The Journal of Pediatrics

Volume 150, Issue 3, Pages, 213-324 (March 2007)

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THE EDITORS’ PERSPECTIVES

“Bad to the Bone”

Regular readers of The Journal cannot have missed the explosion of interest in bone mineralization studies in children with various chronic disorders. Our understanding of this topic has deepened, and it is recognized that the different modalities employed in the measurement of bone density (DEXA, qualitative CT, and speed of sound [SOS]) do not measure exactly the same thing; each has its advantages and disadvantages, depending upon the situation.

A nice example of this is found in a study by DiVasta et al in Boston in this issue of The Journal. These workers examined a cohort of teenagers with anorexia nervosa, a condition known to be associated with abnormalities in bone mineralization. The short version of their conclusions is that SOS is not the appropriate modality for this population. The reason for this is not clear, but may relate to the effect of changes in other tissue compartments (e.g. fat) in the measurement.

—Thomas R. Welch, MD
page 286

The car seat challenge - What makes sense

The standard of care prior to discharge of a preterm infant is a test of cardiorespiratory stability in the car seat to be used for transporting the infant home. Some infants do have cardiorespiratory events when placed in car seats. The car bed, which allows the infant to be flat, is viewed as a good alternative for discharge. Salhab et al performed a high quality randomized-control trial comparing predischarge respiratory events for preterm infants placed in car seats or car beds. They found no differences in events. In an editorial, Greenberg points out that there is no evidence of the validity of the “car seat challenge,” even though the evaluation is endorsed by the American Academy of Pediatrics. Perhaps it is time to evaluate the utility of car seat assessments prior to discharge of preterms. It may be more effective to simply recommend limited automobile travel for preterms in car seats, along with continual observation during travel to protect the infant from cardiorespiratory events.

—Alan H. Jobe, MD, PhD
page 224 (article)
page 215 (editorial)
How to treat the PDA for the best outcome

The options for many years for the treatment of the PDA in very low birth weight infants have been surgical ligation or indomethacin therapy. For some clinicians, the surgical option is preferable to the possible toxicities associated with indomethacin. Other clinicians do not have good access to PDA ligation or prefer the simplicity of indomethacin therapy. The recent availability of ibuprofen for ductal closure has not changed that equation. The TIPP trial demonstrated that there were not large differences in neurodevelopmental outcomes for infants receiving indomethacin relative to placebo. Depending on how they interpret the results, clinicians use the TIPP trial to justify or avoid the prophylactic use of indomethacin. The results of the new analysis of the TIPP trial by Kabra et al further complicate clinical decisions. Infants who received PDA ligation had less favorable neurodevelopmental outcomes, and BPD and ROP were more common after PDA ligation. These associations are consistent with other reports that anesthesia and surgery in the newborn period are associated with adverse long-term outcomes. The more we know about options to close the PDA, the less secure we are in how to best select the intervention.

—Alan H. Jobe, MD, PhD

Increased pneumothorax with elective C-section

The rate of elective C-section is increasing in the United States and is very high in some other countries. Although a repeat C-section after a previous C-section is the most common indication for an elective C-section, the number of C-section deliveries for no apparent medical reason or at parental request is increasing. The number of C-sections prior to 39 completed weeks of pregnancy also is increasing. The rationale for some of these operative deliveries is to minimize risk for the fetus by avoiding labor. Zanardo et al report that the risk of a symptomatic pneumothorax requiring medical intervention increased to 2.9 per 1000 for elective C-section relative to rates of 1.5 per 1000 for emergency Cesarean section and 0.4 per 1000 for vaginal delivery. Pneumothorax was much more frequent for elective C-sections done prior to 38 weeks gestation. These results are not surprising as others have documented increased respiratory distress and problems with neonatal adaptation after elective C-section. Although infrequent, these adverse outcomes need to be balanced against the risks of labor and a vaginal delivery.

—Alan H. Jobe, MD, PhD
Age under 60 months and underlying neurologic or neuromuscular disorder increase risk for influenza-related hospitalization

In a retrospective cohort study over four influenza seasons, and including 842 children hospitalized and confirmed to have influenza, Newland et al found that the age of 6 to 60 months and underlying neurologic or neuromuscular disorder were independently associated risk factors for hospitalization. Odds ratios for hospitalization for these groups were several-fold higher than those of healthy older children and children without these disorders. Data support current influenza vaccine recommendations and underscore urgency for implementation.

—Sarah S. Long, MD

The course of West syndrome

West syndrome (infantile spasms) is an unusual but generally devastating epileptic syndrome presenting in infancy. Although occasionally one component of an underlying disorder (such as chromosomal derangements or metabolic diseases), the disorder is idiopathic (“cryptogenic”) in a number of children.

Much of our contemporary knowledge of West syndrome comes from work by Hamano et al in Japan. In the current issue of *The Journal*, this group addresses the question of factors that might predict the developmental outcome of children with cryptogenic West syndrome. These workers reviewed the records of 32 patients with an average age of over 8 years. Specifically, they looked for differences between children with a normal developmental outcome and those with delays.

Children with normal developmental outcome had a shorter lag between the onset of spasms and the institution of treatment (a variety of agents, including anticonvulsants, intravenous gamma globulin, and ACTH). Delayed children were also more likely to have other seizures types associated with their infantile spasms, and to have EEGs that evolved to show frontal lobe activity.

Given the size of the group studied, as well as the careful data collection by this group, this should be a valuable paper for the clinician who is counseling a family with a child in whom this frightening diagnosis is made. Although it is not clear from this study whether the “short interval” observation is a surrogate for something else or a direct effect of early treatment, the study also suggests that this is a diagnosis that should be pursued vigorously once suspected.

—Thomas R. Welch, MD

Gastric aspiration in SIDS

SIDS cannot be reliably assigned as the cause of death without a complete assessment of the circumstances of the death and a thorough autopsy. A major initial concern about the very successful “Back to Sleep” campaign in the United States was that infants would aspirate if placed on their backs, despite epidemiological data to the contrary from elsewhere in the world. The fear of aspiration persists, and an autopsy finding of aspiration is routinely discounted as a post-mortem finding, particularly if resuscitation was attempted. Krous et al now report that some infants who died of SIDS and who did not receive resuscitative attempts had findings suggesting that aspiration may have contributed to the death. However, supine sleeping position did not increase the identification of aspiration. “Back to Sleep” is the best defense to SIDS and does not increase the risk of aspiration.

—Alan H. Jobe, MD, PhD
AMSPDC: Current Initiatives and Future Opportunities
F. Bruder Stapleton, MD, Seattle, Washington

EDITORIALS

The Challenge of Car Safety Seats
James M. Greenberg, MD, Cincinnati, Ohio

Patent Ductus Arteriosus: Evidence for and against Treatment
Ronald I. Clyman, MD, and Nancy Chorne, MD, San Francisco, California

Assessment of Vascular Function: Pulse Wave Velocity
Bruce S. Alpert, MD, and R. Thomas Collins, MD, Memphis, Tennessee, and Philadelphia, Pennsylvania

MEDICAL PROGRESS

Family Functioning in Children with Chronic Illness Compared with Healthy Controls: A Critical Review
Catherine B. McClellan, PhD, and Lindsey L. Cohen, PhD, Columbia, South Carolina, and Atlanta, Georgia

ORIGINAL ARTICLES

Car Seat or Car Bed for Very Low Birth Weight Infants at Discharge Home
Walid A. Salhab, MD, Asif Khattak, MD, Jon E. Tyson, MD, MPH, Sharon Crandell, MD, Jan Sumner, PNP, Beverly Goodman, PNP, Linda Fisher, PNP, and Karen Robinson, NNP, Dallas and Houston, Texas

John G. Frohna, MD, MPH, Ann Arbor, Michigan

Neurosensory Impairment after Surgical Closure of Patent Ductus Arteriosus in Extremely Low Birth Weight Infants: Results from the Trial of Indomethacin Prophylaxis in Preterms
Nandkishor S. Kabra, MD, Barbara Schmidt, MD, MSc, Robin S. Roberts, MSc, Lex W. Doyle, MD, Luann Papile, MD, Avroy Fanaroff, MD, and the Trial of Indomethacin Prophylaxis in Preterms (TIPP) Investigators, Hamilton, Ontario, Canada, Melbourne, Australia, Albuquerque, New Mexico, and Cleveland, Ohio
Early Inhaled Nitric Oxide Therapy for Term and Near-Term Newborn Infants with Hypoxic Respiratory Failure: Neurodevelopmental Follow-Up
G. Ganesh Konduri, MD, Betty Vohr, MD, Charlene Robertson, MD, Gregory M. Sokol, MD, Alfonso Solimano, MD, Joel Singer, PhD, Richard A. Ehrenkranz, MD, Nalini Singhal, MD, Linda L. Wright, MD, Krisa Van Meurs, MD, Eileen Stork, MD, Haresh Kirpalani, MD, Abraham Peliowski, MD, Yvette Johnson, MD, and the Neonatal Inhaled Nitric Oxide Study Group, Milwaukee, Wisconsin

Aspiration of Gastric Contents in Sudden Infant Death Syndrome without Cardiopulmonary Resuscitation
Henry F. Krous, MD, Homeyra Masoumi, MD, Elisabeth A. Haas, MPH, Amy E. Chadwick, BA, Christina Stanley, MD, and Bradley T. Thach, MD, San Diego and La Jolla, California, and St. Louis, Missouri

50 Years Ago in The Journal of Pediatrics—Editor’s Column: The Story of Aspirin
Bonita Stanton, MD, Detroit, Michigan

Association between Brachial-Ankle Pulse Wave Velocity and Cardiovascular Risk Factors in Healthy Adolescents
Jee-Aee Im, PhD, Ji-Won Lee, MD, Jae-Yong Shim, MD, PhD, Hye-Ree Lee, MD, PhD, and Duk-Chul Lee, MD, PhD, Seoul, Korea

The Influence of Timing of Elective Cesarean Section on Risk of Neonatal Pneumothorax
Vincenzo Zanardo, MD, Ezio Padovani, MD, Carla Pittini, MD, Nicoletta Doglioni, MD, Anna Ferrante, MD, and Daniele Trevisanuto, MD, Padua, Verona, and Udine, Italy

Respiratory Health in Prematurely Born Preschool Children with and without Bronchopulmonary Dysplasia
E. J. L. E. Vrijlandt, MD, PhD, H. M. Boezen, PhD, J. Gerritsen, MD, PhD, E. F. Stremmelaar, MD, and E. J. Duiverman, MD, PhD, Groningen, The Netherlands

Characteristics of Children Receiving Proton Pump Inhibitors Continuously for Up to 11 Years Duration
Eric Hassall, MBChB, FRCP, Wendy Kerr, RN, BSN, and Hashem B. El-Serag, MD, MPH, Vancouver, British Columbia, Canada, and Houston, Texas

The Contribution of the DLG5 113A Variant in Early-Onset Inflammatory Bowel Disease
R. K. Russell, MRCPCH, H. E. Drummond, BSc, E. R. Nimmo, BSc, MSc, PhD, N. Anderson, BSc, PhD, D. C. Wilson, MD, FRCPCH, P. M. Gillett, MBChB, FRCPCH, P. McGrogan, MBChB, MRCP, K. Hassan, MBBS, FRCPCH, L. T. Weaver, MD, FRCPCH, W. M. Bisset, MD, FRCPCH, G. Mahdi, FRCPCH, and J. Satsangi, DPhil, FRCP, Edinburgh, Glasgow, and Aberdeen, United Kingdom

50 Years Ago in The Journal of Pediatrics—Explosion of Nursing Bottles
Bonita Stanton, MD, Detroit, Michigan

Characteristics of Children with Vomiting after Minor Head Trauma: A Case-Control Study
Liviana Da Dal, MD, Barbara Andreola, MD, Paola Facchin, MD, Marzia Gregolin, MD, Andrea Vianello, MD, and Pier Antonio Battistella, MD, Padova, Italy

Temporal Trends in the Treatment of Pediatric Type 1 Diabetes and Impact on Acute Outcomes
Britta M. Svoren, MD, Lisa K. Volkering, BA, Deborah A. Butler, MSW, Elaine C. Moreland, MD, Barbara J. Anderson, PhD, and Lori M. B. Laffel, MD, MPH, Boston, Massachusetts, Birmingham, Alabama, and Houston, Texas

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50 Years Ago in *The Journal of Pediatrics*—Loeffler’s Pneumonia Associated with Hypogammaglobulinemia

Alan P. Knutsen, MD, St. Louis, Missouri

Skeletal Measurements by Quantitative Ultrasound in Adolescents and Young Women with Anorexia Nervosa

Amy D. DiVasta, MD, MMSc, Julie Ringelheim, BA, Stephanie K. Bristol, BS, Henry A. Feldman, PhD, and Catherine M. Gordon, MD, MSc, Boston, Massachusetts

Prospective Study of Infantile Hemangiomas: Demographic, Prenatal, and Perinatal Characteristics

Anita N. Haggstrom, MD, Beth A. Drolet, MD, Eulalia Baselga, MD, Sarah L. Chamlin, MD, Maria C. Garzon, MD, Kimberly A. Horii, MD, Anne W. Lucky, MD, Anthony J. Mancini, MD, Denise W. Metry, MD, Brandon Newell, MD, Amy J. Nopper, MD, and Ilona J. Frieden, MD, Washington, DC, Indianapolis, Indiana, Milwaukee, Wisconsin, Barcelona, Spain, Chicago, Illinois, New York, New York, Kansas City, Kansas, Cincinnati, Ohio, Houston, Texas, and San Francisco, California

