correlation was present in those patients with coronary arterial involvement.

| Table II. Comparison of patients with and without coronary artery involvement |
|----------------------------------|------------------|------------------|
| Age (y)                          | 11.9 ± 5.1 (6–19) | 11.7 ± 2.9 (8–23) |
| Weight (kg)                      | 41.3 ± 20.7 (20.8–73.2) | 37.9 ± 10.9 (20.4–83) |
| Height (cm)                      | 143.8 ± 19.5 (120–169.2) | 146.3 ± 14.3 (134.3–178) |
| Body mass index (BMI) (kg/m²)    | 18.6 ± 4.2 (15.2–28.2) | 17.3 ± 2.1 (14.1–26.7) |
| BMI-SDS                          | 0.9 ± 0.6 (0.3–1.6) | 0.7 ± 0.4 (0.3–1.3) |
| Systolic blood pressure (mm Hg)  | 108.2 ± 13.7 (100.8–134.5) | 106.5 ± 12.2 (92.4–128.2) |
| Diastolic blood pressure (mm Hg) | 64.1 ± 11.6 (53.9–86) | 64.9 ± 12.9 (54–92) |
| HbA1c (%)                        | 4.9 ± 0.9 (4–5.8) | 4.3 ± 0.9 (3.3–5.3) |
| Total cholesterol (mg/dL)        | 168.0 ± 28.4 (140–182) | 164.3 ± 18.4 (140.4–181.1) |
| LDL-cholesterol (mg/dL)          | 90.4 ± 24.7 (65–116.2) | 101.2 ± 25.2 (72.2–117) |
| HDL-cholesterol (mg/dL)          | 45.3 ± 12.4 (28–58.7) | 52.2 ± 14.6 (32.1–62) |
| Triglycerides (mg/dL)            | 120.7 ± 64.2 (67–185.2) | 125.7 ± 68.2 (67–189) |
| Intima-media thickness (IMT) (mm)| 0.459 ± 0.019 (0.44–0.49) | 0.436 ± 0.018 (0.41–0.44)* |
| IMT-SDS                          | 1.7 ± 0.6 (0.8–3.4) | 1.2 ± 0.6 (0.1–2.2)* |
| BRS (msec/mm Hg)                 | 21.05 ± 9.6 (10.2–37.4) | 22.1 ± 8.8 (5.8–47.4) |

BRS, baroreceptor sensitivity; IMT-SDS, standard deviation score of the intima-media thickness.

*P < .05.
There was no difference between patients and controls in BRS. Impairment of the baroreflex sensitivity was not detectable. Blood pressure levels were within normal limits in all patients and healthy controls.

**DISCUSSION**

The present study revealed signs of subclinical atherosclerosis in a group of children after Kawasaki disease. However, impairment of the short-term blood pressure regulation was not found during medium-term follow-up.

Because the carotid IMT in adults is considered a valuable tool for the determination of cardiovascular risk, its use in the pediatric field is growing. The method of measurement of the IMT has been validated in children. Studies have revealed increased IMT in children after Kawasaki disease as well, but data on IMT values compared with the normal population have been lacking.

In our patient group after Kawasaki disease, the significantly increased IMT suggests subclinical atherosclerosis. Children, in whom a dilatation of the coronary arteries had been diagnosed at the time of acute inflammation show an increased IMT compared with the remaining patients. In these children, the inflammatory process was more severe than in the remaining children (increased CRP and ESR). However, a direct correlation of the inflammatory signs to the level of IMT increase could not be found. We suspect that because of the wide range of the CRP and ESR, in our small patient group statistically significant correlations could not be found. We hypothesize that the increased IMT may be caused by a high inflammatory activity resulting in a generalized vasculitis. This relationship has been shown in patients with Takayasu’s arteritis and Behcet’s disease.33,34 In contrast to the changes in the coronary arteries that may be transient, traces of the vasculitis may be permanent in other vessels. The direct effect of a vasculitis may be enhanced by an altered lipid profile, which has been found after Kawasaki disease. It may be that vasculitis and an atherogenic lipid profile interact.

We could not detect a significant correlation between the IMT-SDS and the time interval between the onset of Kawasaki disease and testing. We suppose that our patient and subgroups are too small to reveal statistical significance. However, a slightly increased correlation coefficient in those patients with coronary arterial involvement may be indicative of a relationship. In our patient group, there was a high incidence of those patients presenting with coronary arterial involvement at the time of inflammation when compared with data from the literature.1 The explanation may be that the patients studied were recruited from a pediatric cardiology tertiary healthcare center, which may preferentially attract patients in whom coronary arterial changes are suspected or had been detected previously.

The process of atherosclerosis starts in childhood and is enhanced in the presence of risk factors.7 Beyond a normal increase of the IMT because of an increase of the carotid arterial diameter, IMT may be further increased pathologically during life. Our patients after Kawasaki disease may be at an increased risk for atherosclerotic disease in adulthood. Atherosclerosis-promoting environmental factors such as smoking and obesity may have an additional deleterious impact. Lifelong follow-up visits may be necessary, and special counselling may be wise in patients after Kawasaki disease.

In contrast to the increased IMT values, the short-term blood pressure regulation was normal in our patients. An impairment of the BRS has been associated with the development of systemic hypertension in the normal population.26 As patients after Kawasaki disease showed an increased vascular stiffness, we suspected an impaired BRS in this group. However, the short-term blood pressure regulation is completely normal in these patients.

Study limitations include the small number of patients investigated. As we present a retrospective study, a prospective assessment of the IMT during the different phases of Kawasaki disease is warranted. Additionally, further studies are necessary to determine if increase in the IMT has the same prognostic value on morbidity and mortality as in adult patients. We propose regular follow-up visits in patients after Kawasaki disease. Longitudinal IMT measurements may help to identify patients at particular risk for cardiovascular disease. Those children need to be followed and counselled with regard to atherosclerosis-promoting factors such as obesity, hypercholesterolemia, systemic hypertension, and smoking.

We appreciate the enthusiastic help of Ms. G. Walter.

**REFERENCES**

2. Benser S, McCrindle BW, Silverman ED, Tyrrell PN, Wong J, Yeung RSM.
Are Patients after Kawasaki Disease at Increased Risk for Accelerated Atherosclerosis?

BRIAN W. MCCRINDLE, MD, MPH, SUSAN MCINTYRE, RN, CHRISTOPHER KIM, TAMMY LIN, AND KHOSROW ADELI, PhD

Objective To assess whether patients after Kawasaki disease (KD) have increased risk factors and abnormalities suggestive of early atherosclerosis in systemic arteries.

Study design In a case-control study, we compared 52 patients after typical Kawasaki disease with varying coronary artery involvement (67% males; mean time from illness episode 11.2 ± 3.7 years) studied between 10 and 20 years of age with 60 healthy control subjects (50% males). Brachial artery reactivity (BAR) was assessed using vascular ultrasonography, and atherosclerosis risk assessment was performed. Differences between cases and controls and factors associated with endothelial function in cases were determined.

Results Case patients had lower resting systolic blood pressure ($P < .001$), lower apolipoprotein AI levels ($P < .05$), and higher levels of glycosylated hemoglobin ($P = .007$). There were no significant differences in BAR between case patients and control subjects in response to increased flow ($P = .60$) and nitroglycerine ($P = .93$). For case patients, significant factors in multivariable analysis for lower flow-mediated BAR included higher fasting triglyceride levels ($P = .04$) and lower free fatty acid levels ($P < .001$). No significant relationship was noted with past or current coronary artery involvement.

Conclusion Patients with KD have some abnormalities for risk factors for atherosclerosis, but systemic arterial endothelial dysfunction is not present in the long term. (J Pediatr 2007;151:244-8)

Recent reports have suggested that patients with Kawasaki disease (KD) may be at increased risk for accelerated atherosclerosis. This may be on the basis of ongoing functional and structural abnormalities of affected arteries,1-4 an abnormal profile of known risk factors for atherosclerosis,5-7 or the presence of a state of chronic inflammation.6,8,9 Assessment of the structure and function of the coronary arteries has suggested the presence of long-term abnormalities in segments not previously believed to have been affected.1,4 Non-invasive assessment of other systemic arteries has shown inconsistent abnormalities, and an inconsistent relationship with the degree of coronary artery involvement.7,10-14 We sought to assess whether patients after KD have increased risk factors and abnormalities suggestive of early atherosclerosis in systemic arteries.

METHODS

Study Subjects

Patients were selected from a database of all patients with KD seen at the Hospital for Sick Children between 1982 and 1998, randomly sampling from three groups based on current coronary artery involvement. Healthy control subjects of similar age were concurrently recruited from community groups. All subjects were between 10 and 20 years of age. Participants gave appropriate informed consent, as approved by the Research Ethics Board of the Hospital for Sick Children.

Measurements

The medical records of the patients with KD were reviewed to determine characteristics of the acute KD episode, including initial coronary artery involvement, disease management, and current cardiovascular findings. Standardized atherosclerosis risk factor
Assessments were performed for both case and control subjects. Assessment included recent and past medical history, smoking and smoke exposure, and medication use. The family history of each subject was reviewed for risk factors and cardiovascular disease in primary relatives and parents. Physical activity and dietary questionnaires were administered to both study groups, as well as 3-day dietary food recall records. All participants underwent physical examinations that included Tanner staging and measurement of skinfold thicknesses. Laboratory assessments on all subjects included fasting blood work to assess serum electrolytes, glucose, creatinine, urea, serum hemoglobin A1c, free fatty acids, insulin, C-peptide, lipoprotein profile, apolipoproteins A1, B, and E, lipoprotein (a), homocysteine, and fibrinogen, and 24-hour urinary collection for microalbuminuria. Subjects also underwent 24-hour ambulatory blood pressure monitoring (for further information about methods, see the Appendix; available at www.jpeds.com).

Brachial artery reactivity (BAR) in response to flow-mediated dilation (FMD) and nitroglycerine was assessed in a standardized manner using vascular ultrasonography according to the published methodology of Dhillon et al (Appendix).7,10

**Data Analysis**

Data are described as frequencies, means with standard deviations, or medians with ranges as appropriate. Significant differences between the case patients and control subjects were sought using Fisher’s exact tests, χ² tests, student’s t tests, and Kruskal-Wallis analysis of variance. For patients with KD, relationships between FMD and the category of coronary artery involvement after adjustment for cardiovascular risk factors were sought using multiple linear regression analysis. All analyses were performed with Statistical Analysis Systems software version 9.1 (SAS Institute, Inc., Cary, NC) with default settings.

**RESULTS**

**Characteristics of Study Subjects**

We enrolled 52 patients with KD (67% males). The mean age at the KD episode was 4 ± 3 years, with 96% having typical KD. Treatment included aspirin for 92% and intravenous gamma globulin for 64%. The initial coronary artery involvement showed aneurysms in 37%, ectasia only in 16%, and 47% with no involvement. The mean age at the time of the current study was 15.5 ± 2.3 years, with a mean time since the KD episode of 11.2 ± 3.7 years. The coronary artery involvement at the time of the study showed no involvement in 30 patients, regressed aneurysms in 16, and persistent aneurysms in six patients. One patient was taking warfarin and aspirin, five were taking aspirin only, and one patient was taking atenolol. The mean age at study participation of the 60 healthy control subjects (50% males) was 14.9 ± 2.4 years. Two patients and three control subjects were taking oral contraceptives, and five control subjects were taking methylphenidate.

**Comparison Regarding Atherosclerosis Risk Factors**

A comparison of demographic variables between patients and control subjects showed patients to be significantly less likely to have an obese mother, and more likely to have a hyperlipidemic father (Table I). The groups did not differ regarding height for weight measures, skinfold thicknesses, or self-reported levels of physical activity. There was a nonsignificant trend toward greater time spent in sedentary pursuits (television viewing, computer or videogame use) for the patients with KD. There were no significant differences regarding dietary composition (data not shown).

Regarding laboratory assessments, significant findings for the patients with KD versus control subjects included

### Table I. Comparison of patients with Kawasaki disease and normal control subjects regarding demographics and atherosclerosis risk factor assessment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control subjects</th>
<th>Patients with KD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male:female)</td>
<td>30:30</td>
<td>35:17</td>
<td>.09</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>14.9 ± 2.4</td>
<td>15.5 ± 2.3</td>
<td>.17</td>
</tr>
<tr>
<td>Adiposity measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Z score of BMI</td>
<td>+0.71 ± 1.16</td>
<td>+0.55 ± 1.45</td>
<td>.52</td>
</tr>
<tr>
<td>Mean percentage of ideal weight for height</td>
<td>105 ± 20%</td>
<td>107 ± 19%</td>
<td>.59</td>
</tr>
<tr>
<td>Mean percentile for skinfold thickness</td>
<td>55 ± 28%</td>
<td>55 ± 28%</td>
<td>.97</td>
</tr>
<tr>
<td>Current smoking/smoke exposure</td>
<td>5%</td>
<td>13%</td>
<td>.19</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature CVD in first-degree relative</td>
<td>32%</td>
<td>26%</td>
<td>.54</td>
</tr>
<tr>
<td>Mother:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypertension</td>
<td>7%</td>
<td>10%</td>
<td>.73</td>
</tr>
<tr>
<td>→ on meds</td>
<td>2%</td>
<td>8%</td>
<td>.18</td>
</tr>
<tr>
<td>obese</td>
<td>28%</td>
<td>10%</td>
<td>.02</td>
</tr>
<tr>
<td>hyperlipidemia</td>
<td>7%</td>
<td>12%</td>
<td>.51</td>
</tr>
<tr>
<td>→ on meds</td>
<td>0%</td>
<td>6%</td>
<td>.10</td>
</tr>
<tr>
<td>Father:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypertension</td>
<td>7%</td>
<td>12%</td>
<td>.70</td>
</tr>
<tr>
<td>→ on meds</td>
<td>2%</td>
<td>4%</td>
<td>.59</td>
</tr>
<tr>
<td>obese</td>
<td>17%</td>
<td>8%</td>
<td>.26</td>
</tr>
<tr>
<td>hyperlipidemia</td>
<td>10%</td>
<td>38%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>→ on meds</td>
<td>2%</td>
<td>4%</td>
<td>.59</td>
</tr>
<tr>
<td>Median physical activity (hours per week)</td>
<td>9.5 (0.45)</td>
<td>9.5 (0.75)</td>
<td>.90</td>
</tr>
<tr>
<td>Total activity</td>
<td>15 (2.5, 50)</td>
<td>25 (0.75)</td>
<td>.07</td>
</tr>
<tr>
<td>Total activity of other family members</td>
<td>8 (0.22)</td>
<td>7 (0.37)</td>
<td>.78</td>
</tr>
</tbody>
</table>

*BMI, body mass index; CVD, cardiovascular disease or event; KD, Kawasaki disease; meds, medications.*
lower levels of apolipoprotein A1 and higher levels of hemoglobin A1c (Table II). Compared with local normal values, 7% of patients with KD versus 10% of control subjects had an abnormally low apolipoprotein A1 level, and no patient or subject had an abnormally high hemoglobin A1c level. There were no significant differences in lipid profiles; however, patients with KD demonstrated a tendency toward a more atherogenic profile, with lower high-density lipoprotein (HDL) and higher total and low-density lipoprotein (LDL) cholesterol, as well as higher triglycerides.

Baseline resting systolic and diastolic blood pressures were significantly lower for patients with KD, and there was a trend toward lesser nighttime fall in systolic pressure on 24-hour ambulatory blood pressure monitoring, but neither overall daytime nor nighttime blood pressure values were significantly different (Table III). Compared with published normal values, only three control subjects (5%) and no patient with KD had resting systolic blood pressure above the 95th percentile based on height, and only one control subject and no patient with KD had resting diastolic blood pressure above the 95th percentile based on height.15

Regarding the assessment of BAR, there were no clinically or statistically significant differences with regards to FMD or nitroglycerine-mediated dilatation between patients and control subjects (Figure 1).

Factors Associated with Endothelial Function for Patients with KD

Within the group of patients with KD, factors associated with endothelium-dependent FMD were assessed, particularly any association with coronary artery involvement category. There was no significant relationship to either the age of the patient or the date at diagnosis, sex, number of days of fever, number of diagnostic criteria, the maximum erythrocyte sedimentation rate and the maximum platelet counts, and treatment with intravenous gamma globulin or aspirin. BAR was not significantly related to coronary artery involvement category (Figure 2).

Likewise, there was no relationship between FMD and age or Tanner staging at the time of the study, and adiposity as assessed as a percentage of actual weight for ideal weight based on height percentiles, body mass index, or skinfold thickness percentiles. Regarding the relationship between FMD and the assessed atherosclerosis risk factors, there was no significant association with family history, self-reported physical activity and sedentary pursuit times, current smoking and smoke exposure, or dietary composition. Lower FMD was significantly associated with dietary intake, including higher caloric intake \( (r = -0.31; P < .05) \), higher percent calories from fat \( (r = -0.33; P = .04) \) and higher intake of saturated fat \( (r = -0.31; P < .05) \). There was no significant relationship with fasting total cholesterol, LDL or HDL cholesterol, or apolipoproteins A1 or B, or lipoprotein (a). Lower FMD was significantly associated with higher fasting triglyceride levels \( (r = -0.28; P < .05) \), with 23% of patients...
having a fasting triglyceride level above 1.30 mmol/L. Regarding other laboratory variables, FMD was not significantly associated with fasting insulin or insulin C-peptide levels, hemoglobin A1c, homocysteine or fibrinogen levels, or urinary microalbumin. Lower FMD was significantly associated with higher fasting serum glucose (r = -0.30; P = .04) and lower free fatty acid levels (r = 0.56; P < .001), with no patient having abnormally high glucose and 10% having high free fatty acid levels.

In multivariable analysis (model $R^2 = 0.37$), only higher fasting triglyceride levels ($P = .04$) and lower free fatty acid levels ($P < .001$) were independently related to lower FMD. After adjustment for these significant factors, as well as for age and sex, there remained no significant relationship between coronary artery involvement category and FMD ($P = .18$). This remained true even when the categories of persistent and regressed coronary artery involvement were grouped together ($P = .12$).

**DISCUSSION**

Patients who have had KD may be at increased risk for accelerated atherosclerosis because of a number of potential mechanisms. First, the arterial damage secondary to the disease process itself may alter the arterial structure and function in such a way as to initiate and propagate the atherosclerotic disease process. Second, possible ongoing inflammation secondary to the disease process could further promote atherosclerosis, as well as cause alterations in traditional and non-traditional atherosclerosis risk factors. Third, patients who have had KD may be predisposed to having other types of atherosclerosis risk factors.

We noted few significant differences in atherosclerosis risk factors between patients with KD and healthy control subjects. Adiposity measures were similar, with both groups showing higher than normal body mass index. Patients tended to be more sedentary, had lower apolipoprotein AI and higher hemoglobin A1c levels, and despite lower resting blood pressure levels they had a tendency toward less nighttime fall. Earlier studies have shown that HDL cholesterol levels may be depressed acutely, but there is controversy whether this persists in the long term. Mitani and colleagues, as a part of study of inflammation late after KD, noted no differences between patients with KD and control subjects regarding body mass index, systolic blood pressure, and total cholesterol and HDL cholesterol levels. Cheung et al noted no significant differences regarding body mass index, systolic and diastolic blood pressure, and total cholesterol and LDL cholesterol levels. Patients both with and without coronary artery aneurysms had significantly higher levels of apolipoprotein B and lower levels of HDL cholesterol and apolipoprotein AI compared with the normal control subjects. Noto et al noted that patients with KD had higher levels of glycosylated hemoglobin.

The observation of HDL cholesterol and glycosylated hemoglobin abnormalities may be evidence for the presence of a persistent state of inflammation, and inflammation has been implicated as a mechanism for the development of atherosclerosis. Suzuki et al noted evidence of inflammation at autopsy in the otherwise normal coronary arteries of a patient 13 months after KD. Recent reports have noted higher levels of inflammatory markers only in those patients with KD with persistent coronary artery lesions. A limitation of our study was that we did not measure inflammatory markers.

Systemic endothelial dysfunction did not appear to be present after KD, and FMD was not significantly related to patient and KD characteristics, similar to our previous report with smaller numbers of subjects. Dhillon et al first reported decreased FMD, but they did not find any relationship to coronary artery involvement. In contrast, Ikemoto et al recently reported decreased FMD only in those patients with KD with moderate or severe coronary artery abnormalities. Abnormalities of carotid intima-media thickness, arterial stiffness, and impaired fibrinolytic capacity have also been reported in patients with KD with and without coronary artery complications. Discrepancies between our results and other reports may relate to differences in the patient with KD and control subject populations, or the ultrasonography assessments.

FMD was found to be significantly related to blood glucose, triglyceride, and free fatty acid levels, an observation that has not been previously reported. The positive correlation between free fatty acid concentrations and FMD is surprising, considering that previous studies have suggested that elevated...
levels cause endothelial dysfunction. However, it should be noted that Steinberg et al could not find any relationship between fasting free fatty acid concentrations and FMD. Fasting free fatty acid levels exhibit so much variability in concentration and in composition that it is difficult to reconcile conflicting results of studies. Although most studies have shown that high free fatty acid levels have an inverse correlation with FMD, some have shown contradictory results. Observations that saturated and trans-fatty acids do not impair FMD are attributed to older subjects, positioning of the cuff used to measure FMD, and time of measurement. In a separate investigation, long-chain fatty acids were found to attenuate FMD. Fatty acids have also been observed to play a role in increased FMD in hand veins of study subjects via a cyclooxygenase-dependant mechanism. No consensus has been reached as to the effect of free fatty acids on FMD, and our findings indicate that further study is indicated.

For patients who have had KD, the degree of coronary artery involvement does not appear to be significantly associated with systemic endothelial function, even after adjustment for atherosclerosis risk factors. General assessment and counseling regarding healthy lifestyles is indicated.

REFERENCES

Protocol for Assessment of Brachial Artery Reactivity

1. Imaging and analysis equipment. The brachial artery was scanned above the antecubital fossa of the right arm using high-resolution vascular ultrasonography (ATL 3000 ultrasound machine, 7-15-MHz linear-array transducer, Advanced Technology Laboratories, Bothel, Wash). Longitudinal, electrocardiogram-gated, end-diastolic images were acquired of the brachial arterial diameter over a 1- to 2-cm segment, and computer-assisted edge detection brachial analysis software (DEA, Vasometrix, Montreal) was used to measure the brachial artery diameters.

2. Stimulus protocol. All patients were assessed after an overnight fast, with measurements taken between 8 and 10 AM and after the patient had rested for at least 10 minutes in the supine position. Brachial artery imaging was recorded on Super VHS videotapes, for 30 seconds (baseline), and after 5 minutes of reduced blood flow (induced by inflation of a pneumatic cuff placed at the mid upper arm to 20 mm Hg above resting systolic blood pressure), recorded for 3 minutes after release of the cuff. Flow-mediated (endothelium-dependent) vasodilation (FMD) was assessed as percentage change from baseline to maximal diameter of the brachial artery with reactive hyperemia. After a further 10-minute supine rest, the brachial artery imaging was recorded for a further 30 seconds (repeat baseline), then for 1 minute, at 3 to 4 minutes after a single 400-μg dose of sublingual glyceryl trinitrate (GTN). GTN-mediated (endothelium-independent) vasodilatation was assessed as percentage change from baseline to maximal diameter of the brachial artery post-GTN. All scans were performed by experienced vascular sonographers, and measurements were obtained afterward using the automatic edge-detection algorithms with pre-defined acceptable confidence intervals by a single observer.

Protocol for Assessment of 24-hour Ambulatory Blood Pressure Monitoring

1. Measurement protocol and settings. A Spacelab ambulatory blood pressure monitor model #90217 (www.spacelabs.com) was used. An appropriate-sized blood pressure cuff was placed on the nondominant arm, and recordings started in the morning after clinical assessment. Monitors were set to record blood pressure every 15 minutes from 7 AM to 10 PM, and every 30 minutes from 10 PM to 7 AM. Analysis of recordings was performed using computer software specific to the monitor.

2. Patient instructions. All patients were given written instructions and a diary to record events hourly (eg, walking, sleeping, watching television, doing exercise). If symptoms occurred, they were instructed to push the event button to initiate a recording. Patients were instructed that the monitor would beep before a recording would occur, and then they were to keep still, try to relax, and stop any activities while a recording was being made. They were to check occasionally to ensure that tubing was not kinked. During sleep the monitor was to be kept under a pillow to minimize noise. Patients were instructed to turn the monitor off at the end of the 24-hour monitoring period, and return it.
High-Dose Ibuprofen in Cystic Fibrosis: Canadian Safety and Effectiveness Trial

LARRY C. LANDS, MD, PHD, RUTH MILNER, PHD, ANDRÉ M. CANTIN, MD, DAVID MANSON, MD, AND MARY COREY, PHD

Objective  To assess the effectiveness and safety of high-dose ibuprofen when used as part of routine therapy in patients with cystic fibrosis (CF).

Study design  In this multicenter, double-blinded, placebo-controlled trial, a total of 142 patients age 6 to 18 years with mild lung disease (forced expiratory volume in 1 minute [FEV1] > 60 predicted) were randomized to receive either high-dose ibuprofen (70 subjects, 20 to 30 mg/kg/twice daily, adjusted to a peak serum concentration of 50 to 100 μg/mL) or placebo (72 subjects) for a 2-year period. The primary outcome was the annualized rate of change in FEV1% predicted.

Results  The patients in the high-dose ibuprofen group exhibited a significant reduction in the rate of decline of forced vital capacity percent predicted (0.07 ± 0.51 vs –1.62 ± 0.52; \( P = .03 \)), but not FEV1%. The ibuprofen group also spent fewer days in hospital after adjusting for age (1.8 vs 4.1 days per year; \( P = .07 \)). A total of 11 patients (4 in the ibuprofen group and 7 in the placebo group) withdrew due to adverse events.

Conclusions  High-dose ibuprofen has a significant effect on slowing the progression of lung disease in CF and generally is well tolerated. (J Pediatr 2007;151:249-54)

Cystic fibrosis (CF) is the most common lethal genetic disorder affecting the Caucasian population, with an incidence of about 1:3200 live births in North America. Although median survival in CF is now in the fourth decade of life, most patients eventually succumb to progressive respiratory disease.

Lung disease in CF is characterized by an exuberant neutrophilic inflammation. A study of alternate-day prednisone administration demonstrated beneficial effects on lung function. However, the presence of adverse events, including growth retardation and cataracts, limits the ability to use systemic corticosteroids therapy for prolonged periods. A recent 6-month trial with azithromycin, a macrolide, demonstrated beneficial pulmonary effects. The effect of azithromycin on the rate of decline in pulmonary function, which will have a long-term impact on survival, was not evaluated, however. A 48-week trial of inhaled nebulized hypertonic saline solution failed to slow the rate of decline in lung function.

In 1995, Konstan et al demonstrated that high-dose ibuprofen therapy could slow the progression of lung disease in CF, especially in children. Analyzed as a change in the rate of progression of lung disease (percent of forced expiratory volume in 1 minute [FEV1%] predicted), this therapy has shown promise. In the earlier study, however, the sample size was only 49 children under age 13 years, and 90% came from 1 center. Furthermore, concerns over the safety of long-term use of high-dose ibuprofen has limited its use.

To investigate the long-term use of ibuprofen in a larger population, we undertook a multicenter, double-blinded, randomized clinical trial to examine the effectiveness and safety of high-dose ibuprofen in children with CF when used as part of routine care.

METHODS

This was a multicenter, double-blinded, placebo-controlled trial.
Patients

The diagnosis of CF was based on a sweat chloride concentration >60 mmol/L and a compatible clinical history. Children were recruited from 12 CF centers across Canada between September 1998 and August 2000. These centers were estimated to be able to enroll at least 6 patients who met the inclusion and exclusion criteria for the trial. Children were eligible if they were age 6 to 18 years and had an FEV₁ of >60% predicted⁵ at the time of entry into the trial, with no hospitalizations in the previous 2 months. Children were excluded if they had taken systemic corticosteroids or non-steroidal anti-inflammatory agents for more than 1 month in the past year; had a hepatic, renal, or hematologic disorder or coagulopathy; had documented evidence of peptic ulcer disease (endoscopy) or allergic bronchopulmonary aspergillosis; or had a history of hypersensitivity reaction to nonsteroidal anti-inflammatory agents. The study received ethical approval or had a history of hypersensitivity reaction to nonsteroidal anti-inflammatory agents for more than 1 month in the past year; had a hepatic, renal, or hematologic disorder or coagulopathy; had documented evidence of peptic ulcer disease (endoscopy) or allergic bronchopulmonary aspergillosis; or had a history of hypersensitivity reaction to nonsteroidal anti-inflammatory agents. The study received ethical approval in each of the participating centers, and written informed consent was received for all participants.

Sample Size

Our sample size was based on the effect of placebo treatment on the slope of the FEV₁ in the intention-to-treat pediatric group of Konstan et al.⁶ Because post hoc subgroup analysis in that study may have overestimated the degree of response, we based our sample size estimate on a more conservative expected difference between the groups (4% for control vs 2% for treated). Using a mixed-model regression analysis⁵ and a standard deviation for the slope of 7.5%/year, we found that a 2-year study with 80% power required 220 patients in each study arm (2-sided α = 0.05).

Allocation

Within each clinic, patients were allocated using a predefined block-randomization schedule. Randomization tables were prepared by the central pharmacy in Toronto, and coded packages of ibuprofen or placebo tablets were shipped to the recruiting clinic to be dispensed to the patients. Patients, caregivers, and study personnel were all blinded to treatment assignment. The central pharmacy kept the coded treatment assignment list on which individual assignments were sealed in a special form. Breaking of the code involved tearing off a cover sheet for the individual study subject by 1 of 2 designated research pharmacists. During the study, the code was broken for an individual patient only if requested by the Safety and Monitoring Committee. It was broken for all patients at study termination. No stratification was performed, and no subgroup analysis was planned.

Intervention

Dose. All patients underwent a baseline pharmacokinetic study (baseline concentration and every hour for 3 hours), using 200-mg tablets (Upjohn-Pharmacia) at a dose of 20 to 30 mg/kg to a maximum of 1600 mg. All ibuprofen levels were analyzed by high-pressure liquid chromatography in the laboratory of J.V. Aranda (Division of Clinical Pharmacology and Toxicology, Children’s Hospital of Michigan, Detroit, MI). The number of assigned pills was then adjusted by the coordinating pharmacist to provide a peak plasma concentration of 50 to 100 μg/mL for each patient in the study. The number of pills was adjusted regardless of whether the patient was subsequently assigned to active treatment or to placebo, and dosages were not rechecked. The patient was then instructed to take the prescribed number of pills (ibuprofen or placebo) twice daily.

Participating centers were advised about possible interactions between ibuprofen and intravenous aminoglycosides, resulting in renal insufficiency.¹⁰ Centers were advised that study medication could be stopped during intravenous aminoglycoside administration. Advice on adjusting for other concomitant medications was not given. If a center decided to continue study medication during this time, then close monitoring of renal function was advised. Pharmacokinetic studies were to be repeated if any patient experienced a weight change of >25% during the 2-year study period; this did not occur, however.

Measurements

Patients were examined for the trial every 6 months for 2 years, but could be seen more often at the discretion of the treating center. At each visit, standing height was measured with the patient in stocking feet using a stadiometer, and weight was measured on an electronic balance with the patient lightly dressed. Height and weight were used to calculate standardized z-scores and percent of ideal body weight, using the Centers for Disease Control 2000 growth standards.¹¹ Expiratory spirometry was measured at each center using the same device at each visit and reported as a percentage of predicted value.⁸ Each center was responsible for conducting these tests using American Thoracic Society guidelines.¹² The raw values were processed centrally to calculate the percent predicted values.

At each visit, blood work was conducted to screen for complications; liver function (aspartate aminotransferase [serum glutamic oxaloacetic transaminase], alanine aminotransferase [serum glutamic pyruvic transaminase], gamma glutamyl transferase, total bilirubin), renal (serum electrolytes, blood urea nitrogen, creatinine, microscopic urinalysis), hematologic function (hemoglobin, white blood cell count, platelet count), and coagulation (prothrombin time/partial thromboplastin time) were assessed in each center. Values were considered abnormal as defined by AIDS Clinical Trial Group (ACTG) criteria (available at http://www.rcc.tech-res.com).

Chest radiographs were performed at each visit. The films were read independently by a radiologist (D.M.) using the standard CF chest radiograph scoring system developed by Brasfield et al.¹³

Compliance

At each visit, the pill containers were returned to the local pharmacist and new pills were issued for the next 6
months of the study. The containers were returned to each center’s pharmacist for counting, at which point compliance was assessed. We estimated that 60% of the pills would be consumed; Konstan et al. found compliance rates of 68% in the ibuprofen group and 72% in the placebo groups, with no variation by age. For a study of real-world clinical effectiveness, we considered that compliance assessment using pill counts was simpler and less expensive than random blood testing for ibuprofen.

Adverse Event Recording

At each visit after randomization, an adverse event questionnaire was completed by interview with the local study coordinator, using the diary to assist memory. The coordinator also recorded the number of hospital admissions and length of stay, along with any concomitant therapy, including antibiotics and inhaled anti-inflammatory agents, such as corticosteroids.

The common adverse events related to ibuprofen are primarily gastrointestinal symptoms, such as epigastric discomfort, heartburn, cramping, and gastric or duodenal ulceration. However, many of these symptoms are known to occur in patients with CF as part of the natural history of the disease. We used the adverse symptom questionnaire of Konstan et al. and recorded the incidence of symptoms at each visit.

Patient Withdrawal

A patient could withdraw from the trial at his or her discretion, or could be withdrawn at the discretion of the treating physician if any of the following occurred:

1. Abdominal discomfort resolving with drug removal but recurring with drug reintroduction.
2. Upper gastrointestinal bleeding, documented by radiology or endoscopy. Monitoring for fecal occult blood was not included because although it is a relatively simple and inexpensive test, it is overly sensitive and most likely would trigger many further, more complex investigations.
3. Visual disturbances (eg, blurred or diminished vision, scotomata, or changes in color perception), resulting in immediate drug cessation and ophthalmologic examination. Medication could be restarted if the ophthalmologic examination suggested that the disturbance could be explained by a cause other than study medication.
4. If changes in renal, hepatic, or hematologic function occurred that could be classified in the mildly toxic range (according to ACTG Pediatric Toxicity tables), and remained in this range two weeks later while the subject remained on the study medication. If the abnormalities persisted, then the drug was discontinued, if no reasonable alternative explanation existed. If values were above those in the ACTG mild range, then the study drug was stopped immediately.

The Safety Monitoring Committee decided a priori to stop the trial if (1) the number of subjects voluntarily withdrawing from the trial exceeded 20% of those enrolled; (2) after breaking the blinding code for the above-mentioned adverse effects, the treatment group had a 20% higher incidence of these effects compared with controls; or (3) after breaking the code, the incidence of life-threatening adverse events requiring admission to an intensive care unit or hospital were 5% higher in the treatment group. No interim analysis was planned a priori.

Data Analysis

An intention-to-treat analysis was performed on all available information on each subject, including those subjects who did not complete 2 years of study follow-up. Baseline data were assessed for balance between groups. The primary outcome variable, the annual rate of change in FEV₁%, was analyzed using a mixed-model analysis of variance. Mixed-model analysis allows for efficient use of all data, because the mean slopes are not distorted by subjects with incomplete data. This model effectively weights the contributions of individuals with shorter follow-up or missed observations, ensuring that the estimates of mean and variance of the slope are not biased. The mixed model was also used to analyze secondary outcomes, including predicted FVC%, anthropometric data, and chest radiograph scores. The number of hospitalizations, adverse effects, and use of concomitant therapy were compared by χ² analysis. The number of days in the hospital per year of follow-up was analyzed by Poisson regression, with Pearson adjustment for overdispersion where indicated.

Role of Funding Sources

The sponsors of the study and the company supplying the study medication played no role in study design, data collection, data analysis, data interpretation, or writing of this report.

RESULTS

A total of 142 patients (70 in the ibuprofen group and 72 in the placebo group) were enrolled in the trial (Figure 1). Recruitment was stopped at that point, because a survey of participating centers revealed that prolonging the recruitment period would produce no significant increase in enrollments. The groups had similar baseline characteristics (Table I). At study enrollment, the patients had mild lung disease (mean FEV₁ >90%) and were reasonably well nourished, with mean z scores for height and weight approximately 1/2 standard deviation below the normal median values for age and sex.

The difference in mean annual rate of decline in FEV₁% predicted was not statistically significant (2.69 ± 0.57 for placebo vs 1.49 ± 0.57 for ibuprofen; P = .14). However, a significant decrease in the annual rate of decline of FVC% predicted was seen in the ibuprofen group (1.62 ± 0.52 for placebo vs 0.07 ± 0.51 for ibuprofen; P = .03) (Figure 2). There were no significant differences in changes in the predicted maximum midexpiratory flow (FEF₂₅₋₇₅%) (data not shown).
Chest radiograph scores were available for 62 participants receiving placebo and 60 participants receiving ibuprofen. The mean scores at baseline demonstrated moderate abnormality compared with a perfect score of 25 and did not differ between the groups (placebo, 19.5 ± 2.2; ibuprofen, 19.7 ± 2.1). The mean changes in radiograph scores over the course of the study were not significantly different between the 2 groups (placebo, 0.6 ± 2.3; ibuprofen, 0.5 ± 2.2; *P* = .9).

Nutritional status (weight and body mass index z scores) did not change significantly in either group over the course of the study.

The frequency of hospitalization was quite low and did not differ significantly between the 2 groups (1 or more hospitalizations over the 2-year period, 36% in the placebo group vs 27% in the ibuprofen group [*P* = .3]; 1 or more respiratory hospitalizations, 26% vs 20% [*P* = .4]; 1 or more gastrointestinal hospitalizations, 6% vs 4% [*P* = .7]). Total days spent in the hospital during the randomized follow-up period were 561 for the placebo group and 248 for the ibuprofen group. Poisson regression analysis of days per year of follow-up, with a Pearson adjustment for overdispersion, gave hospitalization rates of 4.1 days per year in the placebo group and 1.8 days per year in the ibuprofen group (*P* = .07).

Post hoc analysis of days in the hospital revealed a significant age factor (*P* = .026); that is, older patients spent more days in the hospital than younger patients. Including age in the Poisson regression model explained more of the variance, and the treatment group difference was significant (*P* = .024). This analysis suggests that the doubling of the days spent in the hospital for patients in the placebo group represents a true treatment effect.