Developmental Outcomes of Cryptogenic West Syndrome

Shin-ichiro Hamano, MD, Satoshi Yoshinari, MD, Norimichi Higurashi, MD, Manabu Tanaka, MD, Motoyuki Minamitani, MD, PhD, and Yoshikatsu Eto, MD, PhD, Saitama and Tokyo, Japan

Increased Prevalence of Thyroid Autoimmunity and Hypothyroidism in Patients with Glycogen Storage Disease Type I

Daniela Melis, MD, PhD, Rosario Pivonello, MD, PhD, Giancarlo Parenti, MD, Roberto Della Casa, MD, Mariarosaria Salerno, MD, Gaetano Lombardi, MD, PhD, Gianfranco Sebastio, MD, Annamaria Colao, MD, and Generoso Andria, MD, Naples, Italy

Neurologic Complications in Children Hospitalized with Influenza: Characteristics, Incidence, and Risk Factors


**SPECIAL ARTICLE**

Pediatrics Workforce: A Look at Developmental-Behavioral Pediatrics Data from the American Board of Pediatrics

Linda A. Althouse, PhD, and James A. Stockman, III, MD, Chapel Hill, North Carolina

**CLINICAL AND LABORATORY OBSERVATIONS**

Neonatal Cholestatic Jaundice as the First Symptom of a Mutation in the Hepatocyte Nuclear Factor-1β gene (HNF-1β)

Dominique Beckers, MD, Christine Bellanné-Chantelot, PharmD, PhD, and Marc Maes, MD, PhD, Yvoir, Belgium, Paris, France, and Brussels, Belgium

Transient Neonatal Hypothyroidism is Associated with Elevated Serum Anti-Thyroglobulin Antibody Levels in Newborns and Their Mothers

Arash Ordookhani, MD, Parvin Mirmiran, PhD, Paul G. Walfish, CM, MD, and Fereidoun Azizi, MD, Tehran, Iran, and Toronto, Ontario, Canada
Clinical Research Abstracts for Pediatricians

Insights

Multislice Spiral Computed Tomography in a Neonate with Vein of Galen Aneurysmal Malformation

Jun Muneuchi, MD, Kunitaka Joo, MD, Kunimi Higashiyama, MD, and Akira Mizushima, MD, Fukuoka, Japan

Corrections

Recombinant Human Insulin-Like Growth Factor I (rhIGF-I) and rhIGF-I/rhIGF-Binding-Protein-3: New Growth Treatment Options?

(AL Rosenbloom, J Pediatr 2007;150:7-11)

The Natural History of Euthyroid Hashimoto’s Thyroiditis in Children

(Radetti et al, J Pediatr 2006;149:827-32)

Duration of Illness is an Important Variable for Untreated Children with Juvenile Dermatomyositis


Letters

The following section is available in the online version of The Journal.

Down Syndrome and GATA1-Related Transient Leukemia

Claudio Sandoval, MD, and Sharon R. Pine, PhD, Valhalla, New York

Nasal Potential Difference in Cystic Fibrosis Diagnosis of Very Young Children

Isabelle Sermet-Gaudelus, MD, PhD, Emmanuelle Girodon, MD, Frédéric Huet, MD, PhD, Rola Aboutaam, MD, Stéphanie Bui, MD, Eric Deneuville, MD, Marcel Guillot, MD, Stéphanie Vrielynck, MD, Gérard Lenoir, MD, and Aleksander Edelman, PhD, Paris, Créteil, Dijon, and Lisieux, France

Reader Services

Information for Readers

Announcements

Guide for Authors

Available at www.jpeds.com
March 2007

Miami Children’s Hospital 42nd Annual Pediatric Postgraduate Course “Perspectives in Pediatrics” and Pediatric Board Review Dates. March 16-22, 2007, InterContinental Hotel Downtown, Miami, FL. Adolescent Medicine, Allergy, Immunology, Cardiology, Dermatology, Gastroenterology, Genetics, Hematology/Oncology, Infectious Diseases, Nephrology, Neurology, Neurosurgery, Nutrition, Ophthalmology, Orthopedics, Pediatric Surgery, Plastic Surgery, Preventive Medicine/Community Pediatrics, Psychiatry, Radiology, and more. For more information, contact Riccardo Firmino, Conference Management Office, Miami Children’s Hospital; phone: 305-756-0791; E-mail: rfirmino@firminousa.com; Website: www.ppgcepip.com.

The Spectrum of Developmental Disabilities XXIX. March 26-28, 2007, Johns Hopkins University School of Medicine, Baltimore, MD. For more information, contact the Office of Continuing Medical Education; phone: 410-955-2959; E-mail: cmenet@jhmi.edu; Website: www.hopkinscme.net.

April 2007

2007 Regional Conference on Child Health Psychology. April 26-28, 2006, Westin Hotel, Cincinnati, OH. Sponsored by the Division of Behavioral Medicine and Clinical Psychology at Cincinnati Children’s Hospital Medical Center in cooperation with the Society of Pediatric Psychology and the Ohio Chapter of the Society for Developmental and Behavioral Pediatrics. For more information visit www.cincinnatichildrens.org/spp-conference.

May 2007

The Programme for Global Paediatric Research Symposium: “Global Childhood Diseases Which Can Impair Development” and Workshop: “Outcome Studies.” May 8-9, 2007, Toronto. Sponsored by The Programme for Global Paediatric Research. PGPR’s fifth symposium will be held May 8, 2007 in conjunction with the annual meeting of the Pediatric Academic Societies. To register for the PAS Meeting, at which this symposium will be held, please go to www.pas-meeting.org. To register for the follow-up workshop on May 9, 2007, please contact Alvin Zipursky, Chair and Scientific Director; phone: 416-813-8762; E-mail: Alvin.zipursky@sickkids.ca; Website: www.globalpaediatricresearch.org.

18th Annual Spring Conference on Pediatrics. May 16-19, 2007, Marriott Frenchman’s Reef Beach Resort, St. Thomas, United States Virgin Islands. Sponsored by Symposis Medicus. For more information, contact Symposis Medicus; phone: 925-969-1789, 800-327-3161; E-mail: info@symposiamedicus.org; Website: www.symposiamedicus.org.

July 2007

29th Annual Aspen Conference on Pediatric Gastrointestinal Disease: Pediatric Gastrointestinal Disease and Intestinal Transplantation. July 22-27, 2007, Snowmass Conference Center, Snowmass (Aspen), CO. Sponsored by Cincinnati Children’s Hospital Medical Center. The conference will be devoted to the diagnosis and management of gastrointestinal disease in children. Specific topics include inflammatory bowel disease (diagnosis, complications, and management), diarrhea (acute and chronic), celiac disease, h. pylori and peptic ulcer disease, gastroesophageal reflux, abdominal pain/irritable bowel syndrome, constipation, obesity and NAFLD/NASH, TPN-associated cholestasis, allergic gastroenteropathies, motility disorders, short gut syndrome/NEC, pancreatic disease/cystic fibrosis, and various aspects of small bowel transplantation. For more information, contact Laura Werts, CME Office, Cincinnati Children’s Hospital Medical Center; phone 513-636-6732; E-mail: laura.werts@cchmc.org; Website: www.cincinnatichildrens.org.

August 2007


2007-2008 Certifying Examinations of the American Board of Pediatrics

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AMSPDC: Current Initiatives and Future Opportunities

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The Association of Medical School Pediatric Department Chairs (AMSPDC) was founded in 1964 with a mission to “foster the advancement of education and research in the field of child health and human development.” In 1997, the name of the organization was changed from the Association of Medical School Pediatric Department “Chairmen” to “Chairs” to recognize the membership more appropriately. Currently, AMSPDC has 147 members throughout the United States, Canada, and Puerto Rico. The organization conducts an annual meeting with the Pediatric Scientist Development Program and meets triennially with the affiliated Council on Medical Student Education in Pediatrics (COMSEP). AMSPDC also is an active member of the Federation of Pediatric Organizations and the Pediatric Public Policy Council. The organization is governed by an executive committee of 6 members serving staggered 3-year terms, a secretary/treasurer serving a 6-year term, and the past-president, president-elect, and the president, each serving 2-year terms.

It has been my privilege to serve as president of AMSPDC from March 2005 to 2007. Each president aspires to accomplish certain objectives during the 2-year term, in addition to addressing important anticipated and unexpected issues arising in academic pediatrics. My priorities were to evaluate the turnover of leadership within pediatric departments and assess factors leading to chair satisfaction and burnout, to evaluate and enhance the value of our annual meeting, and to work with other pediatric organizations to establish an organization or forum for pediatric subspecialty organizations that could address cross-cutting subspecialty issues (eg, timing of fellowship offer dates). My first priority led to a review of the turnover of pediatric chairs from 1993 to 2003. We found a high turnover rate for pediatric chairs (average 17% annual turnover) and a mean tenure for this cohort of chairs of 5.6 years. Despite a growing representation of women among pediatric faculty, the number of women chairs actually decreased from 13 to 11 chairs during the time of the study; furthermore, women chairs had an average time in position of only 3.4 years. Many departments had multiple leaders during the 10-year period. Six departments had 4 different leaders, and 3 departments had 5 leaders during the 10-year study period. These data stimulated us to survey our membership to determine factors related to burnout and job satisfaction and to consider ways we can support our membership, particularly chairs early in their careers. Although most chairs are satisfied with their positions, our survey identified many chairs as having burnout. Burnout was most common in chairs early in their careers.

For many years, AMSPDC has provided a leadership and management program for new chairs every 3 years. Because of the rapid turnover of pediatric chairs, materials from this meeting are being made available on request to new or established chairs, and the content of the program is being reevaluated. Perhaps more important, a mentoring/advice program for chairs is being developed and will become part of our annual meeting. We hope that by identifying and addressing key stressors, chairs will have less burnout and develop longer and more rewarding careers as departmental leaders.

My second priority was to use our annual meeting to allow more discussion and networking among our membership. Our program committee has developed meetings that provide additional time for group discussions and recommendations about important current issues in academic medicine. In our 2006 meeting, we discussed issues related to career and research development, faculty satisfaction and burnout, and the role of the chair in mentoring students and residents. We also discussed the importance of collaboration between pediatric departments and other academic units, such as the institution’s medical school and the Department of Public Health. Additionally, we examined the role of the chair in faculty evaluation and the importance of supporting junior faculty members.

From the Department of Pediatrics, Ford/Morgan Endowed Chair, University of Washington School of Medicine, Seattle, Washington (J Pediatr 2007;150:213-4)
success for women in pediatrics, competency-based versus time-based certification, resident and fellowship education, and the need for an enduring subspecialty forum. After our meeting, the women chairs within AMSPDC published a paper addressing important barriers to the success of women faculty and giving recommendations to address work/life balance and family issues in pediatrics. In their review, women chairs focused on 4 areas: options to work part-time, availability of day care, flexibility in career paths for physician-scientists, and attracting more women into academic leadership positions. In addition, we conducted a survey of family-centered practices among AMSPDC departments to make best-practices available to all academic pediatric departments; a manuscript is now in press.

Finally, AMSPDC has joined with the Association of Pediatric Program Directors (APPD), the Pediatric Academic Society Alliance Societies, and FOPO to consider an organization to encourage communication between pediatric subspecialty societies and to host a forum at the 2006 Pediatric Academic Societies (PAS) meetings to discuss the creation of a Council of Pediatric Specialties. The strong support garnered at that PAS meeting led to an organizational meeting and the creation of the Council of Pediatric Subspecialities in September 2006. This effort will be discussed in more depth in a future publication. One of the important issues to be addressed by the Council will be the timing of pediatric fellowship offers. On the basis of discussions at our 2006 AMSPDC annual meeting, the executive committee of AMSPDC has agreed to provide initial financial support for the founding of the Council (in partnership with the APPD).

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Chairs not only continue to provide leadership in education and research, but they also lead clinical programs in highly competitive and often under-funded markets.

There has been no shortage of important topics within academic pediatrics for AMSPDC to address during my 2 years as president. Issues such as graduate medical education funding for children’s hospitals, Medicaid reimbursements, Hurricane Katrina relief, the organization of the FOPO and creation of the FOPO executive director position, medical student education and web-based teaching tools, funding for pediatric scientists, and review of the pediatric residency and fellowship curriculum were and/or remain important areas for AMSPDC to address in partnership with other pediatric organizations. I believe that clinical reimbursement for both primary care and subspecialty pediatricians, NIH funding of pediatric physician scientists, and the added teaching requirements for the proposed expansion of medical school enrollments will be among the top challenges facing pediatric chairs in the near future.

Clearly the demands on chairs of pediatric departments have changed and expanded since the inception of AMSPDC in 1964. Chairs not only continue to provide leadership in education and research, but they also lead clinical programs in highly competitive and often under-funded markets. In addition, many chairs provide significant hospital administrative leadership, especially in departments based at children’s hospitals. Although the initial vision of AMSPDC in 1964 is still relevant, AMSPDC appropriately has broadened its vision to assist chairs in serving their multiple departmental roles. A re-evaluation of the mission statement and the goals of AMSPDC is timely in light of the growing leadership demands on pediatric chairs. A strategic planning process is being developed by the executive committee.

Despite the significant challenges facing pediatric chairs and academic medicine in general, the dynamic discussions at our annual meetings and my personal conversations with fellow chairs give me great confidence that academic pediatric departments have talented and thoughtful leaders. AMSPDC is an important organization to sustain and support these leaders in their important work.
The Challenge of Car Safety Seats

In newborn intensive care units and special care nurseries throughout the United States, the discharge process typically includes a ritual known as the car seat challenge. The preterm infant, now of sufficient health and size to safely venture home, is first placed in a car seat, connected to a vital signs monitor and pulse oximeter, and then observed for an extended period of time. If specified parameters are achieved, the infant is deemed ready to safely travel in a car seat without the risk of untoward cardiopulmonary compromise.

Given the “objective” data obtained from a car seat challenge (number of apneic episodes, oxygen saturation values, and so on) one might suppose that the test is based on carefully considered scientific evidence. However, reviews of published literature speak to a different story.\(^1,2\)

The car seat challenge appears to originate from the practice of apnea monitoring and related testing popularized in the 1980s to determine readiness for discharge from the neonatal intensive care unit. No published evidence demonstrates that normal studies predict safe discharge. Similarly, little if any objective evidence supports the use of a car seat challenge to confirm safe infant automobile travel. The lack of evidence has not inhibited clinicians. Most nurseries discharging preterm infants use car seat challenge protocols, perhaps under the assumption that they represent a standard of quality care for newborn infants.

Protocols for car seat challenges are poorly standardized; an informal survey conducted during the preparation of this editorial identified observation times ranging from 30 minutes to 5 hours, along with a dizzying array of criteria for passing or failure. And what if the infant fails? Some re-test until the infant passes. Occasionally, a discharge is delayed for a day or two until the infant is rechecked and passes. Others simply discharge in a car bed under the assumption that it is safer. But once again, no objective studies have evaluated this question.

In this issue of The Journal, Salhab et al\(^3\) present a well-designed study to test the hypothesis that car beds present a safe alternative for infants failing their car seat challenge. Their work is important because they test the validity of an assumption in clinical practice, namely that infants who have apneic events in car seats, will not experience such problems when placed in a car bed. Their findings, that infants experiencing apneic events in car seats will also have these events with the same frequency in car beds, convey an important lesson for those of us who hope to practice evidence-based medicine. A recent report by Kinane et al\(^4\) reached a similar conclusion.

Often we pursue clinical practices that are not based on evidence, but rather clinical intuition. Sometimes our intuition is based on logical inference from laboratory-based investigation. Sometimes, the origin of our practices is murky. This should not make us feel bad; there is much in medical practice based upon experience, logical inference, and the like. However, we must resist the temptation to indefinitely embrace practices without appropriate study. In 2006, Vain et al\(^5\) published results of their large, well-designed, prospective, randomized controlled study of suctioning on the perineum for infants born through meconium-stained amniotic fluid. Their study tested the hypothesis that suctioning would not affect the incidence of meconium aspiration syndrome and found that this was indeed the case. Like car seat challenges and car beds, suctioning was an established practice thought to be useful but never carefully studied.

Neonatology would benefit from more studies like those led by Salhab, Kinane, and Vain. These investigators are to be commended for their willingness to resist the siren song of established practice to ask important clinical questions. Our zeal to do the right thing for our patients is always best focused through the lens of careful inquiry.

So what do we do about car seat challenges? Clearly many questions remain. Automobile travel is a fact of modern life. Yet newborn infants, particularly those born prematurely, are probably not designed to ride in cars for extended periods.\(^3,6\) How long is safe and what restraint devices might be best are important areas for investigation. In the meantime, we might consider changing the notion of a car seat challenge to a car seat orientation. The American Academy of Pediatrics\(^7\) recommends that we evaluate cardiorespiratory stability through a “period of observation in a car safety seat” at discharge. Educating parents about proper positioning to support airway patency is certainly useful. We can also advise them to limit the duration of automobile travel with these vulnerable offspring, as well as the importance of close observation. Long trips should be discouraged, or if unavoidable, interrupted with frequent rest stops. Beyond these recommendations, we
Numerous studies have shown that a prolonged, persistent left-to-right shunt through a patent ductus arteriosus (PDA) shortens the life span of animals and humans. In preterm infants, a persistent PDA is a result in large part of alterations in prostaglandin metabolism. Inhibition of prostaglandin production with indomethacin has been the mainstay of preterm PDA treatment since the mid 1970s. In recent years there has been a growing debate about whether or not to treat a persistent PDA during the neonatal period. Preterm infants have a high rate of spontaneous PDA closure during the first 2 years. Therefore, early treatment runs the risk of exposing infants to drugs or procedures they might not need. In this issue of The Journal, the report by Kabra et al fans the flames of this controversy. In the following review, we will examine the evidence for and against PDA treatment during the neonatal period.

Although a persistent PDA is associated with several important neonatal morbidities, its role in causing these morbidities is currently in question. Based on existing clinical trials, it is hard to tell whether the reported association between a persistent PDA and other neonatal morbidities is a result of the left-to-right PDA shunt itself, the therapies used to treat it, or the immaturity of the infant who is likely to develop a PDA. Only one randomized, controlled trial, performed more than 25 years ago, was designed specifically to examine the role of a persistent untreated PDA in neonatal morbidity. The investigators found that a persistent PDA increased pulmonary morbidity and prolonged the need for respiratory support. The trial size was too small to examine the PDA’s effect on other neonatal morbidities.

Unfortunately, the vast majority of PDA treatment trials were never designed to examine the role of a persistent PDA in neonatal morbidity; they were designed to assess the relationship between “timing,” or initiation, of treatment and efficiency of PDA closure. All of the trials utilized “backup treatments” to close the PDA if it persisted beyond several days. These timing trials can give us information about the role of a PDA in producing morbidity, only if the morbidity’s appearance and/or underlying cause occur during the period of PDA exposure (between the initial and backup treatments) (Figure). On the other hand, these trials tell us nothing about the role of the PDA in morbidities that occur after infants have received their backup treatment, or in morbidities that occur before the trial begins (Figure).

What information can be gleaned from these timing trials? There are basically two types of timing trials: prophylactic (where treatment starts within 24 hours of birth) and symptomatic (where treatment starts when symptoms appear: lactic, symptomatic, or late lactic). Both, those that occur before birth and those that occur after birth, could be detected in these prophylactic trials. Morbidities affected by the PDA (or its treatment) that could be detected in prophylactic trials are those that occur between birth and the time of backup treatment (2–3 days after birth) (Figure). Both, the individual prophylactic trials and the evidence from other studies, support the use of indomethacin to close a persistent PDA in preterm neonates.

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Lactic trials and a meta-analysis of their results (reviewed in references 9 and 10) consistently show that prophylactic use of indomethacin increases the effectiveness of pharmacologic closure and decreases the need for surgical ligation, decreases the incidence of early, serious pulmonary hemorrhages, and decreases the incidence of serious (grades 3/4) intracranial hemorrhage (ICH). Indomethacin’s ability to reduce grade 3/4 ICH appears to be independent of its effect on PDA closure. This action only occurs when indomethacin is administered in a prophylactic mode, and has not been observed with other cyclooxygenase inhibitors, such as ibuprofen.11

SYMPOMATIC TREATMENT TRIALS

Like the prophylactic trials, the symptomatic treatment trials can only detect PDA-related morbidities that occur between the time of initial treatment (>2 days after birth) and the time of backup closure (Figure). In these trials, infants were exposed to a symptomatic PDA for varying time spans before backup closure was invoked (mean [range] = 5 [1-14] days). For the purposes of discussion, we analyzed only those trials that waited at least 6 days (mean = 9 ± 3 days) before resorting to backup closure.8,12-14 By doing this, we hoped to maximize our ability to detect any detrimental effects of a PDA on a particular morbidity.

PULMONARY MORBIDITY

Five of the seven trials that reported pulmonary morbidity8,12-17 (and a meta-analysis of the seven trials) showed that exposure to a symptomatic PDA, for at least 6 days, prolonged the need for supplemental oxygen and/or mechanical ventilation. Information about longer exposures to a PDA can be found in studies of preterm baboons. These studies provide evidence for more long lasting pulmonary morbidity following exposure to a persistent PDA. Premature newborn baboons, exposed to a moderate-size PDA shunt for 14 days, have altered pulmonary mechanics and arrested alveolar development.19 Arrested alveolarization is the histologic hallmark of the “New Bronchopulmonary Dysplasia.”20 Pharmacologic closure of the PDA significantly increases alveolarization (alveolar surface area and branching) and prevents the deterioration in pulmonary function.19

NECROTIZING ENTEROCOLITIS

There is little evidence to support or refute the role of a PDA in necrotizing enterocolitis (NEC). A meta-analysis of the trials8,13,15,16,18 that delayed backup treatment for at least 6 days showed that early treatment of a PDA may decrease the incidence of NEC, but only among infants <1000 g birth weight. This analysis has some uncertainty because it is heavily weighted by a single study;18 no significant association between a PDA and NEC was found when this study was removed from the analysis.

RETINOPTHY OF PREMATURITY (ROP)

No causal role has been found for a PDA in ROP.

MORBIDITIES ASSOCIATED WITH INDOMETHACIN

Any discussion of PDA treatment must consider the possibility of treatment-related morbidities. Although none of the treatment trials were specifically designed to examine the incidence of morbidities caused by indomethacin or surgery, the prophylactic treatment trials do provide some information about those associated with indomethacin. In these
trials, <50% of control group infants were exposed to indomethacin (compared with 100% in the prophylactic group) (see reference 9). Therefore, one might expect that if indomethacin produced significant problems, some noticeable differences would be apparent between the groups. Transient alterations in renal function and urine excretion are common problems with the initial doses of indomethacin (this appears to be less of a problem with ibuprofen). These renal abnormalities return to normal after the initial doses of indomethacin or with drug discontinuation.21 Indomethacin, by itself, does not appear to increase the incidence of other neonatal morbidities (eg, NEC, gastrointestinal perforation, ROP, chronic lung disease [CLD], or cerebral white matter injury9). However, an increased incidence of gastrointestinal perforations has been observed when indomethacin and postnatal steroids are administered simultaneously.22,23 Although indomethacin’s cerebral vasoconstrictive effects are frequently cited as a concern for neonatologists,24,25 a recent Cochrane systematic review found that indomethacin prophylaxis is more likely to decrease rather than increase the incidence of periventricular leukomalacia.9 Studies of neurodevelopmental outcome26-28 also are reassuring. There is no evidence that prophylactic indomethacin has any adverse effect at 18 months29; in fact, there is evidence that it may have long-term benefits at 4.5 and 8 years.27,28

MORBIDITIES ASSOCIATED WITH LIGATION

What happens when pharmacologic treatment fails to close the PDA? Surgical ligation of a PDA is associated with its own set of morbidities: thoracotomy, pneumothorax, chylothorax, infection, and vocal cord paralysis. More than 50% of infants with birth weights ≤1000 g will require inotropic support for profound hypotension during the postoperative period.30 In addition, neonatal transport to another facility may be required if surgical expertise is not readily available. The article by Kabra et al7 in the current issue of The Journal raises even more concerns about the use of surgical ligation in the neonatal period. They found an increased incidence of neurodevelopmental abnormalities, in addition to CLD and ROP, among infants treated with ligation. This is consistent with prior reports that link sensorineural abnormalities with surgical procedures in the neonatal period.31,32 These findings are still quite preliminary. The observational design of Kabra’s study makes it impossible to determine if surgical ligation plays a causative role or is simply a surrogate marker for infants who are more critically ill or who have a developmental profile that leads to increased morbidity. In addition, other observational studies have failed to find a similar connection between surgical ligation and neurodevelopmental abnormalities or ROP.33 Although the link between neurodevelopmental abnormalities, ROP, and ligation may be somewhat tenuous, stronger evidence exists for a causal relationship between ligation and CLD.33 One trial in humans has compared surgical ligation with pharmacologic closure34; infants who were surgically ligated required longer durations of continuous positive airway pressure than those treated with indomethacin (P = .06). Recent findings in premature baboons support the concept that surgical ligation may have a detrimental effect on lung function and growth. Although pharmacologic closure prevents the arrest in alveolar development caused by a PDA,19 no benefit on alveolar growth has been observed following surgical ligation.35,36

Based on this review we offer the following conclusions. A moderate left-to-right PDA shunt alters pulmonary mechanics, increases the risk of pulmonary hemorrhage, and alters alveolar surface area (at least in preterm baboons). If left untreated, prolonged exposure to the left-to-right shunt can lead to congestive failure, pulmonary hypertension, and death. We suggest that pharmacologic treatment of a PDA in the newborn period offers measurable benefits without an increase in clinically significant adverse effects. If pharmacologic treatment is to be used, early treatment is more likely to result in successful ductus closure. In certain settings (where ICH, pulmonary hemorrhage, and PDA ligations are frequent occurrences), indomethacin prophylaxis may even be a preferred alternative. On the other hand, ductus ligation, although eliminating one potential cause for neonatal morbidity, may introduce its own set of problems. Further investigations will be needed to determine which infants are most likely to benefit from surgical ligation and which infants might best be left untreated when pharmacologic approaches are no longer an option.