A total of 18 patients (9 in each group) did not complete the full 2 years of follow-up. Eleven withdrew due to adverse events (4 in the ibuprofen group and 7 in the placebo group); Table II presents results in the order in which the patients withdrew. As far as we know, all centers discontinued the study drug during treatment with intravenous aminoglycosides. There were no changes in renal,

### Table I. Subject baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo group (n = 72)</th>
<th>Ibuprofen group (n = 70)</th>
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<tbody>
<tr>
<td>Age</td>
<td>11.1 ± 3.1</td>
<td>12.0 ± 3.3</td>
</tr>
<tr>
<td>Height z score</td>
<td>−0.50 ± 0.97</td>
<td>−0.52 ± 0.91</td>
</tr>
<tr>
<td>Weight z score</td>
<td>−0.48 ± 0.96</td>
<td>−0.44 ± 0.97</td>
</tr>
<tr>
<td>Weight, % of ideal</td>
<td>101 ± 13.0</td>
<td>102 ± 14.6</td>
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<tr>
<td>Body mass index z score</td>
<td>−0.28 ± 0.91</td>
<td>−0.21 ± 0.95</td>
</tr>
<tr>
<td>FEV1,% predicted</td>
<td>91.0 ± 17.4</td>
<td>92.3 ± 18.4</td>
</tr>
<tr>
<td>FVC,% predicted</td>
<td>96.2 ± 18.0</td>
<td>95.2 ± 14.0</td>
</tr>
</tbody>
</table>

All values are mean ± standard deviation.

### Table II. Adverse events leading to study withdrawal

<table>
<thead>
<tr>
<th>Patient</th>
<th>Event</th>
<th>Group</th>
<th>Time in study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Conjunctivitis</td>
<td>Ibuprofen</td>
<td>4 months</td>
</tr>
<tr>
<td>2</td>
<td>Abdominal cramps, nausea, diarrhea</td>
<td>Ibuprofen</td>
<td>2.5 months</td>
</tr>
<tr>
<td>3</td>
<td>Abdominal pain, gastritis</td>
<td>Placebo</td>
<td>14 months on and off</td>
</tr>
<tr>
<td>4</td>
<td>Epigastric pain, nausea, diarrhea</td>
<td>Placebo</td>
<td>3 weeks</td>
</tr>
<tr>
<td>5</td>
<td>Abdominal pain, reflux esophagitis</td>
<td>Placebo</td>
<td>12 months</td>
</tr>
<tr>
<td>6</td>
<td>Abdominal pain, admitted with hepatitis</td>
<td>Placebo</td>
<td>9 months on and off</td>
</tr>
<tr>
<td>7</td>
<td>Nausea, vomiting, tinnitus</td>
<td>Ibuprofen</td>
<td>18 months</td>
</tr>
<tr>
<td>8</td>
<td>Reactive arthritis</td>
<td>Placebo</td>
<td>8 months</td>
</tr>
<tr>
<td>9</td>
<td>Elevated liver enzyme levels</td>
<td>Placebo</td>
<td>18 months on and off</td>
</tr>
<tr>
<td>10</td>
<td>Gastrointestinal bleeding</td>
<td>Ibuprofen</td>
<td>23.5 months</td>
</tr>
<tr>
<td>11</td>
<td>Abdominal pain</td>
<td>Placebo</td>
<td>1.5 months</td>
</tr>
</tbody>
</table>
hepatic, or hematologic values that warranted discontinuation of the study drug.

There were no differences in the percentage of patients taking concomitant therapy (anti-inflammatory, inhaled corticosteroids, inhaled or oral antibiotics, bronchodilators, pancreatic enzymes, vitamins) at the beginning of the trial or any time during the study. There was no discernible center effect for any of the outcomes.

**DISCUSSION**

We found that high-dose ibuprofen significantly slowed the decline in FVC in a group of children and adolescents with CF who initially had well-preserved lung function. The ibuprofen group had fewer days spent in the hospital. Ibuprofen generally was well tolerated, with only 4 subjects withdrawing due to adverse events.

Our findings are consistent with those of Konstan et al., who found that children with mild lung disease benefited the most from this therapeutic strategy. Compared with their patients, the patients in the current study were younger and had better initial lung function and nutritional status. However, their placebo group, whether taken as the entire group or limited to those under age 13 years, had greater annual losses in lung function (FEV1, 3.6%/year for all vs 4.2%/year for those under age 13) compared with our group (−2.7%/year). When it became clear after 1 year of enrollment that we could not achieve our projected sample size, the investigative team, after consulting with the Safety Monitoring Committee, decided to continue the underpowered study, with the main focus on safety outcomes.

We encountered few adverse events leading to withdrawal. The main impediment to recruitment was similar to that reported for previous studies, concerns about the risk of adverse events, especially gastrointestinal events. One patient experienced significant gastrointestinal bleeding. At the time of the event, we were not advising any prophylactic therapy, such as H2 antagonists; but after the event, on the advice of the Safety Monitoring Committee, all centers were advised that they could prescribe H2 antagonists for gastrointestinal protection. We do not know the extent of adherence to this advisory. A recent single-center study of high-dose ibuprofen did not find any improvement in lung function, but did report significant adverse events, primarily gastrointestinal. In that study, the sample size was not powered to detect significant declines in lung function, and only 4 of 9 patients with significant gastrointestinal complaints received H2 antagonists or other gastrointestinal protection.

More recently, concern has been expressed about the long-term use of nonsteroidal anti-inflammatory drugs, including ibuprofen, and the risk of cardiovascular events. This may be related to the relatively low dosage of these medications prescribed to treat conditions other than CF. Konstan et al. have demonstrated that low-dose ibuprofen can actually increase neutrophil recruitment; however, when peak serum levels of 50 to 100 µg/mL are achieved, neutrophil recruitment is diminished in both CF and healthy subjects. Therefore, low-dose ibuprofen actually may be proinflammatory.

One other impediment to using high-dose ibuprofen is the need for therapeutic monitoring, including pharmacokinetics every 2 to 3 years and monitoring for adverse renal, hepatic, and hematologic effects. The costs of such monitoring and of the ibuprofen itself are relatively minor compared with those for most current therapies, however.

We did not achieve our recruitment goals, and our control group did better than we had predicted when calculating our required sample size. Nonetheless, we did achieve a virtual stoppage (<0.1%) in the rate of decline in FVC, along with fewer days in the hospital after adjusting for age. Due to a wide variance in the rate of decline in FEV1, our 45% decrease in the rate of decline in the ibuprofen group was not statistically significant. To detect a significant change in the rate of decline of FEV1 requires a study lasting at least 1 year with a relatively large sample size. As general results for patients with CF continue to improve, the sensitivity of spirometry as an outcome measure diminishes, yet no new markers have been firmly established. However, our results demonstrate that adverse events occurred less often with ibuprofen than perceived by the treating community in CF.

In summary, high-dose ibuprofen in patients with CF was found to be safe and to have a positive impact on the rate of decline in lung function and on the duration of hospitalization. This study supports and extends the original observations of Konstan et al. Slowing the rate of progression will result in enhanced longevity and quality of life for patients with CF.

**REFERENCES**


**APPENDIX**

**Investigators Recruiting Patients in Their Center**

Danny Vaze, Janeway Hospital

Dan Hughes, IWK Health Centre

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Normand Petit, Centre Hospitalier Rouyn-Noranda

Larry Lands, Montreal Children’s Hospital

Jacques-Edouard Marcotte, Hôpital Ste Justine

Ian Maclusky, Toronto Hospital for Sick Children

Linda Pedder, McMaster University Medical Centre

Bryan Lyttle, Children’s Hospital of Western Ontario

Vijay Kumar, Sudbury Regional Hospital

Kumar Ramlall, Royal University Hospital

Mark Montgomery, Alberta Children’s Hospital
Primary Sclerosing Cholangitis in Childhood is Associated with Abnormalities in Cystic Fibrosis–Mediated Chloride Channel Function

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Objective To determine whether primary sclerosing cholangitis (PSC) in childhood is associated with abnormalities in cystic fibrosis transmembrane conductance regulator (CFTR).

Study design Subjects with PSC diagnosed in childhood (n = 20) were recruited from Children's Hospital. Subjects had testing with sweat chloride concentration, nasal transmembrane potential difference, and extensive genetic analysis of the CFTR gene. Disease control subjects consisted of 14 patients with inflammatory bowel disease alone and no liver disease. t Tests were performed to determine statistical significance.

Results In the PSC group, CFTR chloride channel function (ΔChloride free + isoproterenol) was markedly diminished at −8.6 ± 8.2 mV (reference range: −24.6 ± 10.4 mV). In contrast, disease control subjects had normal function, at −17.8 ± 9.7 mV (P = .008). Sweat chloride concentration in subjects with PSC was greater than in disease control subjects (20.8 ± 3.4 mmol/L vs 12.0 ± 1.6 mmol/L, P = .045). Comprehensive CFTR genotyping revealed that 5 of 19 (26.3%) subjects with PSC had a CFTR mutation or variant, compared with 6 of 14 (42.9%) disease control subjects.

Conclusions There is a high prevalence of CFTR-mediated ion transport dysfunction in subjects with childhood PSC. (J Pediatr 2007;151:255-9)

Cystic Fibrosis (CF) is characterized by abnormal secretion of fluid, electrolytes, and macromolecules by exocrine glands. To date, close to 1200 CF-causing mutations have been reported.1 In addition to the formation of inspissated secretions, cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction results in an excessive host inflammatory response.2,3

Primary sclerosing cholangitis (PSC) is a slowly progressive cholestatic disease of unknown cause, characterized by fibroobliterative inflammation of the biliary tract. Although the underlying cause and pathogenesis of PSC is not known, it is associated with inflammatory bowel disease (IBD) in approximately 80% of cases.4 Conversely, only about 4% of patients with IBD have or will have PSC, and it is impossible to predict who will do so.

PSC and CF have features in common. Chronic low-grade inflammation and damage to bile ducts characterize both conditions. Due to their similarities, studies have examined the prevalence of CFTR mutations in adults with PSC. In one study, only 1 of 19 subjects with PSC had neither a CFTR mutation/variant nor the M470V genotype.5 CFTR function in these patients was decreased as measured by nasal transmembrane potential difference (NTPD). Another study failed to demonstrate an association of common CF disease–causing mutations with PSC.6 However, exhaustive genotyping as well as functional analyses were not performed in that study.

In the current study, we hypothesized that a defect in CFTR mediated chloride channel function is present in subjects with PSC diagnosed in childhood (<18 years) as well as functional analyses were not performed in that study.
compared with disease control subjects with IBD and no liver disease. In contrast to the previous adult study by our group in a separate set of patients, subjects with PSC diagnosed in childhood may have no CFTR dysfunction. Alternatively, genetic diseases may be more likely to manifest in children than in adults if there are more severe mutations with a further decrease in CFTR function.

METHODS

Patient Selection and Study Design

This study was conducted at Children’s Hospital Boston and Beth Israel Deaconess Medical Center in Boston. Institutional review board approval was obtained at both hospitals. Written informed consent was obtained from the parents or guardians of the children who served as subjects of the investigation and, when appropriate, from the subjects themselves. Children with PSC diagnosed before the age of 18 years were recruited. The criteria for the diagnosis of PSC included presence of typical cholangiographic abnormalities of PSC involving bile ducts segmentally or extensively by endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP), and/or liver biopsy demonstrating typical features of PSC. Patients were excluded if they had other liver disease, such as viral hepatitis, drug-induced liver disease, and metabolic or hereditary liver disease by conventional clinical, laboratory, and histologic criteria. PSC with features of autoimmune hepatitis (overlap syndrome) was not used as an exclusion criterion, as this is thought to be a subset of PSC. For entry into this study, subjects with PSC had to be at least 12 years of age, as this was the lower age limit to reliably tolerate NTPD. Disease control subjects were age-matched subjects with IBD and no liver disease. Disease control subjects had normal alanine aminotransferase and γ-glutamyl transferase levels and did not undergo routine biliary imaging or liver biopsies. Diagnostic criteria for this group included clinical, radiologic, and/or histologic evidence of either ulcerative colitis or Crohn disease. There was no exclusion based on sex, race, and ethnic background. Subjects had functional testing for CFTR consisting of NTPD and sweat chloride measurements and underwent complete CFTR gene sequencing for mutations.

Sweat Chloride

All patients underwent sweat chloride testing by the quantitative pilocarpine iontophoresis method, described by Gibson and Cooke, at Children’s Hospital Boston. Results were classified as abnormal (>60 mmol/L), borderline (40 to 60 mmol/L), or normal (<40 mmol/L). These reference values are based on those recommended by the consensus statement from the United States Cystic Fibrosis Foundation, in which the diagnostic criteria have been revised to include the “atypical” CF phenotype.

Nasal Transmembrane Potential Difference

Nasal transmembrane potential difference was performed as described by Knowles et al. Basal potential difference (infusion PD) and the response to inhibition by perfusion of amiloride (ΔAmil) was recorded to reflect activity of inwardly directed sodium transport. A chloride-free solution was perfused with amiloride to measure basal chloride secretion, and a maximal chloride secretory response (ΔCl-free + Iso) was then elicited by perfusing with isoproterenol. ΔCl-free + Iso was considered to be abnormal if it was outside the 99% probability limits (7.65 to 22.6 mV) for healthy control subjects. Reference ranges were established from healthy individuals analyzed in a previous study from our group. NTPD testing was performed in the same time period by the same operator and was not blinded to diagnosis.

Analysis of the CFTR Gene for DNA Alterations

Patients underwent an exhaustive search for DNA alterations in the CFTR gene with multiplex, heteroduplex gel (mHET) analysis as previously described. PCR-amplified DNA fragments corresponding to all the CFTR exons, their flanking intron sequences, and the promoter region (up to 1 kb upstream of exon 1) were examined by mHET and sequencing analyses. The estimated detection rate for this protocol is 95% of known CFTR gene mutations. In addition, variants in the polythymidine tract (5T, 7T and 9T) of intron 8 and the M470V (1540A→G) polymorphism in exon 10 were studied. Abnormalities in these loci produce either less amounts of correctly spliced CFTR (T-tract) or subfunctional CFTR (M470V). Other genetic liver disease modifiers such as α-1-antitrypsin were not assessed.

Statistical Analysis

All phenotype measurements by NTPD were described as mean ± SD. Sweat chloride concentration was the average of both arms and expressed as mean ± SEM. t Tests were performed to determine statistical significance between groups.

RESULTS

Demographics

Twenty subjects with PSC were recruited, 19 of whom completed NTPD. There was a variable degree of portal tract fibrosis in the patients with PSC, with some having mild fibrosis and others more advanced disease and portal-to-portal tract bridging fibrosis. Seven of 20 subjects with PSC had recent autoimmune markers. The diagnosis of overlap syndrome with autoimmune hepatitis in 4 patients was based on characteristic biopsy features accompanied by positive autoimmune markers. Fourteen disease control subjects were recruited, 12 of whom completed NTPD (Table I).

Phenotype Testing

The sweat chloride concentration in subjects with PSC was greater than in disease control subjects (20.8 ± 3.4
Table I. Demographics of PSC subjects and disease control subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PSC</th>
<th>IBD and no liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>17.9 ± 0.8</td>
<td>17.5 ± 0.4</td>
</tr>
<tr>
<td>Sex</td>
<td>Male: 15, Female: 5</td>
<td>Male: 6, Female: 8</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian: 19, Black: 1, Other: 0</td>
<td>Caucasian: 12, Black: 0, Other: 2</td>
</tr>
<tr>
<td>IBD</td>
<td>Ulcerative colitis: 13, Crohn disease: 5, None: 2,Overlap syndrome: 4, Sinusitis/asthma: 5</td>
<td>Ulcerative colitis: 3, Crohn disease: 11, None: 0,Overlap syndrome: 0, Sinusitis/asthma: 5</td>
</tr>
<tr>
<td>Family history of CF</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Family history of PSC</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Age at the time of enrollment is expressed as the mean ± SEM. Overlap syndrome is sclerosing cholangitis with features of autoimmune hepatitis based on liver biopsy.

mmol/L vs 12.0 ± 1.6 mmol/L, 
With regard to NTPD, the maximum baseline potential difference was normal in both groups. Baseline potential difference in subjects with PSC was −26.5 ± 7.0 mV and in disease controls −22.3 ± 6.1 mV (normal reference range: −23.0 ± 8.1 mV). The response to inhibition of sodium uptake (ΔAmiloride) was also normal in both groups, with subjects with PSC at 15.0 ± 6.9 mV and disease control subjects at 11.8 ± 4.8 mV (normal reference range: 13.7 ± 5.2 mV). CFTR chloride channel function (ΔChloride free + isoproterenol, which reflects maximum CFTR-mediated chloride conductance) was markedly diminished in subjects with PSC, at −8.6 ± 8.2 mV compared with disease control subjects, in whom values were normal (−17.8 ± 9.7 mV, P = .008) (normal reference range: −24.6 ± 10.4 mV) (Figure, A). The individual values are shown in the Figure (B). There was no correlation between severity of liver disease by biopsy and degree of CFTR dysfunction, although the numbers were small.

Genetic Testing

For purposes of definition, mutations are defined as CF-causing changes; variants are associated with decreased CFTR function and/or present in other CFTR-associated diseases; polymorphisms are changes not linked to specific diseases. Comprehensice CFTR genotyping revealed that 5 of 19 (26.3%) subjects with PSC had a CFTR mutation or variant, compared with 6 of 14 (42.9%) disease control subjects (Table II). The R75Q variant was common in both groups of subjects and is currently not listed as a CF causing mutation, although its contribution to CF-like phenotypes cannot be excluded. Homozygosity for 470V (GG) at the 1540 locus produces a less functional CFTR protein variant and was identified in 4 of 19 subjects with PSC compared with 2 of 14 disease control subjects. Eight of 19 subjects with PSC had a polymorphism, as did 6 of 14 disease control subjects. Three disease control subjects had the T-tract 5/7. There is little data regarding the frequency of CFTR mutations/variants/polymorphisms in normal populations. The data indicate the following frequencies: IVS8T5, 3% to 5%, depending on population; R75Q, 3% to 6%, depending on population; 1716G−A, 1% to 2% (personal communication from Julian Zielenski, Hospital for Sick Children, Toronto, Canada).
DISCUSSION

In this prospective study, we have demonstrated an increased prevalence of CFTR functional abnormalities in subjects with PSC diagnosed in childhood compared with disease control subjects. The mean values for the impairment in the chloride secretory response observed in subjects with childhood PSC was intermediate to that expected in patients with classic CF and healthy control subjects. It is noteworthy that 11 of 19 subjects with PSC had very low isoproterenol stimulated chloride secretory responses. The mean value of $8.6 \text{ mV}$ was lower than that seen in our previous study of adults with PSC ($14 \text{ mV}$ median $[9, -20, \text{ interquartile range}]$). $^5$ NTPD values are not known to change as a function of age in older children and adults (personal communication from Peter Durie and Lynda Ellis, Hospital for Sick Children, Toronto, Canada).

A reduced chloride response has been reported in other single organ disorders associated with CFTR dysfunction, such as congenital bilateral absence of the vas deferens,$^{14}$ idiopathic pancreatitis,$^{10}$ and chronic rhinosinusitis.$^{15}$ NTPD is more sensitive than sweat testing for the assessment of chloride ion secretion in disease states characterized by single organ involvement associated with mild CFTR dysfunction. Hence, it is not surprising that most subjects with PSC had negative sweat tests. However, the mean sweat chloride value in subjects with PSC was greater than in disease control subjects.

Although the sample size was too small for a valid correlation, exhaustive CFTR genotyping was not a reliable

### Table II. Genotype-phenotype correlation

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Mutations/Variants</th>
<th>Polymorphism</th>
<th>1540 locus</th>
<th>T Tract</th>
<th>Sweat chloride (mmol/L)</th>
<th>ΔCl + Iso (mV)*</th>
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<tbody>
<tr>
<td>PSC</td>
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<td>1</td>
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<td>2</td>
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<td>7/7</td>
<td>NP</td>
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</tr>
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<td>6</td>
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<td>7/7</td>
<td></td>
<td></td>
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<tr>
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</tr>
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</tr>
<tr>
<td>13</td>
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<td>-3.8</td>
</tr>
<tr>
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</tr>
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<td>AG</td>
<td>7/9</td>
<td></td>
<td>21.6</td>
<td>-1.8</td>
</tr>
<tr>
<td>18</td>
<td>1001 + 11C/T</td>
<td>AG</td>
<td>7/9</td>
<td></td>
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</tr>
<tr>
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<tr>
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<td>7/7</td>
<td></td>
<td>10.8</td>
<td>-30</td>
</tr>
<tr>
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<tr>
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<td>125G/C</td>
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<td></td>
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<td>-33</td>
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<td>5/7</td>
<td>4</td>
<td>-14</td>
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</table>

Subjects with IBD were disease control subjects. CFTR mutations shown in bold are E725K, S1235R, and 2752 - 26A → G. The 1540 locus is presented as genotype AA, AG (M470V), or GG (470V).

*(ΔChloride free + isoproterenol). NP (not performed). Subjects 4 and 8 had no IBD. Subjects 7, 8, 12, and 16 had overlap syndrome.
predictor of phenotype in this study. There were several variants detected that are not true CF-causing mutations. It is important to point out that what may be regarded as a variant, that is, not proven to be a disease-causing mutation leading to the classic form of CF, may be a causative mutation leading to the expression of disease in other milder CF related disorders, or “CFTR-opathies,” such as idiopathic pancreaticiti.10 The polymorphisms identified in our study are also important because they could affect CFTR function, in part through potentiating mutations or variants. Some of the exonic and intronic polymorphisms may actually disrupt yet unknown sequence elements playing a role in regulating transcription or splicing of the gene. It is interesting to note that CFTR variants and mutations were detected in disease control subjects as well. Because the onset of PSC in patients with IBD is variable, it is possible that disease control subjects may develop this condition in the future. None of the patients in this study met the CF Consensus criteria for the diagnosis of classic CF.

A conceptual model of cholangiopathies was recently described.16 PSC probably represents a common phenotypic end point arising from the interaction of multiple environmental and genetic factors. Its strong association with IBD (90% in this cohort) suggests that chronic portal bacteremia may provide an initial insult to cholangiocytes. Bacterial overgrowth in the CF intestine, as recently shown in CF mice,17 may also play a causative role as an instigating factor. The fact that only 4% of patients with IBD will have PSC may be related to CFTR dysfunction resulting in an excessive host inflammatory response attributable to increased levels of proinflammatory cytokines and neutrophils.2,3 Further support for the concept that CFTR dysfunction in the setting of colitis predisposes to bile duct injury comes from experiments with exon 10 cftr−/− mice, in which induction of colitis with dextran sodium sulfate results in a mononuclear cell infiltrate in the portal tracts in conjunction with bile duct proliferation.18 This was not observed in wild-type control mice. Peroxisome proliferator activated receptor (PPAR)-α abnormalities may play a role in contributing to this excessive inflammatory response, as shown in this CF mouse model of bile duct injury.19 Thus, abnormal qualitative or quantitative innate immune responses to an insult in the liver may predispose to the development of PSC.

We conclude that NTPD has identified a subgroup of subjects with PSC diagnosed in childhood who have CFTR-mediated ion transport dysfunction as compared with disease control subjects. PSC is a genetically complex disease with no simple mendelian pattern of inheritance. CFTR may play a role as a modifier in the development of PSC, but this may not be the only mechanism and does not exclude other independent or coexistent environmental or genetic factors or disorders of immune regulation. Genotyping did not identify an increase in disease proven CFTR mutations, which is not unexpected, given the fact that these individuals do not have the classic form of CF.

REFERENCES


Clinical Trial of Safety and Efficacy of IHN-A21 for the Prevention of Nosocomial Staphylococcal Bloodstream Infection in Premature Infants

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Objective To determine if IHN-A21, an intravenous immune globulin (IGIV) derived from donors with high titers of antibody to surface adhesins of Staphylococcus epidermidis and S aureus prevents late-onset sepsis (LOS) in very low birth weight (VLBW) infants.

Study design In this double-blind, placebo-controlled study, infants with birth weights 500 to 1250 g were randomized to receive up to four doses of IHN-A21 (Veronate®) or placebo. The primary objective was to determine the safety and efficacy of IHN-A21 versus placebo for prevention of S aureus LOS in VLBW infants.

Results A total of 1983 infants from 95 neonatal intensive care units were randomized, and received at least one dose of study drug. S aureus LOS developed in 50 of 989 (5%) and 60 of 994 (6%) infants who received placebo or IHN-A21, respectively (P = .34). No differences were found in the frequencies of LOS caused by coagulase-negative staphylococci (CoNS), Candida spp, or overall mortality. No adverse events were statistically significantly associated with IHN-A21 infusions compared with placebo.

Conclusion IHN-A21 failed to reduce the incidence of staphylococcal LOS or candidemia in premature infants. (J Pediatr 2007;151:260-5)
teins, clumping Factor A and Ser-Asp dipeptide repeat G, that are found in >95% of strains of \textit{S. aureus} and most strains of \textit{S. epidermidis}, respectively.\textsuperscript{13-15} These antigens play an important role in the adherence of bacteria, which is the initiating step in establishing infection. Donors for INH-A21 represent approximately 2% of the normal blood donor population with the highest levels of antibodies to either antigen. Compared with seven lots of commercially available IGIV from five manufacturers, INH-A21 contains 2- to 5-fold higher levels of anti-clumping Factor A and 1.75- to 6-fold higher titers of anti-Ser-Asp dipeptide repeat G (data on file). We report results from a randomized, double-blind, multicenter, placebo-controlled study designed to determine the safety and efficacy of INH-A21 versus placebo for prevention of LOS as a result of \textit{S. aureus} in VLBW infants.

METHODS

Patients and Eligibility

This clinical trial was conducted at 95 study centers in the United States and Canada between May 26, 2004 and January 21, 2006. Premature infants between postnatal days 3 to 5 (beginning at hour 49 and through hour 120 after delivery) were eligible for enrollment if they met the following criteria: birth weight \( \geq 500 \) and \( \leq 1250 \) g and expected to survive at least 4 weeks and to require intravenous access for 10 to 14 days. Infants were excluded if there was evidence of active sepsis (defined by one of the following: culture-proven early-onset sepsis and not clinically stable, or clinical signs of sepsis and blood cultures pending), severe congenital anomaly, congenital immunodeficiency, evidence of significant fluid overload or volume depletion, or serum creatinine >1.6 mg/dL. Infants were excluded who had received or were likely to receive another IGIV product or immune globulin before first infusion of study drug or were receiving antibiotics for prevention of catheter-related or nosocomial infections.

Study Design, Study Groups, and Randomization

Following informed consent, infants meeting entry criteria were randomized (1:1) to receive 1.5 mL/kg of study drug INH-A21 (750 mg/kg) or placebo (0.45% NaCl). Infants were randomized using a standard block randomization, stratified within site and birth weight group (500-900 g and 901-1250 g). Infants received up to four infusions of study drug on study days 1, 3, 8, and 15, provided intravenous access was present for general medical care. Infusions were administered by a rate-escalation protocol as described previously.\textsuperscript{12} The dose selected and infusion schedule were based on results from a previous dose-escalation study and population pharmacokinetic modeling of anti-staphylococcal antibodies.\textsuperscript{12,16} Infants were followed for up to 70 days at the enrolling institution, or up to the time of discharge home, permanent transfer to another hospital, or death.

The protocol, study design, and parental consent forms were approved by the Institutional Review Board at each participating institution. An independent Data and Safety Monitoring Board reviewed available safety data and infection rates at predefined intervals. The study was conducted according to the guidelines of Good Clinical Practice as established by the International Conference on Harmonization (http://www.fda.gov/cder/guidance/959fnl.pdf).

Outcome Measures

The primary outcome was the proportion of infants with LOS caused by \textit{S. aureus}. Sepsis for known bacterial or fungal pathogens was defined as the presence of clinical signs and one positive blood culture or culture from an otherwise sterile site (cerebrospinal fluid; peritoneal, pleural, or joint fluid; but not urine). For CoNS, the diagnosis of sepsis was considered “definite” when clinical signs of sepsis were present and accompanied by two documented cultures for CoNS obtained within a 24-hour period. Cultures could be two separate blood samples or one blood culture plus a culture from an otherwise sterile site (excluding urine, superficial soft tissue, or upper respiratory tract). The diagnosis was considered “probable” if clinical signs were present with one positive blood culture and antibiotics were administered on four or more consecutive days. Clinical signs of infection considered indicative of infection included: hyperglycemia (>140 mg/dL), increased apnea, leukocytosis (white blood cell count >20,000 cells/mm\(^3\)), neutropenia (absolute neutrophil count <1,500/mm\(^3\)), temperature instability, hypotension, increased respiratory support, lethargy, unexplained metabolic acidosis, increased band-to-mature neutrophil ratio (>0.2), pulmonary infiltrates on chest roentgenogram, inflammation at a vascular line site, or gastrointestinal symptoms.\textsuperscript{3} Secondary outcomes of the trial included the proportions of infants with \textit{Candida} bloodstream infection (BSI), all CoNS sepsis (definite and probable), all staphylococcal sepsis, and mortality. Vital signs were monitored throughout the infusion, and concomitant medications and adverse events were monitored during the study. Specific diagnoses related to prematurity (morbidity associated with prematurity) were recorded and included anemia, hyperbilirubinemia, patent ductus arteriosus, apnea, bradycardia, periventricular or intraventricular hemorrhage, retinopathy of prematurity, air leak syndrome, feeding intolerance, gastroesophageal reflux, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia, respiratory distress of prematurity, cystic periventricular leukomalacia, progressive hydrocephalus, and focal gastrointestinal perforation (not associated with NEC). Adverse events were defined as serious if they resulted in death, were immediately life-threatening, or required intervention by procedure or surgery.

Statistical Analysis

The primary analysis compared the proportion of infants with \textit{S. aureus} sepsis in each treatment group. Only the first episode of sepsis for each infant was analyzed. The null hypothesis that the proportions in the two treatment groups were the same was tested using a Cochran-Mantel-Haenszel \( \chi^2 \) statistic controlling for birth weight group, with a two-
sided α of 0.05. The study had 90% power to detect a 50% reduction in S aureus LOS, assuming a 6% incidence rate in the placebo group. The analysis was performed using the intent-to-treat population defined as all infants who were randomized and received at least one infusion of study drug.

The Cochran–Mantel–Haenszel χ² test statistic controlling for birth weight group was used to compare secondary outcomes, adverse events, and morbidities associated with prematurity by treatment group. Analyses within each birth weight stratum were conducted using a Pearson’s χ² test.

Two-sided significance tests were used throughout, with a P value ≤ .05 being declared statistically significant for the primary hypothesis. Other P values are presented as descriptive statistics. No attempts were made to adjust for multiple testing. The analysis was conducted using the SAS software version 8.02 (SAS Institute Inc., Cary, NC).

RESULTS

Subjects

From 95 neonatal intensive care units in the US and Canada, 2017 infants were enrolled. Thirty-four infants did not receive any infusion of study drug (INH-A21 or placebo), usually because they became clinically unstable, and were not included in the analysis (Figure 1). Among the 1983 infants enrolled who received at least one infusion of study drug, 989 and 994 received placebo and INH-A21, respectively. The mean and median ages at the time of the first infusion were 4.2 and 4.0 days, for placebo and INH-A21, respectively. There were no significant differences by birth weight, gestational age, sex, or maternal race between the two groups (Table I). Overall, infants received a mean of 3.4 complete study-drug infusions, with a mean of 3.6 infusions per infant among those with birth weights 500 to 900 g and 3.3 infusions for those infants with birth weights 901 to 1250 g. There was no difference in mean number of infusions between placebo and INH-A21 groups.

Primary Outcomes

Overall, 110 (6%) infants developed at least one episode of S aureus LOS: 50 (5%) among the placebo and 60 (6%) among the INH-A21 recipients (P = .34; Table II). Oxacillin resistance was present in 27 (23%) of 116 tested S aureus isolates; two strains had mixed sensitivities, and two isolates were not tested. The time of onset of S aureus LOS was similar between the two treatment groups (Figure 2; available at www.jpeds.com). The median (and ranges) time to S aureus LOS was 18 days (range 1-70 days) and 19 days (range 2-70 days) for placebo and INH-A21 recipients, respectively. No difference was seen between treatment groups in frequency of S aureus infections by birth weight stratum: 33 infections occurred in the placebo group and 39 infections in the INH-A21 group for infants with a birth weight of 500 to 900 g (P = .48). There was no difference in infection rate analyzed by the number of infusions received for the overall population or by treatment group (data not shown).

Table I. Summary of selected characteristics of the treatment groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N = 989)</th>
<th>INH-A21 (N = 994)</th>
<th>P value*</th>
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<tr>
<td>Estimated gestational age (wk; mean ± SD)</td>
<td>26.8 (2.2)</td>
<td>26.8 (2.2)</td>
<td>.76</td>
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<tr>
<td>Male sex, n (%)</td>
<td>504 (51%)</td>
<td>487 (49%)</td>
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<tr>
<td>Birth weight (g; mean ± SD)</td>
<td>896 (197)</td>
<td>891 (204)</td>
<td>.36</td>
</tr>
<tr>
<td>Maternal use of antibiotics,† n (%)</td>
<td>572 (58%)</td>
<td>583 (59%)</td>
<td>.75</td>
</tr>
<tr>
<td>Cesarean delivery, n (%)</td>
<td>715 (72%)</td>
<td>700 (70%)</td>
<td>.36</td>
</tr>
<tr>
<td>Apgar score at 5 min mean (± SD)</td>
<td>7.3 (1.7)</td>
<td>7.3 (1.7)</td>
<td>.72</td>
</tr>
<tr>
<td>median</td>
<td>8</td>
<td>8</td>
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<td>Maternal race/ethnicity, n (%)</td>
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<td>Caucasian, non-Hispanic</td>
<td>535 (54%)</td>
<td>524 (53%)</td>
<td>.74</td>
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<tr>
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<td>279 (28%)</td>
<td>285 (29%)</td>
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</tr>
<tr>
<td>Hispanic</td>
<td>115 (12%)</td>
<td>134 (14%)</td>
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</tr>
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</tr>
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<td>7 (&lt;1%)</td>
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<td>8 (&lt;1%)</td>
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<tr>
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<td>0 (0%)</td>
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*P values corresponds to a test of no difference between treatments using either a Cochran–Mantel–Haenszel test (general association) stratified by birth weight group for categorical variables, or an analysis of variance model with treatment and birth weight group as fixed effects for continuous variables.

†Use of antibiotics within 24 hours before delivery by the mother.
Bloodstream Infection

S aureus† 50 (5%) 60 (6%) .34
Any CoNS 227 (23%) 247 (25%) .32
Definite CoNS‡ 92 (9%) 107 (11%) .28
Probable CoNS§ 154 (16%) 148 (15%) .67

All staphylococcal infection
S aureus and definite CoNS 139 (14%) 160 (16%) .20
Candida spp† 264 (27%) 285 (29%) .32
Mortality 73 (7%) 57 (6%) .13

*P value corresponds to a test of no difference between treatments using a Cochran-Mantel-Haenszel test (general association) stratified by weight group.
†All infections other than CoNS are defined as clinical signs of infection plus at least one positive culture from blood or an otherwise sterile site.
‡A definite CoNS infection is defined as clinical signs of infection plus at least two positive blood cultures or at least one positive blood culture and one otherwise sterile site culture. The two positive cultures must be drawn within 24 hours of one another.
§A probable CoNS infection is defined as documented evaluation for infection, plus one positive blood culture, plus clinical signs of infection, plus antibiotics for ≥4 days.

Secondary Outcomes

No difference was found between the two groups for any secondary outcome. Among the placebo recipients, 92 infants developed definitive CoNS LOS compared with 107 infants receiving INH-A21 (P = .28). Thirty-six infants developed Candida BSI. Antifungal prophylaxis had been administered to 65 placebo and 68 INH-A21 recipients (7% each). Among 1850 infants who did not receive antifungal prophylaxis, 30 of 924 (3%) placebo and 32 of 926 (3%) INH-A21 recipients developed Candida BSI. There were 130 deaths in the study population through study day 70, with no significant differences between the treatment groups (P = .13). The number of infants with sepsis caused by other organisms included Escherichia coli (n = 63, 3%), Klebsiella sp (n = 38, 2%), Enterobacter sp (n = 36, 2%), Pseudomonas sp (n = 35, 2%), and Serratia (n = 18, 1%), with no significant differences by treatment group (Table III; available at www.jpeds.com).

Adverse Events

There were no differences between treatment arms in the total numbers of adverse events, serious adverse events (SAEs), adverse events considered related to treatment, or adverse events leading to interruption of infusion or permanent discontinuation of study drug (Table IV; available at www.jpeds.com). The most common SAEs were NEC, gastrointestinal perforation (not NEC), retinopathy of prematurity, pneumothorax, sepsis, hydrocephalus, and bradycardia, with no differences between the two groups (Table V). Four SAEs among placebo recipients were considered possibly related to study drug by the investigator (two NEC, one intestinal perforation, and one air embolism) compared with two such events among INH-A21 recipients (one NEC and one pulmonary hemorrhage). Frequencies of the 16 pre-specified common morbidities of prematurity were not statistically significantly different between the two treatment groups (Table VI; available at www.jpeds.com).

DISCUSSION

The potential to prevent infection in a high-risk population of premature infants through administration of immune globulin has been attractive for several reasons. The neonate born before 32 weeks gestation is deficient in IgG. Specific antibody is believed to be a critical component of host defense against staphylococci, which represent the most common pathogens for LOS. ¹⁷⁻²⁰

Multiple trials have attempted to reduce LOS by administration of IGIV. ⁷,¹⁰,¹¹,²¹⁻²³ The meta-analysis by Ohlsson and Lacy ⁹ concluded that IGIV could decrease nosocomial infections in this population, but it would not affect mortality. An approach using IGIV derived from donors with high levels of pathogen-specific antibody, however, had not been studied.

The adhesion proteins, microbial surface components recognizing adhesive matrix molecules (MSCRAMMs), are surface-expressed virulence factors, and animal models have demonstrated the ability of antibody to prevent infection. ²⁴ In addition, a Phase II trial with INH-A21, although not powered for statistical significance, showed trends for reduction of S aureus LOS and Candida BSI in premature infants.¹² In the current large, adequately powered, randomized clinical trial, we were unable to demonstrate clinical benefit from infusion of IGIV with elevated levels of antibody against surface antigens of S epidermidis and S aureus.

The changes in the infusion schedule between the Phase II trial and the current trial do not explain the apparent difference in efficacy between the two trials. The lots of INH-A21 used in the current trial had 50% to 75% higher levels of anti-MSCRAMM antibodies than the single lot...
used in the previous Phase II trial. Based on population pharmacokinetic modeling, the levels of anti-staphylococcal antibodies likely were higher at all time points compared with those observed with the previous schedule. Because the mean time to onset of *S aureus* LOS was approximately 3 weeks, we also do not believe that the time of initiation of infusions explains the lack of effect.

Reduction of infections in premature infants through administration of IGIV may not be as simple as supposed previously. Risk factors for LOS are complex, involving the environment, immune status of the infant, and risk factors for hospital acquired infections; and they may not be addressed by administration of IgG. Although opsonic activity generally is accepted as being critical, there is no evidence to support a quantitative link between measured opsonic activity and risk of infection for premature infants. Levels of IgG antibodies and opsonic activity to staphylococci either at birth or during the first 2 postnatal weeks do not differ between infants who develop CoNS sepsis and those who do not. In term infants, antibody can be protective for certain pathogens, but this has not been shown for staphylococci or premature infants. In the end, the lack of efficacy for INH-A21 may rest with the selected target. Antibodies directed against capsular polysaccharide and protein targets are both opsonic, but clinical efficacy only has been achieved to date with anti-capsular polysaccharide antibodies. However, anti-capsular polysaccharide antibodies to *S aureus* have failed to protect patients in recent clinical trials.

The safety profile of INH-A21 is similar to that reported in other studies of IGIV in neonates. Acute renal failure and aseptic meningitis, reported among adults but not neonates, were not observed. Neutropenia, anecdotally reported to be associated with IGIV use in neonates, was reported in 4% of infants in each treatment group.

LOS continues to be a major health risk for premature infants. Our data are consistent with studies showing the predominance of gram-positive organisms as causative agents. The percentage of infants affected by *S aureus* was similar to that seen in our prior Phase II study and is higher than that reported by older studies, but it is consistent with that recently reported by Healy et al. We may be observing the infection point of the return of *S aureus* as a major pathogen among neonates. Clearly, the need for new strategies to reduce staphylococcal LOS persists.

The authors specifically acknowledge Amy Burdan for medical writing assistance in preparing the manuscript.

REFERENCES

of neonates against early-onset disease caused by this pathogen. J Infect Dis 2004;190:928-34.


Figure 2. Time of onset of *S. aureus* infections. Number of infections occurring among patients randomized to placebo (hatched bars) or INH-A21 treatment (open bars) during each time interval.

### Table III. Number of infants with non-staphylococcal and non-candidal bloodstream infections. A count of patients

<table>
<thead>
<tr>
<th>Organism</th>
<th>Placebo (n = 989)</th>
<th>INH-A21 (n = 994)</th>
<th>Total (n = 1983)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><em>Enterobacter</em> sp</td>
<td>15 (2)</td>
<td>21 (2)</td>
<td>36 (2)</td>
</tr>
<tr>
<td><em>Enterococcus</em> sp</td>
<td>29 (3)</td>
<td>25 (3)</td>
<td>54 (3)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>31 (3)</td>
<td>32 (3)</td>
<td>63 (3)</td>
</tr>
<tr>
<td>Group B <em>streptococcus</em></td>
<td>9 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>11 (&lt;1)</td>
</tr>
<tr>
<td><em>Klebsiella</em> sp</td>
<td>23 (2)</td>
<td>15 (2)</td>
<td>38 (2)</td>
</tr>
<tr>
<td><em>Pseudomonas</em> sp</td>
<td>23 (2)</td>
<td>12 (1)</td>
<td>35 (2)</td>
</tr>
<tr>
<td><em>Serratia</em> sp</td>
<td>9 (&lt;1)</td>
<td>9 (&lt;1)</td>
<td>18 (&lt;1)</td>
</tr>
<tr>
<td><em>Viridans streptococcus</em></td>
<td>7 (&lt;1)</td>
<td>4 (&lt;1)</td>
<td>11 (&lt;1)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (2)</td>
<td>21 (2)</td>
<td>41 (2)</td>
</tr>
<tr>
<td>Alpha hemolytic streptococcus</td>
<td>1 (&lt;1)</td>
<td>3 (&lt;1)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>0 (0)</td>
<td>2 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Gram-negative coccus</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Gram-positive rods</td>
<td>4 (&lt;1)</td>
<td>4 (&lt;1)</td>
<td>8 (&lt;1)</td>
</tr>
<tr>
<td>Other gram-negative bacillus</td>
<td>8 (&lt;1)</td>
<td>5 (&lt;1)</td>
<td>13 (&lt;1)</td>
</tr>
<tr>
<td>Other gram-positive coccus</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Viral pathogen</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Not specified</td>
<td>4 (&lt;1)</td>
<td>5 (&lt;1)</td>
<td>9 (&lt;1)</td>
</tr>
</tbody>
</table>

### Table IV. Summary of adverse events

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Placebo (n = 989)</th>
<th>INH-A21 (n = 994)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>883 (89%)</td>
<td>890 (90%)</td>
<td>.85</td>
</tr>
<tr>
<td>Within 48 h of infusion</td>
<td>629 (64%)</td>
<td>662 (67%)</td>
<td>.15</td>
</tr>
<tr>
<td>Considered drug-related</td>
<td>60 (6%)</td>
<td>68 (7%)</td>
<td>.48</td>
</tr>
<tr>
<td>Leading to interruption or discontinuation of infusion</td>
<td>47 (5%)</td>
<td>59 (6%)</td>
<td>.24</td>
</tr>
<tr>
<td>Leading to permanent discontinuation of infusion</td>
<td>65 (7%)</td>
<td>54 (5%)</td>
<td>.28</td>
</tr>
<tr>
<td>Any SAE</td>
<td>182 (18%)</td>
<td>164 (16%)</td>
<td>.24</td>
</tr>
<tr>
<td>Within 48 h of infusion</td>
<td>43 (4%)</td>
<td>48 (5%)</td>
<td>.61</td>
</tr>
<tr>
<td>Considered drug-related</td>
<td>3 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
<td>.65</td>
</tr>
</tbody>
</table>

*P value corresponds to a test of no difference between treatments using a Cochran-Mantel-Haenszel test (general association) stratified by weight group.

### Table VI. Common morbidities of prematurity identified in study patients*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n = 989)</th>
<th>INH-A21 (n = 994)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air leak syndrome</td>
<td>119 (12%)</td>
<td>131 (13%)</td>
<td>.43</td>
</tr>
<tr>
<td>Anemia</td>
<td>857 (87%)</td>
<td>854 (86%)</td>
<td>.63</td>
</tr>
<tr>
<td>Apnea</td>
<td>908 (92%)</td>
<td>909 (91%)</td>
<td>.77</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>960 (97%)</td>
<td>954 (96%)</td>
<td>.18</td>
</tr>
<tr>
<td>Chronic lung disease‡</td>
<td>740 (75%)</td>
<td>746 (75%)</td>
<td>.90</td>
</tr>
<tr>
<td>Cystic periventricular</td>
<td>41 (4%)</td>
<td>39 (4%)</td>
<td>.80</td>
</tr>
<tr>
<td>leukomalacia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeding intolerance</td>
<td>823 (83%)</td>
<td>828 (83%)</td>
<td>.96</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>343 (35%)</td>
<td>320 (32%)</td>
<td>.24</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>34 (3%)</td>
<td>35 (4%)</td>
<td>.92</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>861 (87%)</td>
<td>869 (87%)</td>
<td>.81</td>
</tr>
<tr>
<td>Patent ductus rrtersiosus</td>
<td>446 (45%)</td>
<td>456 (46%)</td>
<td>.73</td>
</tr>
<tr>
<td>Progressive hydrocephalus</td>
<td>48 (5%)</td>
<td>47 (5%)</td>
<td>.89</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>947 (96%)</td>
<td>952 (96%)</td>
<td>.98</td>
</tr>
<tr>
<td>Necrotizing enterocolitis (Stage ≥2)</td>
<td>84 (8%)</td>
<td>71 (7%)</td>
<td>.10</td>
</tr>
<tr>
<td>Intraventricular hemorrhage (Grade I-IV)</td>
<td>347 (35%)</td>
<td>317 (32%)</td>
<td>.13</td>
</tr>
<tr>
<td>Retinopathy of prematurity (Stage I-5)</td>
<td>406 (41%)</td>
<td>424 (41%)</td>
<td>.45</td>
</tr>
</tbody>
</table>

*Patients with more that one morbidity for a particular condition are counted only once for that condition.

†P value corresponds to a test of no difference between treatments using a Cochran-Mantel-Haenszel test (general association) stratified by weight group.

‡Defined as use of oxygen on postnatal day 28.
Nebulized Hypertonic Saline in the Treatment of Viral Bronchiolitis in Infants

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Objective To investigate the use of nebulized 3% hypertonic saline (HS) for treating viral bronchiolitis in moderately ill hospitalized infants by a prospective, randomized, double-blinded, controlled, multicenter trial.

Study design A total of 96 infants (mean age, 4.7 months; range, 0.3 to 18 months) admitted to the hospital for treatment of viral bronchiolitis were recruited from 3 regional pediatric centers over 3 bronchiolitis seasons (December 2003 to May 2006). Patients were randomized to receive, in a double-blind fashion, repeated doses of nebulized 3% HS (treatment group) or 0.9% normal saline (NS; control group), in addition to routine therapy ordered by the attending physician. The principal outcome measure was hospital length of stay (LOS).

Results On an intention-to-treat basis, the infants in the HS group had a clinically relevant 26% reduction in LOS to 2.6 ± 1.9 days, compared with 3.5 ± 2.9 days in the NS group (P = .05). The treatment was well tolerated, with no adverse effects attributable to the use of HS.

Conclusions The use of nebulized 3% HS is a safe, inexpensive, and effective treatment for infants hospitalized with moderately severe viral bronchiolitis. (J Pediatr 2007;151:266-70)

Respiratory syncytial virus (RSV) accounts for the majority of viral bronchiolitis cases, although other viruses, including human metapneumovirus, adenovirus, parainfluenza, rhinovirus, and influenza, also play important roles.1-3 Given that virtually all children become infected with RSV by age 2 years and that at least 1% of these children will develop bronchiolitis sufficient to require hospitalization,4 the burden of this disease is high, accounting for up to 17% of all infant hospitalizations,5 at an annual cost of more than $500 million in the United States alone.6

Despite the high prevalence and morbidity of bronchiolitis, therapy remains controversial and without widely accepted therapeutic guidelines other than supportive care.7,8 Bronchiolitis is characterized by airway plugging with sloughed epithelium, mucus, and edema rather than bronchospasm.9,10 Nevertheless, the use of nebulized bronchodilators continues to be common,11,12 despite extensive evidence supported by 3 meta-analyses that the benefits are limited, short term, and do not justify routine use.13-15 Similarly, although steroids might reasonably be expected to decrease the inflammatory response in bronchiolitis, published data are conflicting, with equally well-designed studies concluding that steroids may be either effective16-18 or ineffective.19-21 The primary treatment, therefore, remains largely supportive, with administration of fluids and supplemental oxygen, observation, and mechanical ventilatory support as needed.8,22

Several reports over the last decade have demonstrated that inhalation of nebulized 6% to 10% hypertonic saline (HS) improves both immediate and long-term clearance of small airways in patients with cystic fibrosis.23-26 The exact mechanism is unknown but is thought to facilitate removal of inspissated mucus through osmotic hydration, disruption of mucus strand cross-linking, and reduction of mucosal edema.27,28 In otherwise

| ANOVA | Analysis of variance |
| HS | Hypertonic saline |
| KGH | Kingston General Hospital |
| LOS | Length of stay |
| NS | Normal saline |
| RDAI | Respiratory Distress Assessment Instrument |
| RSV | Respiratory syncytial virus |
| SaO2 | Oxygen saturation |
| SKMC | Sheikh Khalifa Medical City |
| VGH | Victoria General Hospital |
healthy infants hospitalized with viral bronchiolitis, the regular administration of nebulized 3% HS combined with epinephrine decreased length of stay (LOS) by approximately 22% compared with infants receiving the same dose of epinephrine mixed in 0.9% normal saline (NS).29 Similarly, in ambulatory infants with mild bronchiolitis, inhalation of nebulized 3% HS (with terbutaline) improved clinical scores but did not produce a decrease in hospital admission rate.30 Both of the aforementioned studies used 3 times per day dosing, which is significantly less than the 3 to 6 times per hour regimens often used to deliver nebulized medication to children in respiratory distress.31-33

The purpose of the present study was to investigate the addition of frequently nebulized 3% HS to standard therapy of moderately ill infants hospitalized with typical viral bronchiolitis in a prospective, randomized, double-blind, controlled fashion. The primary objective was to compare the LOS of these infants with that of a control group of infants receiving standard therapy plus frequently nebulized NS.

METHODS

Patients

Infants up to age 18 months who were admitted to the hospital for the treatment of moderately severe viral bronchiolitis were eligible for study. The diagnosis of moderately severe bronchiolitis required a history of a preceding viral upper respiratory infection, the presence of wheezing or crackles on chest auscultation, plus either an oxygen saturation (SaO₂) of <94% in room air or significant respiratory distress as measured by a Respiratory Distress Assessment Instrument (RDAI)24 score of ≥4. In brief, 6 separate assessments of retractions and auscultatory findings are made and assigned a numerical score; the sum of these scores provides the RDAI score ranging from 0 to 17, with increasing scores indicating increasing respiratory distress.

Exclusion criteria included a history of any of the following: previous episode of wheezing, chronic cardiopulmonary disease or immunodeficiency; critical illness at presentation requiring admission to intensive care; the use of nebulized HS within the previous 12 hours; or premature birth (gestational age ≤ 34 weeks).

Setting

The study was conducted at 3 regional tertiary care hospitals: Sheikh Khalifa Medical City (SKMC), Abu Dhabi, United Arab Emirates; Victoria General Hospital (VGH), Victoria, British Columbia, Canada, and Kingston General Hospital (KGH), Kingston, Ontario, Canada. VGH and KGH serve multiethnic populations in the west coast and central regions of Canada, respectively. Data were collected during the winter bronchiolitis seasons between December 2003 and April 2006.

Study Design

Patients admitted to hospital with bronchiolitis were assessed within 12 hours for entry into the study. If inclusion/exclusion criteria were satisfied, then informed consent was obtained, and the patient was randomized to receive treatment with 4 mL of nebulized study solution containing either 3% HS (study group) or NS (control group). The study solution was administered in a double-blind fashion every 2 hours for 3 doses, followed by every 4 hours for 5 doses, followed by every 6 hours until discharge. After study enrollment, any additional (nonprotocol) treatments were at the sole discretion of the attending physician, who was blinded to the study treatment. If additional treatments included nebulized medication, the medication was nebulized in 4 mL of the assigned study solution (ie, HS or NS). All inhaled therapies were delivered to a settled infant from a standard oxygen-driven hospital nebulizer through a tight-fitting face-mask, or head box, whichever was better tolerated by the infant.

Patients were randomized independently at each study site to receive either HS or NS using a computer-based randomization program. Study solutions were prepared by a research pharmacist and were identical in appearance and odor. The identity of the study solutions was blinded to all participants, care providers, and investigators. Clinical response was determined by the designated study physician using RDAI scores and SaO₂ readings at study entry and then at least once daily.

Determination of LOS

LOS was defined as the time between study entry (within 12 hours of admission to the hospital) and the time at which the infant either reached protocol-defined discharge criteria as measured by the study physician or was discharged from the hospital on independent clinical grounds by the attending physician, whichever came first. Protocol-defined discharge criteria required both an RDAI score <4 and an SaO₂ of at least 95% in room air for 4 hours.

Ethics

The study was approved by the ethics and human research committees of the 3 participating hospitals. Informed written consent was obtained from at least 1 parent of each infant before enrollment.

Statistical Strategy

A reduction in LOS of 1 day was previously proposed as being clinically significant32 and was adopted in this study. It was anticipated that this would require a sample size of approximately 46 patients per trial arm, for 80% power, to show a P value ≤ .05. This number is based on a prestudy mean LOS at the largest study hospital (SKMC) of 4.1 ± 1.7 days (unpublished data). Data were entered into an Excel spreadsheet (Microsoft Corp, Redmond, WA) and imported into SPSS version 12.0.1 software (SPSS Inc, Chicago, IL).
for analysis on an intention-to-treat basis. Descriptive analyses were completed overall and also for the control and study groups separately. The χ² test (Fisher’s exact) was used to examine the association between categorical variables and group, and independent sample t tests and Levene’s test for equality of variance were used to assess the association between numeric variables and group. One-way analysis of variance (ANOVA) was used to compare data from the 3 groups separately. The equivalence of variance (ANOVA) was used to compare data from the 3 groups separately. The results, the patients were divided into 3 age groups (0 to 6 months, 7 to 12 months, and 13 to 18 months), and the effects of age and treatment were tested in a 2-way ANOVA.

RESULTS

Study Population

A total of 96 previously well infants (mean age, 4.7 ± 4.2 months; range, 10 days to 18 months) with viral bronchiolitis were enrolled from 3 centers during the bronchiolitis seasons from December 2003 to May 2006. Thirty-two infants were enrolled from the 2 Canadian sites (VGH and KGH), and 64 infants were enrolled from SKMC. Forty-seven infants were randomized to the HS treatment group, and 49 were randomized to the NS control group. Five infants (2 from the HS group and 3 from the NS group) were withdrawn at parental request before study completion but were included in the final intention-to-treat analysis.

The HS and NS groups were comparable at baseline and typically presented on the fifth day of illness (range, 1 to 14 days) with borderline hypoxia (mean SaO₂, 95%; range, 85% to 100%) and moderate respiratory distress (mean clinical score, 8 out of 17; range, 4 to 17) (Table I). Some 69% of all tested infants were positive for RSV. Subset comparison of the SKMC and Canadian sites revealed minimal differences at baseline (Table II; available at www.jpeds.com). Although the Arab infants tended to be sicker (RDAI 8.9 ± 2.9 vs 6.2 ± 1.9; P < .001) and more likely to receive previous treatment with a bronchodilator (98% vs 70%; P < .001), all other measurements were comparable.

Treatment Received

After enrollment, all treatments (protocol and add-on) received by infants in the HS and NS groups were comparable (Table III). The infants received a mean of 9 nebulizations of study solution per day delivered alone (38% of treatments) or co-administered with albuterol (salbutamol; 37%), racemic epinephrine (racepinephrine; 23%), or inhaled steroid (3%). Subset comparison of the SKMC and Canadian sites revealed minimal differences in the treatments received (Table IV; available at www.jpeds.com). Treatment at SKMC was more likely to include antibiotics (P = .002) as well as the addition of racemic epinephrine to the inhaled study solution (P = .003).

Adverse Effects of HS

All participants tolerated therapy without apparent adverse effects and were eventually discharged after achieving full recovery. No infants were withdrawn by the medical staff due to clinical deterioration or the need for intensive care support. Although 5 infants were withdrawn at parents’ request because of perceived adverse effects of therapy, only 2 of these infants were receiving HS. One of these infants (a 2-month-old male) cried very vigorously during his third inhalation (HS alone) and again with his fifth inhalation (HS with racemic epinephrine) and was withdrawn at that time. This was not associated with any significant acute change in his clinical condition, and he was eventually discharged on day 6. The second infant (a 3-month-old female) was withdrawn because of agitation after her second inhalation (HS

| Table I. Patient demographics and illness status at baseline |
|-----------------|-----------------|--|
|                | HS (n = 47)     | NS (n = 49)     | P  |
| % male         | 57%             | 61%             | .84|
| Age (months)   | ± 4.3 ± 3.7     | ± 4.6 ± 4.7     | .54|
| Duration of illness before admission (days) | ± 4.5 ± 2.3 | ± 4.0 ± 2.4 | .30|
| Respiratory distress clinical score | ± 7.8 ± 2.5 | ± 8.1 ± 3.3 | .69|
| % SaO₂ in room air | 94.9 ± 3.9 | 95.2 ± 3.4 | .71|
| Infants treated with bronchodilator before study entry (%) | 37 (86%) | 41 (91%) | .52|
| Infants treated with systemic steroids before study entry (%) | 1 (2.5%) | 1 (2.4%) | 1.0|
| Infants treated with antibiotics before study entry (%) | 6 (15%) | 4 (9.8%) | .52|
| Infants tested for RSV | 40 | 40 | 1.0|
| RSV positive (%) | 25 (62%) | 30 (75%) | .39|

*Sample sizes vary slightly for the individual comparisons due to missing data.

| Table III. Treatments received during the study |
|-----------------|-----------------|--|
|                | HS (n = 47)     | NS (n = 49)     | P  |
| Study solution alone (nebulizations/day) | 3.2 ± 3.0 | 3.8 ± 4.1 | .46|
| Albuterol + study solution (nebulizations/day) | 3.1 ± 3.5 | 3.6 ± 3.6 | .49|
| Racemic epinephrine + study solution (nebulizations/day) | 2.7 ± 3.7 | 1.6 ± 2.4 | .13|
| Steroids + study solution (nebulizations/day) | 0.39 ± 0.83 | 0.26 ± 0.60 | .42|
| Total nebulizations/day | 9.1 ± 3.0 | 9.2 ± 4.5 | .93|
| Number of patients given any systemic steroid (%) | 8 (17%) | 7 (14%) | .78|
| Number of patients given any antibiotic (%) | 5 (11%) | 10 (20%) | .26|

*Sample sizes vary slightly for the individual comparisons due to missing data.
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Response to Therapy

The endpoint of LOS was identified by the attending physician using clinical grounds alone (45% of patients) or by reaching protocol-established discharge criteria as measured by the study physician (55% of patients), whichever came first. One-way ANOVA confirmed that the LOS did not differ significantly between study sites for either the NS group (P = .12) or the HS group (P = .44).

Infants in the control group had a mean LOS of 3.5 ± 2.9 days, whereas infants treated with nebulized 3% HS were discharged on average 1 day sooner, with a 26% reduction in LOS to 2.6 ± 1.9 days (P = .05). There was a trend toward greater improvement in infants under age 6 months, but this difference did not attain statistical significance (P = .17). The percentage of patients from each group remaining in hospital each day is shown in the Figure.

DISCUSSION

This study demonstrates that inhaled 3% HS is an effective treatment for infants up to age 18 months hospitalized with viral bronchiolitis. Repeated inhalations of nebulized HS reduced the LOS by approximately 1 day, from 3.5 ± 2.9 to 2.6 ± 1.9 days. This is a clinically relevant benefit with the potential for widespread impact on the treatment of bronchiolitis.

The infants that we studied came from a population that was geographically and ethnically very diverse. Nevertheless, these infants were very similar to those described in other bronchiolitis studies, with a slight male predominance (62%), primary infection with RSV (69%), mean age of 4.7 months, and LOS in the control group of 3.5 to 4 days. Strict inclusion and discharge criteria were used to minimize possible confounding effects of uncharacterized and evolving wheezing phenotypes and to minimize between-site variability. The clinical scoring system chosen has been widely used in other studies on bronchiolitis and has been proposed to be the scoring system of choice for further studies. Therefore, our findings should be universally applicable to other previously healthy infants hospitalized with moderately severe viral bronchiolitis.

The majority of our patients received bronchodilators before study entry. In addition, although our study protocol did not require or encourage the co-administration of bronchodilator with the study solution, blinded attending physicians prescribed bronchodilators approximately 5 times per day. This finding was not unexpected, because the use of bronchodilators in bronchiolitis remains widespread, with some reporting it in more than 80% of patients. It is also possible that attending physicians prescribed bronchodilators to prevent possible adverse effects of HS. Although inhalation of HS may cause bronchoconstriction in asthmatics and co-administration with a bronchodilator is often recommended, others have reported that inhalation of 4.5% to 7% HS (without a bronchodilator) can be performed safely in healthy nonasthmatic children or in children with moderately severe small airway obstruction secondary to cystic fibrosis. In our study, there were no apparent adverse effects attributable to the use of HS without a bronchodilator, although the numbers were insufficient to allow further exploration of this issue. However, there was no increase in add-on bronchodilator therapy in the treatment group, suggesting that the use of HS in this setting was not associated with a clinically significant increase in lower airway obstruction.

The use of inhaled HS in the treatment of viral bronchiolitis in hospitalized infants is a novel therapy that was first reported in 2003 and recently strengthened with the publication of a 2-year extension of the original study. These authors demonstrated that 3 times a day dosing with 4 mL of 3% HS containing 1.5 mg of epinephrine compared with the same dose of epinephrine in NS reduced the LOS from 3.6 ± 1.6 days to 2.8 ± 1.3 days, a 22% improvement (P < .05). They included epinephrine to prevent possible adverse effects of HS and attributed the beneficial effects in the treatment group to the presence of HS. Our study was very similar but differed primarily in the inclusion of slightly older infants (up to age 18 months), plus the much more frequent dosing of HS (9.1 ± 3.0 inhalations/day). In our hands, increasing the frequency of inhaled HS produced a further reduction in the LOS to 26%, but this reduction was not significant compared with 3 times a day dosing.

The routine use of 3% HS in the treatment of infants hospitalized with bronchiolitis has the potential for enormous economic benefit. A 26% reduction in LOS not only will return infants to home and their parents to work a day sooner,
but also will also substantially reduce hospital costs. The estimated hospital costs for bronchiolitis in the US, which includes the widespread use of bronchodilators nebulized with NS, exceed $580 million per year. Therefore, the substitution of NS with the comparably priced 3% HS, with the subsequent reduction in LOS, has the potential to save the US healthcare system more than $150 million annually.

In summary, inhaled 3% HS is a safe, inexpensive, and effective treatment for previously well infants admitted to the hospital with moderately severe viral bronchiolitis. Further research is needed to determine the optimal dosing and to identify whether there is any benefit from co-administered bronchodilator.

We thank Jaishen Rajah, Senior Consultant in Paediatrics, SKMC, for his initial statistical guidance.

REFERENCES

Table II. Site-specific patient demographics and illness status at baseline

<table>
<thead>
<tr>
<th></th>
<th>SKMC (n = 64)*</th>
<th>VGH + KGH (n = 32)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>% male</td>
<td>59</td>
<td>59</td>
<td>1.0</td>
</tr>
<tr>
<td>Age (months)</td>
<td>4.4 ± 4.3</td>
<td>5.3 ± 4.1</td>
<td>.34</td>
</tr>
<tr>
<td>Duration of illness before admission (days)</td>
<td>4.2 ± 2.6</td>
<td>4.2 ± 1.9</td>
<td>.87</td>
</tr>
<tr>
<td>Respiratory distress clinical score</td>
<td>8.9 ± 2.9</td>
<td>6.2 ± 1.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% oxygen saturation in room air</td>
<td>94.7 ± 3.8</td>
<td>95.8 ± 3.3</td>
<td>.17</td>
</tr>
<tr>
<td>Previous treatment with bronchodilator (%)</td>
<td>98</td>
<td>70</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous treatment with systemic steroids (%)</td>
<td>3.4</td>
<td>0.0</td>
<td>.91</td>
</tr>
<tr>
<td>Previous treatment with antibiotics (%)</td>
<td>15.5</td>
<td>4.3</td>
<td>.27</td>
</tr>
<tr>
<td>Tested for RSV (%)</td>
<td>89.7</td>
<td>87.5</td>
<td>.74</td>
</tr>
<tr>
<td>RSV positive (%)</td>
<td>62.1</td>
<td>61.3</td>
<td>.94</td>
</tr>
</tbody>
</table>

*Sample sizes vary slightly for the individual comparisons due to missing data.

Table IV. Site-specific treatments received

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SKMC (n = 64)*</th>
<th>KGH + VGH (n = 32)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study solution alone (nebulizations/day)</td>
<td>2.4 ± 2.4</td>
<td>6.0 ± 4.1</td>
<td>.03</td>
</tr>
<tr>
<td>Albuterol + study solution (nebulizations/day)</td>
<td>3.8 ± 3.8</td>
<td>2.4 ± 2.4</td>
<td>.12</td>
</tr>
<tr>
<td>Racemic epinephrine + study solution (nebulizations/day)</td>
<td>2.9 ± 3.6</td>
<td>0.48 ± 1.0</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Steroids + study solution (nebulizations/day)</td>
<td>0.24 ± 0.72</td>
<td>0.48 ± 0.72</td>
<td>.77</td>
</tr>
<tr>
<td>Total nebulizations/day</td>
<td>9.4 ± 3.8</td>
<td>8.9 ± 4.1</td>
<td>.71</td>
</tr>
<tr>
<td>Number of patients given any systemic steroid (%)</td>
<td>10 (16%)</td>
<td>5 (16%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Number of patients given any antibiotic (%)</td>
<td>15 (23%)</td>
<td>0 (0%)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

*Sample sizes vary slightly for the individual comparisons due to missing data.
Deaths and Injuries Attributed to Infant Crib Bumper Pads

BRADLEY T. THACH, MD, GEORGE W. RUTHERFORD, JR, MS, AND KATHLEEN HARRIS

Objective  To document deaths attributed to bumper pads and injuries from their use that are potentially preventable.

Study design  The US Consumer Product Safety Commission maintains files on cases voluntarily reported to them of deaths and injury related to commercial products. These cases represent an unknown fraction of total occurrences. We searched this database for deaths related to crib bumpers for the years 1985 to 2005. We also searched other Consumer Product Safety Commission databases for crib-related injuries that potentially might have been prevented by bumpers. Additionally, we examined 22 retail crib bumpers and described features that could be hazardous.

Results  Twenty-seven accidental deaths reported by medical examiners or coroners were attributed to bumper pads. The mechanism of death included suffocation and strangulation by bumper ties. Twenty-five nonfatal injuries were identified, and most consisted of minor contusions. All retail bumpers had hazardous properties.

Conclusions  These findings suggest that crib and bassinet bumpers are dangerous. Their use prevents only minor injuries. Because bumpers can cause death, we conclude that they should not be used. (J Pediatr 2007;151:271-4)

Most infant cribs sold in the United States are used with bumper pads. Whether crib bumper pads pose a risk to infants for accidental suffocation is controversial. Recently, the Juvenile Product Manufacturing Association (JPMA) asked the US Consumer Products Safety Commission (CPSC) to review crib deaths involving suffocation or strangulation. On the basis of their own analysis of an unpublished CPSC review, representatives of the JPMA independently concluded, "there were no deaths directly related to the traditional use of crib bumper pads." However, several organizations, including the CPSC and the American Academy of Pediatrics, have stated that crib bumpers are a potential risk when they are "pillow like." In addition, the First Candle Sudden Infant Death Syndrome Alliance cautions that bumper pads should be "thin, firm but not pillow like." These are subjective assessments and open to interpretation; thus caregivers may have difficulty in applying these criteria to their purchases of bumper pads. Because there are no detailed and systematically gathered data on hazards of crib bumper pads, we searched for cases of accidental death attributed to crib bumpers in CPSC databases.

Also, because crib bumpers are intended to reduce the risk of injury, we searched CPSC's injury database for non-fatal crib injuries that conceivably might have been prevented by crib bumpers. Finally, we have examined crib bumpers currently on the market for features that might be construed as pillow-like or otherwise potentially dangerous.

METHODS

Bumper-related suffocation deaths were identified through a search of CPSC databases from Jan 1, 1985, through Dec 31, 2005, made available to the public. Three CPSC databases were searched. These include the Death Certificate, Injury and Potential Injury Incidents, and In-Depth Investigations databases. The CPSC receives death certificates from all 50 states, the District of Columbia, and New York City; these include deaths from all suffocation codes, with the exception of the suffocation code for “falling earth” that was in use with the International Classification of Diseases, Ninth Revision coding system. This information is stored in the Death Certificate database. The CPSC also collects information on deaths from medical examiners, coroners, and other sources such as police and fire departments and media articles that are stored in the Injury and Potential Injury Incidents database or stored in the In-Depth Investigations database. The information in the 3 databases contains unique information about deaths and duplicates

See editorial, p 237

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reports that may provide additional information about deaths. Because the CPSC does not receive all deaths reported in the United States, the deaths in the study should be considered a minimum number.

The databases were searched for the keywords “bumper,” “pad,” and “padding” for deaths involving infants aged from 1 month through 2 years. The search was not restricted in sleeping location, external cause of death code, or other identifier. Deaths identified in all of the databases were combined and sorted by state, age, and sex to identify duplicate cases, and deaths were removed that were duplicates or out-of-scope (eg, mattress pad, heating pad), yielding a final dataset of 27 deaths.

Crib-related injury cases were identified though CPSC’s National Electronic Injury Surveillance System (NEISS). NEISS is a probability sample of US hospital emergency departments stratified by emergency department size and geographic location. This database was searched from Jan 1, 2000, through Dec 31, 2004, by using product codes for cribs, portable cribs, crib extender rails or youth bed rails, and cribs not specified for infants aged ≤6 months. This age range was selected because after 6 months it is doubtful that bumpers would prevent head injury because most infants can raise their heads above the bumper pad. Although it is possible to determine national estimates using the NEISS, we made no attempt to do so because of the small number of cases identified.

Files on these deaths and injuries were obtained and reviewed. Cases with evidence of non-traditional use of bumper pads were excluded.

The authors assessed infant bumpers for sale at a St. Louis, Missouri, retail store; 22 different bumpers were examined and graded for softness, potential space between bottom of bumper and mattress, bumper width, and length of fabric fasteners that attach the bumper to the crib. Softness was graded on a scale of 1 to 3, with 3 being the consistency of a comforter or soft pillow and 1 being that of a typical couch cushion. We considered a typical cushion to be firm enough to provide comfort when a person otherwise would be sitting on or against a hard surface. It was obvious that softness varied a great deal from bumper to bumper. However, the site of the investigation necessitated a subjective assessment of this property.

RESULTS

In this search, we found 27 cases of infant death involving bumper pads or similarly padded bassinets (4 of the 27 cases). In 26 cases, a death scene investigation was conducted. In 1 case, it was uncertain whether a formal investigation was made. Additionally, CPSC personnel conducted an additional scene investigation in 18 of the 27 cases. In all cases except 1 (#14), an autopsy was performed.

Three types of infant death involving crib bumpers pads were found: 1) face against bumper (Figure 1); 2) infant wedged between bumper and other object (Figure 2), and 3): bumper tie around infant’s neck. There were 11 deaths in type 1 cases; 13 deaths in type 2 cases, and 3 deaths in type 3 cases (Table I; available at www.jpeds.com).

There were 25 non-fatal crib injuries in the database (Table II; available at www.jpeds.com). It was unclear in most reports whether bumpers were present or not. Summaries in Tables I and II are those of the medical examiner or other health care workers (Table II).

Twenty-two different crib bumper pads were evaluated for relevant properties at a retail outlet store in St. Louis (Table III; available at www.jpeds.com).

DISCUSSION

Recently, the Canadian Healthy Environment and Consumer Safety Bureau in a brief report cited 23 “incidences” involving bumper pads, including 1 suffocation and 1...
strangulation death.\(^5\) The present report provides details of multiple infant deaths in which crib or bassinet bumper pads were thought to play a causal role. Also, it is a report of nonfatal injuries that might have been prevented had crib bumper pads been used. It must be emphasized that our search of the crib database reveals only an undetermined fraction of the actual incidents occurring in the United States in the period studied, because incidents are inconsistently reported to the CPSC and may or may not be published in media sources. Data on accidental deaths from US Vital Statistics are not coded by product. Thus CPSC data is the only resource at the national level with codes allowing for the identification of bumper-related deaths. The degree of underreporting is indicated by cases coming from only 17 states, with some states with large populations (New York, Texas) contributing only 1 case each and other less-populated states (Wisconsin, Missouri) reporting 3 cases each.

It is important to consider limitations of our study. Underreporting of cases is one obvious limitation. In addition, scene investigations and autopsies were performed by different individuals, so there was no consistent protocol for these procedures.

We have divided the bumper- and padded bassinet-related deaths into 3 categories. The first are those in which the infant’s face was in close contact with the bumper surface, and death was either judged or could be assumed to be caused by asphyxia possibly resulting from re-breathing expired air or by nasal and oral compression.\(^6\)\(^10\) From past studies, the softest of the retail bumpers examined that had the characteristics of comforters or soft pillows would pose the greatest risk for this type of death.\(^6\)\(^10\) Case #6 in Table I is of particular interest because the bumper had a plastic covering, and it was suggested in the death scene report that moisture on the plastic caused the face to adhere to the bumper surface. This indicates that applying a nonporous covering over a bumper might not make it safer.

Half the cases were in category 2. Here the infant’s head was determined to be wedged between a bumper and another surface. Death caused by wedging is a traditional diagnosis, and cases continue to be reported.\(^11\)\(^13\) An important contributing factor in wedging deaths is that many infants lack the motor development needed to extricate themselves.\(^14\) Death presumably results from asphyxia caused by re-breathing, nose and mouth compression, or a combination of these. Wedging occurs when the baby pushes his/her head into a narrow space between 2 surfaces. An important feature of the surface is that it is elastic and can spring back to its original shape after deformation. This characteristic provides the force pressing against the infant’s head, which causes the entrapment. Couch cushions are elastic and are universally recognized as a common cause of wedging deaths.\(^12\)\(^13\) Because the firmer and thicker retail bumpers we evaluated were elastic, like couch cushions, we deemed them to be more hazardous for wedging than the softer thinner bumpers. Considering this, it would not seem to be helpful to suggest that crib bumper pads be firm.\(^4\)

The last category of death was strangulation. Infant deaths involving neck compression by cords, ribbons, or bands of various kinds is well-recognized, and frequent warnings to eliminate this hazard have been issued in past years. Current manufacturing standards state that “ribbons, strings, and ties on bumper guard should not exceed 9 inches.”\(^15\) It is relevant that in our own survey of commercially available bumpers there were 2 with fabric fasteners longer than 9 inches (case #5 and #10). Therefore, a strangulation hazard may still exist for some bumpers on the market.

In theory, bumpers prevent injury from a baby’s head hitting crib bars or from extremities projecting through the bars. We cannot tell from the reports of crib injuries how effective bumpers are in protecting infants, because we do not know whether a bumper was present. The exception is the 1 case in which, ironically, the infant’s knee was reportedly confused when it struck a crib bumper pad (Table II, case #14). In the remaining cases, contusions and abrasions to the face and head conceivably could have been prevented had a bumper been in place. However, it is unclear whether a bumper would have prevented an arm or leg from passing through the crib rails, because we found an open space between the bumper and the crib mattress in all the bumper pads we examined. It is conceivable that a bumper might have contributed to the arm and leg injuries because it could provide a mechanism for limb entrapment. This could amplify the force on the limb exerted by an infant struggling to free itself. The seven reported cases of limb fractures or closed head injury were likely not caused by accidents. It is difficult to imagine an infant exerting a force sufficient to cause a limb fracture or hitting its head against a wooden slat with force enough to cause closed head injury. Currently, such cases would immediately raise a pediatrician’s suspicion of intentional injury.

In summary, we report a number of fatal accidental infant deaths directly attributable to crib bumper pads. In direct contradiction to the JPMA interpretation of a CPSC staff data review that there were no incidents directly related to normal bumper use, we found 27 cases of death reported in the same CPSC databases. Moreover, an examination of commercial bumper pads indicates that these products continue to have characteristics that appear to be dangerous. Furthermore, a review of cases of non-fatal injuries in cribs indicates that these are not serious and might or might not have been prevented by bumper pads. This case series provides evidence that the risks from crib bumper pads or padded bassinettes (death) outweigh the possible benefits provided by such padding (minor bruises and contusions). Furthermore, our data does not suggest any way in which changes in bumper design can reduce risk of death. We conclude that bumpers should not be placed in cribs or bassinetts.