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Assessment of Vascular Function: Pulse Wave Velocity

In recent years, several non-invasive techniques have been developed and tested to measure vascular properties that may predict later-onset cardiovascular morbidity and mortality. Among these properties are arterial compliance, distensibility, and stiffness. These measures represent different facets of arterial structure and function. Three different approaches of investigation have been developed in adults: analysis of pressure waves; vessel diameter changes in response to pressure changes; and measuring pulse wave velocity.

Arterial pulse waveform analysis is performed by application tonometry, which requires a transfer function to derive central aortic waveforms. The derivation and validation procedures require intra-arterial catheter measurements, excluding this technology for children, who cannot be enrolled in such studies.

Arterial distensibility is the change in vessel size (diameter as a proxy for cross-sectional area) in response to pressure change. It is a reciprocal of arterial stiffness, estimating vessel elastic properties. The vessel diameters are measured with ultrasound scanning. Studies in adults have shown impairments in patients with hypertension, diabetes mellitus, and dyslipidemia. The measures also predict future adverse cardiovascular outcomes. Few studies have been performed in children, but the results have shown data that parallel adult study results. The limitations to this technique include the precision with which vessel measurements must be done and the

extrapolation of the vascular pressures obtained at a site distant from the ultrasound scanning measures. In addition, the process of pressure application at the skin over the artery will alter the vessel shape and pressure waveform.

In this issue of *The Journal of Pediatrics*, Im et al report their findings of brachial-ankle pulse wave velocity (baPWV) and its correlations with known risk factors for cardiovascular disease (CVD) in a population of healthy Korean adolescents.\(^1\) Pulse wave velocity (PWV) measurement as a surrogate for arterial stiffness was first reported in 1922, but only recently were automated devices produced to measure it. It is now recognized as being a highly sensitive measurement of arterial tree stiffness and a strong predictor of CVD mortality in adults. It is non-invasive and has been validated repeatedly in adults. PWV increases as arteries become more damaged and stiffer. Therefore PWV is highly associated with atherosclerotic and hypertensive vessel pathologies. Blancher et al have stated that PWV is the strongest independent predictor of clinical cardiovascular morbidity.\(^2\)

There are several methodologies to measure PWV, but each detects the onset of the pressure wave form in relation to an electrocardiogram time point. The distance along the arterial tree is measured/estimated and the velocity calculated.

Studies in adults are now plentiful and have been performed in patients with many chronic diseases known to increase cardiovascular pathology. Studies in children are limited, but have been performed in healthy volunteers and patients with diabetes mellitus, neurofibromatosis, snoring, Kawasaki’s disease, polyarteritis nodosa, and coarctation of the aorta after surgical repair.

The automated system used by Im et al uses oscillometric pressure cuffs to obtain measurements at the brachia and ankles. The results from this technique give higher PWV values compared with carotid-femoral measurements, because baPWV reflects wavefront transmissions in both central (elastic) and peripheral (muscular) arteries. Our laboratory recently reported baPWV measures in 205 normotensive, healthy adolescents.\(^3\) We found that baPWV was greater in male patients than in female patients, and, probably more importantly, higher in African-American than Caucasian volunteers between the ages of 12 and 21 years. Our results were similar to those found in another biracial community in the Southern United States.\(^4\)

The results reported by Im et al confirm our earlier findings and those of Niboshi et al,\(^5\) who compared male and female adolescents. Their group was able to measure the associations of baPWV to many recognized cardiovascular risk factors, including body mass index, waist circumference, waist-hip ratio, systolic and diastolic blood pressure, insulin measures, triglyceride levels, C-reactive protein levels, and homocysteine levels. In separate analyses by sex, other risk factors were also significantly related to baPWV.

Im et al used the exclusion criterion of a resting blood pressure >140/90 mm Hg to define hypertension. This threshold is an adult criterion for hypertension and would indicate significantly elevated blood pressure (clinical hypertension) in some of the age groups represented. Because percentile blood pressure measurements based on sex, age, and height\(^6\) are typically used in the United States to define hypertension in pediatric populations, the use of such an adult threshold is likely to have allowed subjects to participate who had elevated blood pressure on the basis of appropriate percentile standards. This does not invalidate the findings presented in this paper. However, it likely would, to some extent, change the statistical significance of the sex differences reported for baPWV because the presence of blood pressure elevation is known to increase PWV significantly.

The value of a totally non-invasive marker for later-onset CVD is, as the current media commercial says, “priceless.” If primary care physicians could screen youth for early signs of atherosclerosis and implement early, effective interventions, morbidity and mortality from CVD, the leading cause of death in Westernized societies, could be substantially reduced. More data are needed from populations worldwide for a “normal control” database. Longitudinal studies from childhood would establish the true value of baPWV in preventive cardiology. The data extant suggest that PWV is a useful research method and perhaps should become a more routine screening test in high-risk populations of youth.

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Advances in medical care and technology have increased the lifespan and decreased the disease-related suffering of children with chronic illnesses. In addition to physical health outcomes, health care professionals are increasingly evaluating other parameters, such as child and family adjustment. Among these psychosocial factors, family functioning is a key variable that has been shown to play an essential role in children’s adjustment to chronic illness.

Family functioning is a broad concept and is often used as an umbrella term encompassing numerous constructs, including parents’ satisfaction with their parenting role, positive parent–child interactions, family communication, family adaptability, and family cohesion. Research has shown that families of a child with a chronic illness may have deficits in family cohesion, family adaptability, parent-child interactions, family conflict, and family problem-solving skills. Understanding the nature and development of these problems in family functioning is critical to formulating effective interventions.

Although we know that family functioning is related to the well-being of children with chronic illness, we lack a clear understanding of whether families of chronically ill children are significantly more likely to have difficulties in functioning compared with families of healthy children. In this article we review the research into the functioning of families with children with a range of chronic illnesses compared with healthy controls, critique these studies, highlight parallels across the literature, and provide directions for future study.

The inclusion of demographically matched healthy control groups allows researchers to eliminate a number of methodological limitations and draw strong conclusions regarding the impact of childhood illness on family functioning. This is particularly important with measures of family functioning that were not recently normed, or were normed with a group that is significantly different from the sample being studied. For example, researchers examining family functioning in the predominately African-American sickle cell disease (SCD) population have stressed the importance of including a demographically matched healthy comparison sample rather than relying on the norm–group statistics for comparisons. Including this group allows researchers to better distinguish the disease-specific effects on family functioning independent from the sociocultural influences, such as ethnic minority socioeconomic status. A review of studies of chronic illness adjustment and family functioning indicates that previously established differences are not significant when healthy controls are included.

We selected cystic fibrosis (CF), juvenile rheumatoid arthritis (JRA), type 1 diabetes/juvenile-onset diabetes, asthma, hemophilia, and SCD for this review because these are some of the most common chronic childhood illnesses and represent a broad spectrum of disease. Although there are differences across these 6 groups, there are similarities in chronicity, creation of disability, and need to adhere to demanding regimens.

**REVIEW INCLUSION CRITERIA**

Articles included in the review were identified through searches in MEDLINE or PsycINFO databases. The following search terms were used: “cystic fibrosis,” “juvenile rheumatoid arthritis,” “diabetes,” “asthma,” “hemophilia,” and “sickle cell disease.” These terms were combined with the search terms “family functioning,” “family coping,” and “family adjustment.” Additional inclusion criteria were that the study focused on pediatric rather than adult chronic illness, and a healthy control group was included. A total of 15 articles were identified (Table; available at www.jpeds.com). Given the small number of studies and range of measures, evaluating this body of work by meta-analysis was not feasible.
Cystic Fibrosis

The literature on families with a child with CF reports varying findings regarding the impact of chronic illness on family functioning. Research shows that parents of children with CF report higher parenting stress compared with parents of healthy children. In addition, mothers of children with CF report decreased time available to spend with their spouses. Spieth et al.8 found similar results and concluded that families of a child with CF score significantly lower than healthy control families in domains of communication, interpersonal involvement, affect management, behavior control, and role allocation.

Some research indicates that having a child with CF might not impair family functioning, however. For example, 2 studies have shown no differences in family functioning between families with children with CF and families of physically healthy children.9,10 Further, on an in vivo problem-solving task, families of adolescents with CF were more likely to be categorized as good problem solvers than were families of healthy adolescents.9 Cowen et al11 found that fathers of young children with CF are more likely to report positive family functioning than are fathers of healthy children.

Type 1 Diabetes Mellitus

For the most part, the research has found few differences in family functioning comparing families of children with type 1 diabetes mellitus with families with physically healthy children.12-14 However, mothers of children with diabetes report having less time to engage in activities with their children compared with mothers of healthy children.13 Parents of children with type 1 diabetes also report different family values than families of healthy children; specifically, they are more likely to describe their families as less achievement-oriented compared with families of physically healthy children.13

Juvenile Rheumatoid Arthritis

Research comparing families with a child with JRA and healthy families indicates a general lack of differences.15-17 It is notable that Huygen et al.16 separately examined families of children (age 6 to 11 years) and families of adolescents (age 12 to 16 years) and found results suggesting that families with children with JRA, but not those with adolescents with JRA, had greater family cohesion and less family adaptability than families without children with JRA.16

Sickle Cell Disease, Hemophilia, and Asthma

There are few studies comparing family functioning in SCD, hemophilia, or asthma with healthy controls. Two studies comparing functioning in families of children with SCD and healthy families have provided divergent conclusions, possibly due to the geographical differences between the samples and the incorporation of extensive cultural sensitivity training and monitoring of the data collectors in one study but not the other. The better functioning found by Midence et al.18 could reflect a pattern whereby parents demonstrate increases in family protectiveness and a resultant decrease in reporting of family conflict, whereas the emphasis that Noll et al.19 placed on cultural sensitivity training might have resulted in families of children with SCD feeling less threatened and more open.

Because hemophilia occurs predominately in males, research in this area highlights the importance of considering the role of the child’s sex in family functioning issues. A study found that the parents of boys with hemophilia reported a greater total number of family functioning difficulties, but the small sample size kept these differences from being statistically significant.20 Research investigating family functioning in the pediatric asthma population found heightened mother-reported problems with social support, child behavior, and stressful events, but no significant differences on measures of family functioning.10,12 (For more details, see the Table, available at www.jpeds.com.)

CRITICAL EVALUATION

In summarizing the results that can be drawn from this body of literature, it is essential to consider the findings in light of methodological limitations. Most of the investigations reviewed herein used a single measure of family functioning, and 2 of the studies obtained only mothers’ reports.8,10,13-18,20-22 Family functioning is a multifaceted concept, and multiple measures are needed to capture its important dimensions. Measuring other domains, such as children’s medication adherence and parental depression, might be important because they can influence family functioning and child behavior.23,24 Other research has shown that parents’ reports of activities may not accurately reflect true behaviors. For example, Quitter et al.24 found that mothers of children with CF do not perceive their parenting role differently than mothers of healthy children; however, behavioral assessment revealed significant differences in the activities of the 2 groups. These findings support the need for multiple informants and multiple methods of assessment when investigating family functioning.

Another limitation of this research is the extreme variation in the age of the participants. Illness-related issues that impact family functioning might differ across age groups and developmental periods. For example, whereas families of children with CF and those with healthy children may face many of the same stressors, the declines in health associated with increased age in individuals with CF may be an important variable when investigating family functioning. Similarly, parents of adolescents with type 1 diabetes and JRA may experience greater conflict associated with treatment adherence issues than they had faced when their children were younger. By collapsing across large age ranges, researchers may have diluted possible effects.

Most of the studies selected healthy controls similar in age, sex, and ethnicity to the chronically ill children. Unfortunately, few studies considered additional variables when
matching. For example, only 2 studies considered the number of other children in the home and whether any of these other children also had significant medical diagnoses. By matching not only basic demographics, but also other important variables, researchers are better able to attribute any differences between the families to disease status.

Most of the studies neglected to include how illness-related factors, such as disease severity and time since diagnosis, relate to family functioning. Families might have increased difficulties when a child is first diagnosed with a chronic illness. The relationship between childhood chronic illness and family functioning may have been less apparent because time since diagnosis, disease severity, and extent of disease activity were not considered.

RECOMMENDATIONS FOR FUTURE RESEARCH

Future examinations of family functioning and childhood chronic illness should include multimethod assessments of family functioning. Ideally, research examining family functioning should include reports of family functioning from all members of the family, in addition to observational measures to directly assess family interactions. Observational measures of family functioning can identify objective indices of family functioning, which cannot reliably be obtained through ratings. Although observational data can be time-consuming and expensive to collect, it can provide researchers and clinicians with objective and quantifiable data to use in evaluating changes over time and responses to intervention.

Multisite research, rather than sampling from a single clinic group, will allow researchers to increase the size of their samples and the generalizability of their findings. Along with the site from which participants are drawn, other participant characteristics also deserve consideration in future research, including the impact of previous parenting experience on family functioning, the child’s sex and ethnicity, and whether additional children with chronic physical or mental illnesses reside in the home.

Although difficult to conduct, longitudinal investigations of family functioning are needed to explore the processes by which chronic childhood illnesses influence family functioning. Evaluating families as they progress from initial diagnosis to key developmental phases (eg, school entry and adolescence) may help identify the periods of greatest challenges and aid in developing protocols to mediate these threats to optimal family functioning. In addition, longitudinal research aids identification of the roles of other variables, such as disease severity, in predicting family functioning.