REFERENCES

3. Task Force on Sudden Infant Death Syndrome. The changing concept of sudden infant death syndrome: diagnostic coding shifts, controversies regarding the sleeping...


### Table I. Medical examiners' summaries of deaths

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>“Face obstructed by crib bumper pad—positional asphyxia. A male infant, age 2 months, died after he was found with his face against a bumper pad in his crib at home by his mother.”</td>
</tr>
<tr>
<td>2</td>
<td>“Died of asphyxiation caused by pressure against an overstuffed crib bumper during sleep. A 7-month-old female was found unresponsive in her crib by her mother. The victim was placed on her back in the crib.”</td>
</tr>
<tr>
<td>3</td>
<td>“A coroner determined a 7-month-old male infant died in a crib due to positional asphyxiation—face in corner of crib against bumper pad. Victim was on his back with head turned to right, and his face was up into the corner of the bumper pad.”</td>
</tr>
<tr>
<td>4</td>
<td>“This incident involved the death of a 4-month-old infant due to positional asphyxia. The infant was found unresponsive by his mother. He had crawled face first into the corner of his crib with his nose and mouth pressed against the protective bumpers.”</td>
</tr>
<tr>
<td>5</td>
<td>“A 14-month-old baby boy died sleeping in a crib with his face pressed firmly against a bumper pad.”</td>
</tr>
<tr>
<td>6</td>
<td>“Baby got face into plastic bumper pad of cradle. Crib pad was much too large for this size of bed. Night was very hot, and it was felt that the crib pad adhered to the victim due to the heat. Baby got face into plastic bumper pad. Anoxia consistent with accidental suffocation.”</td>
</tr>
<tr>
<td>7</td>
<td>“A 13-month-old male was found dead in his crib while he and his mother were visiting at his grandmother’s house. The infants face was resting against a properly installed plastic bumper pad.”</td>
</tr>
<tr>
<td>8</td>
<td>“A 3-month-old male died of SIDS in his crib with his face against the bumper pad.”</td>
</tr>
<tr>
<td>9</td>
<td>“A 2-month-old female was found dead in her wicker infant basket for a nap after being fed at noon. She was found on her stomach, head turning to the left with face pressed slightly against the padded basket liner. The medical examiner found no anatomic cause and attributed the death to probable suffocation.”</td>
</tr>
<tr>
<td>10</td>
<td>“A 2-month-old male died of anoxia when he was sleeping and his face was pressed against the bumper of the ‘bassinet/cradle’. The victim was dead on arrival. Note: Mother stated that the baby died due to the tilt of the bassinet/cradle.”</td>
</tr>
<tr>
<td>11</td>
<td>“Baby suffocated at home in the corner of the crib against the crib bumper. Suffocation—accidental.”</td>
</tr>
<tr>
<td>12</td>
<td>“Baby found face down in crib, pinned between bumper pad and sibling sister. A male infant, age 4 months, placed for a nap in a crib with a twin sister was found wedged between the bumper pad and his sister. Cause of death asphyxia due to positional crib accident.”</td>
</tr>
<tr>
<td>13</td>
<td>“A 4-month-old male was found dead in his crib at home. Reports indicated that the victim became wedged between the mattress and the bumper pad of his crib. The death was declared an accident; cause of death was listed as asphyxia by suffocation.”</td>
</tr>
<tr>
<td>14</td>
<td>“A 10-month-old male died of positional asphyxia, wedged between his crib railing and a dresser 6 inches away. He apparently stood on the crib bumper pads and climbed over the crib railing.” Author’s note: This case indicates yet another hazard of bumper use. The bumper allowed the infant to climb from a relatively safe environment into a hazardous one.</td>
</tr>
<tr>
<td>15</td>
<td>“Found unresponsive wedged between pillow and bumper pad. Positional asphyxia. Note: Mother reported the baby’s head had slipped off the edge of the pillow. His head was wedged between the pillow and the bumper pads inside the bed.”</td>
</tr>
<tr>
<td>16</td>
<td>“Seven-month-old girl was placed in her crib for a nap after being fed by her mother. Child was found later in her crib with her head wedged between the mattress and the bumper pad attached to side slats. Child was pronounced dead at arrival at hospital.”</td>
</tr>
<tr>
<td>17</td>
<td>“Found by mother with face wedged between crib mattress and bumper pads. COD: asphyxias.”</td>
</tr>
<tr>
<td>18</td>
<td>“An 11-month-old female slid off the bed mattress. The crib bumper pad is believed to have become caught around the victim’s neck, and as she slid forward and she was unable to breathe and suffocated. The cause of death is mechanical asphyxia, the manner of death is considered accidental.”</td>
</tr>
<tr>
<td>19</td>
<td>“A 2-1/2-month-old male died due to probable suffocation. According to an investigator with the sheriff’s department, the infant’s mother found him face down in his crib. The investigator stated the baby’s head had caught between a baby blanket and the bumper pads in his crib. He was pronounced dead at the scene.”</td>
</tr>
<tr>
<td>20</td>
<td>“Face wedged in crib between pillow, mattress, and bumpers, external facial compression (suffocation).”</td>
</tr>
<tr>
<td>21</td>
<td>“An 8-month-old female died after being trapped tight against a side rail padding and mattress in her crib.”</td>
</tr>
<tr>
<td>22</td>
<td>“A 6-day-old female was found not responsive in her infant basket. She was on her stomach with her head turned to one side. Her face was pressed into the crevice between the basket mattress and padded sideriner. After an autopsy was preformed, the medical examiner ruled that death was caused by probable suffocation due to an external airway obstruction.”</td>
</tr>
<tr>
<td>23</td>
<td>“The baby was found wedged between adult pillows and crib bumper. The baby had originally been placed on her side and was found on her stomach.”</td>
</tr>
<tr>
<td>24</td>
<td>“A 2-month-old male was found dead in his crib. Autopsy examination revealed no cause of death, but findings frequently seen in sudden infant death syndrome. Based on circumstances surrounding the death as currently known, this death meets the criteria for sudden infant death syndrome.” Author’s note: The original death scene investigation makes no mention of infant’s head position at death, and so the medical examiner lacked this important information. A subsequent CPSC death scene investigation (Figure 2) indicated that the baby’s face was covered by a comforter, and his head was wedged between the mattress and the bumper pads.</td>
</tr>
<tr>
<td>25</td>
<td>“A 6-month-old female was strangled by the strings of her bumper pads while sleeping in her full size crib. She had placed her head through a loop formed by the tied fabric attachment strings of the bumper pad.”</td>
</tr>
<tr>
<td>26</td>
<td>“Asphyxiation by string-ligature. Father noted the string around baby’s neck. He pulled baby from crib, pulling the string from the bumper pad in the process. Police surmise that the baby had grasped the loosened tie in his hand then rolled over pulling the tie across the front of his neck. A mark was made.”</td>
</tr>
<tr>
<td>27</td>
<td>“Tie of bumper pad became tangled around neck. Cerebral anoxemia and anoxia; ligature compression of vessels.”</td>
</tr>
</tbody>
</table>
Table II. Consumer Product Safety Commission file summaries of crib accidents

<p>| 1.  | “Patient struck face on side of a crib at home, contusion on face.” |
| 2.  | “Child has a dent in side of head after pushing against bars of crib at home.” |
| 3.  | “Hit head on crib Dx. Head abrasion.” |
| 4.  | “Patient struck left knee against side of a crib, knee contusion.” |
| 5.  | “Patient fell forward in crib, bumping head on crib at home 7 days ago; head injury, head contusion.” |
| 6.  | “Four-month-old male, contusion to head, hit head on crib.” |
| 7.  | “Patient was in crib; mom came home, and patient had a bump on her forehead. Dx: mild head injury.” |
| 8.  | “Patient sustained head injury hit head on crib.” |
| 9.  | “Patient hit head against metal bassinet at home 2 days ago, has abrasion in forehead, crying, minor head injury, abrasion.” |
| 10. | “Contusion to head when struck on crib.” |
| 11. | “Patient’s legs were sticking out of crib bars this AM. Now his hip is making a popping sound. DX: sprain right leg.” |
| 12. | “Mother states child hit face on side of crib. Dx: nasal contusion.” |
| 13. | “Patient hit mouth on crib and sustained cut injury to inner mouth.” |
| 14. | “Knee contusion—hitting bumper pads in baby bed-home.” |
| 15. | “Left arm caught between bars in crib, contusion left arm.” |
| 16. | “Trauma (R) forearm; patient got forearm stuck in the baby crib rail, crying and pain. Patient got arm stuck in crib, was alone in bedroom, strain elbow.” |
| 17. | “Contused head on bassinet.” |
| 18. | “Patient caught arm in crib at home, not using arm; nursemaids elbow.” |
| 19. | “Fx (Left Forearm), patient got her arm caught in the rails of the crib, cried a lot of pain.” |
| 20. | “Patient got leg caught in crib, twisted thigh, arrives with swollen thigh, Lt femur fracture.” |
| 22. | “Patient’s arm got stuck between crib and wall, and father states he heard a crack. Dx: Lt humerus fracture.” |
| 23. | “Patient pushed against crib, dad heard snap. Femur fractured.” |
| 24. | “Patient hit head on crib; closed head injury.” |</p>
<table>
<thead>
<tr>
<th>Softness scale</th>
<th>Thickness (inches)</th>
<th>Length of bands attaching bumper to crib bars (inches)</th>
<th>Potential for head wedging</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>1-1/16</td>
<td>6-1/2</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1-1/4</td>
<td>8</td>
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<td>3</td>
<td>1</td>
<td>1-3/4</td>
<td>8-1/4</td>
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<td>4</td>
<td>2</td>
<td>1-3/4</td>
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<td>22</td>
<td>3</td>
<td>1-3/4</td>
<td>8-1/2</td>
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</table>

In the assessment of softness, 1 is the hardest and 3 the softest; 2 is intermediate. The hardest and thickest (>2 inches) bumpers were deemed to have the highest potential for wedging.
Insulin Resistance in Adolescents

ANN M. RODDEN, DO, VANESSA A. DIAZ, MD, MS, ARCH G. MAINOUS III, PHD, RICHELLE J. KOOPMAN, MD, MS, AND MARK E. GEESY, MS

Objectives To investigate the relationship of other body mass index (BMI) ranges with Homeostasis Model Assessment–Insulin Resistance (HOMA-IR), a surrogate marker for insulin resistance in adolescents.

Study design Cross-sectional analysis of a nationally representative sample of 1837 nondiabetic, nonpregnant 12 to 19 year old persons from the National Health and Nutrition Examination Survey, 1999-2002. The main outcome measurement of insulin resistance was calculated as HOMA-IR > 3.16.

Results Having a BMI ≥75th percentile is associated with a high HOMA-IR levels. As the BMI percentile increases, the odds of high HOMA-IR levels increase (BMI percentile 75-84.9, OR 4.277, 95% CI 2.090-8.752; BMI percentile 85-94.9, OR 4.299, 95% CI 2.158-8.563; BMI ≥95th percentile, OR 17.907, 95% CI 11.360-28.228).

Conclusion Adolescents with BMI percentile of 75 to 84.9, which represents approximately 1.2 million US adolescents, have not previously been identified as having higher HOMA-IR levels. (J Pediatr 2007;151:275-9)

The proportion of adolescents who are overweight has risen from 6% in the 1970s to 17% in 2004.1-3 The classification of obesity for children and adolescents differs from that of adults. Instead of having set body mass index (BMI) levels (obese is a BMI ≥30, overweight a BMI of 25-29.9 for adults), children and adolescents are characterized by BMI percentiles. Being overweight is defined as a BMI of greater than or equal to the 95th percentile of Centers for Disease Control and Prevention (CDC) growth charts, and risk of being overweight is defined as a BMI percentile between 85 and 94.9. Normal weight is characterized as being between the 5th and 85th percentile.4

Being overweight is an established risk factor for insulin resistance, a precursor of type II diabetes mellitus, as well as hypertension, coronary heart disease, stroke, and cancer.5-9 It is unclear however, whether contemporary classifications of levels of BMI as overweight or risk of overweight are the only levels of BMI to have independent risk for insulin resistance because these are arbitrary classifications based on percentiles.

The purpose of this study is to evaluate the association of BMI with an insulin resistance surrogate marker among adolescents while controlling for factors that are related to insulin resistance. In particular, we examine the prevalence of higher Homeostasis Model Assessment–Insulin Resistance (HOMA-IR) levels at specific BMI levels that consist of overweight, risk for overweight, and several groupings in the "normal" BMI category in a nationally representative sample of adolescents.

METHODS

Study Population

Data from the 1999-2002 National Health and Nutrition Examination Survey (NHANES) were analyzed. NHANES included participants from a nationally representative sample of non-institutionalized residents of the United States. The survey was conducted by the National Center for Health Statistics (NCHS) and included laboratory and interview information.

Samples were weighted to be representative of the US population so population estimates could be made. The NHANES sampling weights account for unequal proba-
Abilities of selection as a result of planned oversampling, sample design, and nonresponse, and they were matched to known population control totals to be representative of the US population. Sample weights also account for missing data.

A fasting sample of adolescents between 12 and 19 years of age had laboratory tests obtained for further evaluation. Adolescents were excluded from this sample if they were currently pregnant or had previously been informed by a physician that they had diabetes.

Demographic Data

Persons were categorized based on self report as non-Hispanic White, non-Hispanic Black, or Hispanic. The poverty income ratio (PIR) was available from the NHANES data. This ratio takes into consideration the annual income before taxes of the family, adjusting for family size. A value ≤ 1.00 was considered below the official poverty threshold.

Body Mass Index

BMI was calculated from the measured weight and height (kg/m²) collected by protocol. The CDC 2000 growth chart guidelines for grouping BMI percentiles by age in adolescents were used. Adolescents were grouped into the following categories by BMI percentile: <50, 50.0-74.9, 75-84.9, 85-94.9 (risk for overweight), and ≥95 (overweight).

Dietary Variables

Dietary history for the 24 hours before the interview was gathered in person by trained dietary interviewers using a multiple pass method. A standard set of measuring guides were used to help the respondent report the volume and dimensions of the food items consumed to simplify portion size estimation. The dietary recalls were further characterized as reliable and meeting the minimum criteria by the NCHS if ≥ 25% of foods were missing descriptive information, ≥ 15% were missing amounts, and the respondent remembered at least one food item per meal. Persons with unreliable data as determined by the NCHS were excluded. The total daily carbohydrate intake in grams was quantified from this 24-hour dietary recall.

Physical Activity

Each participant was asked a series of questions pertaining to physical activity. Typical physical activity levels were determined from these questions. These categories consist of little or no regular recreation, sport, or physical activity; regular recreation or work-related physical activity of any time period during the week; regular, heavy physical activity <1 hour a week; and regular, heavy physical activity 1 hour or more a week.

Cardiovascular Fitness

The cardiovascular (CV) fitness test consisted of a submaximal exercise test performed by trained health technicians. Each participant performed a treadmill protocol chosen based on age, sex, BMI, and self-reported physical activity. An estimated maximal oxygen uptake was calculated based on...
heart rate measurements during the submaximal testing. Each participant’s CV fitness was categorized as low, moderate, or high, based on the estimated maximal oxygen uptake for age and sex.  

Homeostasis Model Assessment—Insulin Resistance (HOMA-IR)  
The gold standard for measuring insulin sensitivity is the hyperinsulinemic-euglycemic clamp technique, which is invasive, expensive, and time-consuming to perform. Because the NHANES collected fasting laboratory data, fasting glucose and insulin were obtained on participants. Although HOMA-IR is not the gold standard, HOMA-IR is able to be used in large populations of adolescents as a screening tool for insulin resistance. In the adolescent population, the homeostatic model assessment has been identified as being one of the best non-invasive techniques with sensitivity and specificity of 76% and 66%, respectively, with a cutoff value of 3.16. This differs from the value found to be useful in adults of >2.50. Consequently, we will consider the HOMA-IR cutoff value of 3.16 to be high HOMA-IR. HOMA-IR was calculated as fasting insulin (μU/mL) × fasting glucose (mg/dL) divided by 22.5.

Data Analysis  
Because of the complex survey design of the NHANES 1999–2002, univariate analysis and descriptive statistics were performed using SUDAAN software (Research Triangle Institute, Research Triangle Park, NC). Associations between variables and BMI percentiles were assessed using χ² tests. Associations between high HOMA-IR and variables also were assessed using χ² tests and t tests when appropriate. A P value < .05 was considered significant.

We assessed predictors of high HOMA-IR in these nondiabetic 12 to 19 year olds using a logistic regression. An unadjusted model and a model adjusting for the demographics only were initially performed. The final adjusted model assessed the relationship of high HOMA-IR levels with BMI controlling for age, sex, ethnicity, PIR, and carbohydrates, along with self-reported physical activity and CV fitness. The total daily carbohydrate intake was included in the final adjusted model because it has been found to be statistically significant in previous studies evaluating insulin resistance.

RESULTS  
Table I shows the characteristics of the unweighted study population of 1837 persons representing a weighted population of 31,285,208 adolescents between 12 and 19 years of age. The average age was 15.4 years, which was similar across all BMI categories. Overweight and risk for overweight adolescents reported less physical activity than normal weight adolescents. Overall, the majority of normal-weight adolescents were classified as being of moderate fitness on the CV fitness test. More than half of those considered overweight achieved low CV fitness test results.

Table II compares the same population by HOMA-IR levels. More than a third of Hispanic and Non-Hispanic Black adolescents had HOMA-IR >3.16. Adolescents with high HOMA levels tended to report less activity (P = .005) and performed worse on the CV fitness test (P < .001). The prevalence of high HOMA-IR in the adolescent population with BMI ≥95th percentile was 73%. This decreased to 37.8% of adolescents in the BMI group with a percentile of 85 to 94.9. In the BMI percentile weight category with a BMI percentile of 75 to 84.9, which is characterized as normal weight, almost 34% of adolescents in this group also had high HOMA-IR levels. The amount of high HOMA-IR levels decreased below the 75th percentile BMI to about 10%.

In all three models noted in Table III, a BMI ≥75th percentile was associated with high HOMA-IR levels. The odds of having high HOMA-IR in the final adjusted model was similar in adolescents with a BMI percentile of 75 to 84.9 (OR 4.277, 95% CI 2.090-8.752) and a BMI percentile of 85 to 94.9 (OR 4.299, 95% CI 2.158-8.563).
DISCUSSION

Adolescents with BMI percentile of 75 to 84.9, which represents approximately 1.2 million US adolescents, have high HOMA-IR levels. Although several previous studies have identified an increase in insulin resistance in the overweight and risk for overweight adolescent populations,9,13,14 this is the first study to show high HOMA-IR levels in the BMI percentile of 75 to 84.9, a group considered to be “normal weight.” Adolescents with insulin resistance tend to have higher total cholesterol with lower high-density lipoprotein, higher fasting triglycerides, and higher systolic blood pressure.9 This study demonstrated that more than 8.5 million US adolescents have high HOMA-IR levels. Many of these persons may not be identified based on our current BMI categorizations because more than 3.2 million adolescents who are considered to be of normal weight have high HOMA-IR levels. Of these adolescents, more than 1.2 million are in the BMI percentile group of 75 to 84.9. In fact, the proportion of adolescents with high HOMA-IR levels in this BMI group is similar to the proportion in the risk for overweight group. Adolescents in the BMI percentile range of 75 to 84.9 have conventionally been considered “normal weight.” Our findings suggest that the prevalence of high HOMA-IR levels in this “normal weight” group is similar to that of those considered at risk for overweight. Thus, a BMI ≥75th percentile is associated with high HOMA-IR levels, and these adolescents may benefit from counseling on diet and exercise.

Other factors such as diet, exercise, and physical activity were controlled for in the analysis because they are known to be related to insulin resistance. The percentage of energy intake from carbohydrates has been noted to be related to increased insulin resistance in an adult population.12 Cardiovascular (CV) fitness, a measure of a person’s maximal oxygen consumption during exercise and physical activity may be related to insulin resistance.15 A third of adolescents have low CV fitness levels.16 This is associated with an increased prevalence of cardiovascular disease risk factors.16,17 Similarly, a sedentary lifestyle, a factor distinct from CV fitness, is associated with obesity, diabetes, and cardiovascular disease, and it is very prevalent in adolescents.18-20

A BMI >75th percentile is associated with higher HOMA-IR. Identifying persons with insulin resistance at an early age may allow for preventive measures to be discussed and implemented. Lifestyle interventions have been attempted in adults with insulin resistance and have reduced the

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Table III. Association between HOMA-IR and BMI in nondiabetic adolescents age 12 to 19 years*

<table>
<thead>
<tr>
<th>BMI percentile</th>
<th>Odds ratio (95%CI)</th>
<th>Adjusted for demographics*</th>
<th>Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>50-74.9</td>
<td>1.577 (0.902-2.757)</td>
<td>1.539 (0.863-2.746)</td>
<td>1.742 (0.960-3.163)</td>
</tr>
<tr>
<td>75-84.9</td>
<td>5.066 (2.872-8.937)</td>
<td>4.328 (2.412-7.766)</td>
<td>4.277 (2.090-8.752)</td>
</tr>
<tr>
<td>Age</td>
<td>0.952 (0.877-1.094)</td>
<td>0.949 (0.862-1.043)</td>
<td></td>
</tr>
</tbody>
</table>

Sex

- Male
- Female 1.156 (0.868-1.540) 1.044 (0.678-1.610)

Ethnicity

- Non-Hispanic
- White
- Non-Hispanic 1.267 (0.895-1.792) 1.243 (0.808-1.914)
- Black
- Hispanic 1.457 (1.002-2.120) 1.509 (0.981-2.320)

PIR

- <1.0 2.466 (1.495-4.074)
- ≥1.0 1.045 (0.635-1.721)

Activity

- Little 1.888 (1.233-2.890)
- Regular 4.378 (1.357-14.120)
- Heavy <1 h/wk 1
- Heavy ≥1 h/wk 1

CV fitness

- Low 1.572 (0.853-2.898)
- Moderate 1.032 (0.535-1.991)
- High 1
- Carbohydrates 1.000 (0.998-1.002)

*Adjusted for age, sex, and ethnicity.
†Adjusted for age, sex, ethnicity, PIR, carbohydrates, physical activity, and CV fitness.
incidence of diabetes compared with placebo treatment.\textsuperscript{21,22} In the Diabetes Prevention Program Trial comparing placebo, metformin, and lifestyle changes, the people in the lifestyle changes arm had a reduced incidence of diabetes.\textsuperscript{21} Recently a randomized, controlled trial of metformin demonstrated improvement in BMI and fasting insulin in overweight adolescents.\textsuperscript{23} If people at risk for disease could be identified earlier in life, these lifestyle and medical interventions might prevent diabetes, heart disease, strokes, and even cancer.

There are limitations to this study. First of all, there is still no universally accepted definition for insulin resistance in adolescents. However, this study uses HOMA-IR, which has been identified in previous studies as more reliable than other non-invasive tests in the adolescent population.\textsuperscript{11} Several laboratory modalities and values have been noted that use non-invasive measurement techniques to identify this intermediary state known as insulin resistance.\textsuperscript{11,24,25} Compared with other tests such as the quantitative insulin sensitivity check index (QUICKI) and fasting glucose/insulin ratio (FGIR), HOMA-IR has been found to be more reliable in adolescents.\textsuperscript{11} Second, physical activity was assessed based on self-report. Because it might be expected that respondents overreport physical activity, lower levels of physical activity may still be beneficial. Third, insulin resistance may be a transient process during puberty because of hormonal changes. Tanner stages were not collected in the 1999-2002 NHANES, so this could not be controlled for in the analysis. HOMA-IR values tend to peak at 13 years of age in girls and 14 years in boys.\textsuperscript{26} To adjust for these peaks, the analysis was performed with age categorized as 12 to 14 and 15 to 19 years old, and it did not affect the results (analysis not included).

This study suggests that adolescents with a BMI percentile of 75 to 84.9 should be considered a group that includes persons who may need counseling about diet and exercise similar to those with a BMI $\geq 85^{\text{th}}$ percentile. Further studies are needed to develop effective lifestyle or medical interventions for this group.

**REFERENCES**

A Cognitive Behavioral Therapy Program for Overweight Children

ERICA L. T. VAN DEN AKKER, MD,* PATRYCJA J. PUIMAN, MD,* MIEKE GROEN, MSC, RENIER TIMMAN, PHD, MIEKE T.M. JONGEJAN, MD, PHD, AND WIM TRIJSBURG, PHD†

Objective To assess the 1-year results of a multidisciplinary, cognitive behavioral therapy treatment program for overweight and obese children.

Study design Children (n = 73; 8 to 15 years old) participated in a prospective study aimed at reduction of the body mass index–standard deviation score (BMI-SDS), adapting a healthy lifestyle and creating a positive self-image and higher self-esteem, by use of a group approach and parental involvement. Reduction in BMI-SDS and percent overweight were measured and analyzed by use of MIXED modeling.

Results The participants achieved a 0.6 BMI-SDS reduction, comparable to a weight loss of 18.7% after 1 year (P < .0001). The proportion of dropouts was 33%. Compared with the follow-up group, dropouts were older, increased in BMI-SDS before start of treatment, and were less successful in BMI-SDS reduction during treatment.

Conclusions This treatment program had a positive effect on BMI-SDS in overweight and obese children at 1-year follow-up. Differences between the characteristics of the dropout and follow-up group may reflect predictor variables for treatment outcome. (J Pediatr 2007;151:280-3)

Worldwide the growing incidence of obesity and overweight in children is a reason for concern.1-3 Obese children are likely to become overweight or obese adults, with an increased risk of diabetes mellitus type 2, cardiovascular disease and death.4-7 Even more alarming is the rising prevalence of abnormal glucose tolerance, dyslipidemia, and hypertension among obese children.8,9 One of the key elements in the battle against obesity is early treatment to prevent comorbidity and risk of becoming obese adults.

Obesity treatment aims at lifestyle changes and has an overall low success rate.10 From previous studies we have learned that treatment programs for overweight and for obese adults are less successful than those designed for children.11 This is not surprising, taking into account that eating habits and exercise patterns are developed at a young age. Therefore lifestyle changes are easier to achieve when sedentary behavior and unhealthy dietary habits have not yet fully developed. Cognitive behavioral therapy in children is reported as one of the most successful methods for reducing overweight and obesity.10,12 Nonetheless, when treating obese children, family engagement and group therapy appear to positively influence success rates.13-15

Since 1995, the pediatric department of the Sint Franciscus Hospital in Rotterdam, the Netherlands, has had a cognitive behavioral outpatient treatment program for overweight and obese children, in which parental involvement and a group approach are imbedded. This program is called the “Dikke Vrienden Club” (DVC), which translates into “Big Friends Club,” with a pun on “close” friends intended. Both overweight and obese children between 8 and 15 years of age can take part in this program. The DVC aims at reduction of body mass index (BMI), adapting a healthy lifestyle and creating a positive self-image. In this article we present 1-year follow-up results of this program.

METHODS

Study Population
All children who participate in the DVC program are between 8 to 15 years old and are overweight or obese, defined as a BMI standard deviation score (BMI-SDS) of more

<table>
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<tr>
<th>BMI</th>
<th>Body mass index</th>
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<tr>
<td>BMI-SDS</td>
<td>Body mass index–standard deviation score</td>
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DVC Dikke Vrienden Club (Big Friends Club)
than 1.1 and 2.3, respectively. The exclusion criteria were overweight caused by a somatic treatable disorder, mental retardation, behavioral problems defined as a score exceeding 70 on the “child behavioral checklist” (CBCL),16,17 being insufficiently fluent in the Dutch language, and insufficient motivation of parents or the child to actively participate in the program.

Design

The DVC focuses on 4 elements: (1) Teaching children about a healthy diet and physical exercise. (2) Coping with psychosocial consequences of overweight and obesity. (3) Creating a positive self-image and higher self esteem. (4) Reducing BMI-SDS, preferably by maintenance of weight during growth.

Participants are referred by a physician or may contact the pediatric department themselves. During the first outpatient clinic visit, a pediatrician will conduct an interview and physical examination to exclude somatic disorders that might cause overweight or obesity. In addition, the parents and the child are evaluated for motivation to participate in the treatment. When this is found to be sufficient, they are asked to sign a consent form and declaration of intent. The children are then placed on the 3-month waiting list.

DVC groups comprise 8 to 10 children. The program provides for an intake session, 8 children-sessions and 2 parent-sessions during the first 12 weeks. The meetings are led by a team consisting of a psychologist, a dietician, and a physiotherapist. Both at the start and the end of this intensive 12-week period, the children are seen by the DVC-team and a pediatrician.

The program uses different behavioral therapy techniques such as operant and cognitive therapy strategies. The first 90 minutes of the children-sessions are dedicated to normal eating and exercise behavior and strategies to deal with difficulties concerning eating or physical inactivity. By providing group therapy, the children can recognize and share their concerns and learn from each other. Gradually their eating and exercise behaviors will change, first by extrinsic reinforcement and later on by intrinsic reinforcement. Furthermore, attention is paid to the psychosocial aspects of obesity like being picked on by peers. The last hour of each session is led by the physiotherapist. By creating positive exercise experiences through games and sports, the children improve their physical condition and exercise behavior. Implementing more exercise in daily life and therefore decreasing sedentary behavior is another goal of this part of the session.

The role parents play in their child’s lifestyle is emphasized. Hence, 2 parent-sessions are scheduled. The first takes place before the children’s first session. In this session the DVC team explains the DVC-key elements and the content of the program. During the session the parents learn about a healthy diet, normal exercise behavior, psychosocial aspects of obesity, and the fact that obesity increases the risk of physical and psychological morbidity. Part of the session is devoted to changing interaction patterns between the parents and their children by teaching them how to support their child instead of controlling them, how to give positive feedback, and how to apply positive reinforcement. The second parent-session takes place 4 weeks later. During this session the parents are invited to ask questions and to share their problems. The DVC team stimulates the parents to search for answers within the group to increase the parent’s problem-solving capacity.

After the intensive 12-week period, the children are awarded an A-diploma if they managed to decrease their BMI-SDS. To support each other after the intensive period, the children are paired into age-matched buddy-teams. They find emotional support and help by contacting each other when necessary. The buddy-team–system is a tool to reach the set eating and exercise goals. It enhances self-control and shifts the extrinsic reinforcement provided by the DVC team and the parents to intrinsic reinforcement. At 6 months and 12 months after start of the program, children-parent-sessions aimed at prevention of relapse are organized. The goals are evaluated and the children receive feedback on their diet and exercise pattern. All together, the children, parents and the DVC team try to solve the problems that arose during the past months. The main purpose of these 2 sessions is reinforcement of the key elements of the DVC program. Additionally, B- and C-diplomas are awarded during these sessions for children who retained or further reduced BMI-SDS.

In between, the children are seen by a pediatrician 6, 9, and 12 months after the start of the program, and height and weight are measured. At these occasions the children receive individual feedback about their weight change. Children who did not return at the end of the 12-week period, or who did not show up for the follow-up visits were classified as drop-outs.

Measurements

Data were collected at 4 time points: first outpatient clinic visit (t = -3 months); intake at start of the DVC program (t = 0); end of the 12-week intensive program (t = 3 months); and 1 year after start of the program (t = 12 months) (Figure). Height was measured in the upright position and defined in centimeters. Weight was measured in kilograms by a digital scale (SECA, Hamburg, Germany). BMI was calculated as bodyweight (kg) divided by height in meters squared (m²). BMI standard deviation score (BMI-SDS) represents an age- and sex-specific standard deviation. The BMI-SDS was calculated with the software program Growth Analyser version 3.5 (Dutch Growth Foundation, Rotterdam, the Netherlands; www.growthanalyser.org). Percent overweight was calculated using the following equation: 100 × (actual weight - 50th percentile weight-for-height)/ 50th percentile for weight for height. The weight-for-height growth charts are based on nationally collected data.18

Statistical Analysis

The course of BMI-SDS was analyzed with the PROC MIXED procedure in SAS 8.2 (SAS Institute, Cary,
NC). ¹⁹ This analysis method allows the use of incomplete cases. First, a saturated MIXED model was postulated, including the BMI-SDS as dependent variable, and the main effects time, squared time, age, sex, and the interaction effects between these main effects. Then the covariance structure and random part of the model were determined, by use of the restricted maximum likelihood function. Finally, insignificant interaction effects were removed step by step from the fixed part of the model. The ordinary maximum likelihood function was used to determine the difference between the saturated and the final model. SPSS 12.0.1 (SPSS, Chicago, IL) was used for relations between dropout and BMI-SDS increase (Fisher’s exact test). Relation between age and dropout was analyzed with an independent sample $t$ test. $P$ values < .05 were considered statistically significant.

**RESULTS**

Seventy-three children (53 girls) participated in the DVC from 1999 to 2003 (Table I). Mean age was 10.5 years (range 8.0–14.0 years). Mean BMI at inclusion was 27.3 kg/m² (range 22.4–40.0) and mean BMI-SDS was 2.6 (range 1.8–3.6). Seventy participants (96%) completed the 12-week program. One year later, 49 (67%) children came back for follow-up; the other 24 (33%) were considered dropouts. Mean BMI-SDS showed a significant reduction of 0.3 BMI-SDS (range 0.18–1.8; $P = .0001$) (Table I, Figure). This decrease is comparable to the BMI-SDS decrease after the 12-week program ($P < .0001$) (Table I, Figure).

In the analysis of changes in BMI-SDS, the saturated fixed model ($-2$ log-likelihood $= -7.7$) was not significantly better than the final model ($-2$ log-likelihood $= -3.4$; $\chi^2 (5) = 4.3; P = .51$). The variables of the final MIXED model are presented in Table II.

For the follow-up group, those children who attended the 1-year follow-up visit, the treatment resulted in a significant decrease of 0.6 mean BMI-SDS (range $-2.0$–$0.16$) ($P < .0001$) (Table I, Figure). This decrease is comparable to a mean weight loss of 18.7%. Forty-five children (92%) managed to reduce their BMI-SDS, 33 of whom achieved this reduction by losing weight. The other 12 children gained weight, but the BMI-SDS decrease was accomplished by height gain. Four children in the total follow-up group (8%) had a BMI-SDS elevation with a mean of 0.1 SDS in comparison to the end of the intensive 12-week program.

The children who did not attend the 1-year follow-up visit were already less successful during the first 3 months of the DVC program. The mean BMI-SDS for this dropout group increased between the first outpatient clinic visit ($t = 0$) and the intake session at start of the study ($t = 0$) ($P < .001$). During the 12-week program, the dropout group decreased less in BMI-SDS, than non-dropouts (Figure). Dropout was also related to age at start, with a higher mean age for dropouts compared to the follow-up group ($P < .01$). Analyses showed that 62% of children aged 12 years or

### Table I. Characteristics study population

<table>
<thead>
<tr>
<th></th>
<th>Follow-up (SD)</th>
<th>Drop-outs (SD)</th>
<th>$P$ value</th>
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</thead>
<tbody>
<tr>
<td>Girls</td>
<td>$n = 49$</td>
<td>$n = 24$</td>
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<tr>
<td>$t = 3$ months</td>
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</tr>
<tr>
<td>Age (years)</td>
<td>10.0 (8-13)</td>
<td>11.4 (8-14)</td>
<td>.001†</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.4 (42.4-107.4)</td>
<td>72.4 (54.4-113.8)</td>
<td>.002†</td>
</tr>
<tr>
<td>BMI-SDS</td>
<td>26.6 (22.4-36.2)</td>
<td>28.7 (24.1-40.0)</td>
<td>.01†</td>
</tr>
<tr>
<td>$t = 3$ months</td>
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<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.0 (42.6-111.8)</td>
<td>75.1 (56.4-117.2)</td>
<td>.001†</td>
</tr>
<tr>
<td>BMI-SDS</td>
<td>26.8 (21.8-36.8)</td>
<td>29.3 (24.2-41.4)</td>
<td>.003†</td>
</tr>
<tr>
<td>$t = 3$ months</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.4 (36.1-103.9)</td>
<td>73.6 (54.9-113.5)</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>BMI-SDS</td>
<td>24.8 (20.6-34.0)</td>
<td>28.6 (23.7-40.1)</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>$t = 3$ months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.4 (35.0-111.1)</td>
<td>72.4 (30.7-113.3)</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>BMI-SDS</td>
<td>2.0 (0.8-3.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Fisher's exact test, 2-sided.
†Student's $t$ test.
‡$n = 21.$

### Table II. Final MIXED model parameters of BMI-SDS decrease

<table>
<thead>
<tr>
<th>Effect</th>
<th>Estimate</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>3.68</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex</td>
<td>−0.24</td>
<td>.013</td>
</tr>
<tr>
<td>Age</td>
<td>−0.007</td>
<td>.018</td>
</tr>
<tr>
<td>Dropout</td>
<td>0.19</td>
<td>.047</td>
</tr>
<tr>
<td>Time linear</td>
<td>0.69</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Time quadratic</td>
<td>−0.56</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Time cubic</td>
<td>0.088</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Dropout-time linear</td>
<td>−0.10</td>
<td>.20</td>
</tr>
<tr>
<td>Dropout-time quadratic</td>
<td>0.083</td>
<td>.012</td>
</tr>
</tbody>
</table>

Figure. Dropout group versus follow-up group.
older dropped out, compared with 21% of younger children. No different effect of the treatment was found for boys and girls. Characteristics of the follow-up and dropout groups are summarized in Table 1.

**DISCUSSION**

Overall, the overweight and obese children participating in the DVC program achieved a mean BMI-SDS reduction of 0.6 at 1-year follow-up. When converted to percent overweight, the BMI-SDS reduction results in an 18.7% loss of percent overweight. This means that a shift from a mainly obese group to a predominantly overweight group had occurred. The 18.7% reduction is higher than that found in most other studies. Three other studies using an approach similar to ours reported 12-month success rates ranging from 5.8% to 13.1% weight reduction.\(^2\)\(^3\)\(^4\)\(^5\)\(^6\) One of these also used the BMI-SDS and found a decrease of 0.38 BMI-SDS.\(^7\) In this study, the intensive 12-week program, the decline in overweight persisted until 1-year follow-up. Other studies describing long-term follow-up all show BMI-SDS reduction during the intensive treatment program, yet this is not always maintained during follow-up.\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)

Only 3 participants in our study dropped out during the intensive 12-week program. However, the 33% dropout rate after 1 year shows that the full program might not suit all children. Only 1 other study with a 1-year follow-up reported a dropout rate of 22%.\(^13\) In our study, the dropouts were older than children in the follow-up group. Therefore the DVC program might be more effective in younger children. Another study also reported success rates that were higher for children under 14 years of age compared with older children.\(^14\) In contrast, a 2-year follow-up study reported better results for older and more overweight children.\(^15\) We identified 2 other predictors for dropout: mean BMI-SDS increasing during the waiting list period and achieving less reduction in mean BMI-SDS during the intensive 12-week treatment period. On the basis of these findings, we suggest that the characteristics of the dropout group in the DVC program may reflect predictor variables for treatment outcome. Further identification of predictor variables could be helpful in designing treatment programs focused on children’s individual needs. Some subgroups might benefit more from an individual or more intensive program.

Comparison of our findings to those from other studies is complicated by several factors. First, definitions of overweight and obesity lack uniformity. Use of the BMI-SDS as a standard international definition for childhood overweight and obesity, as proposed by Cole et al,\(^2\) will enable comparison of study results. Second, study results do not always permit conclusions about dropout rates or rates of successfully treated children. This study was neither randomized nor controlled. However, from our waiting list data and from patient-controlled studies performed by others, we know that BMI-SDS reduction is not achieved without treatment.\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)

In conclusion, children who participated in this cognitive behavioral therapy program declined in overweight at 1-year follow-up. Further follow-up studies are needed to see what perspective the DVC program offers on long-term weight control. In addition, further identification of predictor variables could lead to better and more individually based recommendations on different treatment programs, and therefore increase the chances of success.

**REFERENCES**

Objective. To assess whether socioeconomic position, maternal intelligence (IQ), and the home environment are interrelated to cognitive development in childhood.

Study design. Prospective cohort study (n = 723) with cognitive tests at ages 2, 4, 7, and 11 to 13 years.

Results. There were statistically significant positive associations of father’s occupational prestige, Home Observation for Measurement of Environment (HOME) score, and maternal IQ with cognitive performance in childhood. After adjustment for confounding factors, there was an increase in cognitive development by 0.8 to 2.0, 2.9 to 4.8, and 4.2 to 9.0 points for a 10-unit increment in father’s occupational prestige, maternal IQ, and HOME score, respectively.

Conclusions. These results demonstrate that socioeconomic position, maternal IQ, and the home environment are independently and positively predictive of children’s cognitive development. These findings provide additional rationale for implementing social policies that reduce socioeconomic inequalities.

Childhood intelligence (IQ) is a predictor of various health outcomes in adulthood (eg, cardiovascular disease, some cancers, diabetes, suicide, motor vehicle injuries, and premature deaths).1-6 Hence, a better understanding of the determinants of child IQ should assist in the reduction of lifetime risks to health.

Several explanations for the association between IQ and adult health have been advanced,7 including that IQ is 1) a predictor of health-favoring social circumstances in later life (eg, high educational attainment and high job status); 2) a cumulative index of psychological and physiological insults (eg, birth complications, suboptimal postnatal care, and illness); 3) an intrinsic indicator of general body integrity (as measured via the brain’s capacity to process information rapidly, correctly, and reliably); 4) a proxy for stress management skills—people with higher intelligence scores may be less likely to place themselves in stressful environments or cope better if they do; or 5) an asset for optimal interpretation of health prevention messages—children who scored highly in intelligence tests were more likely to give up smoking in adult life.8

The relative roles of socioenvironmental and genetic factors in cognitive development remain unresolved. Although a proportion of the variation in human intelligence may be attributable to genetic factors,9 socioenvironmental factors are important determinants of childhood IQ and are modifiable through a range of early-years intervention strategies such as early childhood education and care.10,11 A number of studies have examined the link between socioeconomic characteristics and cognitive development.12-14 In general, children in disadvantaged families manifest poorer cognitive performance than do those in better-off families. However, few studies have adjusted satisfactorily for parental and environmental factors that may confound the relation between socioeconomic backgrounds and cognitive development. For example, children in disadvantaged families may be more exposed to environmental neurotoxins such as lead and other chemicals and may have poorer quality of home environment.15-21

In this study, we examined the association of socioeconomic position, maternal IQ, and the home environment with cognitive development during childhood, using data from a prospective cohort study design that enabled adjustment for a wide range of confounding factors.
METHODS

The primary objective of the Port Pirie Cohort Study was to examine the relation between exposure to environmental lead and child development. The children living in and around the lead-smelting town of Port Pirie, South Australia, were followed from birth to age 11 to 13 years. Details of the research design have been reported elsewhere.17-21

Sample

Of the 723 live births who were originally recruited in the Port Pirie Cohort Study, 601, 548, 494, and 375 were followed and assessed, respectively, at ages 2, 4, 7, and 11 to 13 years. The children who were evaluated at each age differed little from those lost to follow-up on most characteristics, including sociodemographic, environmental, and biomedical factors, except that they lived in families with slightly higher social class than those lost to follow-up.17-21 For example, possible loss to follow-up bias was evaluated at age 11 to 13 years. The results show that 55 children lost to follow-up were in families that either left the Port Pirie district or could not be contacted despite intensive efforts (ie, 11.7% of the base population), although a small number of families (7.8%) simply discontinued their participation.19

Measurements of Socioeconomic Characteristics

A crude measure of children’s socioeconomic position often used in Australia is the Daniel Scale,22 which is based on the hierarchy of the father’s occupational prestige and is used as an approximate indicator of family income. The Daniel score is inversely related to occupational prestige, that is, the higher the Daniel score, the lower the prestige. For example, a manufacturing worker was scored much higher than a professional occupation (eg, manager or engineer). The Daniel score of each family at birth was used in this study, as some evidence suggests that the father’s social class at birth is an important predictor of child’s IQ.13,23 Two important predictors of children’s abilities are the Home Observation for Measurement of the Environment (HOME) inventory24 and maternal IQ. The HOME inventory was used to assess each child’s caregiving environment, when each child was 3 years of age. Maternal IQ was measured with the Wechsler Adult Intelligence Scale-Revised,25 whereas the children were in the age range of 3 to 5 years. Maternal IQ rather than maternal education was used in this study because the former combines both inherited and acquired cognitive capacity and is a better integrated predictor of children’s IQ than is the latter.

Measurement of Cognitive Function

Each child’s abilities were assessed by using the Bayley Scales of Infant Development at age 2 years,26 the McCarthy Scales of Children’s Abilities at age 4 years,27 and the revised version of the Wechsler Intelligence Scale for Children (WISC-R) at ages 7 and 11 to 13 years.28 The Bayley Scales of Infant Development, which comprises two standardized scores, the Mental Development Index (MDI) and Psychomotor Development Index, is suitable for children ages 30 months and younger. Only MDI scores were used in this study because MDI score primarily reflects cognitive abilities. The McCarthy Scales of Children’s Abilities, which are applicable to children 3 to 7 years old, comprises five scales: verbal, perceptual performance, quantitative, memory, and motor. The first three of those scales combined form the general cognitive index. The WISC-R was used to assess the cognitive function of each child at ages 7 and 11 to 13 years. The WISC-R is a test of general intelligence developed for use with children ages 6 to 16 years. All children were assessed at each age by a research psychologist who was unaware of children’s socioeconomic characteristics.

Confounders

Information was also collected on the following potential confounding variables: child’s sex, birth weight, head circumference, birth length, Apgar score at 5 minutes after birth, presence of neonatal jaundice, maternal age, duration of gestation, maternal smoking and drinking habits, parental marital status, and lifetime average blood lead concentration up to age 2 years. Birth weight was measured in the clinical setting and recorded in grams. Duration of gestation was calculated from the date of the last menstrual period reported by the mother and checked against medical records. The child’s head circumference and birth length were also measured immediately after delivery. To assess early-life exposure to environmental lead, sequential blood samples were collected from the pregnant women, the umbilical cord, at 6, 12, and 24 months, and then periodically from the young child. The lifetime average blood lead concentration up to 2 years was used in this study because we had previously found that lead exposure in the first 2 years of life is most critical to cognitive development.17-21

Analysis

We first examined univariate relations between socioeconomic characteristics and cognitive development. All available data were retrieved for the 601 children whose cognitive function was initially assessed at age 2 years. Analysis of variance was used to test for linear trend across groups defined on the basis of the quintiles, separately for each of three indices: the Daniel Scale, the HOME score, and maternal IQ. Covariates that might confound the association between socioeconomic characteristics and cognitive function were explored. Multiple linear regression model was then used to examine the association of occupational prestige, maternal IQ, and home environment, with cognitive development as measured at ages 2, 4, 7, and 11 to 13 years, after adjustment for a range of potential confounding factors.
RESULTS

Overview of the Predictors of Cognitive Development

The mean value of cognitive scores at ages 2, 4, 7, and 11 to 13 years was 109.2, 107.1, 104.7, and 100.0, respectively. The father’s occupational prestige, HOME score, and maternal IQ were clearly associated with cognitive function at all ages examined (P ≤ .01), and there appeared to be a consistent dose–response relationship (Figure 1).

Daniel Scale and Cognitive Development

Table I (available at www.jpeds.com) presents a statistically significant positive association between father’s occupational prestige and children’s cognitive function at ages 2, 4, 7, and 11 to 13 years in simple (unadjusted) regression analyses. Children whose father’s occupational prestige was low had poorer cognitive function than those whose father’s occupational prestige was higher. The strength of the association decreased slightly after adjustment for a range of putative confounders (model I).

The association between father’s occupational prestige and children’s cognitive function was attenuated by adjustment for maternal IQ (model II) and quality of home environment (model III). However, the relation remained statistically significant or marginally significant.

Maternal IQ, Quality of Home Environment, and Cognitive Development

Similar patterns were observed for maternal IQ (Table II; available at www.jpeds.com) and quality of home environment (Table III; available at www.jpeds.com). Statistically significant and positive associations were observed for those two indices across different ages in simple (unadjusted) regression analyses. Children whose mother’s IQ or quality of home environment (HOME score) was low had poorer cognitive function than those whose mother’s IQ or HOME score was higher. The magnitude of the association decreased slightly after adjustment for a set of confounders (models I through III). However, after that adjustment there remained a statistically significant association of mother’s IQ and HOME score with children’s cognitive development across childhood.

Socioeconomic Position, Maternal IQ, Quality of Home Environment, and Cognitive Development: A Comparison

Further analyses display a consistent relation between these predictors and cognitive development after adjustment for confounding factors in the final model. For example, for every 10-unit increase in father’s occupational prestige, children’s cognitive performance increased by 0.8 (95% CI: −0.7 to 2.3), 1.5 (95% CI: 0.1 to 2.9), 2.0 (95% CI: 0.5 to 3.4), and 1.1 (95% CI: −0.4 to 2.6) points at ages 2, 4, 7, and 11 to 13 years, respectively. There was a similar pattern for the effect of maternal IQ on cognitive performance by age. For every 10-unit increase in HOME scores, children’s cognitive performance improved by 9.0 (95% CI: 5.4 to 12.7), 7.7 (95% CI: 4.2 to 11.3), 4.2 (0.7 to 7.6), and 6.2 (95% CI: 2.5 to 9.9) points at ages 2, 4, 7, and 11 to 13 years, respectively (Figure 2).

DISCUSSION

In this cohort of children, socioeconomic position, maternal IQ, and the quality of home environment were consistently associated with cognitive development, even after adjustment for a wide range of confounders. Our results indicate that the three measures of socioeconomic characteristics have an independent impact on childhood cognitive development. In general, the higher the occupational prestige and maternal IQ, and the better the home environment, the higher the children’s cognitive function.

We also found that the association between socioeconomic position and cognitive development was markedly attenuated by adjustment for maternal IQ and quality of home environment. It suggests that it is important to take these factors into account in the assessment of the association between socioeconomic position and childhood intelligence. The results of this study also indicate that other parental factors (eg, parental smoking behavior) and environmental variables (eg, lead exposure) are unlikely to explain the association between socioeconomic characteristics and cognitive development. Further, there were different patterns for the effects of HOME score versus maternal IQ or father’s occupational prestige on cognitive performance (Figure 2). This suggests that the quality of home environment may influence cognitive development through different mechanisms and/or pathways to maternal IQ or father’s occupational prestige. In particular, it appears that the quality of home environment has maximal impact in early childhood, and the other two variables have maximal impact in later childhood.

Several studies have examined the association between socioeconomic status and cognitive function. Kaplan et al undertook a population-based study of 496 Finnish men ages 58 and 64 for whom there were data on parent’s socioeconomic position, their own education level, and performance on neuropsychological tests. They reported childhood socio-
economic position to be positively associated with cognitive function in adulthood. Jeffers et al. examined the combined effect of social class and birth weight on cognitive development and found that the postnatal socioeconomic environment has a substantial impact on cognitive function through to early adulthood. More recently, Lawlor et al. reported that father’s social class at the time of birth was an important predictor of childhood intelligence, even after adjustment for maternal characteristics and perinatal and childhood factors. Our findings are essentially consistent with the findings of these studies. Although both maternal IQ and quality of home environment are important determinants of children’s cognitive function, there are few empirical data on how these factors inter-relate to each other. The results of this study demonstrate that maternal IQ and quality of home environment tend to have independent impacts on children’s cognitive development.

There are three major strengths in this study. We systematically examined the inter-relations between socioeconomic characteristics and cognitive development after adjustment for a wide range of confounding factors (including parental smoking and lead exposure). Second, a relatively homogenous community-based sample was used. For example, all children involved in the study were Caucasian, and therefore the assessment is unlikely to be confounded by cultural factors. Finally, internationally standardized tests of cognitive function were used at various ages, and stringent quality control procedures were implemented in this study.

This study has three possible limitations. First, follow-up bias could have arisen if the children who left the study differ—in the relation that they display between their socioeconomic characteristics and cognitive development—from those who remained in the study. However, any such bias is unlikely to be substantial because our analyses showed that the children who were evaluated at ages 11 to 13 years did not differ significantly from those lost to follow-up on most characteristics, including sociodemographic, environmental, and biomedical factors, except that fathers of the children remaining in the cohort had slightly higher occupational prestige than those lost to follow-up. Therefore, to maximize available information, we used the total dataset available at each age (2, 4, 7, and 11 to 13 years); the longitudinal analysis of only those subjects who contributed data at all four ages revealed a similar pattern. Second, there is no recognized gold standard for measuring socioeconomic characteristics. We used the Daniel scale, the HOME score, and maternal IQ to measure child’s socioeconomic characteristics. Nevertheless, these indices may not fully reflect all potentially relevant childhood socioeconomic background, and residual confounding (eg, by paternal IQ) may exist. Finally, this study is unavoidably unable to distinguish between a genetic and an environmental effect of maternal IQ on cognitive development.

The findings of this study have two important public health implications. First, socioeconomic attributes appear to be independently and positively predictive of children’s cognitive function. The association between socioeconomic characteristics and cognitive development is unlikely to be explained by other parental factors (eg, parental smoking behaviour) and environmental variables (eg, lead exposure). Second, socioeconomic characteristics may directly or indirectly contribute to the documented relation between childhood intelligence and adult morbidity and mortality as they are major determinants of cognitive development.

The authors particularly wish to thank the families who participated in this study.
REFERENCES

### Table I. Regression coefficients (95% CI) of father’s occupational prestige as a predictor of cognitive development

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Unadjusted</th>
<th>Model I</th>
<th>Model II</th>
<th>Model III</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.28</td>
<td>0.26 (0.14, 0.37)</td>
<td>0.16 (0.02, 0.31)</td>
<td>0.08 (−0.07, 0.23)</td>
</tr>
<tr>
<td>4</td>
<td>0.34</td>
<td>0.27 (0.15, 0.39)</td>
<td>0.22 (0.08, 0.37)</td>
<td>0.15 (0.01, 0.29)</td>
</tr>
<tr>
<td>7</td>
<td>0.33</td>
<td>0.31 (0.19, 0.43)</td>
<td>0.24 (0.09, 0.38)</td>
<td>0.20 (0.05, 0.34)</td>
</tr>
<tr>
<td>11–13</td>
<td>0.30</td>
<td>0.23 (0.11, 0.36)</td>
<td>0.15 (−0.01, 0.30)</td>
<td>0.11 (−0.04, 0.26)</td>
</tr>
</tbody>
</table>

*Model I: Variables that were adjusted for included child’s sex, birth weight, head circumference, birth length, Apgar score at 5 minutes, neonatal jaundice, maternal age, duration of gestation, maternal smoking and drinking habits, parental marital status, and lifetime average blood lead concentration up to age 2 years; model II: all the variables in model I plus maternal IQ; model III: all the variables in model II plus HOME.

### Table II. Regression coefficients (95% CI) of maternal IQ as a predictor of cognitive development

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Unadjusted</th>
<th>Model I</th>
<th>Model II</th>
<th>Model III</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.44</td>
<td>0.43 (0.27, 0.58)</td>
<td>0.40 (0.25, 0.56)</td>
<td>0.29 (0.13, 0.45)</td>
</tr>
<tr>
<td>4</td>
<td>0.56</td>
<td>0.50 (0.35, 0.64)</td>
<td>0.45 (0.30, 0.60)</td>
<td>0.34 (0.18, 0.50)</td>
</tr>
<tr>
<td>7</td>
<td>0.57</td>
<td>0.57 (0.43, 0.71)</td>
<td>0.53 (0.39, 0.67)</td>
<td>0.48 (0.33, 0.63)</td>
</tr>
<tr>
<td>11–13</td>
<td>0.46</td>
<td>0.41 (0.26, 0.56)</td>
<td>0.41 (0.25, 0.56)</td>
<td>0.32 (0.16, 0.48)</td>
</tr>
</tbody>
</table>

*Model I: Variables that were adjusted for included child’s sex, birth weight, head circumference, birth length, Apgar score at 5 minutes, neonatal jaundice, maternal age, duration of gestation, maternal smoking and drinking habits, parental marital status, and lifetime average blood lead concentration up to age 2 years; model II: all the variables in model I plus Daniel scores; model III: all the variables in model II plus HOME.

### Table III. Regression coefficients (95% CI) of quality of home environment as a predictor of cognitive development

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Unadjusted</th>
<th>Model I</th>
<th>Model II</th>
<th>Model III</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1.21</td>
<td>1.13 (0.85, 1.41)</td>
<td>1.03 (0.74, 1.33)</td>
<td>0.90 (0.54, 1.27)</td>
</tr>
<tr>
<td>4</td>
<td>1.38</td>
<td>1.16 (0.87, 1.45)</td>
<td>1.05 (0.75, 1.35)</td>
<td>0.77 (0.42, 1.13)</td>
</tr>
<tr>
<td>7</td>
<td>1.02</td>
<td>0.82 (0.53, 1.11)</td>
<td>0.65 (0.35, 0.95)</td>
<td>0.42 (0.07, 0.76)</td>
</tr>
<tr>
<td>11–13</td>
<td>1.06</td>
<td>0.95 (0.66, 1.24)</td>
<td>0.86 (0.55, 1.16)</td>
<td>0.62 (0.25, 0.99)</td>
</tr>
</tbody>
</table>

*Model I: Variables that were adjusted for included child’s sex, birth weight, head circumference, birth length, Apgar score at 5 minutes, neonatal jaundice, maternal age, duration of gestation, maternal smoking and drinking habits, parental marital status, and lifetime average blood lead concentration up to age 2 years; model II: all the variables in model I plus Daniel scores; model III: all the variables in model II plus maternal IQ.
A Randomized, Controlled Trial of Tonsillectomy in Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome

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Objective We carried out a prospective, randomized, controlled trial to clarify the effect of tonsillectomy on the clinical course of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome.

Study design Twenty-six consecutive children (mean age 4.1 years) with at least 5 PFAPA attacks were recruited from 3 tertiary care pediatric hospitals during 1999-2003 and randomly allocated to tonsillectomy or follow-up alone. They were all followed up with symptom diaries for 12 months. Tonsillectomy was allowed after 6 months in the control group if the attacks recurred.

Results Six months after randomization all 14 children in the tonsillectomy group and 6/12 children in the control group (50%) were free of symptoms (difference 50%, 95% confidence interval 23% to 75%, \( P < .001 \)). Tonsillectomy was performed on 5/6 of the patients in the control group who still had symptoms after 6 months. The remaining unoperated child in the control group had recurrences of the fever episodes throughout the follow-up, but the symptoms became less severe, and the parents did not choose tonsillectomy.

Conclusion Tonsillectomy appeared to be effective for treating PFAPA syndrome. The fever episodes ceased without any intervention in half of the control subjects. We conclude that although the mechanisms behind this syndrome are unknown, tonsillectomy can be offered as an effective intervention for children with PFAPA. (J Pediatr 2007;151:289-92)

Periodic fever syndrome refers to recurrent bouts of fever at regular intervals without any definitive infection. The most usual type in children is periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome, characterized by periodic episodes of high fever lasting 3 to 6 days and recurring regularly every 3 to 8 weeks, often associated with aphthous stomatitis, pharyngitis, and adenitis. PFAPA was first described by Marshall et al1 in 1987, and larger series of patients have been described since then.2-4 PFAPA is sporadic, but 3 familial types of periodic fever syndrome with underlying genetic abnormalities have been characterized, that is, Mediterranean fever (MEFV), hyperimmunoglobulinemia D syndrome (HIDS) and tumor necrosis factor receptor–associated periodic syndrome (TRAPS).5-7

The cause of PFAPA syndrome is unknown. Affected children are healthy between episodes and the prognosis is excellent even when the recurrent bouts of fever last for years.4 No amyloidosis or other complications have been reported, even though they are possible in familial types of periodic fever syndrome, such as in MEFV.8 Treatment with antipyretics is of limited value and antimicrobial agents are ineffective,3 and although a single dose of a corticosteroid (1 to 2 mg/kg prednisone) leads to rapid resolution of the fever in most patients,3,4 it does not prevent subsequent episodes. The only therapies found to induce remission in at least some patients are continuous cimetidine therapy9 and tonsillectomy,2-4 but no randomized, controlled studies have been published on their efficacy. We carried out a prospective, randomized, controlled trial to clarify the effect size of tonsillectomy on PFAPA.

METHODS

Patients Consecutive children with at least 5 PFAPA attacks were recruited from 3 tertiary care pediatric hospitals from 1999 to 2003. The criteria for an attack were high fever

<table>
<thead>
<tr>
<th>HIDS</th>
<th>Hyperimmunoglobulinemia D syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEFV</td>
<td>Mediterranean fever</td>
</tr>
<tr>
<td>PFAPA</td>
<td>Periodic fever, aphthous stomatitis, pharyngitis and adenitis</td>
</tr>
<tr>
<td>TRAPS</td>
<td>Tumor necrosis factor receptor–associated periodic syndrome</td>
</tr>
</tbody>
</table>

From the Departments of Pediatrics (M.R., M.U.) and Otorhinolaryngology (J.L.), University of Oulu, the Departments of Pediatrics (E.S., H.S.) and Otorhinolaryngology (P.M.), University of Helsinki and the Department of Pediatrics (A.P.-L., O.R.), University of Turku, Finland.

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(≥38.5°C) of unknown origin recurring with a typical, regular pattern and asymptomatic intervals of 2 to 5 weeks. Accompanying signs of aphthous stomatitis, pharyngitis, and adenitis were recorded. Thirty-five children were evaluated, and the parents of 28 of these gave written consent for participation in the study (Figure). The protocol was acceptable to the Ethical Committee of the Northern Ostrobothnia Hospital District. The 28 children had had an average of 9 febrile episodes (range 4 to 20) before recruitment, with fever lasting for a mean of 3.6 days (range 2 to 6) with a mean interval of 25.6 days (range 18 to 28). In 41% of cases the fever was the only symptom during the episodes (Table), 29% had exudative tonsillitis during at least 1 of the episodes and 21% had either cervical lymphadenopathy, aphthous stomatitis or pain in the mouth or throat. One child had a sibling with PFAPA. Two children whose parents were not willing to participate also had a sibling who had had PFAPA that had been cured after tonsillectomy. The parents of these children wanted tonsillectomy to be performed as soon as possible.

Serum levels of immunoglobulins G, A, M, E, and D were measured in 20 of 26 children and were within the age-adjusted normal values in all cases. Either the sedimentation rate or the C reactive protein (CRP) and blood leukocyte count during an episode was available for 24 of 26 children (Table).

### Intervention and Follow-up

The participants were randomly allocated to either the treatment group, for tonsillectomy to be performed within 1 month, or the control group (Figure). They were then all followed up with symptom diaries filled in by the parents for 1 year. Tonsillectomy was allowed after 6 months in the control group if the child’s symptoms still persisted.

### Outcome Measures and Statistical Methods

The main outcome measure was disappearance of fever episodes according to the symptom diaries. For the sample size calculations we estimated that the fever episodes would disappear in 90% of cases in the tonsillectomy group and in 30% of cases in the control group during the first 6 months of the follow-up. We chose the type I error to be 5% and wanted to be 90% sure when claiming the efficacy to be less than a difference of 60%. With these assumptions, the sample size was calculated to be 12 children per group. To make sure that there would be enough children for analysis in both groups, we chose to enroll 28 children. A balanced randomization was used at each center to minimize bias. The proportion of children with disappearance of symptoms was compared between the treatment groups and the absolute difference and 95% confidence interval (CI) for the difference were calculated. The statistical significance of the difference in proportions was tested with the SND test. The mean number of PFAPA episodes per person-month at risk was determined.
for both treatment groups and the mean difference with CI was calculated. The statistical significance of the difference was tested with the Mann–Whitney U-test.

RESULTS

All 14 children in the tonsillectomy group and 6 of 12 (50%) in the control group were free of symptoms 6 months after randomization (difference 50%, CI 23%-75%; P < .001). Tonsillectomy was performed on 5 of 12 children (42%) in the control group after the follow-up period of at least 6 months because symptoms persisted, after which the symptoms disappeared in all cases. There were no complications after tonsillectomy. One child had persistent fever episodes throughout the follow-up, but the symptoms became less severe, and the parents did not want tonsillectomy to be performed.

Four of the 14 children in the tonsillectomy group had 1 fever episode compatible with periodic fever in 6 months after tonsillectomy (0.05 episodes per person-month at risk), and the 12 children in the control group had altogether 34 such episodes in the same time interval (0.44 episodes per person-month at risk, difference 0.40, 95% CI 0.17 to 0.62; P = .007).

There were no significant differences in the outcome between the children who had periodic fever with or without aphthous stomatitis, pharyngitis, tonsillitis or lymphadenitis. In the tonsillectomy group 7 of 14 (50%) had fever as the only symptom during episodes (Table) and all of them had a successful outcome. In the control group, there were 4 of 12 (33.3%) children with fever as the only symptom during the episodes. In 2 of them, the fevers disappeared spontaneously during the 6-month follow-up, in 1 child tonsillectomy was performed because of persisting symptoms, and 1 child’s parents did not choose tonsillectomy. The 6 children in the control group who were cured without any intervention did not differ in age, sex, or features of the PFAPA attacks from the 6 in whom the attacks recurred.

DISCUSSION

Tonsillectomy appeared to be an effective treatment for PFAPA syndrome, although half of the children in the control group had self-resolution during the follow-up of 6 months. The mean number of PFAPA episodes per person-month at risk during the 6 months of the follow-up was reduced from 0.44 to 0.05 as a result of tonsillectomy. This striking effect has been found previously in some retrospective patient series.2,3,10,11 Galanakis et al.2 in a retrospective evaluation of the preoperative symptoms of 40 children who underwent tonsillectomy for recurrent pharyngitis, found that 15 (37.5%) of them had a history compatible with PFAPA syndrome, and all of these were symptom-free after tonsillectomy.

The cause of PFAPA syndrome is unknown. Some clinical features resemble 3 familial types of periodic fever syndrome, that is, MEFV, HIDS, and TRAPS,5–7 but the episodes do not appear as regularly in these as they do in PFAPA. Cyclic neutropenia is a rare syndrome with profound neutropenic episodes causing fever, pharyngitis, lymphadenopathy, and pyogenic infections at intervals of 21 to 24 days. The occurrence of cyclic neutropenia is most often familial, however, and it can be differentiated easily from PFAPA syndrome by means of serial leukocyte counts just before the fever. The diagnosis is confirmed by bone marrow examination and genetic testing.5,7

The diagnosis of PFAPA syndrome is based on the clinical picture and the exclusion of other diseases causing recurrent episodes of fever. The children in our series had aphthous stomatitis, cervical lymphadenopathy, and pharyngitis reported less often than the patients described in the literature, and exudative tonsillitis reported more frequently. Signs of mild pharyngitis and lymphadenitis are not very easy to discover in small children and we think it is possible that some of those localizing signs have been missed by physicians. There were 2 children whose symptoms had begun at an older age than is stated in the diagnostic criteria published by Thomas et al.3 Both these patients had a typical clinical picture, however, and were cured by tonsillectomy, as was the one with a sibling with a history of PFAPA. A limitation of the study is inability to confirm cases other than by compatible symptom complex. Additionally, parents and investigators, obviously, were not blinded to treatment group.

Even though epidemiologic data are lacking, PFAPA cannot be said to be a rare syndrome in children. Patients are otherwise healthy, and they have no tendency to suffer from recurrent infections in general. Their growth and psychomotor development are normal. On the other hand, the periodic fevers associated with PFAPA may persist for years when untreated.3 Recognition of the syndrome brings significant relief to the parents and eliminates unnecessary courses of antimicrobial therapy. Single-dose prednisone therapy (1 to 2 mg/kg) has been recommended as first-line medication,3,5 but repeated doses of prednisone have led to a decrease in the interval between episodes5,7 and may cause other well-known systemic side-effects in small children. The fear of these side effects results in a poor compliance.31 Tonsillectomy proved to be very effective for treating PFAPA syndrome and was readily accepted by most of the parents. In this series the parents of 1 child preferred the symptoms of PFAPA over tonsillectomy. The parents of 1 child had earlier experience of tonsillectomy and PFAPA syndrome, and they chose tonsillectomy for their child as soon as possible and were not willing to participate in this study because of the possibility of being randomized into the control group. We conclude that tonsillectomy can be offered as an effective treatment when discussing treatment for children with this peculiar syndrome.

REFERENCES

50 Years Ago in The Journal of Pediatrics

STERIOD THERAPY FOR RHEUMATIC FEVER
McCue, CM. J Pediatr 1957;50:255-61

Although the incidence of rheumatic fever had been declining in the United States for more than 30 years, in the 1950s it remained a feared illness. Aspirin was available to treat systemic and articular manifestations of the disease, but its efficacy in carditis was uncertain. Many affected children were left with disability, and some died of their illness.

The report by Dr. McCue describes her experience with glucocorticoids to treat 94 children with acute rheumatic fever at the Medical College of Virginia during the years 1950 to 1957. Not all the children had carditis, but of those who did, some had pericarditis or severe congestive heart failure. Rheumatic fever was diagnosed using contemporary Modified Jones Criteria and treated using a protocol that evolved during the course of the study. Most patients received between 200 to 300 mg of cortisone or 60 mg prednisone orally for 21 days, followed by a 60-day taper. Outcome was judged according to grade of heart murmur, radiographic size of the cardiac silhouette, and survival. This was an uncontrolled study. However, of 36 patients with carditis who began treatment during the first 28 days of illness, 74% were judged to be either free of heart disease or greatly improved, a significantly better outcome when compared with a group of patients treated 10 years earlier. Furthermore, dramatic responses were observed in individual cases, some of which attending physicians judged to be life-saving.

Dr. McCue’s report was one of several studies from the same era, which included larger controlled, multicenter trials. Taken together, these studies failed to establish the superiority of glucocorticoids over aspirin for treatment of acute rheumatic carditis. Since their publication, the incidence of rheumatic fever has continued to decline in most industrialized countries. In contrast, it remains endemic in much of Africa, Asia, and South America, where it far exceeds Kawasaki disease as the most common cause of acquired heart disease in childhood. Because of this, it is rather disturbing that, despite advances in cardiac imaging and development of newer immunosuppressive medications, no therapy has ever been convincingly shown to reduce the risk of heart valve lesions in acute rheumatic carditis.

Efforts are underway to develop a vaccine against group-A streptococcus, the microorganism that elicits the immunologic response that causes rheumatic fever. However, until an efficacious, non-rheumatogenic vaccine becomes available, the need for an effective and affordable treatment for rheumatic carditis will remain as urgent as it was in 1957.

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REFERENCE
Effect of Prebiotic Supplementation and Calcium Intake on Body Mass Index

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Objective To assess the effects of a prebiotic supplement and usual calcium intake on body composition changes during pubertal growth.

Study design We measured anthropometry and body fat with dual-energy X-ray absorptiometry in 97 young adolescents who were randomized to receive either a daily prebiotic supplement or maltodextrin (control) for 1 year.

Results Subjects who received the prebiotic supplement had a smaller increase in body mass index (BMI) compared with the control group (BMI difference 0.52 ± 0.16 kg/m², P = .016), BMI Z-score (difference 0.13 ± 0.06, P = .048) and total fat mass (difference 0.84 ± 0.36 kg, P = .022). The prebiotic group maintained their baseline BMI Z-score (0.03 ± 0.01, paired t test, P = .30), although BMI Z-score increased significantly in the control group (0.13 ± 0.03, P < .001). In considering subjects whose usual calcium intake was ≥700 mg/d, those who received the prebiotic supplement had a relative change in BMI that was 0.82 kg/m² less than control subjects (P < .01), and BMI Z-score that was 0.20 less than control subjects (P = .003). Differences tended to be maintained 1 year after supplementation was stopped.

Conclusion Prebiotic supplementation and avoidance of a low calcium intake can have significant effects in modulating BMI and other body composition changes during puberty. (J Pediatr 2007;151:293-8)

Although the optimal calcium intake is uncertain, few challenge the concept that very low calcium intakes during puberty have long-term detrimental health effects on bone.1,2 We have shown that the use of a prebiotic (a food substance that promotes the growth of potentially beneficial bacteria in the intestines), specifically an inulin-type fructan (ITF), was associated with increased calcium absorption and bone mineralization in nonobese pubertal children.3

It has been hypothesized that increased dietary calcium leads to decreased weight gain and lower body mass index (BMI) in adults via an effect on fat cells,4,5 although a recent systematic review did not confirm this relationship.6 The relatively few data available in children suggest a similar benefit in both young children and adolescents.7-11

Prebiotics may also play a role in weight maintenance.12-14 Although few data exist regarding the mechanism of this effect, it appears to involve both fiber and hormonal effects, which increase the sense of satiety and lead to long-term decreases in undesired weight gain.14,15 An interaction between prebiotic supplementation and calcium intake on body composition has not been previously considered.

As part of our blinded, randomized controlled trial of prebiotic supplementation and bone mineralization, we obtained longitudinal anthropometry, dietary, and body composition data in those supplemented and the control group.5 That trial was not specifically designed to evaluate body composition or BMI as related to either diet or prebiotic supplementation. Thus subjects were unlikely to have altered their dietary pattern on the basis of an expectation that enrollment in the study would lead to body fat changes.

In this report, we have used the data from that trial, including a post-supplementation follow-up, to examine the effects of prebiotic supplementation and usual diet on weight and body composition changes during puberty. We hypothesized that this analysis would demonstrate that both calcium intake and prebiotic supplementation would be related to study changes in total body fat, BMI and BMI Z-score and that these would be related to each other such that higher calcium intakes were associated with an enhanced prebiotic effect on BMI.
METHODS

By public advertising, we identified 50 girls and 50 boys for this study. Of these 97 subjects (49 boys and 48 girls) completed the 1-year study intervention study. All subjects were between 9.0 to 13.0 years of age and were selected to approximately match the ethnic distribution of the greater Houston area. All subjects received a screening physical examination including Tanner staging before inclusion in the study. To be enrolled, subjects had to be healthy, nonobese, Tanner stage 2 or 3, and girls had to be premenarchal. Written informed consent was obtained from a parent or legal guardian for each subject; written assent was obtained from all of the study subjects. The Institutional Review Board of Baylor College of Medicine and Affiliated Hospitals approved this protocol.

Within 8 weeks of the screening visit described above, subjects were admitted for 24 hours to the General Clinical Research Center of Texas Children’s Hospital in Houston, TX. During this stay, measurements of calcium absorption and dual-energy X-ray absorptiometry (DXA) measurement of bone mineralization, as well as body fat determination were carried out.

At the end of this baseline study, subjects were randomized, in a double-blinded fashion, and stratified by sex to 1 of 2 carbohydrate supplement groups; either 8 g/d of a prebiotic, ITF (Beneo Synergy1, Orafti, Tienen Belgium), or 8 g/d of a maltodextrin control. The ITF prebiotic was a co-spray dried 1:1 mixture of oligofructose (average degree of polymerization, DPav = 4) and long-chain inulin (DPav = 25). Subjects were instructed to mix the carbohydrate supplement with calcium-fortified orange juice and to drink it with breakfast daily for 12 months. The supplemented juice (180-240 mL/d) provided approximately 80 to 110 kcal/d and the prebiotic 12 kcal/d (1.5 kcal/g). The maltodextrin control provided approximately 32 kcal/d (4 kcal/g). The energy contribution of the juice, but not the supplements, was included in the energy intake calculations.

To provide some dietary variation, subjects were also allowed to use milk to mix the carbohydrate supplement. Dietary recalls and discussions with families demonstrated that all subjects primarily used orange juice, and this accounted for more than 95% of total study days. Twelve months after the initial baseline study, subjects returned for a follow-up visit in which anthropometry and DXA measurements were performed. Subjects then discontinued the supplement, and follow-up anthropometry and DXA measurements were performed 12 months later (2 years after enrollment).

At the screening visit, a dietary history was obtained to determine what subjects usually ate on a normal day. Food preferences were also obtained. Inpatient menus for the overnight study visit were based on this reported typical calcium intake. All foods and beverages during the inpatient and outpatient visits were pre-weighed and post-weighed to accurately determine intake. Subjects were instructed to keep weighed food records for 2 days after the first overnight visit and for 2 days after the 1-year visit. Subjects were called at home every 2 months during the 1-year period to obtain a 24-hour dietary recall of the previous day’s intake and to ensure that the subject maintained a relatively consistent calcium intake. Energy intake was not regulated during any time of the study. Another 24-hour dietary recall was obtained at the 2-year follow-up visit. Dietary intake data were collected with Nutrition Data System for Research software versions 4.03 and 4.05, developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN.

Because of the possibility that the study intervention lead to a change in dietary intake, we utilized the intake values at the one-year visit (both dietary recall and in-patient and outpatient weighed diet averages) as the primary study dietary variable for energy and calcium intake. Data from the 1-day weighed inpatient food record at the 1-year visit along with the 2-day weighed home food records at this visit were pooled. This average value was used to represent the dietary intake at the end of 1 year of supplementation.

Whole body fat was determined by use of a Hologic QDR-4500A DXA absorptiometer (Hologic, Inc, Waltham, MA) scanning in the fan-beam mode. Total body fat was calculated as the product of body weight and body fat percentage (DXA). BMI Z-scores were calculated from the online database of our institution.

Statistical comparisons between prebiotic and control groups were made by use of the generalized linear model (analysis of variance) function of SPSS 13.0 for Windows (SPSS, Inc., Chicago, IL). For each analysis the final value was used as the dependent variable, and the initial value used as a covariate in analyses.