Conducting methodologically sound, high-quality research in this area might make it possible to determine whether families with chronically ill children are indeed at increased risk for problematic functioning. Such research also would bolster the current understanding of the process by which families confront stressful events and how these events relate to their functioning. In addition, assessment work in this vein should highlight directions for intervention and provide recommendations to other families about how to navigate stressful life events.

REFERENCES

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Car Seat or Car Bed for Very Low Birth Weight Infants at Discharge Home

WALID A. SALHAB, MD, ASIF KHATTAK, MD, JON E. TYSON, MD, MPH, SHARON CRANDELL, MD, JAN SUMNER, PNP, BEVERLY GOODMAN, PNP, LINDA FISHER, PNP, AND KAREN ROBINSON, NNP

Objective To compare the incidence of apnea, bradycardia, or desaturation in a car seat with that in a car bed for preterm very low birth weight (<1500 g) infants.

Study design Infants were studied for 120 minutes in a car seat and in a car bed. Apnea (>20 seconds), bradycardia (heart rate <80/min for >5 seconds), desaturation (SpO2 <88% for >10 seconds), and absent nasal flow were monitored.

Results We assessed 151 infants (median birth weight, 1120 g [range, 437 to 3105]; median birth gestational age, 29 weeks [24 to 34]) in both devices. Twenty-three infants (15%) had ≥1 event in the car seat compared with 29 (19%) in the car bed (P = .4). Time to first event was similar in the car seat and car bed (mean, 54 to 55 minutes). In logistic regression analyses, bronchopulmonary dysplasia was a significant predictor for a car seat event and a lower gestational age at birth was a risk factor for a car bed event.

Conclusions We found no evidence that an event is less likely in a car bed than in a car seat. Whichever device is used, very low birth weight infants require observation during travel. (J Pediatr 2007;150:224-8)

In 1990, the American Academy of Pediatrics recommended that all newborn infants discharged from hospitals should be transported in infant car safety seats.1 However, 12% to 30% of premature infants have been reported to have episodes of desaturation and bradycardia while in car seats,2-5 and studies by Bull et al6 suggest that a car bed can be adapted to accommodate very small infants. Based largely on these studies, the American Academy of Pediatrics in 1996 recommended that each preterm infant be monitored in a car safety seat before hospital discharge and that infants with documented desaturation, apnea, or bradycardia should travel in a supine or prone position in a car bed.7,8 This recommendation is based on an assumption that these events are less likely in a car bed than in a car seat. Yet, there are no studies with preterm infants comparing the incidence of these events in a car seat with that in a car bed, particularly among very low birth weight (VLBW) infants, who are most likely to have these episodes.

We conducted a two-center, cross-over trial to determine whether preterm VLBW infants at discharge home had fewer events when placed supine in a car bed than in a car seat. We hypothesized that these infants have fewer events in a car bed than in a car seat. Our secondary objectives were to relate the duration of time in a car seat or bed to the likelihood of these episodes and to evaluate risk factors for their occurrence.

METHODS

Population To increase the sample size and the generalizability of the findings, the study was conducted in two hospitals: Parkland Memorial Hospital (Dallas, Texas), a county hospital with a largely inborn population, and Memorial Hermann Children’s Hospital (Houston, Texas), a private hospital with a substantial proportion of maternal and neonatal referrals. All VLBW infants weighing ≤1500 g at birth and at <37 weeks’ gestational age (GA) became eligible when they were nearing discharge. At both hospitals, infants are considered ready for discharge when weighing >1800 g, are nipple-feeding well, have appropriate weight gain, and are free of apnea or bradycardia for ≥5

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days. Informed parental consent was obtained for all participants, and the study was conducted as approved by the local institutional review board.

Assessment Procedures

Because some infants (for example, those referred from other communities) may travel in a car seat for 2 hours, enrolled infants were studied for 120 minutes in a car seat and 120 minutes in a car bed. At least 1-hour recovery time was allowed between assessments. Depending on the availability of the research staff, the second assessment occurred as much as 24 hours after the first assessment. As is routine practice in our centers, both assessments occurred within 72 hours before the scheduled discharge for each infant. All study sessions occurred at a minimum of 30 minutes after feeding. Baseline data were recorded for 5 minutes before placement in the car seat or the car bed. Whether the infant was placed in the car seat first or the car bed first was randomly assigned by using sequentially numbered, sealed, opaque envelopes prepared by means of a random-number table by an investigator unin- volved in the care of the subjects. Infants were assessed in the Cosco infant car seat and in the Cosco Ultradreamride car bed. In the car seat, infants were reclined at a 45 degree angle and supported with cotton rolls, as recommend for positioning of the head and neck. In the car bed, the infants were placed supine.

Each infant was monitored in both devices with a pulse oximeter, a cardiopulmonary monitor, and a nasal flow detector. Apnea, bradycardia, oxygen saturation, and nasal airflow were assessed by using the Eventlink 511 monitor by CAS Medical Systems, Inc (Branford, Conn). The 511 Monitor displays beat-to-beat heart rate, respiratory rate through thoracic impedance, oxygen saturation, and captures nasal airflow, electrocardiogram, pulse rate, and respiratory waveform. In addition, this monitor allows event detection and storage, based on adjustable parameters. The 20 seconds before the event is saved as the baseline, and the recording continues for 30 seconds after the event. Captured data can be reviewed and printed. In the absence of a clearly defined lower oxygen saturation limit in convalescent VLBW infants, we selected 88% as a lower cutoff. The monitor was set to identify apnea for 88% lasting for 10 seconds or more.

It was difficult to predetermine an appropriate sample size because of the lack of data regarding the incidence of adverse events in safety devices in VLBW infants. Therefore, we determined the proportion of infants in the car seat arm of the study who had an event during the first 6 months into the study (18%). To avoid bias in determining the sample size, we remained blinded to the findings in the car bed arm. To identify a 50% reduction in the proportion of infants with events in the car bed, we selected a sample size of 154 patients (two-tailed analysis; α error = 0.05; β error = 0.2).

Because each infant served as his or her own control, the proportion of infants with an event in the car seat was compared with that in the car bed by using the McNemar test for paired observations. The time to the first event was compared by using the Student t test. The mean oxygen saturation in the car seat and the car bed at baseline and at 30-minute intervals were compared by using the Friedman repeated-measures analysis of variance on ranks with the Dunn method for multiple comparisons. The oxygen saturations were compared at each time point by using the Wilcoxon signed rank test. χ² analysis and the Mann-Whitney rank sum test were used to compare infants with events versus those with no events in the car seat and the car bed. The Sigma Stat 3.1 software package (SPSS, Chicago, Ill) was used in the above analyses. All tests were two-tailed, with the type I error of 0.05.

Separate logistic regressions models were used for car seats and car beds to relate the likelihood of events to various risk factors: center, birth weight, GA, total ventilation days, BPD, grade III/IV intracranial hemorrhage, duration of apnea of prematurity, chronological age and weight at the time of test. Backward elimination procedures were used to deter-
mine the risk factors that best predict an event in the car seat or car bed. Adjusted odds ratio (OR) and 95% Wald confidence intervals (CI) were calculated for the significant risk factors. The SAS 9.1.3 software package (Cary, NC) was used in all logistic analyses.

RESULTS

Between February and December 2002, 178 infants met inclusion criteria. Consent was obtained for 160, and 7 were not studied because they were discharged earlier than planned. The data could not be analyzed for two infants because of monitor malfunction. Thus, we assessed 151 infants; 77 were randomly assigned to the car seat first and 74 to the car bed first. The median (range) birth weight was 1120 g (437 to 3105); weight at study, 2545 g (1750 to 5670); GA at birth, 29 weeks (24 to 34); and GA at study, 38 weeks (31 to 56); 49% were boys; 54% were Hispanic; 29% were African American, 16% were Caucasian, and 1% were other racial groups.

Forty-three (28%) of the infants had at least one event in either or both transportation devices; 23 (15%) had an event in the car seat; and 29 (19%) had an event in the car bed (Table I). The absolute difference is 4% (95% CI = −4% to 12%, P = .4). In neither study hospital did events occur less commonly in a car bed than in a car seat (17.5% vs 16.5% at Parkland; 22% vs 13% at Hermann). The number of infants with events that prompted a nursing intervention (repositioning, suctioning, oxygen administration) was also comparable: 9 (6%) in the car seat versus 5 (3%) in the car bed (95% CI = −2% to 7%, P = .30). Two patients, one with each device, were removed from the device and retuned to a crib because of continued desaturation despite nursing interventions. No infant required intubation or bag and mask ventilation.

The type of events was comparable for the car seat and car bed (Table II). No infant who received nursing interventions had electronic monitoring or clinically recognized episodes at enrollment in the study. The one infant receiving xanthine therapy at enrollment had no event in either device. The events requiring intervention in the car bed were attributed to emesis (n = 2), airway obstruction secondary to flexion of the neck (n = 1), previously undetected anemia (n = 1), or viral illness (n = 1). The events requiring intervention in the car seat were attributed to emesis (n = 2), flexion of the neck (n = 3), or anemia (n = 1) or had an unclear cause (n = 3).

The mean time to first event was almost identical in the car seat and car bed (mean ± SD = 55 ± 42 vs 54 ± 34 minutes, respectively; range = 1 to 117 minutes for both devices). The car seat and car bed were also similar in the proportion of infants whose first event occurred after 60 minutes of observation (40% vs 52%) and after 90 minutes (30% vs 10%) (P > .05).

The median oxygen saturation (available for 146 infants) decreased from 100% at baseline to 98% at 120 minutes in the car seat (P < .001). The minimum oxygen saturation values at baseline, time zero, 30 minutes, 60 minutes, 90 minutes, and 120 minutes were 93%, 92%, 89%, 89%, 85%, and 90%, respectively. Oxygen saturation in the car bed decreased from 100% at baseline to 99% at 120 minutes (P < .001). The minimum oxygen saturations were 90%, 90%, 91%, 90%, 90%, and 91% at baseline, time zero, 30 minutes, 60 minutes, 90 minutes, and 120 minutes, respectively. Three infants in the car seat each had one oxygen saturation <90% recorded; none was recorded for infants in the car bed. Paired comparison of the median oxygen saturation of the two transportation devices revealed similar values at baseline, zero, 30 minutes, and 60 minutes; but lower values in the car seat than car bed at 90 minutes: 98% (96% to 100%) versus 99% (97% to 100%), P = .004; and 120 minutes: 98% (97% to 100%) versus 99% (97% to 100%), P < .001.

For the car bed, infants with at least one event were of lower GA, birth weight, and had longer mechanical ventilation than infants without events (Table III). For the car seat, BPD and GA approached statistical significance. In multivariable analysis, a lower GA at birth was the only predictor for a car bed event (OR, 1.28; 1.06 to 1.54, P < .01) per week decrease in GA; the presence of BPD was the best predictor for a car seat event (OR, 2.65; CI 1.03 to 6.81, P = 0.04).

DISCUSSION

To our knowledge, this is the first randomized study comparing responses of infants to car beds and car seats. Our study has three major findings: (1) As reported by other investigators,2-5 apnea, bradycardia, and desaturation episodes may still occur at discharge when VLBW infants are placed in a transportation device, particularly among infants who were born most prematurely or who are recovering from BPD; (2) we found no evidence that these episodes are less likely in a car bed than a car seat; (3) a brief observation period in a transportation device is not sufficient to identify infants at

| Table I. Distribution of infants according to device and whether an event occurred |
| Car seat | Infants with ≥1 event | Infants with no event |
| Car bed | Infants with ≥1 event | 9 | 20 |
| Infants with no event | 14 | 108 |

| Table II. Type of adverse events | Number of infants |
| Car seat | Car bed |
| Central apnea | 7 | 5 |
| Obstructive apnea | 3 | 5 |
| Mixed apnea | 2 | 7 |
| Bradycardia | 5 | 8 |
| Oxygen desaturation | 20 | 27 |

Some infants are included in more than one category.
risk, but the longer these infants remain in such devices, the more likely oxygen saturation is to fall.

The proportion of our VLBW infants with one or more episodes—15% in the car seat and 19% in the car bed—is in the range previously reported for premature infants observed in car seats.2-4,12 This proportion may be higher in populations whose mean birth weight and GA is lower or whose incidence of BPD is higher. Although most events resolved spontaneously, 6% of infants in the car seat and 3% of those in the car bed received nursing intervention to terminate events. Although other investigators have noted that VLBW infants have subclinical events well past term,13,14 the testing in this study may have unmasked a new or underlying problem that had been missed by the caregivers before the test.

The appropriate period of observation in a car seat or car bed is unclear.15 Most reports have involved a 90-minute interval,2-4,12 although shorter periods may be used in clinical practice. A short observation period may not detect infants at risk, whereas a long period adds burden on the nursery staff and may prompt continued hospitalization of infants who experience minor episodes but could be safely discharged. The time to first event approached 1 hour, with a wide range (1 to 117 minutes) for both transportation devices. The optimal observation period in a transportation device and the proper interpretation of the results cannot be well defined without further study of the reliability of findings and their relation to the risk of important events while riding in a car.

Our results for oxygen saturation monitoring are similar to those of Merchant et al,12 who reported a significant decline in the mean to 94% during a 90-minute car seat test. These declines may have little clinical significance. However, 7% of their infants and 2% of ours had oxygen saturation values <90%. The difference between studies may reflect the use of continuous recording in the study of Merchant et al and a difference in nursing attention to optimize positioning. Oxygen saturation <85% has been associated with reduced cerebral oxygenation in VLBW infants.16 The potential significance of these events on the short- and long-term outcomes of VLBW infants is unclear.