The principle model used included the initial height Z-score, the Tanner breast stage after 1 year, and the calcium and energy intake after 1 year. The initial height Z-score adjusted for size difference at the start of the study but was not a significant factor in any outcomes. The Tanner stage at 1 year was significantly related to changes in BMI and BMI Z-score (P < .05) in most of the analyses. A significant interaction was found between energy intake and prebiotic use, but not between energy use and calcium intake or calcium intake and prebiotic use for BMI and BMI Z-score outcomes. Therefore only the energy intake and prebiotic use interaction were included in the final model. The effect of calcium intake on changes in body composition was assessed by including this as a continuous independent variable or a dichotomous independent variable (with cutoffs of either 700 mg/d, 800 mg/d, or 900 mg/d).

We also evaluated whether a significant change in body composition had occurred during the year of the study in either of these groups. As BMI normally increases during puberty, we evaluated the age and sex normalized value, the BMI Z-score, to determine whether a potentially undesirable increase in BMI had occurred in either group. BMI z-score at the start and end of the study were compared in each of the 2 groups individually with a paired t test.

Two subjects (both in the control group) had a baseline BMI Z-score <1.65. Analyses were carried out with and
Table I. Baseline anthropometry before supplementation with prebiotic or control

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prebiotic (n = 48)</th>
<th>Non-prebiotic (control) (n = 49)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>11.8 ± 0.2</td>
<td>11.4 ± 0.2</td>
<td>.02</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>42.6 ± 1.3</td>
<td>41.3 ± 1.3</td>
<td>.46</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>149.1 ± 1.3</td>
<td>148.3 ± 1.3</td>
<td>.67</td>
</tr>
<tr>
<td>Weight Z-score</td>
<td>0.2 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>.56</td>
</tr>
<tr>
<td>Height Z-score</td>
<td>0.0 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>.14</td>
</tr>
<tr>
<td>Tanner stage (2/3)</td>
<td>34/11</td>
<td>37/12</td>
<td>.61</td>
</tr>
<tr>
<td>M/F</td>
<td>25/23</td>
<td>24/25</td>
<td>.76</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.99 ± 0.37</td>
<td>18.62 ± 0.37</td>
<td>.49</td>
</tr>
<tr>
<td>BMI Z-score</td>
<td>0.26 ± 0.18</td>
<td>0.20 ± 0.18</td>
<td>.73</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>24.7 ± 0.9</td>
<td>24.5 ± 0.9</td>
<td>.89</td>
</tr>
<tr>
<td>Total fat mass (kg)</td>
<td>10.7 ± 0.6</td>
<td>10.4 ± 0.6</td>
<td>.69</td>
</tr>
<tr>
<td>Calcium intake (mg/d)</td>
<td>904 ± 45</td>
<td>882 ± 45</td>
<td>.73</td>
</tr>
<tr>
<td>Energy intake (kcal/d)</td>
<td>2287 ± 67</td>
<td>2195 ± 66</td>
<td>.33</td>
</tr>
</tbody>
</table>

*One missing case (control) for body fat and total fat mass. Data are mean ± SEM. Tanner stage refers to breast/penile as stages 2 or 3.

without these subjects included in the analysis because of the possibility of the higher BMI Z-score subjects affecting the results. Omission of these subjects did not substantially change the results, and the results are presented with all subjects included.

All data are presented as mean ± SEM. Values of P < .05 were considered significant.

RESULTS

A total of 97 subjects, 48 who received the prebiotic supplementation and 49 who received the control completed the 1-year study. Of these, follow-up data were available at 2 years for 89 subjects, 44 of whom had received the prebiotic supplementation. Sex and ethnicity were considered in the analysis and were not found to be significantly related to any of the outcomes of the study and thus dropped from the analysis.

Anthropometric characteristics of the study subjects are shown in Table I. By study design, there were no subjects enrolled with a BMI Z-score >2.0 (maximum was 1.86; 2 subjects had a BMI Z-score ≥1.65 representing the 95th percentile). One subject with a BMI Z-score of −2.13 was the only subject with a BMI Z-score <−2.0.

Results for the effect of prebiotic supplementation on the basis of this model are shown in Table II. The increment in BMI over the study year was 0.73 kg/m² for the prebiotic group and 1.24 kg/m² for the control group (Difference 0.52 ± 0.16 kg/m², P = .016). Omitting calcium intake from the analysis negligibly changed the relative prebiotic effect on BMI by 0.01 kg/m². The same negligible effect of including calcium intake in the model on the other body composition outcomes was found.

In the prebiotic group no significant increase in BMI Z-score occurred during the study (0.03 ± 0.01; P = .30); in contrast BMI Z-score increased significantly in the control group (0.13 ± 0.04; P = .001).

We did not find any significant relationship between the baseline BMI Z-score (P = .66) or whether the subject tended to be overweight at the start of the study (BMI Z-score >1.0, P = .84) on the effect of the prebiotic on changes in BMI Z-score. Omitting the 2 subjects (both control group) with a baseline BMI Z-score ≥1.65 or the 1 subject (control group) with a BMI Z-score <−2.0 similarly had no substantial effect on the findings or their statistical significance.

To examine the effect of the prebiotic on body composition at different energy intakes, we modeled the data identically as before but omitted energy intake and the energy intake-prebiotic interaction as covariates. For BMI, the between-group differences became 0.49 ± 0.022 kg/m², P = .026 and for BMI Z-score, 0.123 ± 0.06, P = .062, values virtually identical to the analysis that had included energy intake and energy intake-prebiotic interaction (Table II). Thus, although there was a statistically significant interaction of energy intake with prebiotic use, the effect of energy intake and the interaction with prebiotic supplementation on the overall differences were small.

We found a P = .08 for the effect of calcium intake on BMI and BMI Z-score when calcium intake was considered as a continuous linear covariate. However, when calcium intake was considered as a nonlinear dichotomous variable and subjects were categorized as having higher or lower relative calcium intakes using cutoff points of 700 mg/d, 800 mg/d or 900 mg/d, the results depended on the cutoff point selected. A highly significant (P < .01) effect of calcium intake on BMI and BMI Z-score was seen (Table III) in a model with 700 mg/d intake or 800 mg/d intake as cutoff points. In both cases, the change in BMI, BMI Z-score, fat mass, and weight over the study year were significantly less for subjects above the calcium intake cutoff point than for those below it. Use of a calcium intake cutoff point of 900 mg/d showed no significant effect of calcium intake on BMI or BMI Z-score. Omitting the 2 subjects with a BMI Z-score ≥1.65 or the subject with a BMI <−2.0 had a very small effect on the results.

Use of the prebiotic had no significant effect on body composition outcomes for calcium intakes <700 mg/d (Figure). This value was chosen based on the findings in Table III that there was a nonlinear effect of calcium intake on body composition with an effect seen at intakes as low as 700 mg/d as a cutoff point. The rationale for the use of cutoff points was the likelihood that the nonlinear effects would not allow for identification of the calcium effect. Furthermore, cutoff values are often used in establishing dietary requirement and nutritional guidelines. In subjects with calcium intakes ≥700 mg/d, the prebiotic supplementation was associated with a BMI difference of 0.82 kg/m², BMI Z-score difference of 0.2, fat mass difference of 1.3 kg, and a body weight of 2.0 kg compared with those not receiving the prebiotic (values lower for prebiotic group, all P < .01, except BMI, P < .001).
the prebiotic supplement. Maintenance or slightly increased during the year after stopping intake in BMI increased, the magnitude of each effect was calcium intake values in those who received prebiotics and those who had a


of about 0.6 to 0.8 kg/m². We found that the prebiotic interventions were avoided.

linear fashion by the dietary intake of calcium such that the increase during pubertal growth in primarily nonobese young adolescents. This effect was significantly modified in a non-linear fashion by the dietary intake of calcium such that the maximum benefit to the prebiotic occurred when low calcium intakes were considered as a group. Because the calcium intake assessments used were at a single time point, although robust and reflective of dietary recall data, weighed diets, and their inpatient dietary records, the specific value at which a calcium effect could be seen and the magnitude of the effect should be interpreted cautiously. Nonetheless our data dem-

Follow-up data were available for 89 of the 97 (43 prebiotic) subjects at 2 years. The prebiotic intervention had been stopped after 1 year and DXA and anthropometry were performed 12 months later. We found a BMI difference of 0.68 ± 0.36 kg/m², P = .061 for the prebiotic effect, and 0.91 ± 0.41, P = .03 for the calcium effect on BMI (lower values in those who received prebiotics and those who had a calcium intake ≥700 mg/d). Therefore, although the variability in BMI increased, the magnitude of each effect was maintained or slightly increased during the year after stopping the prebiotic supplement.

DISCUSSION

We found that supplementation with a prebiotic, in addition to its benefit to bone mineralization, had a significant benefit in the maintenance of an appropriate BMI increase during pubertal growth in primarily nonobese young adolescents. This effect was significantly modified in a non-linear fashion by the dietary intake of calcium such that the maximum benefit to the prebiotic occurred when low calcium intakes were avoided.

BMI normally increases during puberty at a yearly rate of about 0.6 to 0.8 kg/m².18 We found that the prebiotic group had an increase in BMI of about 0.7 kg/m² during the supplementation year, consistent with expected increases during puberty and that the control group had an increase of 1.2 kg/m². We further considered the effect on the age- and sex-normalized BMI, the BMI Z-score. The changes in BMI Z-score demonstrated no significant change in the BMI Z-score in the prebiotic group compared with a significant increase in the Z-score of the control group during the study year. Thus the overall greater increase in BMI during the year in the control group was likely not ideal. It is not clear why the control group had an increase in BMI Z-score, although this may be related to overall trends toward increased BMI currently. It is possible that it was related to the placebo. Regardless, further data are needed to determine whether an actual decrease in BMI could be achieved with prebiotic supplementation or only a limitation in an undesirable increase in BMI.

The calcium effects were more difficult to quantify because this was not a calcium intervention trial. There was a significant interaction of calcium intake with prebiotic supplementation, but only when subjects with low intakes of calcium were considered as a group. Because the calcium intake assessments used were at a single time point, although robust and reflective of dietary recall data, weighed diets, and their inpatient dietary records, the specific value at which a calcium effect could be seen and the magnitude of the effect should be interpreted cautiously. Nonetheless our data dem-

Table II. Effect of supplementation on body composition after 1 year*

<table>
<thead>
<tr>
<th></th>
<th>Prebiotic (n = 48)</th>
<th>Control (n = 49)</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI Z-score</td>
<td>0.25 ± 0.045</td>
<td>0.38 ± 0.044</td>
<td>0.13 ± 0.06</td>
<td>.048</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.52 ± 0.15</td>
<td>20.03 ± 0.15</td>
<td>0.52 ± 0.21</td>
<td>.016</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>47.7 ± 0.4</td>
<td>49.0 ± 0.4</td>
<td>1.3 ± 0.6</td>
<td>.048</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.7 ± 0.3</td>
<td>155.7 ± 0.3</td>
<td>0.0 ± 0.5</td>
<td>.99</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>23.3 ± 0.4</td>
<td>24.2 ± 0.4</td>
<td>-0.8 ± 0.6</td>
<td>.14</td>
</tr>
<tr>
<td>Total fat mass (kg)</td>
<td>11.24 ± 0.25</td>
<td>12.07 ± 0.25</td>
<td>0.84 ± 0.36</td>
<td>.022</td>
</tr>
</tbody>
</table>

*One missing case (control). Evaluation of each outcome was done with a model in which the covariates were the baseline height Z-score, the energy and calcium intake at 1 year, the Tanner stage at 1 year, and the interaction of the prebiotic and energy intake. Each model individually included the baseline value for the dependent variable. The interaction of energy intake and prebiotic supplementation was significant, P < .01 for each body composition variable.

Table III. Study year differences in change in BMI Z-score, BMI, total fat mass, and weight in subjects consuming a calcium intake below the cutoff point compared with those consuming calcium intakes above the cutoff point

<table>
<thead>
<tr>
<th>Calcium intake cut-off*†‡</th>
<th>700 mg/d§</th>
<th></th>
<th>800 mg/d§</th>
<th></th>
<th>900 mg/d</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference</td>
<td>P value</td>
<td>Difference</td>
<td>P value</td>
<td>Difference</td>
<td>P value</td>
</tr>
<tr>
<td>BMI Z-score</td>
<td>0.20 ± 0.07</td>
<td>.008</td>
<td>0.17 ± 0.07</td>
<td>.014</td>
<td>0.08 ± 0.07</td>
<td>.28</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.67 ± 0.25</td>
<td>.006</td>
<td>0.54 ± 0.22</td>
<td>.015</td>
<td>0.25 ± 0.23</td>
<td>.28</td>
</tr>
<tr>
<td>Total fat mass (kg)</td>
<td>1.02 ± 0.42</td>
<td>.016</td>
<td>0.58 ± 0.36</td>
<td>.13</td>
<td>0.13 ± 0.40</td>
<td>.74</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>1.3 ± 0.7</td>
<td>.076</td>
<td>1.2 ± 0.6</td>
<td>.06</td>
<td>0.6 ± 0.7</td>
<td>.37</td>
</tr>
</tbody>
</table>

*Values shown are the difference between changes during the study year in the body composition parameters for subjects with calcium intakes lower than the indicated cut-off compared to those with higher intakes. No significant effects were seen using any cutoff >900 mg/d. All values are positive, indicating a larger change (increase) in those with intakes below the cut-off compared to those above the cut-off.
†Total sample was 97 subjects (one missing for total fat mass). Covariate model included prebiotic supplementation, height Z-score, Tanner stage, energy intake and interaction of energy intake and prebiotic supplementation.
‡n = 23 below cut-off, n = 74 above.
§n = 40 below cut-off, n = 57 above.
†n = 54 below cut-off, n = 43 above.
onstrate that calcium intake values below about 800 mg/d were associated with a greater increase in BMI than greater intakes and that the benefit to prebiotic supplementation was greater when calcium intake is not low. The mechanism of a potential calcium effect on weight, however, is likely related to a direct effect on fat cell metabolism.4,5

These findings of a beneficial effect of avoidance of a low calcium intake on maintenance of BMI are consistent with our hypothesis and with a recent study in which adolescents in Brazil in the lowest quartile of calcium intake had a significantly greater BMI than those in the highest quartile.11 Lappe et al8 found no effect of calcium intake on weight gain in girls during puberty but the non-supplemented group had an average intake above the level found to have an effect in our data. Dixon et al7 found an inverse relationship between BMI and calcium intake, but only in 7- to 10-year-old children without hypercholesterolemia. Our data are consistent with these results, but we did not evaluate lipid status in our study subjects and thus cannot identify a specific relationship between lipid status and prebiotic supplementation.

Figure. Effects of prebiotic supplementation versus control on body composition outcomes in 97 subjects (96 for fat mass). Covariate model included prebiotic supplementation, height Z-score, Tanner stage, energy intake and interaction of energy intake and prebiotic supplementation. Differences not significant for all results in <700 mg/d calcium intake comparisons. *P < .01. **P < .001.

A single study of preschool children reported that a 300-mg increase in calcium intake was associated with 1 kg less body fat.5,7 Our data found a 1.0-kg difference in body fat mass in those with calcium intakes >700 mg/d compared with those with lower intakes and a 0.8-kg difference in those who received the prebiotic. Combination of a calcium intake >700 mg/d and prebiotics led to a 1.3 kg difference in fat mass. These data are consistent with the earlier study in preschool children. In contrast, Phillips13 did not find a relationship between body fat percentage or BMI and dairy food intake during pubertal development in nonobese girls.

A limitation in this study was the lack of control of energy intake during the study. We did not regulate or investigate the consequences to the whole diet of the supplemental orange juice provided with the study. The increment in calories from the maltodextrin (control) was <2% of the mean caloric intake and much less than the intake from the orange juice. It is unlikely to have contributed substantially to the increase in BMI Z-score that occurred in that group.

We did not specifically recruit overweight or obese subjects because of the potentially confounding effect of these on bone mineral metabolism changes; however, we found no effect of baseline BMI Z-score on the prebiotic effect. Energy expenditure was not assessed, nor was physical activity estimated. We used multiple methods to assess dietary intakes. However, all such methods are limited in their ability to assess long-term intakes and therefore may not represent exact measures of usual intake. We did not have dietary data available at 2 years, so we cannot determine whether the trend toward a persistent benefit was associated with dietary changes.

The mechanism of the prebiotic effect on BMI and body fat has only minimally been evaluated to date. In a rat model, ITF regulates appetite via increases in gastrointestinal peptides that modulate food intake such as glucagon-like peptide-1.12 A recent pilot study involving 10 young adults suggested that prebiotics reduce hunger and food consumption.13 The lack of a significant increase in BMI Z-score in the prebiotic group despite the supplementation with both the prebiotic and with juice implies an overall regulatory effect on energy intake associated with the diet or with the prebiotic. In our study, although energy intake was assessed at the beginning and end of the study, the tools used and the assessment methods would not be able to identify small changes in intake over a long period of time.

Our findings demonstrate the potential for dietary interventions such as calcium and prebiotic supplementation to assist in maintaining appropriate rates of increase in BMI during puberty in nonobese young adolescents, as well as their known benefits for bone and gastrointestinal health. Controlled trials evaluating other population groups, including those who are more overweight and combining these interventions with exercise and behavior modification should be conducted to evaluate the overall potential optimal strategy for decreasing the risk of excessive increase in BMI during early adolescence.
The authors would like to acknowledge the assistance of Leslie Cruz, Penni Hicks, PhD, and Adrianne Morse in data analysis and E. O’Brian Smith, PhD for statistical advice. Orange juice used in the study was provided by The Coca-Cola Company, Houston TX and the inulin-type fructan by Orafti, Tienen, Belgium.

REFERENCES
Long-Term Follow-Up in 12 Children with Pulmonary Arteriovenous Malformations: Confirmation of Hereditary Hemorrhagic Telangiectasia in all Cases

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Objective To assess whether pulmonary arteriovenous malformation (PAVM) is associated with hereditary hemorrhagic telangiectasia (HHT).

Study design This study was a review of 12 children (sex ratio = 1) including family history, mutation analysis, and long-term follow-up.

Results Five children were under age 3 years when PAVM was diagnosed. Presentations included pulmonary symptoms (n = 8), cerebral abscess (n = 2), and transient ischemic attack (TIA) (n = 1); 1 patient was asymptomatic. Nine of the 12 children (75%) had a family history of PAVM. The diagnosis of HHT was confirmed in all cases. A mutation in ENG was found in 9 of the 10 children available for testing. No mutation in ACVRL1 was found. During long-term follow-up (mean, 16 years), the following complications occurred: TIA (n = 2), hemoptysis (n = 2), and cerebral abscess (n = 2). Nine children experienced recurrence of PAVM. The children with no recurrence were those without a family history of PAVM.

Conclusions The diagnosis of HHT should be considered in a child with an apparently isolated PAVM. Because serious complications may occur at any age, we recommend screening for PAVM and long-term follow-up in children from families with HHT, especially those with an ENG mutation. (J Pediatr 2007;151:299-306)

Pulmonary arteriovenous malformations (PAVMs) are abnormal vascular connections between pulmonary arteries and veins that provide a direct, capillary-free communication between the pulmonary arterial and pulmonary venous circulations, leading to hypoxemia, dyspnea, exercise intolerance, and cyanosis. These pulmonary symptoms seem to correlate with the degree of right-to-left shunting present.1 Furthermore, large, subpleural, thin-walled PAVMs may rupture into the pleura, leading to spontaneous hemotorax, or central PAVMs may rupture into the bronchi, leading to massive hemoptysis. These hemorrhagic complications occur in ~15% of untreated patients.1-6 Paradoxical embolism to the systemic circulation also can occur due to the direct connection between the pulmonary artery and vein, leading to such neurologic complications as cerebral abscess (septic emboli), transient ischemic attack (TIA), or stroke (thromboemboli) in about 40% of adults with untreated PAVMs.1-6

Studies based mainly on adults have shown that up to 90% of patients with PAVMs actually have hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber disease.4,7-11 Nevertheless, HHT may have remain undiagnosed in a given family at the time of the initial diagnosis of PAVM in a family member.4 HHT is an autosomal dominant hereditary disorder caused by mutation in 1 of 2 genes: ENG, encoding endoglin, or ACVRL1, encoding activin receptor-like kinase 1. Both of these genes are involved in the transforming growth factor-β signaling pathway. Clinical features of
HHT include recurrent spontaneous epistaxis and clinical symptoms related to anemia, mucocutaneous telangiectasia, and visceral arteriovenous malformations in the pulmonary, cerebral, or hepatic vascular bed. A family history of HHT is almost always found but may be neglected. Clinical diagnosis of HHT is considered definite if 2 of the criteria are present, possible when 3 criteria are present, and uncertain when only 1 criterion is present.

The prevalence of PAVMs in HHT patients ranges from 15% to 36% in predominantly adult series. PAVM is most often diagnosed in the second or third decade of life.

Although 92 children with PAVM have been reported since 1965, data on the outcome of PAVMs have been less well described in children compared with adults. Furthermore, family history (including HHT but also PAVM), molecular data, and long-term follow-up are often lacking. In the present study, we report detailed data on 12 children presenting with apparently isolated PAVMs in whom a diagnosis of HHT could be definitely established.

METHODS

Between 1975 and 2000, 12 children were referred to the Department of Medical Genetics of Hôtel-Dieu Hospital in Lyon after diagnosis and initial treatment of PAVMs, to determine whether these apparently isolated lesions could be the lead manifestation of an undetected HHT family disease. Only 1 child (patient 11) belonged to a previously known HHT family; the other children’s families had no previous diagnosis or knowledge of Rendu-Osler-Weber disease.

Pulmonary Investigations

Chest radiograph, room air arterial blood gas or pulse oximetry, hemoglobin level, and pulmonary angiography were performed in all patients. Nine children underwent thoracic computed tomography (CT) or contrast-enhanced pulmonary magnetic resonance angiography (CEMRA). Treatment of PAVMs in Lyon was limited to surgical resection or ligation until 1992, after which most patients have been treated with transcatheter embolotherapy (TCE).

Diagnosis of HHT

A comprehensive family history for epistaxis and other clinical symptoms related to HHT was elicited. The patients and parents underwent physical examination, including an extensive search for telangiectasia (especially at characteristic sites, such as the lips, oral cavity, fingers, and nasal mucosa). We applied the HHT consensus clinical diagnostic criteria to evaluate the certainty of the HHT diagnosis in each patient. When a blood sample was available, mutation analysis (in ENG and ACVRL1) was performed in Lyon.

Written informed consent was obtained from the patients, or from their parents if they were under age 18, in accordance with the French bioethics law.

Follow-Up

Follow-up data were collected for all patients, including assessment for HHT symptoms, assessment of pulmonary symptoms and complications of PAVM, as well as pulse oximetry or arterial blood gas, hemoglobin level, and, more recently, contrast echocardiography. If either test was positive, then thoracic CT was performed. The follow-up period started at the time of the PAVM diagnosis.

RESULTS

Clinical Presentation and Family History

The study group comprised 6 females and 6 males, ranging in age from 1 day to 18 years (Table I). Five children were under age 3 years at the time of PAVM diagnosis. Patients 10 and 12, the aunt and the mother of patient 1, also presented with PAVM before age 18 years. The most frequent presenting complaints were pulmonary symptoms (n = 8; 67%), including dyspnea on exertion, respiratory distress at rest (sometimes occurring during an infectious episode), cyanosis, and hemoptysis. Three children presented with inaugural neurologic complications (25%), 2 with a cerebral abscess (patients 8 and 12) and 1 with a TIA (patient 11). In the latter case, TIA indirectly led to the diagnosis of PAVM, which was eventually considered because the child’s hemoglobin level was increased despite recurrent epistaxis. In the remaining case (patient 9), PAVM was discovered on routine chest radiograph performed for minor thoracic trauma. On clinical examination, 10 children were cyanotic (85%), 5 had clubbing (42%), and 9 had a pulmonary bruit (75%), but examination was unremarkable for the 2 remaining children. Although only 6 patients had telangiectasia or epistaxis at the time of diagnosis, the others developed these clinical features during the follow-up period (Table I).

Long-term follow-up and family history allowed us to confirm the clinical diagnosis of HHT in all children (Table I). Although 11 of the 12 children and their families had never heard of HHT at the time of their first admission to the hospital, the family history revealed relatives with epistaxis or telangiectasia in all families and relatives with PAVM in 8 families (67%) (Table I).

Pulmonary Investigations

Laboratory and imaging findings are shown in Table II. Arterial blood gas measurements with the patient on room air revealed hypoxemia; arterial oxygen tension (PaO₂) ranged from 31.5 to 88 mm Hg (mean, 56 mm Hg). Polycythemia, secondary to chronic hypoxemia, was present in 9 of the 12 children (75%). Chest radiographs were abnormal in all cases, with the most common image a round or oval mass of uniform density. In all patients, the diagnosis of PAVM was confirmed by conventional pulmonary angiography, which revealed large single lesions (15 to 50 mm diameter) in 8 patients (67%), multiple lesions in 3 patients (25%), and diffuse PAVM in only 1 patient (8%). A total of 26 discrete PAVMs were documented, excluding the diffuse PAVMs.
Table I. Clinical features of the 12 children

<table>
<thead>
<tr>
<th>Patient case no.</th>
<th>Sex</th>
<th>Age at PAVM diagnosis</th>
<th>Presenting symptom</th>
<th>Family members with HHT and PAVM</th>
<th>Clinical manifestations of PAVMs</th>
<th>Age of PAVM diagnosis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>1 day</td>
<td>Pulmonary symptoms</td>
<td>+</td>
<td>+</td>
<td>+ 10 years</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>11 months</td>
<td>Pulmonary symptoms</td>
<td>+</td>
<td>+</td>
<td>+ 11 years</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>13 months</td>
<td>Hemoptysis</td>
<td>+</td>
<td>+</td>
<td>+ 13 months</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>26 months</td>
<td>Pulmonary symptoms</td>
<td>+</td>
<td>+</td>
<td>+ 18 years</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>2.5 years</td>
<td>Pulmonary symptoms</td>
<td>+</td>
<td>+</td>
<td>+ 19 years</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>6.5 years</td>
<td>Pulmonary symptoms</td>
<td>+</td>
<td>+</td>
<td>+ 7.5 years</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>10 years</td>
<td>Pulmonary symptoms</td>
<td>+</td>
<td>+</td>
<td>+ 10 years</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>12 years</td>
<td>Cerebral abscess</td>
<td>+</td>
<td>+</td>
<td>+ 18 years</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>12.5 years</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+ 12.5 years</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>15 years</td>
<td>Pulmonary symptoms</td>
<td>+</td>
<td>+</td>
<td>+ 23 years</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>16.5 years</td>
<td>TIA</td>
<td>+</td>
<td>+</td>
<td>+ 30 years</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>18 years</td>
<td>Cerebral abscess</td>
<td>+</td>
<td>+</td>
<td>+ 18 years</td>
</tr>
</tbody>
</table>

Cyanosis, Dyspnea, Clubbing, Pulmonary bruit, Telangiectasia*, Epistaxis*.

<table>
<thead>
<tr>
<th>Number</th>
<th>Family relationship</th>
<th>Clinical manifestations</th>
<th>Age of occurrence.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Her mother (case 12)</td>
<td>Bacterial meningitis</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>Her maternal aunt (case 10)</td>
<td>Pulmonary symptoms</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>Her maternal great-grandfather</td>
<td>Pulmonary symptoms</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>His mother</td>
<td>Pulmonary symptoms</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>His maternal great-aunt</td>
<td>Cerebral abscess</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>The son of the great-aunt</td>
<td>Cerebral abscess</td>
<td>31</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>Her mother</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Her maternal grand-mother</td>
<td>Pulmonary symptoms</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>His father</td>
<td>Pulmonary symptoms</td>
<td>48</td>
</tr>
<tr>
<td>0</td>
<td>4</td>
<td>His grand-mother</td>
<td>50</td>
</tr>
<tr>
<td>0</td>
<td>5</td>
<td>His aunt</td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td>His mother</td>
<td>Pulmonary symptoms</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>Her sister C</td>
<td>Cerebral abscess</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>Her sister D</td>
<td>Pulmonary symptoms</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>Her father</td>
<td>Cerebral abscess</td>
<td>54</td>
</tr>
<tr>
<td>1</td>
<td>His mother</td>
<td>Pulmonary symptoms</td>
<td>33</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>His maternal grandfather</td>
<td>Pulmonary symptoms</td>
</tr>
<tr>
<td>7</td>
<td>His maternal aunt C</td>
<td>Pulmonary symptoms</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>His maternal aunt P</td>
<td>Pulmonary symptoms</td>
<td>31</td>
</tr>
<tr>
<td>7</td>
<td>His first cousin J</td>
<td>Pulmonary symptoms</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>His first cousin F</td>
<td>Hemoptysis</td>
<td>18</td>
</tr>
</tbody>
</table>

*, present.
*Age of occurrence.
Table II. Laboratory, imaging findings and molecular data on the 12 children

<table>
<thead>
<tr>
<th>Patient case no</th>
<th>Laboratory findings</th>
<th>Gene mutation</th>
<th>Imaging findings</th>
<th>PAVM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SaO₂ (%)</td>
<td>PaO₂, mmHg (kPa)</td>
<td>Hb (g/dL)</td>
<td>DNA level</td>
</tr>
<tr>
<td>1</td>
<td>31.5 (4.2 kPa)</td>
<td>178</td>
<td>c.461delG</td>
<td>p.Gly154fsX162</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>15</td>
<td>c.689+2T&gt;C</td>
<td>Exon skipping</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>11</td>
<td>Not available for mutation screening</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>17</td>
<td>c.IA&gt;G</td>
<td>p.M1?</td>
</tr>
<tr>
<td>5</td>
<td>50 (6.65)</td>
<td>17.8</td>
<td>c.277C&gt;T</td>
<td>p.Arg93X</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>40 (5.3)</td>
<td>17.5</td>
<td>Not available for mutation screening</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>32.2 (4.3)</td>
<td>19</td>
<td>No mutation found in ENG or ACVRL1</td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td>16</td>
<td>c.1346_1347delCT</td>
<td>p.Ser449fsX499</td>
</tr>
<tr>
<td>9</td>
<td>89</td>
<td>16.2</td>
<td>c.1134_1977del</td>
<td>Unknown</td>
</tr>
<tr>
<td>10</td>
<td>80</td>
<td>15.7</td>
<td>c.461delG</td>
<td>p.Gly154fsX162</td>
</tr>
<tr>
<td>11</td>
<td>83 (11.07)</td>
<td>17.6</td>
<td>c.1522C&gt;T</td>
<td>p.Gln508X</td>
</tr>
<tr>
<td>12</td>
<td>88</td>
<td>15</td>
<td>c.461delG</td>
<td>p.Gly154fsX162</td>
</tr>
</tbody>
</table>

LLL, left lower lobe; RUL, right upper lobe; LUL, left upper lobe; Hb, hemoglobin.
+ , abnormal; -, negative.
*Not performed.
Most of the PAVMs were located in the lower lobes (20/26; 77%). PAVMs were detectable on thoracic CT scan performed in 7 cases and on CEMRA in 2 cases (patients 2 and 9).

Molecular Testing

A mutation in the ENG gene was found in 9 of the 10 children available for screening. Detailed data are presented in Table II. No mutation in either ENG or ACVRL1 was found in the remaining child. Two patients (3 and 6) had been lost to follow-up when molecular screening was established in 2001.

Treatment and Follow-Up

Initial treatment and follow-up are described in Table III. Surgical resection was carried out in 10 patients (83%), and 2 patients underwent TCE. Surgical procedures included wedge resection and partial or complete lobectomy (Figure). Patients 8 and 9 were treated by TCE and required 4 and 3 TCE sessions, respectively.

The mean follow-up period was 16 years (range, 4 to 26 years), with a total of 190 patient-years. Only 2 patients were lost to follow-up (patients 3 and 6), after 14 and 4 years, respectively. During the follow-up period, 2 patients developed TIAs (3 and 4 years after the initial treatment); patient 8 had a right arm weakness for 24 hours, and patient 11 presented with abnormal gait for 24 hours. Patient 8 had reperfused PAVMs, and patient 11 had a new PAVM; both patients underwent TCE. In patient 9, brain abscess led to the diagnosis of recurrent PAVM 2 years after initial treatment. Two patients (11 and 12) suffered from minor hemoptysis. In all, 9 patients (75%) experienced recurrence of PAVM, consisting of new feeding vessels appearing after surgery or recanalization of embolized vessels and occurring 2

Long-Term Follow-Up in 12 Children with Pulmonary Arteriovenous Malformations: Confirmation of Hereditary Hemorrhagic Telangiectasia in all Cases

![Figure. Anatomic view. A, Voluminous PAVM (star) involving the right upper lobe of patient 3, with appearance of medusa head with large feeding arteries (arrows). B, Left lower lobectomy (star) of patient 7 with an obvious voluminous PAVM (arrow).](image)
to 17 years after the initial PAVM treatment. All of these patients were treated by 1 to 4 TCE sessions, except patient 10, who declined treatment. HHT complications unrelated to PAVM occurred in 4 patients, including multiple liver vascular malformations (patient 5) and cerebral arteriovenous fistulas (patient 6 at 8 years and patient 9 at 13 years).

**DISCUSSION**

Comprehensive family history, careful clinical examination of relatives, and follow-up allowed us to confirm the diagnosis of HHT in all families. Clinical diagnosis of HHT is more difficult in children because of the age-related development of clinical manifestations. All of our 12 patients were carefully examined for subtle manifestations, but most did not display additional features on initial examination. This is in keeping with the classical reports on HHT, showing that only 50% to 60% of HHT patients develop epistaxis before age 20 and about 50% develop telangiectasia before age 30.12,15 Penetrance is estimated as up to 98% after 50 years.

PAVM may occur very early in life and present with serious, sometimes life-threatening, complications. Our series includes a high proportion of early-onset forms; about half of the children were under age 3 years at the time of PAVM diagnosis. Patients were usually older in other recent series.26,27,30 Patient 1 presented with a large PAVM at birth. PAVM has occasionally been reported in newborns.19-21,31 This suggests that, at least in some patients, PAVM develops during intrauterine life. In the present series, the high proportion of symptomatic PAVM (all except 1) likely reflects the fact that HHT was not known, except in 1 family, and that pulmonary screening could not be proposed.

Several recent data from genotype–phenotype correlation studies have strongly established the significantly higher frequency of PAVM as well as complications (including cerebral abscess) in patients with an ENG mutation compared with those with an ACVRL1 mutation.32-36 In our series, the fact that all mutations were found in ENG is unlikely due to a selection bias, because we and others previously showed that ACVRL1 mutations are almost twice as common as ENG mutations.29,37,38 Taken together, and in accordance with the literature, our results suggest that the predominance of PAVM in families with ENG mutations may be even higher for early-onset forms.27 Although there is no specific ENG mutation associated with PAVM, we recently suggested that truncated mutations may be associated with a greater risk of epistaxis and telangiectases in HHT patients.32 Although such a trend was also observed for PAVM, it did not achieve significance. The fact that we did not find any ENG missense mutation in the present series may provide evidence in favor of this hypothesis, but these mutations are less frequent than truncating mutations for this gene.28,29

Eight of the 12 children (67%) had a family history of PAVM. According to some authors, the prevalence of PAVM is about 15% to 20% in unselected patients with HHT, but may reach approximately 35% in HHT families in which at least 1 member has PAVM.3,6,39 This is in accordance with recent data from our group showing that PAVM is often family-clustered, especially in families with an ENG mutation.32 Interestingly, in the present series, the children with no recurrence of PAVM also had no family history of pulmonary involvement.

The treatment of choice (safe, well-tolerated, and effective) for PAVM in adults is TCE using coils or other intravascular devices.1,40-42 TCE is performed for all PAVMs with feeding arteries of at least 3 mm in diameter and has dramatically limited the need for surgery. The first large series of children treated with TCE has recently been published,26 and the improvement of medical survey in children from HHT family members should lead to the increased use of this technique. Antibiotic prophylaxis also should be recommended for all bacteremic procedures, such as dental work, once PAVM has been diagnosed,6,26 to prevent cerebral abscess.

The follow-up period in our series (mean, 16 years) is the longest reported so far, and allowed us to detect 5 recurrences of PAVM occurring more than 10 years after initial treatment. The high recurrence rate (75%) might be related in part to the improved imaging techniques for detection of PAVMs during the follow-up period (some of the PAVMs may have been initially missed), but it raises concerns about the risk of developing novel PAVMs during childhood and adolescence and emphasizes the need for long-term follow-up.

Because PAVM may present with life-threatening complications early in life, and because effective treatment has been described, we advocate screening for PAVM in children of HHT families. Pulmonary screening protocols have been proposed for adults.1,6,15,43,44 We have recently reported that 100% sensitivity and negative predictive value could be obtained in adults when combining anteroposterior chest radiographs with contrast echocardiography.39 A screening algorithm based on the combined use of both tests, followed by chest CT if either test is positive, was suggested. An alternative is screening directly by chest CT. But the algorithm may obviate the need for chest CT in patients without PAVM (the majority of HHT patients). The need to avoid unnecessary chest CT in children is obvious because of radiation-induced cancer.45 Contrast echocardiography is often suggested as a screening tool in children,26 and a preliminary study on a small group of children was reported recently.46 Further studies are needed to determine the most appropriate screening strategy for children. The fact that chest radiography allowed detection of large PAVMs in our patients as well as in those reported earlier suggests that it should be performed at least once during childhood, even in asymptomatic children of HHT families, to detect large PAVMs.1,6,8,9,17 Physical examination and eventually pulse oximetry may be useful to disclose cyanosis, which is often noted in published cases of PAVM in children. Contrast echocardiography seems to be the most appropriate screening test in children. As in adults, definite diagnosis of PAVM relies on chest CT or pulmonary angiography when TCE is indicated.

Despite the fact that most mutations in ENG and ACVRL1 are private (ie, different from one family to another), the recent development of effective molecular tech-
niques will allow physicians to use genetic data for clinical screening of patients from HHT families. Once a pathogenic mutation has been identified in the index case, genetic testing of the other family members is straightforward. Keeping in mind that genetic testing in children should be combined with appropriate counseling regarding medical, ethical, and psychological aspects, this approach may reduce the cost of conventional clinical screening and long-term follow-up, which will be focused on mutation carrier family members.

In conclusion, PAVM may occur very early in life, and serious, sometimes life-threatening, complications may result if they are left untreated. The diagnosis of HHT should be considered in a child with apparently isolated PAVM. Children of HHT families should benefit from PAVM screening and long-term follow-up, especially in families with an ENG mutation or a history of PAVM.

We thank Jean-Pierre Pracros for his helpful comments and Daniel Florot, Benoît Guibert, and Gérard Champsaur for referring some of the families.

REFERENCES


50 Years Ago in *The Journal of Pediatrics*

**Niemann-Pick Disease in a Boy of 16 Months**


In an age in which protein purification and demonstration of human enzymatic activities were still among the most challenging scientific goals, Pansky and Lee described the effect on the electrophoretic mobility of serum proteins of “therapy” in a patient diagnosed with Niemann-Pick disease. The therapies offered were a series of biologicals including vitamins A and B₁₂, adrenocorticotropic hormone, and various antibiotics. The serum proteins were identified solely by their electrophoretic mobilities, and the clinical diagnosis was based on undefined “chemical, histological, physical and marrow findings.” The physician reader 50 years later may derive comfort from the progress that medical science has made not only in accurately defining the diagnostic enzymatic deficiencies of many inherited disorders, among them several forms of Niemann-Pick disease (A, B, and C), but also in having available an enzyme replacement therapy, albeit in human clinical trials, for sphingomyelinase deficiency, the classic form of Niemann-Pick disease. A generation of clinical biochemists carefully elaborated the lysosomal enzyme deficiencies that cause more than 40 lysosomal storage disorders (LSD). A succeeding generation of molecular biologists sequenced the genes that encode these lysosomal enzymes and produced animal models that led to the current understanding of lysosomal storage disease pathophysiology. Although bone marrow transplantation demonstrated long-term efficacy in some patients with LSD, morbidity and mortality in these patients encouraged the search for alternative treatments. From early experiments treating patients with nephropathic cystinosis using cysteamine, a thiol analogue used previously in high-altitude pilots to ameliorate radiation exposure, numerous therapeutic approaches have followed to offer success in decreasing lysosomal storage and conferring clinical benefits. Following the FDA approval in 1992 of glucocerebrosidase purified from human placentas (ceredase), recombinant technology has allowed high-throughput synthesis of an enzyme analogue (cerezyme) in a bioreactor using Chinese hamster ovary cells. These therapies offered the first effective treatments for an intralysosomal enzyme deficiency causing an LSD. Enzyme replacement therapies for Fabry disease, mucopolysaccharidoses types I (Hurler), II (Hunter), VI (Maroteaux-Lamy syndrome), and Pompe’s disease have been FDA approved, and several other disorders, among them Niemann-Pick A/B, are currently in clinical trials. Alternative therapeutic approaches (miglustat) inhibit the biosynthesis of the glycosphingolipid, which accumulates in Gaucher disease, and offer clinical benefits for patients in whom enzyme replacement therapy is not an option. The field of lysosomal storage diseases has been reinvigorated by treatment options born of decades of scientific and clinical investigation. The pediatrician’s recognition of these treatable disorders at an early age is critical to long-term outcome.

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10.1016/j.jpeds.2007.04.025
Duodenogastro-Esophageal Reflux in Children with Refractory Gastro-Esophageal Reflux Disease

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Objective To determine the role of duodenogastro-esophageal reflux (DGER) in the pathogenesis of refractory gastro-esophageal reflux disease (GERD) in children.

Study design Twenty-two patients (12 boys, mean age, 13.2 years) with GERD symptoms that persisted on omeprazole (1 mg/kg) underwent upper gastrointestinal endoscopy and barium x-ray, 24-hour pH and DGER (Bilitec) monitoring, and a 13C octanoic acid gastric emptying breath test.

Results Patients presented mainly with epigastric pain, regurgitation, and nausea. Endoscopy revealed persistent esophagitis in 15 patients (68%). Pathologic acid and DGER exposure were present in 12 (55%) and 15 (68%) children, respectively, with combined pathologic reflux in 10 (45%). Acid exposure did not differ according to the presence of esophagitis, but patients with grade II esophagitis had significantly higher DGER exposure than those without esophagitis (9.1 ± 5.3% vs 26.7 ± 10.9% of the time, P < .05). Gastric emptying rate was not associated to acid or DGER exposure or persisting esophagitis. Symptoms improved after adding a prokinetic drug to the proton pump inhibitor therapy or referral for surgery (n = 5).

Conclusions DGER may play a role in the pathophysiology of proton pump inhibitor–refractory GERD and esophagitis in children. (J Pediatr 2007;151:307-11)

Gastro-esophageal reflux disease (GERD) is defined by the presence of symptoms and lesions that can be attributed to reflux of gastric contents to the esophagus. The pressure of the lower esophageal sphincter, the motility of the esophageal body and the stomach, the composition of the reflux material, and the sensitivity or resistance of the esophageal mucosa to the reflux material are important factors involved in the pathogenesis of GERD-related symptoms and lesions.

The refluxate is not only composed of gastric acid and pepsin but may also contain food and regurgitated duodenal contents. In adults, reflux of duodenal contents into the stomach is a physiological event, both postprandially and at night. Hence, regurgitation of duodenal contents through the pylorus into the stomach, with following reflux into the esophagus, which is called duodenogastroesophageal reflux (DGER), is not unusual. The role of DGER has initially been evaluated by means of endoscopy with biopsies, scintigraphy, aspiration studies, and esophageal pH monitoring. The terms bile reflux and alkaline reflux have been used to describe DGER, but it is now well established that alkaline reflux that is found on pH monitoring is not equivalent to DGER but rather seems to reflect swallowed saliva and esophageal mucosal bicarbonate secretion.

The Bilitec 2000 (Synectics Medical, Stockholm Sweden) device is a fiberoptic spectrophotometric probe developed to quantify DGER in an ambulatory setting. In vitro validation studies confirmed a good correlation between the total bilirubin concentration of aspirated samples and the fiberoptic reading of bilirubin concentration. Moreover, a good correlation was found between total bilirubin content and the concentrations of pancreatic enzymes in aspirated refluxate. Based on these observations, bilirubin seems to be an accurate tracer for DGER monitoring in patients who have normal serum bilirubin levels.

In adults, esophageal exposure to acid and to DGER has been extensively studied by using combined pH and Bilitec monitoring in normal subjects and patients with GERD. Both acid reflux and DGER show a graded increase in severity across the

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<td>GERD</td>
<td>Gastro-esophageal reflux disease</td>
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<td>PPI</td>
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GERD spectrum, and they occur simultaneously in the majority of the reflux episodes. DGER has been identified as a factor that contributes to GERD that is refractory to acid suppressive therapy.16,19-21

METHODS

Study Population
We evaluated consecutive children with refractory GERD symptoms despite omeprazole treatment (1 mg/kg). All children and their parents were asked to stop any medication known to affect gastrointestinal motility or secretion for at least 2 weeks before the study. Inclusion criteria were the presence of GERD symptoms despite the intake of omeprazole, at appropriate doses for at least 2 months, started after an abnormal endoscopy and/or pH-monitoring that established GERD. Exclusion criteria were organic, systemic, metabolic, or neurologic disease and an underlying psychiatric illness. Therefore, all patients underwent a careful history taking, clinical examination, routine biochemistry, and an abdominal ultrasound. A barium swallow was performed to rule out a hiatal hernia, malrotation, or any other anatomic abnormality.

Questionnaire
Before the pH and DGER monitoring study, each patient and his or her parents completed a questionnaire, which evaluated the presence of different typical and atypical reflux symptoms (heartburn, regurgitation, epigastric pain, chest pain, night-time pain, nausea, vomiting, belching, bloating, anorexia, aspiration, throat ache, hoarseness, coughing, and hypersalivation).

Esophagogastroduodenoscopy with Biopsies
A fiberoptic esophagogastroduodenoscopy with biopsies was performed in all patients, after sedation with 0.1 mg/kg midazolam (with a maximum of 5 mg) and 1 mg/kg pethidine (with a maximum of 10 mg) intravenously. The type and location of the mucosal injury were documented and the severity of the damage was graded according to the Savary Miller classification,22 which was still the basis for proton pump inhibitor (PPI) reimbursement in Belgium at the time of the study. During the esophagogastroduodenoscopy, biopsies were obtained from the duodenum, the stomach (antrum), and the distal esophagus.23,24

Ambulatory pH and DGER Monitoring
A Digitrapper MK III (Synectics Medical) with unipolar antimony electrodes calibrated in test solutions (pH 7 and 1) was used for the pH monitoring. The Bilitec 2000 (Synectics Medical), a fiberoptic probe, was used for DGER monitoring. The fiberoptic probe and the pH probe were taped together at the tip. This assembly was introduced through the nose and positioned under fluoroscopic control two vertebrae above the diaphragm.25 During the study, patients received no solid food, fruit juice, or coffee but a fluid food Nutridrink with vanilla taste (Nutridrink, Nutricia, Bornem, Belgium).26 They were admitted to the hospital for the duration of the study but were encouraged to carry out daily activities. Patients and their parents were asked to mark the sleeping, eating, and symptom periods by pressing a button on the data recorder.

The ambulatory recording data were downloaded onto a personal computer and analyzed with the aid of commercially available software (Gastrosoft Inc, Synetics Medical, Irvine, TX). Acid reflux was quantified with the following variables obtained from computerized analysis: number of reflux episodes, number of reflux episodes lasting longer than 5 minutes per hour, and percentage of time with pH \( \leq 4 \). DGER was quantified with the following variables obtained from computerized analysis: number of reflux episodes, number of reflux episodes lasting longer than 5 minutes per hour, and percentage of time with bilirubin absorbance \( \geq 0.14 \). The recording was divided into meal, postprandial (2 hours after a meal), interdigestive, upright, and supine periods.

A patient is considered to have pathologic DGER if the fraction of time that the esophageal mucosa is exposed to a refluxate with a bilirubin absorbance of >0.14 exceeds 4.2% of the total study time.27 Pathologic acid reflux is considered to be present if the fraction of time that the esophageal mucosa is exposed to a refluxate with pH <4 exceeds 4% of the recording time.28

Gastric Emptying Breath Test
Gastric emptying rate was studied by means of the noninvasive \(^{13}\)C octanoic breath test. Octanoic acid, a medium-chain fatty acid marked with a stable \(^{13}\)C isotope, is rapidly absorbed from the duodenum. Because gastric emptying is the rate-limiting step for the absorption of medium-chain fatty acids, the fraction of \(^{13}\)C expired in the breath is a measure for the rate of gastric emptying. The \(^{13}\)C octanoic acid was mixed in a pancake and presented for breakfast after obtaining two basal breath test samples. After feeding, breath samples were collected every 15 minutes during 4 hours. Analysis of the expired \(^{13}\)C fraction in the breath samples was performed by using isotope-ratio mass spectrometry (Gilson ABCA 20-20 stable isotope analyzer and autosampler; Europa Scientific, Crewe, UK), and the gastric emptying time was calculated as previously reported.29

Statistical Analysis
Values are expressed as mean and standard error (SEM) or median and interquartile ranges. Results were compared by using the Student \( t \) test, Mann-Whitney \( U \) test, or \( \chi^2 \) test wherever appropriate. Probability values were considered to be significant at <.05.
RESULTS

Study Population

Twenty-two children (12 girls; mean age, 13.2 ± 2.2 years) with symptoms suggestive of refractory GERD despite at least 2 months of omeprazole therapy (1 mg/kg) were included. Twenty-one children had an abnormal endoscopy before the PPI treatment (grade 1 esophagitis in 7 patients, grade 2 esophagitis in 10 patients, gastritis in 12 patients, and antral erosions in 5 patients). One patient had a normal endoscopy with biopsies but an abnormal pH monitoring (8.2% of time pH < 4). The mean time between the start of the PPI treatment and the DGER monitoring because of symptoms suggestive of PPI refractory GERD was 3.5 months.

Questionnaire

The most prevalent symptoms were epigastric pain, regurgitation, and nausea (Table I). Heartburn is not typically reported by children with GERD, but night-time pain and retrosternal pain were reported in 32% and 36%, respectively, of the patients.

Barium Swallow

All patients underwent a barium x-ray examination of the esophagus, stomach, and duodenum. The barium study did not reveal any anatomic abnormalities except for one child with a small intermittent sliding hernia. In one child with a history of infantile pyloric hypertrophy (at the age of 2 months), the barium examination did not reveal a recurrent pyloric stenosis, and barium emptied normally.

Esophagastroduodenoscopy and Biopsies

All patients underwent a new esophagastroduodenoscopy. Eight patients had a grade I esophagitis and 4 had a grade II esophagitis. Gastritis was noted in 8 children, 3 children had gastric erosions, and duodenal mucosal hyperemia was noted in one child. During the endoscopy, biopsies were obtained from the duodenum, stomach, and distal esophagus. Biopsies showed esophagitis in 3 endoscopy-negative patients, Helicobacter pylori–negative gastritis in 9 patients (5 chronic focal gastritis, 4 reactive gastritis), and duodenitis in 1 patient. No other inflammatory or allergic disorders were noted. In total, endoscopic or histologic esophagitis was demonstrated in 15 patients (68.1%).

Acid and Bile Reflux Testing

The results of esophageal pH and DGER monitoring are listed in Table II. The mean esophageal acid exposure was slightly elevated, and pathologic esophageal acid exposure was present in 12 children (55%). Average esophageal DGER exposure was highly elevated, and 15 patients (68%) had pathologic DGER exposure. Combined pathologic acid and DGER exposure was present in 45% of the children (n = 10), although 2 (9%) had pathologic acid exposure alone and 5 (23%) had pathologic DGER alone. No pathologic reflux was demonstrated in 5 (23%) children (Figure 1).

Acid exposure and DGER exposure were not significantly correlated (r = 0.05, NS). Gastric emptying rate did

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<td>Aspiration</td>
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<th>Table II. Results of pH and DGER monitoring</th>
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<td>% Time pH &lt; 4</td>
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<td>No. of acid reflux episodes</td>
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<td>No. of DGER episodes</td>
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<td>Longest DGER episode (min)</td>
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Data are represented as number/row percentage.

Figure 1. Distribution of findings on combined reflux monitoring in 22 children with PPI-refractory GERD symptoms. Graph shows the proportion of patients with pathologic acid exposure or pathologic DGER exposure or both.
not differ between patients with or without pathologic acid exposure (84 ± 24 vs 86 ± 26 minutes, NS) or with or without pathologic DGER exposure (105 ± 47 vs 76 ± 24 minutes, NS).

Relation Between Endoscopic Esophagitis and Acid or DGER Exposure

Esophageal acid exposure and esophageal DGER did not differ between patients with or without esophagitis (Figure 2). However, patients with grade II esophagitis had significantly higher DGER exposure than patients without esophagitis (9.1% ± 5.3% vs 26.7% ± 10.9% of the time, \( P < .05 \)). Similarly, the duration of the longest DGER episode was significantly longer in patients with grade II esophagitis compared with patients with grade I esophagitis and patients without esophagitis (242 ± 132 vs 28 ± 18 and 61 ± 16 minutes, respectively, \( P < .05 \)).

Relation Between Symptoms and Acid or DGER Exposure

There was no statistical difference in symptom pattern between acid, DGER, or combined reflux patients. In all groups, the most prevalent symptoms were regurgitation, epigastric pain, and nausea.

Clinical Outcomes

After the investigation, initial therapy consisted of prokinetic drug therapy (cisapride or domperidone) in all children. Most children with DGER had better symptom control on a combination of high-dose PPI and prokinetic drug therapy. Eventually, 4 of the children with pathologic DGER were referred for antireflux surgery. One of the children without pathologic DGER was also referred for antireflux surgery because of pathologic acid reflux that persisted during adequate PPI and prokinetic drug therapy. The Nissen fundoplication resolved all symptoms in the group with the pathologic DGER, and the PPI and prokinetic treatment could be stopped.

**DISCUSSION**

The term bile reflux is often used synonymously with DGER because bile acids or bilirubin are the constituents used most often as markers. Studies in the adult population have demonstrated a progressive increase in esophageal exposure to acid and duodenal contents across the spectrum of GERD, with a particularly high prevalence in patients with Barrett esophagus.30,31 Although DGER is also suppressed by PPIs, available literature suggests that PPIs are less efficacious to normalize DGER, compared with their effect on acid reflux.32,33 In adults, DGER has been associated with less complete responsiveness to PPI therapy34 and with persistence of symptoms and lesions during PPI therapy.20

In the past, it has been suggested that an alkaline shift on esophageal pH monitoring might reflect exposure to duodenal content in pediatric GERD.35 However, combined aspiration and pH monitoring studies in adults have shown that this is not the case,36 and the Bilitec 2000 fiberoptic spectrophotometric probe is now considered the gold standard for the evaluation of DGER.37 One previous study evaluated the use of combined pH and Bilitec monitoring in children with GERD symptoms and found that both bile and acid reflux increased with the severity of esophagitis in children, too.36

In the present study, we assessed esophageal acid and DGER exposure in consecutive pediatric patients with GERD that was refractory to standard PPI therapy. The refractoriness is confirmed by the finding of ongoing or recurrent endoscopic esophagitis after a brief interruption of drug intake, despite at least 2 months of PPI therapy in the majority of the children. For ethical reasons, performing DGER monitoring in healthy children is not feasible, and hence normal values for the pediatric population are lacking. We therefore used the upper limit of normal values previously obtained in healthy adults to define pathologic DGER exposure. Using this cutoff, we found pathologic esophageal DGER exposure in 68% of the children, and one third did not have associated pathologic acid exposure. More severe grades of esophagitis were associated with significantly higher DGER exposure, also suggesting the pathophysiologic relevance of DGER in GERD refractoriness in these patients.

The present study has a number of limitations. First of all, due to the setting of this study in a tertiary referral center, this is a highly selected refractory patient population, and the true prevalence of pediatric refractory GERD remains unclear. In the adult population, refractory heartburn and regurgitation are cardinal clinical symptoms suggestive of refractory GERD. In the present study of pediatric refractory GERD, the most frequently reported symptoms were epigastric pain, regurgitation, and nausea. Studies in adults have suggested that symptoms of heartburn and regurgitation occur in relation to both acid or bile reflux, and less typical symptoms such as nausea and vomiting were related to bile reflux alone.39
Second, as the use of solid food during Bilitec monitoring is associated with a high prevalence of meal-impaction artifacts, patients were put on a liquid diet during the study. This is a deviation from normal feeding patterns, and the lack of solid foods may have led to an underestimation of some of the acid and DGER measures. Third, as indicated above, normal values derived in this study were derived from an adult and not a pediatric control population. Finally, and most importantly, as this group of children with refractory GERD was studied after a brief interruption of PPI therapy and in the absence of control DGER data in children whose symptoms responded well to PPIs, we can only speculate on the contribution of DGER to PPI refractoriness in pediatric patients. However, the association of more severe reflux esophagitis with higher DGER exposure is supportive of a pathophysiologic role for DGER in refractoriness. Furthermore, the clinical improvement after addition of prokinetic therapy, or referral for surgery, would also support a role for DGER in ongoing symptoms and lesions despite PPI therapy. Indeed, previous studies in adults have confirmed the value of prokinetic therapy or surgery in the treatment of DGER.

Given its high prevalence in the patient group we studied, nonacid reflux or DGER should be considered in children with refractory symptoms despite adequate PPI therapy. Future studies seem warranted to investigate acid and DGER exposure on PPI therapy and to investigate the response to prokinetic or surgical therapy in children with established pathologic DGER.

REFERENCES


Objective To evaluate the impact of vocal cord dysfunction on feeding in children after cardiovascular surgery.

Study design Of the 2255 children who had cardiovascular surgery between January 2000 to January 2006, 38 (1.7%) had postoperative vocal cord dysfunction confirmed at laryngoscopy. The following data were obtained retrospectively: type of surgery, laryngoscopic examination results, swallowing studies, upper gastrointestinal (UGI) studies, and feeding route: oral, nasogastric tube (NG), and gastrostomy.

Results Surgeries included aortic arch reconstruction (n = 20), patent ductus arteriosus ligation (n = 8), arterial switch (n = 3), cervical cannulation for extracorporeal membrane oxygenation (n = 2), and others (n = 5). A swallowing study confirmed dysfunction in 27 of 29 patients. Gastrostomy was placed in 18/38 patients. At discharge, 18 patients were fed by gastrostomy, 13 orally, 3 by NG, and 4 by combination oral/NG. At a median follow-up of 12 months, 20 were fed orally, 1 by NG, 7 by gastrostomy, 7 by combination gastrostomy/orally, 1 was lost to follow-up, 2 died.

Conclusion Vocal cord dysfunction after pediatric cardiovascular surgery is associated with significant feeding problems and may require prolonged gastrostomy feeding. These findings support aggressive surveillance for vocal cord dysfunction, especially in patients undergoing aortic arch surgery. (J Pediatr 2007;151:312-5)

Postoperative vocal cord dysfunction is a clinically important complication in children undergoing cardiovascular surgery because it may predispose them to aspiration by impairing their ability to protect their airway. Such aspiration may in turn result in significant pulmonary morbidity and in severe cases even prove fatal. There are several possible mechanisms responsible for vocal cord dysfunction, such as operative injury to the recurrent laryngeal nerve, association of the cardiac defect with a congenital laryngotracheal anomaly, prolonged intubation with direct vocal cord trauma, neurodevelopmental delay, poor sucking and swallowing coordination, or even injury from a transesophageal echocardiography probe.1,2 Some children with vocal cord injury undergo placement of a gastrostomy tube to avoid the risk of aspiration; others remain orally fed, but with altered consistency of feeds. Unfortunately, there is relatively little published information pertaining to feeding patterns after diagnosis of postoperative vocal cord dysfunction. In this study we sought to determine the impact of vocal cord dysfunction on feeding in children after cardiovascular surgery to provide some guidance for parents and physicians caring for these children.

METHODS

This study was approved by the Institutional Review Board of the University of Arkansas for Medical Sciences. Medical records of pediatric patients (<18 years) who had heart surgery from January 2000 to January 2006 and had otolaryngology consultation were reviewed. All those who had postoperative vocal cord dysfunction confirmed at laryngoscopy formed the study cohort. The following data were obtained retrospectively: age and weight at surgery, cardiac diagnosis and type of surgery, whether intraoperative transesophageal echocardiography was performed, duration of endotracheal intubation, presence of neurologic injury, laryngoscopic examination results, esophageal swallowing studies, upper gastrointestinal (UGI) studies, duration of hospital stay, discharge and follow-up feeding route: oral, nasogastric tube (NG), gastrostomy.

Laryngoscopic evaluations were performed by a pediatric otolaryngologist by flexible, fiberoptic laryngoscopy. Vocal cord paresis was defined as incomplete abduction...
Vocal Cord Dysfunction and Feeding Difficulties after Pediatric Cardiovascular Surgery

or adduction of the cord. Vocal cord paralysis was defined as complete immobility of the vocal cord. Esophageal swallow studies were performed by a speech pathologist in conjunction with a supervising radiologist. Patients were given barium with 3 different consistencies: thin, nectar, and honey. The swallowing was viewed in a lateral plane with continuous fluoroscopy. Laryngeal penetration was present if the barium bolus entered the glottic aperture but did not pass the level of vocal cords. If the bolus passed across the vocal cords and entered the subglottic area and trachea, it was considered aspiration. Sucking and swallowing coordination were also observed during this study. The study was repeated at an interval recommended by the speech pathologist. A barium contrast UGI study or technetium scanning was performed to identify gastroesophageal reflux on the basis of clinical suspicion.

Recommendations were made by the speech pathologist to alter the feeding consistency if there was aspiration or deep penetration noted with a certain consistency of barium. If the patient had aspiration with all consistencies or had poor suck and swallow coordination in spite of speech therapy, gastrostomy tube placement was considered. In addition, a Nissen fundoplication was performed if there was evidence of significant reflux on UGI or technetium scan. Charts were reviewed to obtain information about the feeding pattern at each follow-up visit with cardiologist, otorhinolaryngologist, or speech pathologist.

RESULTS

From January 2000 to January 2006, 2255 children underwent cardiovascular surgery at our institution. Vocal cord dysfunction was diagnosed in 38 (1.7%). Primary cardiovascular surgeries included coarctation repair in 10, modified Norwood procedure in 10, patent ductus arteriosus (PDA) ligation in 8, arterial switch in 3, cannulation for cerebral extracorporeal membrane oxygenation (ECMO) in 2, systemic-pulmonary shunt in 1, left aortopulmonary collateral ligation in 1, left pulmonary arterioplasty in 1, tricuspid arteriosus repair in 1, and Fontan completion in 1. Many patients had more than 1 cardiac lesion addressed during surgery. The median age at surgery was 13.5 days (1 to 1604 days); median weight was 3.45 kg (0.9 to 14.5 kg). Transesophageal echocardiography was performed during surgery in 11/38 (29%) patients. The median duration of intubation was 10 days (2 to 71 days). The median length of hospital stay was 32.5 days (9 to 107 days). There were 2 deaths: patient 11 died at 3 months of age because of infection of ventriculoperitoneal shunt, and patient 38 died 3 days after Nissen fundoplication and gastrostomy placement. Cause of death of patient 38 was unknown and autopsy was denied by the family (Table I; available at www.jpeds.com).

Five patients had significant neurologic injury diagnosed during surgery. Patient 4 had multiple seizures in the immediate postoperative period and a magnetic resonance imaging (MRI) of the brain showed multiple hemorrhagic infarcts in the white matter. Patient 11 had severe communicating hydrocephalus diagnosed 3 weeks after modified Norwood palliation and underwent a ventriculoperitoneal shunt. Patient 21 who had been on ECMO support for severe pulmonary hypertension was noted to have extensive encephalomalacia involving both cerebral hemispheres on an MRI performed 23 days after being placed on ECMO. This patient had a normal head ultrasound scanning result before being placed on ECMO. Cerebral palsy later developed as a consequence of the patient’s neurologic damage. Patient 23 had extensive encephalomalacia of both cerebral hemispheres with focal encephalomalacia of the right parietal cortex observed on MRI performed a year after initial heart surgery. This patient had heterotaxy syndrome and a very complicated postoperative course including support with ECMO. Also, patient 23 already had a gastrostomy after his initial heart surgery, before the diagnosis of neurologic injury and has continued to be fed by gastrostomy. Patient 27 had a computed tomographic scan of the head performed 1 week before heart surgery that showed focal areas of edema in both cerebral hemispheres suggesting infarction. A follow-up study performed 2 weeks after cardiac surgery showed progressive atrophy and ischemia compatible with hypoxic encephalopathy. This patient has continued to be fed by gastrostomy. Patient 17 had Down syndrome, and patient 33 had Turner syndrome.

The initial laryngoscopic examination showed unilateral vocal cord paresis in 4, bilateral paresis in 1, unilateral paralysis in 30, bilateral paralysis in 2, and left vocal cord paralysis with right vocal cord paresis in 1. Of the 30 patients with unilateral paralysis, 2 patients who had undergone cannulation for cervical ECMO had right vocal cord paralysis and the remaining 28 had left vocal cord paralysis. Positioning of a paralyzed cord was in the paramedian position in all cases. None of the patients had a documented congenital laryngotracheal anomaly, except patient 23 who had laryngomalacia. A follow-up evaluation was available in 9 of 38 patients and showed normal vocal cord mobility in 3 patients, improved mobility in 4, and unchanged in 2. None of our patients underwent a medialization of the paralyzed vocal cord. Tracheostomy was done in 3 patients: patient 16 who had bilateral vocal cord paralysis and subglottic stenosis; patient 21 returned to hospital 6 months after initial discharge with chronic lung disease and severe laryngotracheomalacia and failed several attempts at extubation, thus requiring tracheostomy; patient 31 returned to the hospital 2 weeks after initial discharge with respiratory failure related to prematurity and chronic lung disease and required tracheostomy after prolonged mechanical ventilation and failure to wean from ventilatory support.

Results of esophageal swallow studies, UGI and technetium scanning, gastrointestinal surgery, and the feeding pattern before heart surgery and at the time of discharge are shown in Table I. Before surgery 17 patients had never been fed orally, 16 were being fed orally, 4 by a transpyloric tube, and 1 by a nasogastric tube. Clinical suspicion of swallowing dysfunction was noted in 34 of 38 (89%) patients with vocal cord dysfunction diagnosed at laryngoscopy. A swallowing
Table II. Percentage of patients on various feeding regimens at the time of discharge from the hospital and at last follow-up

<table>
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<th>Feeding management</th>
<th>Hospital discharge status (n = 38)</th>
<th>Last follow-up status (n = 35)*</th>
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<td>37.2%</td>
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<td>Modified oral</td>
<td>18.4%</td>
<td>20%</td>
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<td>Oral/GT or NG combination</td>
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<td>17.1%</td>
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<tr>
<td>All GT or NG</td>
<td>55.2%</td>
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GT, Gastrostomy; NG, nasogastric tube.
*One lost to follow-up; 2 died.

study was done in 29 patients within 30 days after surgery; all were abnormal in terms of aspiration, penetration, or discordant swallowing. Aspiration of varying consistencies of formula was noted in 23; 5 had penetration with thin or nectar consistency, and 1 had delayed swallowing with thin and nectar consistency. Results of a follow-up swallow study were available in 17 patients at a mean follow-up of 6.2 ± 4.1 months from the initial study. It was normal in 8, showed improved swallowing in 4, unchanged in 3, and worsening in 2.

Gastroesophageal reflux was evaluated by UGI in 20 patients and a technetium scan in 3, and both in 2. Of these 25 patients, reflux was identified in 16. Gastrostomy was placed in 18/38 (47%) patients, 16 of whom also underwent Nissen fundoplication. Two patients (31 and 32) with aspiration of all consistencies and no evidence for reflux also had gastrostomy placed.

At discharge, 5 patients were sent home on normal oral feeds, 7 with thickened oral feeds, 5 with combination of nasogastric and thickened oral feeds, 3 were on nasogastric feeds, and 18 patients were fed by gastrostomy (Table II). At a mean follow-up duration of 10 months (3 to 60 months), 1 was lost to follow-up; 13 were on normal oral feeds; 7 were on thickened oral feeds; of the 18 patients who underwent gastrostomy placement, 9 were still fed by gastrostomy; 6 were on combination of gastrostomy and orally fed; 1 had normal swallow function and gastrostomy removal; and 2 died (Table II).

DISCUSSION

The phenomenon of vocal cord dysfunction after pediatric heart surgery is familiar in pediatric cardiac units. Although it is sometimes viewed as relatively trivial in comparison to other possible complications of cardiovascular surgery, it is well known that the probability of aspiration is increased in patients with vocal cord dysfunction because of impaired airway protection.3,4 This potential for pulmonary injury in the setting of vocal cord dysfunction in turn has major implications for feeding strategies in these children. It must be emphasized that every single patient in our study with vocal cord dysfunction had an abnormal swallowing study result. We have demonstrated that only 13% of such children may be normally orally fed by the time of hospital discharge, and that the remaining patients will receive some or their entire nutritional intake as modified oral feeds with or without some sort of feeding tube when they leave the hospital.

A large portion of our study cohort (34/38) had undergone surgery requiring dissection around the aortic arch, ductus arteriosus, or left pulmonary artery. Because the left recurrent laryngeal nerve courses around the ductus arteriosus, surgery involving the ductus, the descending aorta, or the left pulmonary artery may require mobilization of this nerve and put it at risk for injury. It is worth noting that the 2 patients who were placed on cervical ECMO via right cervical incision developed right vocal cord paralysis, the presumable mechanism being injury to the vagus nerve in the carotid sheath. The vagus nerve provides innervation to the right vocal cord via the recurrent laryngeal nerve and could be injured during manipulation of the common carotid artery and internal jugular vein for cervical ECMO. Schumacher et al5 reported 5 similar cases of right vocal cord paralysis after cervical ECMO without any other risk factors and suggested that a laryngoscopic examination should be considered for patients after ECMO.

Similar to our study cohort, previous studies have also demonstrated a high risk for injury to the left recurrent laryngeal nerve during PDA ligation and arch reconstruction.6,7 Skinner at al8 evaluated the incidence and significance of recurrent laryngeal nerve injury and swallowing dysfunction after the Norwood procedure and compared Norwood patients to a group of patients undergoing biventricular aortic arch reconstruction. In this study swallowing dysfunction occurred in 48% of patients, with aspiration in 24%. Unlike other reports, left recurrent laryngeal injury was believed to be an uncommon cause of swallowing dysfunction and was seen in only 9% of their patients. They did not find any difference in incidence of left true vocal cord paralysis and aspiration between those who had Norwood procedure versus those who underwent biventricular repair with aortic arch reconstruction. Kohr et al2 reported dysphagia in 18% of children undergoing cardiac surgery. The risk factors for dysphagia identified in their study included preoperative intubation, age less than 3 years, and use of transesophageal echocardiography in children weighing less than 5.5 kg. Transesophageal echocardiography was used in only 29% of our patients. We do not have a control group to compare whether vocal cord dysfunction was associated with the duration of intubation or intraoperative use of transesophageal echocardiogram. Besides vocal cord dysfunction, other potential risk factors that could contribute to feeding difficulties include abnormal swallowing, gastroesophageal reflux, and splanchic hypoperfusion related to surgery or underlying heart disease. In addition, delayed introduction of oral feedings as seen in 45% of our study cohort can result in significant oromotor and swallowing dysfunction.

Even though we analyzed all patients <18 years old who underwent cardiothoracic surgery, it is important to note that all but 1 of the patients with vocal cord dysfunction were younger than 1 year old. Vocal cord dysfunction related to
congenital heart surgery appears to be extremely uncommon in children over 1 year of age. Zbar et al. studied 17 cases of vocal cord paralysis in infants under 12 months of age. Eight of these children with left vocal fold paralysis had a history of prior thoracic surgery. This study reported a 7.4% postoperative incidence of vocal fold paralysis after ligation of PDA. They concluded that iatrogenic injury of left recurrent laryngeal nerve during heart surgery is the most common cause of vocal cord paralysis in infants and that it persists at an average follow-up of 6 months. However, idiopathic vocal cord paralysis resolved within an average of 6 weeks. In another study Zbar et al. found that the incidence of iatrogenic left vocal cord paralysis was 8.8% in infants undergoing PDA ligation, and the single major risk factor for this was birth weight less than 1 kg. In our study cohort, 3 of the 8 patients who had PDA ligations were premature. These 3 premature infants represent a tiny fraction of the premature neonates undergoing ductal ligation during the period of the study. On the other hand, 20 patients who had complex arch manipulation either as a part of Norwood procedure or coarctation repair developed vocal cord dysfunction. This reflects a much higher incidence of vocal cord dysfunction in these children undergoing more complex repairs. The question of whether the recurrent laryngeal nerve is at less risk during ductal ligation as opposed to arch reconstruction, or whether the consequences of nerve injury are less transient and, hence, magnified in the setting of more complex congenital heart disease remains unanswered.

In a clinical review, Hartle et al. provided an update on management of adult patients with unilateral recurrent laryngeal nerve paralysis as a result of thyroid surgery. They stated that this lesion is frequently well tolerated but may be life threatening because of the possibility of aspiration pneumonia. They recommended surgical treatment with medialization of the paralyzed vocal cord to close the glottic gap on phonation, so that the normal vocal fold can make contact with the paralyzed one. This technique reportedly is simple, has low complication rate and is highly efficient in eliminating aspiration and improving voice quality. In contrast, Bhattacharyya et al. did not find significant improvement in aspiration after vocal cord medialization. There are no conclusive studies regarding use of medialization for unilateral vocal cord paralysis in infants.

A swallowing study is a useful tool for diagnosing aspiration in patients who have vocal cord dysfunction. Aspiration of varying consistencies was noted in 80% of our patients who had a swallowing study. Thus allowing us to appropriately alter their feeding regimen or place a GT. Even though a follow-up swallow study was not available in all patients, 70% showed normal or improved swallowing on a follow-up study at 6 months, emphasizing the need for a continued follow-up evaluation by a speech pathologist. Most of the patients who received a gastrostomy continued to be fed by gastrostomy at the time of last follow-up.

Several limitations of our study are worthy of note, the most important of which is its retrospective nature. Because we did not prospectively evaluate all patients undergoing cardiovascular surgery, we do not know the true incidence of vocal cord dysfunction and have probably underestimated it. Lesser degrees of vocal cord dysfunction or temporary cord dysfunction may have gone undetected in this cohort. Not all patients who had vocal cord dysfunction had evaluation by a swallow study. Also a follow-up swallow study was not done in all those who initially had an abnormal swallow study result. Most patients do not have a follow-up laryngoscopic evaluation to determine the resolution or persistence of vocal cord dysfunction. We are currently prospectively monitoring all patients who have suspicion of vocal cord dysfunction especially after heart surgeries involving great vessels or PDA. These patients are undergoing laryngoscopic evaluations, swallowing study and UGI or technetium scan. A systematic approach like this will allow us to better treat these patients in terms of their feeding and might possibly reduce the duration of hospitalization after heart surgery. This will also enable us to better predict the time course of the cord paresis and the need for gastrostomy feeds.

We thank Carl W. Chipman Jr, RN, for his help with the database.

REFERENCES

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GER, Gastroesophageal reflux; GI, gastrointestinal; GT, gastrostomy; NG, nasogastric tube; NPO, nil per os; PO, per os (oral); TPT, transpyloric tube.
Growing Skull Fracture after Minor Closed-Head Injury

JEAN-RODOLPHE VIGNES, MD, PhD, N. U. OWASE JEELANI, MRCS, MBA, MPhil, ASHFAQ JEELANI, MD, MSc, MRCPCH, MICHIEL DAUTHERIBES, MD, AND DOMINIQUE LIGUORO, MD, PhD

Head injury is a major public health issue due to its prevalence and the associated socioeconomic costs. Its incidence is increasing in urban areas. Minor closed-head injuries (MCHIs) constitute more than 80% of all head injuries. A conservative approach to diagnostic evaluation is generally recommended in infants with MCHI. Skull radiograph (SR) plays a limited role in these cases, except when nonaccidental injury is considered. Growing skull fracture (GSF), a known intracranial complication of head injury, can occur after an MCHI. Unless this diagnosis is considered at initial presentation, a significant delay in detection can occur, resulting in suboptimal management.

To highlight this issue, we present 3 cases of children with a typical MCHI, as defined by previous studies, who subsequently developed GSF. This report emphasizes the importance of initial evaluation in identifying those patients with MCHI at risk of developing intracranial injury. A timely and efficient management plan is recommended.

CASE 1
A 5-day-old term male infant fell from a baby-changing table and cried immediately. The next day, the infant was seen by the family doctor, who noted a subcutaneous parietal hematoma but no other signs of injury or neurologic deficit. No follow-up assessment or investigations were instigated. Five months later, the infant’s mother, concerned about a persistent hematoma (Figure 1A) and progressive lethargy, brought the child for further medical attention. Examination at this point revealed hypotonia with a right incomplete motor deficit. SR revealed a large skull fracture (Figure 1B). Magnetic resonance imaging (MRI) confirmed the presence of a large left temporoparietal meningoencephalocele through the dura, as well as the bone defect, which produced a significant skull deformity (Figure 1C). The assessment protocol for child abuse was followed and yielded negative findings. Electroencephalography (EEG) revealed focal seizure activity requiring medical treatment (sodium valproate).