Bronchopulmonary dysplasia was the only significant predictor for failing a car seat test. Functional residual capacity is reduced in infants with BPD,17 and their tidal volumes decrease after placement in a car seat.4 It is plausible that car seat placement worsened an already compromised pulmonary status in infants with BPD and contributed to the events.

Infants with events in the car bed were of lower GA and birth weight and required longer mechanical ventilation than those with no events, and each 1-week decrease in the GA increased the chance of events by ~30%. These findings outline the precariousness of the cardiopulmonary status of the preterm VLBW infants and are consistent with the lability of the oxygen saturation previously described in this high-risk population.13,14

In conclusion, VLBW infants who are ready for discharge are as likely to have apnea, bradycardia, or oxygen desaturation when placed in a car seat, compared with a car bed. The role of car seats in protecting young infants from injury and death in motor vehicle accidents is well documented.18 However, preterm VLBW infants should be closely observed and travel time limited, irrespective of whether car beds or car seats are used.

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50 Years Ago in The Journal of Pediatrics

A CLINICAL APPROACH TO INFANTILE COLIC: A REVIEW OF NINETY CASES
Breslow L. J Pediatr 1957;50:196-206

In one of the early studies of infantile colic, Breslow evaluated 90 infants with the typical features of colic, who were seen in his private practice. The goal was to evaluate the role played by hunger, feeding technique, and other factors in the cause of colic. He developed a strict protocol that involved instructions regarding feeding techniques, increasing amounts of formula, and then changes in the components of the formula to detect possible intolerance. Although one third of infants appeared to have some intolerance of carbohydrate or fat, the cause of colic could not be identified for more than 40% of the infants.

For those infants who did not respond to the changes in feedings, Breslow advocated small doses of barbiturates or atropine, drugs we now avoid because of their high likelihood of side effects. Over the past 50 years, the pediatric literature is replete with studies trying to find an effective treatment for colic. Even after several systematic reviews, no clear treatment has been identified.

In the absence of formula intolerance, Breslow had the hypothesis that “marked evidence of emotional instability on the part of the parents” may be causal in the development of infantile colic, particularly for those in the group who did not respond to formula changes. Another author, cited by Breslow, noted that colic frequently improved “by substituting a calm nurse for an agitated mother.” Of course, these comments reflect a time when it was thought that a number of unexplained conditions, such as autism, could somehow be caused by parental factors.

Fifty years after Breslow’s study, the cause and treatment of infantile colic remains elusive. However, it seems clear that parental stress is a result of their infant’s colicky behavior and not the cause of it. Given that only a small number of infants will respond to hypoallergenic formula, we now recognize the need to pay as much, if not more, attention to the emotional reactions of the parents and to provide support during these challenging early weeks of an infant’s life.

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10.1016/j.jpeds.2006.09.006
Neurosensory Impairment after Surgical Closure of Patent Ductus Arteriosus in Extremely Low Birth Weight Infants: Results from the Trial of Indomethacin Prophylaxis in Preterms

NANDKISHOR S. KABRA, MD, BARBARA SCHMIDT, MD, MSC, ROBIN S. ROBERTS, MSc, LEX W. DOYLE, MD, LUANN PAPILE, MD, AVROY FANAROFF, MD, AND THE TRIAL OF INDOMETHACIN PROPHYLAXIS IN PRETERMS (TIPP) INVESTIGATORS*

Objectives To determine whether surgical closure of a patent ductus arteriosus (PDA) is a risk factor for bronchopulmonary dysplasia (BPD), severe retinopathy of prematurity (ROP), and neurosensory impairment in extremely low birth weight (ELBW) infants.

Study design We studied 426 infants with a symptomatic PDA, 110 of whom underwent PDA ligation and 316 of whom received medical therapy only. All infants participated in the multicenter Trial of Indomethacin Prophylaxis in Preterms (TIPP) and were observed to a corrected age of 18 months.

Results Of the 95 infants who survived after PDA ligation, 50 (53%) had neurosensory impairment, compared with 84 of the 245 infants (34%) who survived after receiving only medical therapy (adjusted odds ratio, 1.98; 95% CI, 1.18-3.30; \( P = .0093 \)). BPD (adjusted odds ratio, 1.81; 95% CI, 1.09-3.03; \( P = .023 \)) and severe ROP (adjusted odds ratio, 2.20; 95% CI, 1.19-4.07; \( P = .012 \)) were also more common after surgical PDA closure.

Conclusions PDA ligation may be associated with increased risks of BPD, severe ROP, and neurosensory impairment in ELBW infants. (J Pediatr 2007;150:229-34)

Ligation of a patent ductus arteriosus (PDA) is one of the most common types of surgery in preterm babies. The Victorian Infant Collaborative Study Group reported that surgery with general anesthesia during the initial hospitalization increases the risk of neurologic and developmental disability in extremely low birth weight (ELBW) and extremely preterm infants.1,2

We undertook this study to determine whether surgical PDA closure was a risk factor for neurosensory impairment at 18 months in children who were enrolled in the Trial of Indomethacin Prophylaxis in Preterms (TIPP).3 We also examined the impact of PDA ligation on bronchopulmonary dysplasia (BPD) and on severe retinopathy of prematurity (ROP). We chose these 2 morbidities because their incidence may be altered by surgical PDA closure and because they typically develop well after the diagnosis and treatment of a PDA. Both BPD and severe ROP are also independently associated with later death or neurosensory impairment.4 The tendency to resort to PDA ligation reflects local clinical practice and likely varies between hospitals. Our third goal was to estimate how much the frequencies of surgical PDA closures in participating centers contributed to the variation between centers in the incidence of neurosensory impairment.

METHODS

Patients

Infants with birth weights between 500 and 999 g were enrolled in the TIPP study between January 1996 and March 1998.3 The research ethics boards of all clinical centers in Canada, the United States, Australia, New Zealand, and Hong Kong approved the trial protocol, and written informed consent was obtained from a parent or guardian of each

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Management of PDA

PDA was diagnosed with echocardiography and Doppler ultrasound scanning flow studies, which were requested when there was clinical suspicion of the condition. Left-to-right ductal shunting was confirmed with Doppler ultrasound scanning flow echocardiography before drug or surgical therapy. All other management decisions were at the discretion of the local clinicians. Indomethacin was the only drug used for PDA closure.

Outcomes

BPD and ROP were pre-specified secondary outcomes in the TIPP study. All data were collected prospectively in a standardized fashion. BPD was defined as the need for supplemental oxygen at a postmenstrual age of 36 weeks. Infants were screened for ROP by using local nursery protocols, and the diagnosis was made in accordance with the international classification. Severe ROP included unilateral or bilateral disease stages 4 and 5. Infants were also classified as having severe ROP when they received cryotherapy or laser therapy in at least 1 eye.

The primary outcome in the TIPP study was a composite of death before a corrected age of 18 months or survival with ≥1 neurosensory impairments. Neurosensory impairments were defined by the presence of cerebral palsy, cognitive delay, hearing loss requiring amplification, or bilateral blindness. The same long-term outcomes were used in this study. Cerebral palsy was diagnosed when the child had non-progressive motor impairment characterized by abnormal muscle tone and decreased range or control of movements. Cognitive delay was defined as a Mental Development Index score <70 (2 SDs less than the mean of 100) on the Bayley Scales of Infant Development II. The score was assumed to be <70 when the child could not be tested because of severe developmental delay. Sound field audiometry was performed to determine the presence or absence of hearing loss. Infant blindness was defined as a corrected visual acuity <20/200. Follow-up was targeted for a corrected age of 18 months, but the protocol allowed a window of 18 to 21 months (12–21 months for audiometry). Efforts to conduct assessments continued beyond a corrected age of 21 months to maximize completeness. Home visits or assessments in non-study facilities were permitted when necessary.

Statistical Analysis

Infants with a symptomatic PDA were divided in 2 groups: infants who received medical therapy only (PDA-no surgery group) and infants who underwent PDA ligation (PDA-surgical closure group). The prevalence of qualitative baseline factors was compared between the 2 groups with a chi-square test. Means and medians for quantitative baseline factors were compared with the student t test or a non-parametric equivalent. Odds ratios and 95% CIs were calculated to estimate the differences in prognostic risk for infants who underwent PDA ligation, as compared with the infants who received only medical PDA therapy. Logistic function regression was used to compare the rates of poor outcomes with and without adjustment for a pre-specified set of potentially prognostic baseline factors (antenatal steroids, gestational age, sex, multiple births and mother's education) and for the total dose of indomethacin received per kilogram bodyweight between birth and the time the child was discharged from the study center. Logistic regression was also used to determine whether the timing of surgery by week after birth influenced the risk of poor outcome. The relationship between the proportions of ducts closed by surgery and 18-month outcome was investigated by weighted least squares, with study center as the unit of analysis. All analyses were carried out with SAS software version 6.12 (SAS Institute, Cary, NC). All P values were 2-sided and not adjusted for multiple testing. A P value <.05 was considered to be significant.

RESULTS

Study Cohort and Status at First Diagnosis of PDA

Of the 1202 infants who were enrolled in the TIPP study, 9 infants died on their calendar day of birth. Adequate data for analysis of the composite outcome at 18 months were available for 1134 of the remaining 1193 infants (95%). There were 708 infants (62%) without a symptomatic PDA, 316 infants (28%) with PDA who were treated without surgery, and 110 infants (10%) who underwent PDA ligation. Table I shows the baseline characteristics of the infants and their mothers for the 2 subgroups of infants with PDA. The status of the infants was comparable in the 2 groups at the time of their first echocardiographically confirmed diagnosis of PDA (Table II).

Use of Indomethacin for Closure of PDA and Timing of PDA Ligation

A total of 239 of 316 infants (76%) in the PDA-no surgery group and 91 of 110 infants (83%) in the PDA-surgical closure group received indomethacin to treat PDA. The total rates of exposure to indomethacin between birth and discharge from the study center were identical in the 2 groups: 89% of infants in both groups received doses of randomly assigned prophylactic indomethacin, open-label therapeutic indomethacin, or both. However, the median total drug dose per group—including any doses of prophylactic indomethacin—was higher in the PDA–surgical closure group than in the PDA–no surgery group: 0.64 mg/kg body-
weight (interquartile range, 0.37-0.91) versus 0.45 mg/kg bodyweight (interquartile range, 0.29-0.67; \( P = 0.0002 \)).

Nine of the 110 infants (8%) who underwent PDA ligation had the procedure during the first week of life, 31 (28%) during the second week, 32 (29%) during week 3, 21 (19%) during week 4, and 17 (16%) during week 5 or later.

### Risks of Adverse Outcomes after Surgical Closure of PDA

BPD, severe ROP and neurosensory impairment at a corrected age of 18 months, particularly cognitive delay, were more likely to develop in infants whose PDA was closed surgically than in infants whose PDA was managed without...
surgery. This finding remained strong after adjustment for any differences in the groups for the use of antenatal steroids, gestational age at birth, sex, multiple births, mother’s education, and the total dose of indomethacin per kilogram body-weight that infants in both groups received during their stay in the study center (Table III).

Figure 1 shows the risk of death or impairment after PDA ligation for subgroups of infants who had the operation during weeks 1, 2, 3, 4, 5, or later after birth. Although we hypothesized that earlier surgery would lead to better outcomes than delayed surgery, we found little evidence that the timing of the surgery was an important determinant of poor long-term outcome ($P$ [linear trend] = .37).

Incidence of Surgical PDA Closure in Study Centers and its Association with Center-Specific Risks of Neurosensory Impairment

Figure 2 shows the relationships between the rates of surgical PDA closure in each of the 32 study hospitals and the rates of death, the composite of death or impairment, and neurosensory impairment. The incidence of PDA ligation varied greatly in centers, from 0 to >20%. In the analysis that was adjusted only for the number of infants who were enrolled in each center, we observed a significant relationship between the frequency of PDA ligation and the risk of neurosensory impairment at 18 months (Figure 2C). After additional adjustment for the use of antenatal steroids, gestational age at birth, sex, multiple births, and mother’s education, the same trend remained, but the relationship was no longer statistically significant. This suggests that differences in patient population partly explain the variation of PDA ligation rates in centers.

DISCUSSION

In this large international cohort of ELBW infants, surgical closure of a PDA was a strong risk factor for neurosensory impairment at 18 months. Compared with infants whose PDA was treated without surgery, infants who underwent PDA ligation also had increased risks of BPD and of severe ROP. Deaths appeared to be less common in infants who underwent PDA ligation than in infants in the comparison group. This may represent a true beneficial effect of surgical PDA closure on survival, in keeping with a recent report suggesting that the mortality rate is higher in infants whose ductus remains patent after medical treatment.9 Alternatively, the mortality rate in our ligation group may be spuriously low, because deaths could occur only after the surgery, whereas deaths in the comparison group could occur at any time after the first diagnosis of PDA. This bias may have affected our mortality data, but not our estimates of the risk of neurosensory impairment in survivors.