Neurosurgical management comprised duroplasty and cranioplasty. Postoperative outcome was good, and the infant was discharged to home 7 days after the surgery. The infant exhibited early improvement in neurologic status. At 6-month follow-up, persistent mild residual hemiparesis was noted, and EEG showed continuing epileptiform discharges.

CASE 2
A 3-month-old male infant fell from his pram onto the strut of a windowpane. He cried after the fall, and his mother brought him to the emergency department. Examination revealed a right parietal subcutaneous hematoma. The infant had no history of lethargy, irritability, or vomiting, and clinical examination revealed no neurologic deficits. The infant remained well and was discharged to home after 6 hours of observation.

Three months later, the parents noted that the infant was intermittently hypotonic and had a pulsatile collection on his head, which became tense with coughing and crying. An SR showed a large right parietal skull fracture (Figure 2A), and a computed tomography (CT) scan confirmed the diagnosis of a GSF (Figure 2B). A durocranioplasty was successfully performed. The child remained asymptomatic at the 1-year follow up.

CASE 3
A 3-month-old male infant fell from his mother’s arms onto a tiled floor. The infant cried immediately and was brought to the emergency department. Examination revealed a 5-cm-diameter right parietal cephalhematoma. The infant remained alert with no

<table>
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neurologic deficit. Fundoscopic examination was negative. An SR identified a parietal linear skull fracture. A CT scan revealed a cephalhematoma with an underlying cortical contusion and some traumatic subarachnoid blood overlying the contused cortex (Figure 3A).

The infant was observed as an inpatient for 7 days, during which time he remained well. A repeat CT scan showed resolution of the contusions, and he was discharged home. Two weeks later, clinical examination revealed a persistent right parietal pulsatile subcutaneous mass. MRI confirmed the presence of a meningocele (Figure 3B) through the fracture. This was repaired surgically, and the infant was discharged 5 days later. One-year follow up was entirely satisfactory.

**DISCUSSION**

GSF is a rare complication of head trauma. The prevalence ranges from 0.05% to 1.6% of all skull fractures, with 1% typically cited. This figure is an underestimate for the concerned pediatric population, however, because although skull fractures occur in the entire pediatric population, GSFs occur primarily in the first few years of life. Some 90% of GSFs occur before age 3 years, and more than 50% occur before age 12 months. Falling is the most frequent cause of the injury, followed by motor vehicle accidents and birth injury. Nonaccidental injury is another cause than should be considered and excluded. GSFs are generally associated with severe head trauma but can occur with minor head injury, with an associated risk of complications including meningoencephalocele, porencephalic cysts, hydrocephalus, brain atrophy, and functional alterations such as epileptic discharges, neurologic deficit, and psychomotor development delay.

As a general rule in cases of brain injury, early diagnosis and prompt management can help minimize complications and provide the best prognosis. Whereas the primary injury sustained by the brain parenchyma is irreversible, efforts should be geared toward reducing secondary insults. There has been no study specifically comparing outcomes in cases of GSF with early intervention versus delayed intervention, but an understanding of the pathophysiologic mechanisms suggests a more favorable outcome in the former category. Smaller skull and dural defects are easier to repair, and prolonged progressive parenchymal herniation is likely to result in gliotic changes. Our case 3 demonstrated early detection and management with an excellent outcome. In case 1, on the other hand, the delay may be attributed to the residual hemiparesis. In case 2, despite the delay, there was no residual deficit after treatment. Nevertheless, the interval between head injury and diagnosis of GSF continues to vary from the time of initial consultation to a few years.

Age is a significant risk factor for intracranial injury after head trauma, with reports of age cohorts of under 3 months, under 1 year, and under 2 years composing specific risk categories. There is consensus that age under 3 months is almost certainly a risk factor for brain injury after MCHI.

Head injury in the younger age group is distinct from that in older children and adults because of differences in mechanisms and injury thresholds. A normal neurologic examination and maintenance of consciousness do not preclude the presence of significant intracranial injury in pediatric trauma patients. Moreover, 48% of intracranial abnormalities on CT scan are associated with normal initial clinical examination. Some authors feel that the Glasgow coma scale is not sensitive under age 2 years and recommend using the pediatric version of this scale.

Abnormalities of scalp examination may be a marker for intracranial injury in asymptomatic infants. Cephalhematoma, a subperiosteal skull hematoma, typically does not cross suture lines, is painful, and decreases slowly, unlike a strict subcutaneous hematoma. Cephalhematoma is considered an
indirect sign of bone fracture that is a necessary prerequisite to developing a GSF. Previous studies have shown that subcutaneous scalp hematomas, independent of their location, are also strongly associated with skull fracture in infants with head injury, and that skull fractures in turn are closely associated with intracranial pathology. All of our cases presented with scalp hematoma, and this tendency has been corroborated in other studies involving more patients.

Despite the frequent occurrence of MCHI in children, management strategies differ among individuals and institutions. A CT scan is not sensitive enough to detect dural tears at the initial phase and although MRI has greater sensitivity, its use is not routine in cases of head injury, especially in developing countries. Some authors have proposed using B-mode ultrasound for early detection of the dural defect in cases of diastatic skull fractures of posttraumatic collection overlying the skull, but the clinical efficacy of this approach remains to be determined. SR offers a limited role in the evaluation of children with MCHI. It is a radiation source at the time of initial presentation exhibited skull fractures in this subgroup, we recommend that all such patients undergo SR at initial presentation. Demonstration of a fracture mandates close clinical follow-up and a specialist's evaluation. The need for further imaging, such as a CT or MRI, depends on the characteristics of each individual case.

Clinical follow-up over the ensuing weeks should focus on identifying any developing neurologic deficits and on evaluating the scalp hematoma for settling. In cases 1 and 2, the scalp swelling remained persistent and in fact enlarged. In case 1, the neurologic deficit was detected on subsequent examination. In both cases, the diagnosis likely would have been made earlier had adequate follow-up been undertaken.

Finally, the role of parent education should not be underestimated or overlooked. As appropriate, the parents should be informed of the possibility of GSF and instructed to watch for any persistent or progressive scalp swelling and the onset of any neurologic signs and symptoms.

GSF remains a rare but serious complication of pediatric head trauma. Diagnosis and management is typically delayed by the lack of awareness by front-line health care personnel who care for these patients. Although this article highlights a particular high-risk subgroup of infants with MCHI (under age 3 months with cephalhematoma), this complication can occur outside this cohort as well. More work is needed to more accurately define the incidence of GSF, especially in cases of MCHI associated with cephalhematoma. Improved awareness by health care staff and better parent education is essential for prompt diagnosis and treatment to help minimize the detrimental sequelae of this complication.

REFERENCES

In Vivo Proton Magnetic Resonance Spectroscopy Assessment for Muscle Metabolism in Neuromuscular Diseases

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Muscle metabolites were obtained by in vivo proton magnetic resonance spectroscopy of 3 patients with Duchenne muscular dystrophy (DMD), 6 patients with spinal muscular atrophy (SMA), and 10 normal volunteers. Patients with DMD and SMA had lower trimethyl amide (TMA)/water and TMA/total creatine (tCr) ratios but normal tCr/water ratios. (J Pediatr 2007;151:319-21)

Recent reports using in vivo proton magnetic resonance spectroscopy (MRS) have opened up the possibility of monitoring muscle metabolism.1-4 MRS has not yet been used to study muscles with fatty degeneration, however. Muscle atrophy and fatty degeneration are common findings in spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD).5-7 The objectives of this study were to assess the ability of MRS to evaluate metabolic spectra in muscles with fatty degeneration and to compare metabolites in patients with DMD, patients with SMA, and normal controls.

METHODS

Patients

We evaluated 19 MRS studies of 6 patients with SMA type III (4 female and 2 male; mean age, 11 years; range, 4 to 18 years), 3 patients with DMD (3 male; mean age, 9 years; range, 7 to 14 years), and 10 normal volunteers (5 female and 5 male; mean age, 12 years; range, 4 to 18 years) at our hospital between August 2003 and July 2005. We evaluated the functional abilities of lower limbs according to the protocol of Brooke. Informed consent was obtained from all patients and normal volunteers and their parents.

Magnetic Resonance Imaging and MRS

All patients were examined using a 3.0 Tesla whole-body MR system (General Electric Medical Systems, Milwaukee, WI). A built-in body coil for conventional magnetic resonance imaging (MRI) and a knee coil for localization and detection of MRS were used. Both the SMA and DMD groups underwent conventional MRI protocols, including fast spin-echo T2-weighted axial images and spin-echo T1-weighted axial images of upper and lower extremities, before undergoing proton MRS. In the normal volunteers, only T2-weighted axial images and MRS sequences were performed.

Data were collected with standard proton MRS acquisition software provided by the manufacturer. A volume of interest (2 cm × 2 cm × 2 cm) was positioned at the soleus (Figure 1). For localization, spectra were obtained using a point-resolved spin-echo sequence. Water suppression was accomplished using 3 preceding chemical-shift-selective saturation pulses (bandwidth, 60 Hz). The following acquisition measures were used: repetition time (TR), 1.5 seconds; 128 acquisitions; 4 dummy scans; spectral width, 2500 Hz; and 2048 data points. Three echo times (30, 90, and 144 msec) were used on the same volume of interest for each patient.

| DMD | Duchenne muscular dystrophy |
| SMA | Spinal muscular atrophy |
| MRI | Magnetic resonance imaging |
| TCR | Total creatine |
| MRS | Magnetic resonance spectroscopy |
| TMA | Trimethyl amide |

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The MRS analysis package provided by the manufacturer (SAGE 7.1) was used. The raw data was zero-filled once, apodized with a 3-Hz Gaussian filter, Fourier-transformed, and phase- and baseline-corrected. Marquardt curve fitting was performed using a Gaussian line shape to calculate the area under the peak. Total creatine (tCr) and trimethyl amide (TMA) concentrations were measured, and the mean ratios of tCr/water, TMA/water, and TMA/tCr were compared for the different groups.

RESULTS

Spectra of analyzable quality were obtained for the 9 patients and the 10 normal volunteers at 3 echo times separately. All of the spectra of normal volunteers and 7 patients showed peaks of TMA and creatine (Figure 2). TMA peaks could not be detected in 2 other patients (1 DMD, 1 SMA) at the 30-msec echo time, because the peaks could not be differentiated from baseline noise.

The TMA/water ratios in the patients with DMD, those with SMA, and normal volunteers exhibited statistically significant differences at echo times of 30 msec (mean ± standard deviation, 0.00082 ± 0.00045, 0.00135 ± 0.00032, and 0.00273 ± 0.00025; P = .0016), 90 msec (0.00333 ± 0.00221, 0.00547 ± 0.00156, and 0.01091 ± 0.00121; P = .0089), and 144 msec (0.00383 ± 0.00967, 0.01853 ± 0.00684, and 0.03489 ± 0.00530; P = .027). The TMA/tCr ratios also showed statistically significant differences at echo times of 30 msec (0.325 ± 0.154, 0.456 ± 0.109, and 0.817 ± 0.084; P = .014), 90 msec (0.649 ± 0.173, 0.629 ± 0.122, and 1.071 ± 0.095; P = .021), and 144 msec (0.524 ± 0.173, 0.678 ± 0.122, and 1.226 ± 0.095; P = .0017). However, the tCr/water ratios showed no statistically significant differences at echo times of 30 msec (0.00333 ± 0.00129, 0.00467 ± 0.00091, and 0.00336 ± 0.00071; P = .510), 90 msec (0.00457 ± 0.00333, 0.01017 ± 0.00229, and 0.01048 ± 0.00178; P = .287), and 144 msec (0.00970 ± 0.00779, 0.02243 ± 0.00551, and 0.02931 ± 0.00426; P = .113). The Brooke scores of the lower limbs demonstrated significant statistical differences among the patients with DMD, those with SMA, and normal volunteers (3.30 ± 0.58, 2.83 ± 0.41, 1.00 ± 0.00; P < .001).

DISCUSSION

The patients with DMD and those with SMA exhibited significantly lower TMA/tCr and TMA/water ratios compared with normal volunteers, a result compatible with an earlier in vitro proton nuclear MRS study in human patients with DMD.8 The TMA peaks are constituents of phospholipid metabolism and cell membranes, and decreased TMA is considered to be associated with a lower number of cells, reduced rate of membrane synthesis, and decreased cell turnover.9 This decrease in TMA may reflect degenerative changes in the muscles of patients with DMD and SMA.

Compared with normal muscles, the muscles of patients with DMD and SMA were found to have more adipose tissue, which may have rendered the other metabolic peaks undetectable. This made the TMA peaks undetectable in 2 patients at an echo time of 30 msec, but not at longer echo times. This suggests that long echo times are preferable when performing proton MRS studies of muscles with fatty degeneration.

Figure 1. The regions of interest of MRS in the soleus. T1-weighted spin-echo image acquired from a normal volunteer A, and a patient with SMA B.
In conclusion, we have found that in vivo proton MRS has potential in diagnosing or monitoring neuromuscular disease. Proton MRS at longer echo times should allow us to better detect metabolite spectra.

Special thanks to Yuan-Yu Chiau and Feng-O Shu for technical assistance with the MR studies.

REFERENCES

4. Trump ME, Hanstock CC, Allen PS, Gheorghiu D, Hochachka PW. An (1)
ABCA3 Deficiency Presenting as Persistent Pulmonary Hypertension of the Newborn

Annette M. Kunig, MD, Thomas A. Parker, MD, Lawrence M. Nogee, MD, Steven H. Abman, MD, and John P. Kinsella, MD

A newborn with persistent pulmonary hypertension (PH) unresponsive to conventional therapies was found to be homozygous for a mutation in the gene encoding adenosine triphosphate binding cassette protein, member A3 (ABCA3). Most causes of PH respond to lung recruitment, inhaled nitric oxide, and hemodynamic support. When PH is prolonged and does not respond to standard therapies, genetic causes of surfactant abnormalities should be considered in the differential diagnosis.

(from J Pediatr 2007;151:322-4)

A 4.1-kg full-term male infant was delivered at an outlying hospital after an uncomplicated pregnancy and labor. He developed respiratory distress in the delivery room and was initially managed with continuous positive airway pressure. During the first 12 hours of life, his gas exchange worsened, necessitating intubation and mechanical ventilation. A chest radiograph obtained early in the patient’s course showed mild parenchymal lung disease, which did not fully account for the patient’s degree of severe hypoxemia (Figure). Mean airway pressure was 20 cm H₂O at the time of chest radiograph. He was not treated with exogenous surfactant due to his unstable clinical condition, tenuous oxygenation, and chest radiograph inconsistent with typical surfactant deficiency.

The patient was transferred to the Children’s Hospital at age 30 hours for evaluation and management of hypoxemic respiratory failure with progressive deterioration in gas exchange and hemodynamic instability. An echocardiogram on admission revealed a structurally normal heart with bidirectional shunting at the ductus arteriosus and right-to-left shunting at the atrial level consistent with systemic levels of pulmonary artery pressure. His gas exchange and hemodynamics stabilized during treatment with high-frequency oscillatory ventilation (HFOV), inhaled nitric oxide (iNO), and high-dose dopamine infusion. The infant was treated with antibiotics, and infectious causes for pulmonary hypertension (PH) were ruled out with negative blood cultures. A complete family history was obtained, which was negative for respiratory disorders. There was no history of consanguinity.

Hospital Course

Hypoxemic respiratory failure persisted over the first 5 days of life, with little improvement in ventilatory support requirements. Serial echocardiography showed near-systemic levels of pulmonary artery pressure despite iNO treatment. There was no echocardiographic evidence of structural heart disease, severe left ventricular systolic or diastolic dysfunction, or pulmonary venous stenosis to account for the patient’s persistent PH. Due to the severity and persistence of the PH, a lung biopsy was performed at age 6 days to rule out alveolar-capillary dysplasia (ACD); however, the lung histology was not diagnostic for ACD, but rather showed partial desquamation of the respiratory epithelium from membranous and terminal bronchioles. In addition, there was marked alveolar epithelial hyperplasia and moderate widening of alveolar walls without prominent cellular proliferation. This histology suggested a surfactant dysfunction mutation.

Because of a persistent left pneumothorax after the biopsy procedure that contributed to worsening hypoxemia, and in the absence of a diagnosis of severe persistent pulmonary hypertension of the newborn (PPHN), the infant was cannulated for extracorporeal membrane oxygenation (ECMO). Despite ECMO therapy, however, he continued to exhibit evidence of systemic levels of pulmonary artery pressure over a 10-day
course. Brief trials off iNO caused pulmonary artery pressure to rapidly become suprasystemic. Cardiac catheterization to evaluate for discrete pulmonary vein stenosis was declined by the infant’s family.

After discussion with the family regarding the futility of continued ECMO support, therapy was withdrawn, and the patient died. Significant findings at autopsy included hyperplasia and adventitial fibrosis of the pulmonary arteries, as well as right ventricular hypertrophy.

Studies obtained before death did not reveal the most common gene mutation for surfactant protein (SP)-B deficiency. However, electron microscopy of the lung specimen revealed absence of lamellar bodies, a finding consistent with ABCA3 deficiency. In the most severely affected infants with this disorder, normally formed, normally sized lamellar bodies are often absent in the cytoplasm of type II cells. The cytoplasm of type II cells in ABCA3-deficient infants instead may contain small dense bodies that likely reflect abnormally formed lamellar bodies, but the precise nature of these bodies has not yet been determined.1-3

Permission was obtained to enroll the child in a study to identify genetic mechanisms of lung disease. DNA was prepared from peripheral blood leukocytes as described previously,4 and the child was subsequently found to be homozygous for a missense mutation (L326R) in the gene encoding ABCA3.

Clinical Discussion

PPHN is a complex disorder associated with a wide array of cardiopulmonary diseases characterized by marked pulmonary hypertension and altered vasoreactivity, leading to right-to-left shunting of blood across the patent ductus arteriosus and foramen ovale.5,6 For near-term and term newborns with hypoxic respiratory failure and PPHN, therapies including iNO, HFOV, and exogenous surfactant treatment have decreased the use of ECMO over the last decade. Some patients fail to respond to standard treatment with iNO, HFOV, and ECMO, however. Up to 40% mortality has been reported in patients with refractory PH,7 and mortality remains very high in those patients who ultimately require ECMO. Failure to respond to iNO therapy has been associated with alveolar capillary dysplasia, discrete pulmonary vein stenosis, and severe lung hypoplasia, as seen with congenital diaphragmatic hernia. More recently, genetic abnormalities of surfactant function, also known as surfactant dysfunction mutations,8 have been recognized in patients who remain hypoxemic despite a prolonged course of iNO and ECMO.9

The last few years has brought increased recognition of surfactant dysfunction mutations and a better appreciation of their clinical presentation. Often these patients are full-term newborns with hypoxic respiratory failure. SP-B deficiency is characterized by progressive respiratory distress soon after birth, which ultimately leads to respiratory failure and death.10 Chest radiographs typically demonstrate diffuse ground-glass opacities. Patients with SP-C mutations have varied courses ranging from mild respiratory symptoms to severe respiratory failure.10 Radiographically, these patients show diffuse interstitial infiltrates. These surfactant dysfunction mutations are characterized by parenchymal lung disease rather than pulmonary vascular disease, and persistent PH is not commonly reported.

Recently, mutations in the gene encoding the transporter ABCA3 have been reported as a cause of severe neonatal lung disease.11,12 ABCA3 is localized to the limiting membrane of lamellar bodies, organelles containing concentric, onion-like layers of surfactant. Infants with ABCA3 mutations lack typical lamellar bodies, indicating that ABCA3 is critical to their formation.12,13 ABCA3 deficiency is inherited in an autosomal-recessive manner, and the clinical features have not been described in detail. In the limited number of cases of ABCA3 deficiency reported to date, newborns presented with initial signs of respiratory distress syndrome (RDS) and rapidly progressive respiratory failure that was refractory to ventilation and ECMO. Radiographic findings have not been specifically reported but have been described as showing diffuse pulmonary opacification, reticular-granular infiltrates, and air bronchograms consistent with RDS.10 In general severe, prolonged PH has not been reported as a prominent feature in children with ABCA3 mutations. Milder lung disease associated with prolonged survival due to ABCA3 mutations also has been reported recently.4

Here we report a case of ABCA3 deficiency presenting with severe hypoxic respiratory failure and refractory PH. Our patient differed from those previously reported because his primary presentation was severe PH that was unresponsive to traditional therapies, including iNO and HFOV. He did
not present with the typical clinical signs of RDS, and for the first several days of life he had relatively clear lung fields on chest radiographs. He did not develop evidence of parenchymal lung disease until much later in his hospital course, and his initial presentation was severe PH that appeared to be out of proportion to his degree of lung disease.

Information is emerging on the clinical spectrum of patients with surfactant dysfunction mutations. As more patients with these genetic disorders are identified, we may be able to begin to recognize patterns of clinical presentation for these diseases. Surfactant dysfunction mutations are associated with marked changes in the airspaces, alveolar epithelium, and interstitium. Whether or not these diseases are also associated with abnormalities of pulmonary vascular development remains unknown. Our patient failed to respond to iNO despite adequate lung recruitment and cardiac support. The other etiologies of PH that typically fail to respond to iNO were excluded after appropriate evaluation. This case suggests that perhaps iNO nonresponders and/or patients with prolonged, refractory PH should be evaluated for surfactant dysfunction mutations as well. Experience with these rare genetic surfactant abnormalities is limited at this time. Refractory PH may turn out to be common among patients with this disease. Until we understand more about the presentation and clinical course of this disease, it is important to keep a high index of suspicion in patients with severe PH.

We thank the physicians, staff, and consultants involved in the care of this patient. We are grateful to the investigators who provided their time and helpful comments in the preparation of this manuscript.

REFERENCES

A four-year-old girl was admitted with recurrent pneumonias. She was found to have triangular facies, generalized, non-paralytic hypotonia, severe scoliosis, pectal deformity, extreme short stature, and blue scleral hue. Cerebellar signs were absent. Radiographs showed osteoporotic bone with metaphyseal flaring. With this picture, the diagnosis of osteogenesis imperfecta type III was made. MRI of the brain showed severe cerebellar hypoplasia, associated with angulation of the brainstem, but no basilar invagination (Figure).

The recognized neurological complications of osteogenesis imperfecta include cranio-vertebral junction anomalies such as basilar invagination, syringohydromyelia, hydrocephalus, and brainstem compression; there has also been an isolated report of Dandy-Walker malformation.1 There are only two reported cases of cerebellar hypoplasia associated with osteogenesis imperfecta type IV and V.2,3 The proposed mechanism for cerebellar hypoplasia is *in utero* vascular compromise with hypoplastic posterior circulation structures due to associated cranio-vertebral junction anomalies. Neurologic evaluation should be part of a team approach in the management of patients with severe osteogenesis imperfecta types.

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REFERENCES
Adenotonsillectomy less beneficial for sleep apnea in older and obese children


Question In children with obstructive sleep apnea (OSA), are there factors that predict whether symptoms will resolve after adenotonsillectomy (T&A)?

Design Cohort study.

Setting Children’s Hospital, Louisville, Kentucky.

Participants 110 children, age 1 to 16 years (mean age, 6.4 years), along with 22 control children.

Intervention The intervention group underwent 2 polysomnographic evaluations before and after T&A. History of allergy and family history of sleep-disordered breathing was obtained before each polysomnographic evaluation.

Outcome Persistence of sleep-disordered breathing, as defined by an apnea/hypopnea index (AHI) > 5/hour of total sleep time (TST).

Main Results Significant changes in sleep stage percentages and sleep fragmentation were found in the postsurgery study compared with the presurgery study; 25% of the children had an AHI < 1, 46% had an AHI of 1 to 5, and 29% had an AHI > 5 in the postsurgery study. The frequency of children with an AHI > 5/h of TST after surgery was higher in the obese subjects than in the nonobese subjects (36.4% vs 17.6%, P < .05).

Conclusions T&A yields improvements in respiratory abnormalities in children with OSA syndrome, although complete normalization occurs in only 25% of patients. Obesity and AHI at diagnosis are the major determinants of surgical outcome. When normalization of respiratory measures occurs after surgery, normalization of sleep architecture will also ensue.

Commentary OSA is common and potentially harmful. T&A is often used to treat OSA in children. Previous studies have shown that abnormal polysomnographic findings persist after T&A in up to 40% of cases. In the present study, 29% of the patients continued to have more than 5 apneic or hypopneic episodes per hour of sleep time after T&A. Older patients and patients with high body mass index were even more likely to continue to experience OSA after surgery. However, no data on patient symptoms were obtained. It is possible that even patients with an AHI > 5 after T&A experienced improvement in symptoms after the procedure. Notably, children with genetic disorders, cerebral palsy, neuromuscular disease, or any underlying systemic disease were excluded from the study, so it is unclear how these children might benefit from T&A. It also is unclear whether the initial group of 110 patients was chosen prospectively or retrospectively, which could affect the validity of the data. When recommending T&A to parents as a treatment for OSA, physicians need to provide appropriate education so that parents will have realistic expectations. Families should be told that T&A may not cure OSA, particularly in older and obese patients. In addition, this study suggests that postoperative polysomnography should be considered in patients undergoing T&A for OSA.


Question Among young children, how does prevalence of influenza alter the predictive ability of rapid influenza tests?

Design Longitudinal cohort.
Commentary  Influenza is a very common childhood disease, responsible for many pediatric ambulatory visits and hospitalizations during the winter months in the northern hemisphere. This study conveys an important message about interpreting diagnostic tests and reiterates the importance of disease prevalence in test interpretation. That is, when the disease prevalence is low, the PPV of a test also will be low, and when the disease prevalence is high, the PPV will be high. Several important points should be considered when examining the results of the present study. First, although all the tests were compared using a gold standard procedure (viral culture or RT-PCR), several antigen tests with differing performance characteristics, were lumped together. This affects interpretation of the results of a single rapid test used in an institution. Second, to assess whether a test is valid, we need to ask whether the diagnostic test was evaluated in an appropriate spectrum of patients (eg, those in whom it would be used in practice). Rapid tests to either rule in or rule out disease are useful primarily in outpatient settings for such reasons as to reduce the need for further testing and/or antibiotic therapy and to reassure parents. In this study, the rapid tests were performed only on inpatients, and the results were translated to the outpatient population. This limits the generalizability of the results to the outpatient and emergency department settings, where these tests are most often used.

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Failure to respond to name is indicator of possible autism spectrum disorder


Question  Among children at high risk for autism, does failure to respond to name accurately predict a subsequent diagnosis of autism spectrum disorder (ASD)?

Design  Prospective longitudinal study of infants at risk for autism.

Setting  University medical center.

Participants  Infants at risk for autism (55 age 6 months and 101 age 12 months) and a control group at no known risk (43 age 6 months and 46 age 12 months). To date, 46 at-risk infants and 25 control infants have been followed up to 24 months.

Intervention  Experimental task eliciting response-to-name behavior.

Outcome  Autism Diagnostic Observation Schedule, Mullen Scales of Early Learning.

Main Results  At age 6 months, there was a nonsignificant trend for control infants to require a fewer number of calls to respond to name compared with the infants at risk for autism. At age 12 months, 100% of infants in the control group “passed,” responding on the first or second name call, compared with 86% in the at-risk group. Three-fourths of the children who failed the task were identified with developmental problems at age 24 months. Specificity of failure to respond to name was 0.89 for ASD and 0.94 for any developmental delay; sensitivity was 0.50 for ASD and 0.39 for any developmental delay. For a diagnosis of ASD, the likelihood ratios are 4.55 for a positive test and 0.56 for a negative test.

Conclusions  Failure to respond to name by age 12 months is highly suggestive of developmental abnormality but does not identify all children at risk for developmental problems. Lack of response to name is not universal among infants later diagnosed with ASD and/or other developmental delays. Poor response to name may be a trait of the broader autism phenotype in infancy.

Commentary  Developmental pediatricians have advocated for earlier diagnosis of autism because of growing evidence that early intervention may improve long-term outcomes. However, no single diagnostic test has been found to be reliable and valid. Retrospective studies using videotapes of
children subsequently diagnosed with autism have suggested a consistently decreased response to name. This also has been seen in some prospective studies. The current study compared a group of high-risk children (infant siblings of a child diagnosed with autism) with a control group representative of the general population. By age 12 months, children who did not respond to their name were much more likely to be diagnosed with developmental delay or an ASD. Although the sensitivity was low, the specificity was decent, giving a positive likelihood ratio of 4.55 for the diagnosis of ASD. This was a small study, and the authors are still planning to follow all of the children to age 36 months. Larger numbers of children also will produce more stable estimates of sensitivity and specificity. In addition, this test was applied in a group of high-risk children, resulting in spectrum bias, and care needs to be taken when applying this to the general population of patients seen in practice. Nonetheless, response-to-name behavior is an easy and inexpensive test. A high-risk child who fails to respond to his or her name at 12 months should be referred for further testing.

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ALSO NOTED


Delayed clamping of the umbilical cord after delivery results in placental transfusion. In children born vaginally, a 2- to 3-minute delay in clamping can increase the neonate’s blood volume by 20 to 30 mL/kg. The potential benefits and drawbacks of late cord clamping were assessed using meta-analysis. This validation study examined 15 controlled trials involving 1912 newborns. At age 2 to 6 months, those with delayed clamping (>2 minutes) demonstrated increased hematocrit, ferritin, and stored iron levels. Importantly, these children also had a clinically significant decrease in the risk of anemia (relative risk = 0.53; 95% confidence interval = 0.4 to 0.7). Newborns with late clamping were at increased risk for asymptomatic polycythemia, but no other adverse effects were noted. Of note, this study did not address the effect of the current practice of administering oxytocin at the end of labor, and an accompanying editorial does not recommend altering this practice.


Which pain medication (acetaminophen, ibuprofen, or codeine) provides the best analgesia for children with musculoskeletal injuries? This question was investigated by a randomized, controlled trial of children age 6 to 17 years who presented to the emergency department with pain from a musculoskeletal injury sustained in the previous 48 hours. Children were randomized to receive 1 oral dose of acetaminophen 15 mg/kg, ibuprofen 10 mg/kg, or codeine 1 mg/kg. Using a visual analog scale, children rated their own pain. At 30 minutes, there was no statistical difference between pain scores in the 3 groups. However, at 60 or more minutes, patients who had received ibuprofen exhibited significantly greater improvement in pain scores compared with those in the acetaminophen or codeine groups. In addition, more patients in the ibuprofen group had achieved adequate analgesia compared with the other 2 groups (52% vs 36% and 40%; P < .001; NNT = 7 and 9, respectively). Ibuprofen appears to be more effective than acetaminophen or codeine in the treatment of acute musculoskeletal pain, particularly if a fracture is present. However, ibuprofen alone often provides inadequate pain control.
Transfusion threshold in anemic premature infants

To the Editor:

The Iowa and Premature Infants in Need of Transfusion trials did not resolve an important question: “How far can we push the anemic preterm infant before transfusion?” In these trials, the low hemoglobin threshold values for restrictive transfusion practices in preterm infants with no respiratory support were 26% ± 5% and ≤23% (hemoglobin of ≤75 g/L), respectively.

We evaluated cardiac function in stable, very-low-birth weight infants with hematocrit ranges of 14% to 21% and found that these infants have much higher end-diastolic and end systolic diameters and stroke volumes in comparison to infants with higher hematocrit levels. On the basis of echocardiographic measures, we suggested that many stable infants with hematocrit levels ≤21% are in a high cardiac output state. The cutoff values for abnormal end-diastolic and end systolic diameters and stroke volumes were approximately 15 mm, 10 mm, and 2.6 mL/kg, respectively. Because the current “traditional” criteria for packed red blood cell transfusion are not sensitive, new variables are needed to guide the clinician when to transfuse the anemic preterm infant.

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REFERENCES

Reply

To the Editor:

Drs Alkalay and Simmons point out that the lowest safe limits for transfusion are not yet known for preterm newborns. We agree. This reiterates our own cautious conclusion that “transfusion thresholds in ELBW infants can be moved downwards by at least 10 g/L.”1 Pushing the lower limits of transfusion further remains to be tested in randomized controlled trials with clinically meaningful primary outcomes. Although this approach is open to the charge of being a tedious and iterative stepwise procedure, it remains the prudent way forward. In our view, extrapolations to lower guidelines than were tested by the Premature Infants in Need of Transfusion Study and the Iowa study are premature. The situation may be compared with the historical yo-yo-ing back and forth of “appropriate oxygen levels” in the absence of specific targeted trials. It is only now that a series of coordinated international trials is addressing this dilemma in the appropriate manner. They all use clinically relevant primary outcomes.

Alkalay and Simmons also make an interesting proposal that the criteria for establishing transfusion thresholds for preterm newborns should be physiologically based, presumably by use of echocardiography. We are aware of their work cautioning that lower limits of hemoglobin are associated with echocardiographic findings considered abnormal.1 Others have also tried to use physiological measures, including fractional oxygen extraction.2,3 However, use of such surrogate physiological measures have their own issues. For example, is the relative risk of a transfusion better or worse than an adaptation to lower hemoglobin with a raised cardiac output? If surrogate physiological measures are used, they need to be robust and highly predictive of meaningful (preferably long-term) clinical outcomes.3 Ultimately, their use would still require evaluation via randomized controlled trials.

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REFERENCES

The natural history of thyroid autoimmunity and thyroid function in children with type 1 diabetes

To the Editor:

We read with interest the report by Radetti et al1 regarding the natural history of euthyroid Hashimoto thy-
roiditis in children. We have some questions about their data. The criteria for selection of patients and their inclusion in the study have not been made clear. According to the authors, “the presence of Hashimoto thyroiditis was diagnosed on the basis of typical ultrasound imaging findings and presence of thyroid peroxidase antibodies and thyroglobulin antibodies.” Because clinical presence of goiter was not one of the criteria for patient selection, one must surmise that the children at risk were screened by the measurement of thyroid antibodies before they were subjected to a more expensive and involved procedure such as ultrasound imaging. However, in Figures 1, 3, and 4, up to 50% of patients are shown to have normal (grade 0) TPO and TG antibodies. How were these patients identified as having Hashimoto thyroiditis? Also, 2 measurements of any markers of a chronic condition, separated by a few weeks to 32 years, hardly provide information about the “natural history” of the condition especially when the study is conducted in a retrospective manner.

We measured thyroid antibodies (thyrAb) every 3 to 6 months in 236 white, black, and Hispanic (Puerto Rican) children (x = 10.4 years) with type 1 diabetes (T1D) in a 5.5-year prospective study. Initial thyrAb were measured at diagnosis of T1D in 99 children (Group I) and sometime subsequent to diagnosis in 137 children (Group II) (Table). Follow-up was from 1 year to 5.5 years (x = 2.9 years) in 160 children (62 from Group I; 98 from Group II). The prevalence of positive thyroid antibodies at diagnosis of T1D was 17.4%, similar to that reported by others.2-4 There was no significant difference in age between those children with negative and positive thyrAb. The natural history of thyrAb in our population showed that 10% of children demonstrated conversion of their initial thyrAb status. In 7 children, thyrAb were detected intermittently; in 4 initially positive, thyrAb became negative; in 5 initially negative, thyrAb became positive. Fifty children (21%) had positive antibodies at some point during the study. The prevalence of positive thyrAb obtained subsequent to diagnosis of T1D was significantly greater than those obtained at time of diagnosis (P < .05). The highest prevalence of positive thyrAb was in our population of Hispanic children. This is congruent with our data from the Philadelphia Pediatric Type 1 Diabetes Registry that has been maintained since 1985. We demonstrated that Hispanic children in Philadelphia have the highest incidence of T1D of any racial group in the United States.5-7

In children with positive thyrAb, T4 and TSH were measured every 3 to 6 months. Ten children (20%) had normal T4 levels, and their serum TSH levels were 1.5 to 5 times the upper limit of normal; in 70% of these patients, serum levels of TSH normalized without treatment. One of these children had a peak TSH level of 25 mU/L. Although height deceleration has been reported in children with subclinical hypothyroidism,8 it was not demonstrated in our population, nor were there any other signs or symptoms of hypothyroidism. The prevalence of elevated TSH in our population is lower than that reported by Radetti et al,1 yet the prevalence of overt hypothyroidism in our group of patients was similar to the 5.6% in the population described by Radetti et al.1 Of 50 of our subjects who had positive thyrAb at any point in the study, only 3 (6%) developed overt hypothyroidism. Age, duration of diabetes, and level of thyrAb were not associated with the development of overt hypothyroidism.

Our data demonstrate that, as with many autoimmune disorders, there are racial disparities in the prevalence of thyroid autoimmunity in children with T1D. In our population, thyrAb at the time of diagnosis did not always predict subsequent presence or absence of antibodies. Therefore a single measurement of thyrAb at diagnosis of diabetes is not sufficient to identify thyroid autoimmunity. In some children, positive thyrAb occur later, in others positive antibodies may spontaneously remit. We concur with Radetti et al1 that most children with thyroid autoimmunity and TSH levels above normal do not develop overt hypothyroidism. Our data, and those of Moore,9 show that even patients with elevated TSH may have a benign course, and in many subjects (70% of our population) the TSH spontaneously normalizes. Follow-up, rather than empirical treatment of those children may be indicated.
Reply

To the Editor:

We thank Dr. Lipman et al for their interest in our recently published article. In the first part of the letter, they wonder how the diagnosis has been made, in particular because goiter was not present in all children. Obviously the presence of goiter suggested the diagnosis of Hashimoto thyroiditis in most of the children and, in the remaining, it has been made during routine evaluation of children with other known autoimmune disease, such as diabetes and vitiligo. The diagnosis was then confirmed by the typical ultrasound findings together with the presence of thyroid-peroxidase and thyroglobulin antibodies. The presence of at least one antibody was considered necessary, which explains the presence in Figures 1, 3, and 4 of children without one antibody.

The authors also describe the presence of anti-thyroid antibodies and thyroid function in a group of diabetic children followed-up for about 5 years. In agreement with our findings, antithyroid antibodies serum levels, as well as thyroid function largely fluctuated over time with no negative effect on growth. Unfortunately, they never performed a thyroid ultrasound in their patients during follow-up, because, reportedly, the presence of anti-thyroid antibodies alone is not a sufficient criterion for the diagnosis of Hashimoto thyroiditis. Moreover, the prevalence of celiac disease in their diabetic patients is not known. It has been reported, in fact, that, by following a gluten-free diet, anti-thyroid antibodies may disappear.

We are pleased that they do agree with our conclusion that treatment with thyroxine should not be started just when TSH levels are slightly elevated but rather that a watchful observation is recommended.
Additionally, 54 (39%) children with BMI ≥99th percentile had a BMI ≥ 30 kg/m², 13 (9.3%) had a BMI ≥ 35 kg/m², 4 had a BMI ≥ 40 kg/m², and 127 (91%) had a WC ≥90th percentile. Because children at these levels of extreme obesity are at risk for biochemical abnormalities and severe adult obesity,¹ intensive interventions are needed in Mexico to stop this epidemic with its current and potential for future burden to the health care system.

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REFERENCES