These findings question the commonly held view that surgical closure of a PDA is safe in ELBW infants.10-13 Some authors have proposed that PDA ligation is preferable to drug therapy in very small and immature babies,10-13 although others have not shared this opinion.14-16 Limited data are

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**Table III. Risk of adverse outcomes after surgical closure of PDA**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PDA subgroup</th>
<th>Event rate</th>
<th>Unadjusted Odds ratio</th>
<th>Unadjusted $P$ value</th>
<th>Adjusted analyses* Odds ratio (95% CI)</th>
<th>Adjusted analyses* $P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD</td>
<td>PDA-no surgery</td>
<td>127/251 (51%)</td>
<td>1.98</td>
<td>.0057</td>
<td>1.81 (1.09-3.03)</td>
<td>.023</td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>67/100 (67%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe ROP</td>
<td>PDA-no surgery</td>
<td>32/251 (13%)</td>
<td>2.53</td>
<td>.0016</td>
<td>2.20 (1.19-4.07)</td>
<td>.012</td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>27/100 (27%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or neurosensory impairment at 18 months</td>
<td>PDA-no surgery</td>
<td>155/316 (49%)</td>
<td>1.50</td>
<td>.07</td>
<td>1.55 (0.97-2.50)</td>
<td>.069</td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>65/110 (59%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death before 18 months</td>
<td>PDA-no surgery</td>
<td>71/316 (22%)</td>
<td>0.55</td>
<td>.049</td>
<td>0.56 (0.29-1.10)</td>
<td>.095</td>
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<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>15/110 (14%)</td>
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</tr>
<tr>
<td>Neurosensory impairment at 18 months</td>
<td>PDA-no surgery</td>
<td>84/245 (34%)</td>
<td>2.13</td>
<td>.0021</td>
<td>1.98 (1.18-3.30)</td>
<td>.0093</td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>50/95 (53%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cognitive delay</td>
<td>PDA-no surgery</td>
<td>66/239 (28%)</td>
<td>2.11</td>
<td>.0034</td>
<td>1.96 (1.14-3.35)</td>
<td>.015</td>
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<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>41/92 (45%)</td>
<td></td>
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</tr>
<tr>
<td>Cerebral palsy</td>
<td>PDA-no surgery</td>
<td>35/245 (14%)</td>
<td>1.40</td>
<td>.29</td>
<td>1.22 (0.64-2.33)</td>
<td>.55</td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>18/95 (19%)</td>
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</tbody>
</table>

*Analysis adjusted for the use of antenatal steroids, gestational age at birth, sex, multiple births, mother’s education, and total dose of indomethacin received per kg bodyweight between birth and discharge from the study center.
available from controlled clinical trials of surgical PDA closure to inform this debate. We have been able to find only 4 small studies in which preterm infants with PDA were randomly assigned to prophylactic or therapeutic PDA ligation. Long-term outcomes for infants randomized to undergo surgery or medical therapy have not been published. However, Gersony et al observed a higher incidence of severe ROP in infants whose symptomatic PDA was closed surgically compared with infants who received indomethacin. Although the authors of a recent systematic review of this trial were unable to offer any biologically plausible explanation for the adverse effect of PDA ligation on severe ROP, this observation is consistent with our finding of an increased risk of severe ROP after surgical PDA closure.

Our study is the first to describe an association between ligation of PDA and neurosensory impairment later in childhood. However, 2 previous reports by the Victorian Infant Collaborative Study Group have alerted the medical community to the possibility of an adverse relationship between surgery with general anesthesia during the initial hospitalization and sensorineural outcome at 5 years of age in extremely preterm or ELBW infants. Ligation of PDA was the most common type of surgery in the Victorian cohort. Doyle et al offered several possible explanations for the association between surgery and subsequent neurosensory impairment. First, brain injury may have preceded the surgery in some patients; second, infants who underwent surgery may have been sicker; third, perioperative or intraoperative events such as hypothermia, cardiorespiratory instability, or exposure to anesthetic drugs may directly contribute to poor outcome. Anesthetic drugs that are routinely used during neonatal surgeries have been shown to cause apoptotic neurodegeneration in the developing rat brain.

Like Doyle et al, we can only speculate about the possible explanations for the association between surgical PDA closure and neurosensory impairment. The limitations of our study include the lack of information about surgical techniques, use of anesthetic drugs and adverse perioperative or intraoperative events in our database. Our observational study design does not permit us to determine whether the surgical closure of a PDA was a cause or just a marker of poor long-term outcome. However, the strong relationship between PDA ligation and BPD, severe ROP and neurosensory impairment remained after the adjustment for important prognostic baseline characteristics including gestational age and sex and after the adjustment for the differential use of indomethacin that we observed between the medical and surgical PDA groups. We suggest that this ancillary analysis of data from the TIPP study raises questions about the long-term safety of surgical PDA closure in ELBW infants. These questions should be examined in future randomized clinical trials that compare surgical with medical PDA therapy.

Trials are also needed to define when a PDA ligation is indicated and when it is not. In this study, the decision to refer a patient for PDA ligation was not prescribed by protocol for the TIPP study. The locally responsible clinicians decided if and when a PDA should be closed surgically. We were struck by the great variability in the rate of PDA ligation among individual study centers. Rates of surgical PDA closure ranged from 0 to >20%. This variation may be caused by differences in case mix, sampling variability, or differences in clinical practice. Our adjusted analyses suggest that differences in case mix on admission contributed to the observed variability in the frequency of PDA ligations. However, differences in clinical practice may also have played a role.

What are the implications of our findings for the care of very preterm infants? Should clinicians prescribe prophylactic indomethacin to all ELBW infants because this approach has been shown to reduce the rates of surgical PDA closure? We do not recommend the liberal use of prophylactic indomethacin because further analyses of the entire TIPP study cohort have yielded these results: In the 2 subgroups of TIPP study infants who underwent PDA ligation, the incidence of death or neurosensory impairment was 55% (22 of 40 infants) after

Figure 2. Relationship between the rate of PDA ligation in study infants in individual centers and the outcomes of death (A), death or impairment (B), and neurosensory impairment (C). The circles represent the data of individual centers. The area of each circle is proportional to the number of patients enrolled in each center. The fitted weighted regression line is shown along with its P value. After adjustment for antenatal steroid use, gestational age at birth, sex, multiple births, and mother’s education, the P values for death, death or impairment, and neurosensory impairment were .47, .30, and .21, respectively.
indomethacin prophylaxis and 61% (43 of 70) after placebo. In contrast, in the much larger subgroups of TIPP study infants who did not undergo PDA ligation, the incidence of death or neurosensory impairment was 47% (249 of 534) after indomethacin prophylaxis and 44% (218 of 499) after placebo. Therefore, any benefit derived from preventing PDA ligation in a minority of patients appears to be offset by a small adverse effect of prophylactic indomethacin on the long-term outcome of most infants who do not undergo PDA ligation.

In summary, PDA ligation is a risk factor for poor long-term outcome in ELBW infants. Universal indomethacin prophylaxis will prevent a few PDA ligations, but most ELBW infants will not benefit from prophylactic indomethacin and may even be harmed. Controlled trials with long-term follow up are urgently needed to better delineate the role of surgical closure of a PDA in the care of ELBW infants.

REFERENCES

APPENDIX

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Early Inhaled Nitric Oxide Therapy for Term and Near-Term Newborn Infants with Hypoxic Respiratory Failure: Neurodevelopmental Follow-Up

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Objective To report the neurodevelopmental outcome of infants enrolled in a randomized multicenter trial of early inhaled nitric oxide (iNO) in term and near-term neonates with hypoxic respiratory failure and pulmonary hypertension.

Study design Neonates born at ≥34 weeks gestation who required assisted ventilation and had an oxygenation index >15 and <25 were randomized to an early iNO group or a control group. A comprehensive neurodevelopmental assessment of survivors was performed at age 18 to 24 months.

Results The trial enrolled 299 infants, of which 266 (89%) survived to age 18 to 24 months (136 in the early iNO group and 130 in the control group). Follow-up evaluations were done on 234 (88%) of surviving infants. There were no differences between the 2 groups in the incidence of neurodevelopmental impairment (early iNO, 27%; control, 25%) and hearing impairment (early iNO, 23%; control, 24%). Mental development index scores were similar in the 2 groups; however, psychomotor developmental index scores were significantly higher in the control group (early iNO, 89 ± 17.7; control, 93.5 ± 18.4).

Conclusions Early iNO therapy for hypoxic respiratory failure in term and near-term infants is not associated with an increase in neurodevelopmental impairment or hearing loss at 18 to 24 months postnatal age. (J Pediatr 2007;150:235-40)

Inhaled nitric oxide (iNO) therapy reduces the use of extracorporeal membrane oxygenation (ECMO) in term and near-term infants with hypoxic respiratory failure.1-4 Based on initial randomized clinical trials, iNO therapy is commonly used to treat moderate to severe neonatal respiratory failure with an oxygenation index (OI) ≥ 25.5 A review of the previous randomized trials1-4 showed that initiation of iNO therapy at a lower OI is associated with lower ECMO use/mortality. Consequently, we conducted a randomized, multicenter clinical trial of early initiation of iNO therapy for infants presenting with respiratory failure at an OI of 15 to 25 over a 3-year period from July 1998 to May 2001. The primary hypothesis for this study was that initiating iNO at an OI of 15 to 25 compared with use of standard iNO therapy at an OI ≥ 25 would decrease the rate of ECMO/mortality from 35% to 20%. A secondary hypothesis for this study was that early iNO therapy would not increase neurodevelopmental impairment or hearing loss rates among surviving infants at age 18 to 24 months compared with standard iNO therapy. Analysis of the outcomes observed before discharge from the hospital indicated that early iNO therapy did not reduce the combined incidence of ECMO/mortality and that individual ECMO and mortality rates were similar in the 2 groups. Early iNO therapy decreased the progression of respiratory failure to an OI > 25 and then to an OI > 40. Here we report the results of neurodevelopmental follow-up of the surviving infants at 18 to 24 months postnatal age.

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The study was a prospective, randomized, double-masked clinical trial conducted in tertiary care neonatal intensive care units in the United States and Canada. The full details of the trial methods were published previously.6

**Patient Population**

Any infant delivered at ≥34 weeks of gestation with hypoxic respiratory failure secondary to idiopathic pulmonary hypertension, respiratory distress syndrome, perinatal aspiration syndrome, pneumonia/sepsis, or suspected pulmonary hypoplasia was eligible for participation in the trial. Infants were enrolled if they required assisted ventilation with an OI ≥ 15 and < 25 and a fraction of inspired oxygen (FiO2) ≥ 0.8 on any 2 arterial blood gas measurements in a 15-minute to 12-hour window.

Infants were excluded from the trial if they were >14 days of postnatal age, had life-threatening congenital malformations, structural heart disease other than patent ductus arteriosus or patent foramen ovale, congenital diaphragmatic hernia, or previous exposure to iNO therapy. Informed consent was obtained from parents/guardians before randomization, and all of the participating centers obtained approval for the study from the pertinent institutional review boards. The consent form included a plan to obtain detailed neurodevelopmental and hearing assessments at 18 to 24 months postnatal age for surviving infants in the study.

**Randomization**

Infants were stratified by the study center and were randomized to early iNO or to simulated initiation of early iNO. This was done by a central computer accessed by telephone according to a permuted block design developed and implemented by the data-coordination center.

**Follow-Up Assessment**

Surviving infants were scheduled to be seen at age 18 to 24 months for a complete history, physical examination, audiologic assessment, neurologic evaluation, and developmental testing using Bayley Scales of Infant Development.7 Anthropometric measurements were obtained at the follow-up visit, and growth percentiles were plotted using National Center for Health Statistics data. Information about intervening medical problems and socioeconomic data were also collected at this time. The neurologic assessment and developmental evaluations were performed by certified examiners trained to reliability in the examination procedure and were masked to study group assignment. The neurologic evaluation was based on the Amiel-Tison neurologic assessment8 and included an evaluation of tone, strength, reflexes, and posture. Cerebral palsy (CP) was defined as abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture. CP was then classified as mild, moderate, or severe. Mild CP was defined as motor function that slightly interfered with but did not prevent age-appropriate motor activities. The mild CP group included children capable of non-fluent walking, asymmetric walking, or persistent toe-walking with tight Achilles tendons resulting from increased tone; these children did not require an assistive device for walking. Moderate CP was defined as impaired motor function interfering with age-appropriate motor activities and was associated with ambulation requiring an assistive device or no ambulation but the ability to sit independently or with support. Severe CP was marked by impaired function interfering with all age-appropriate motor activity to the point that the child was unable to ambulate or sit, even while supported. For developmental assessment, the Bayley Scales of Infant Development II were administered; from this information, a mental developmental index (MDI) and a psychomotor developmental index (PDI) were derived.

A comprehensive audiologic assessment was done, including speech awareness in the sound field as well as bone conduction, warbled pure-tone thresholds in the sound field at 250 to 4000 Hz, and tympanometry. Responses were compared with previously established norms.9 For the purpose of the study, normal hearing was defined as threshold responses to speech awareness in the sound field and pure-tone thresholds in the sound field at ≤40 decibels. The children were classified into 4 groups: normal hearing, sensorineural hearing loss, conductive loss, and undetermined. A diagnosis of blindness was based on an ophthalmologist report of uncorrectable vision ≤20/200 in the better eye. Neurodevelopmental impairment was defined as the presence of any of the following: moderate or severe CP, Bayley MDI < 70, Bayley PDI < 70, blindness, or permanent hearing impairment requiring amplification.

**Statistical Analysis**

Continuous variables were compared using t-tests or Wilcoxon’s test for nonparametric data. Discrete variables were compared using χ2 tests or Fisher’s exact test as appropriate. A P value < .05 was considered significant. The 95% confidence intervals (CIs) for the differences between continuous and discrete variables were computed; a difference was considered statistically significant if the 95% CI for the difference did not include 0.10

**RESULTS**

A total of 299 infants were enrolled in the original trial (Table I); 30 infants died before discharge (13 in the early iNO group and 17 in the control group). Of the 269 infants who survived to discharge from the hospital, 3 additional infants died before reaching 18 to 24 months postnatal age (1 in the early iNO group and 2 in the control group). Of the remaining 266 infants, 234 (88%; 121 in the early iNO group and 113 in the control group) were seen for follow-up evaluation.

The neonatal characteristics, including birth weight, gestation, and sex distribution, did not differ between the 2 groups (Table I). Infants in both groups were evaluated at similar chronologic and adjusted postnatal ages (Table I).
Although all infants in the early iNO group had received iNO, standard iNO therapy, given at an OI of ≥ 25, was provided to 38% of the surviving infants in the early iNO group and to 50% of the surviving infants in the control group. The number of infants receiving ECMO support was similar in both groups. The 2 groups were similar in terms of ethnic distribution, maternal marital status, and maternal education (data not shown). Overall, 18% of the mothers completed 10 to 12 years of education, 30% had a high school diploma, and 23% attended college.

Information for postdischarge medication use and use of adaptive equipment was collected by a standardized parental questionnaire (Table II). At the time of follow-up evaluation, 35% of the infants in the study were rehospitalized at least once. This is similar to the 36% rehospitalization rate previously reported in the follow-up of cohort from the NINOS trial.1 The most commonly used postdischarge medications included bronchodilators and home oxygen. There were no significant differences between the 2 groups in terms of any medical and community resource needs (Table II). No significant differences in growth measurements were noted between the 2 groups (data not shown). Approximately 20% of the study infants had weight below the 10th percentile, and 15% of the infants had length and head circumference below the 10th percentile.

Approximately 87% of the infants had normal neurologic assessment findings (84% of those in the early iNO group and 91% of those in the control group; Table III). The overall incidence of CP and the incidence of moderate to severe CP did not differ in the 2 groups. There was no difference in the rate of moderate to severe neurologic abnormalities between the 2 groups.

Developmental assessment with the Bayley Infant Development Scale showed no difference in MDI scores between the study groups. The percentage of infants with an MDI score < 70 was similar in the 2 groups. The PDI scores were significantly higher in the control group; however, the percentage of infants with a PDI score < 70 was similar in the 2 groups. Reanalyzing the data after excluding the 12 infants with moderate to severe CP did not significantly affect the trends in MDI and PDI in the 2 groups; the mean MDI score was 85.2 ± 19.9 in the early iNO group, compared with 87.9 ± 18.6 in the control group (P = .26). Approximately 21% of the infants in the early iNO group and 19% of those in the control group had an MDI score < 70. The PDI scores were 91.3 ± 15.3 for the early iNO group and 95.7 ± 15.9 for the control group (P = .006). The percentage with a PDI score < 70 remained similar between the 2 groups, 6.8% in the early iNO group versus 7% in the control group (P = .95). Overall, 203 of the 234 infants seen on follow-up examination underwent a complete audiologic assessment. There was no difference between the 2 groups in the percentage of assessed infants with normal findings or in the incidence of sensorineural or conductive hearing loss. The percentage of infants requiring tympanostomy tube placement was similar in the 2 groups (9.1% in the early iNO group vs 12.6% in the control group). There was no difference between the 2 groups in the incidence of unilateral or bilateral vision loss. We found that 72% of the infants in the early iNO group and 75% of those in the control group were free of neurodevelopmental impairments, including moderate or severe CP, Bayley MDI < 70, Bayley PDI < 70, blindness, or permanent hearing impairment requiring amplification.

Comparing the outcomes for the 46 infants in the early iNO group and 57 infants in the control group who progressed to standard iNO therapy at OI ≥ 25 demonstrated no differences between the 2 groups in terms of the percentage of infants with moderate to severe abnormalities on neurologic assessment. Infants who received standard iNO therapy in the 2 groups also had similar MDI and PDI scores, hearing loss rate, and rate of neurodevelopmental impairment (early iNO group, 34%; control group, 26%; P = .36). Comparing the data for 12 infants in each group who progressed to receive ECMO showed no differences between the 2 groups for these variables.

Exposure to any iNO therapy was not associated with increased neurodevelopmental impairment in the 178 infants who had iNO exposure compared to 56 control infants without iNO exposure. The MDI scores (84.1 ± 19.8 for iNO exposure vs 86.4 ± 22.4 for no iNO exposure; P = .36) and PDI scores (90.8 ± 17.2 for iNO exposure vs 92.6 ± 20.9 for no iNO exposure: P = .13) were similar for the 2 groups. Similarly, neurodevelopmental outcomes for the 24 infants who received ECMO support (MDI, 85.8 ± 23.9; PDI, 92.8 ± 15.3) were similar to those in the 211 infants without ECMO support (MDI, 84.5 ± 20 [P = .66]; PDI, 91 ± 18.5 [P = .68]). We performed secondary analyses of the data to identify any associations between neurodevelopmental im-

### Table I. Neonatal characteristics of the survivors of the early iNO trial evaluated at follow-up

<table>
<thead>
<tr>
<th></th>
<th>Early iNO group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized at study entry, n</td>
<td>150</td>
<td>149</td>
</tr>
<tr>
<td>Age at study entry in hours, median (1st to 3rd quartile range)</td>
<td>28.5 (14-46)</td>
<td>24.8 (12-47)</td>
</tr>
<tr>
<td>Survived to discharge, n (%)</td>
<td>137 (91)</td>
<td>132 (89)</td>
</tr>
<tr>
<td>Survived to age 18 to 24 months, n (%)</td>
<td>136 (90.6)</td>
<td>130 (87.2)</td>
</tr>
<tr>
<td>Evaluated at age 18 to 24 months, n (%)</td>
<td>121 (88.9)</td>
<td>113 (86.9)</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3320 ± 690</td>
<td>3345 ± 552</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>38.5 ± 1.9</td>
<td>38.8 ± 1.9</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>58 (48)</td>
<td>43 (38)</td>
</tr>
<tr>
<td>Chronological age, months</td>
<td>20.9 ± 2.9</td>
<td>20.8 ± 4.1</td>
</tr>
<tr>
<td>Adjusted age, months</td>
<td>20.7 ± 3.0</td>
<td>20.6 ± 4.1</td>
</tr>
<tr>
<td>Received standard iNO, n (%)</td>
<td>46 (38)</td>
<td>57 (50)</td>
</tr>
<tr>
<td>Received ECMO, n (%)</td>
<td>12 (10)</td>
<td>12 (11)</td>
</tr>
</tbody>
</table>

*Infants in either group who progressed to an OI of 25 received standard iNO therapy.
pairments and various adjunctive therapies used during the hospital stay that have been reported to be risk factors for such impairments.12-17 The use of skeletal muscle relaxants (in 134 infants with iNO exposure and 95 infants without exposure) was not associated with increased neurodevelopmental or hearing impairments (data not shown). The 98 infants (43.7%) exposed to postnatal steroids during the hospital stay appeared to have a higher incidence of neurodevelopmental impairments (34.7%) than the infants who had no exposure (19.8%; $P < .01$). However, further analysis of the data revealed that those infants exposed to postnatal steroids were sicker and were more likely to have received volume expanders, vasopressor support, standard iNO therapy, high-frequency oscillation, and longer duration of ventilator support and had a higher incidence of chronic lung disease. A multiple logistic regression analysis model showed that steroid exposure is not an independent risk factor for adverse neurodevelopmental outcome; the odds ratio for neurodevelopmental impairments in the unexposed group was 0.51 with a 95% CI of 0.25 to 1.01 ($P = .053$).

### Table II. Health status outcomes for survivors of the early iNO trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early iNO (n = 121)</th>
<th>Control (n = 113)</th>
<th>$P$ value</th>
<th>95% CI for the difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized since discharge, n (%)</td>
<td>43 (35.3)</td>
<td>41 (36.3)</td>
<td>.87*</td>
<td>-11.1, 13.3</td>
</tr>
<tr>
<td>Home medications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>27 (22)</td>
<td>19 (17)</td>
<td>.29*</td>
<td>-15.7, 4.8</td>
</tr>
<tr>
<td>Diuretics</td>
<td>2 (1.6)</td>
<td>2 (1.8)</td>
<td>1.0†</td>
<td>-4.5, 4.8</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>5 (4.1)</td>
<td>2 (1.8)</td>
<td>.45†</td>
<td>-7.9, 2.8</td>
</tr>
<tr>
<td>Tracheotomy, n (%)</td>
<td>2 (1.7)</td>
<td>0 (0)</td>
<td>.50†</td>
<td>-6.2, 1.8</td>
</tr>
<tr>
<td>Home oxygen, n (%)</td>
<td>14 (11.5)</td>
<td>6 (5.4)</td>
<td>.09†</td>
<td>-13.7, 1.2</td>
</tr>
<tr>
<td>Home ventilator, n (%)</td>
<td>3 (2.5)</td>
<td>0 (0)</td>
<td>.25†</td>
<td>-7.4, 0.9</td>
</tr>
<tr>
<td>Gastrostomy/tube feeding, n (%)</td>
<td>10 (8)</td>
<td>4 (4)</td>
<td>.14*</td>
<td>-11.4, 1.7</td>
</tr>
<tr>
<td>Use of adaptive equipment, n (%)</td>
<td>6 (5)</td>
<td>6 (5.5)</td>
<td>.89†</td>
<td>-6.3, 7.1</td>
</tr>
<tr>
<td>Stroller/wheelchair, n (%)</td>
<td>4 (3.4)</td>
<td>1 (0.9)</td>
<td>.37†</td>
<td>-7.7, 2.1</td>
</tr>
<tr>
<td>Braces/orthotics, n (%)</td>
<td>2 (1.7)</td>
<td>6 (5.5)</td>
<td>.16†</td>
<td>-1.2, 10.0</td>
</tr>
<tr>
<td>Walker, n (%)</td>
<td>0</td>
<td>2 (1.8)</td>
<td>.23†</td>
<td>-1.5, 6.8</td>
</tr>
</tbody>
</table>

*By the $\chi^2$ test.
†By Fisher’s exact test.

### Table III. Neurodevelopmental impairments at age 18 to 24 months in the early iNO and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early iNO (n = 121)</th>
<th>Control (n = 113)</th>
<th>$P$ value</th>
<th>95% CI for the difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral palsy—all degrees, n (%)</td>
<td>10 (8.2)</td>
<td>7 (6.3)</td>
<td>.58*</td>
<td>-9.0, 5.3</td>
</tr>
<tr>
<td>Cerebral palsy—moderate to severe, n (%)</td>
<td>6 (4.9)</td>
<td>3 (2.7)</td>
<td>.50†</td>
<td>-8.2, 3.6</td>
</tr>
<tr>
<td>Any neurologic abnormality, n (%)</td>
<td>20 (16.4)</td>
<td>10 (9.2)</td>
<td>.10*</td>
<td>-16.0, 1.5</td>
</tr>
<tr>
<td>Moderate/severe neurologic abnormality, n (%)</td>
<td>6 (4.9)</td>
<td>3 (2.8)</td>
<td>.51†</td>
<td>-8.0, 3.5</td>
</tr>
<tr>
<td>Bayley MDI, mean/median (SD)</td>
<td>83.3/87 (21.0)</td>
<td>86.1/90 (19.9)</td>
<td>.28‡</td>
<td>-8.0, 2.0§</td>
</tr>
<tr>
<td>MDI &lt; 70, n (%)</td>
<td>28 (25.2)</td>
<td>24 (22.9)</td>
<td>.68*</td>
<td>-13.7, 9.1</td>
</tr>
<tr>
<td>Bayley PDI, mean/median (SD)</td>
<td>89.0/93 (17.7)</td>
<td>93.5/98 (18.4)</td>
<td>.009‡</td>
<td>-9.0, -1.0§</td>
</tr>
<tr>
<td>PDI &lt; 70, n (%)</td>
<td>13 (11.9)</td>
<td>12 (11.4)</td>
<td>.91*</td>
<td>-9.4, 8.5</td>
</tr>
<tr>
<td>Blindness, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>1 (0.8)</td>
<td>1 (0.9)</td>
<td>1.0†</td>
<td>-3.9, 4.4</td>
</tr>
<tr>
<td>Bilateral</td>
<td>4 (3.4)</td>
<td>1 (0.9)</td>
<td>0.37†</td>
<td>-7.7, 2.2</td>
</tr>
<tr>
<td>Hearing status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal hearing</td>
<td>79 (67.6)</td>
<td>76 (76)</td>
<td>.91*</td>
<td>-12.5, 11.0</td>
</tr>
<tr>
<td>Sensorineural loss</td>
<td>7 (6.8)</td>
<td>10 (10.0)</td>
<td>.41*</td>
<td></td>
</tr>
<tr>
<td>Conductive loss</td>
<td>16 (15.5)</td>
<td>7 (7.0)</td>
<td>.055*</td>
<td></td>
</tr>
<tr>
<td>Undetermined/other</td>
<td>1 (0.97)</td>
<td>7 (7.0)</td>
<td>.03†</td>
<td></td>
</tr>
<tr>
<td>Hearing impairment requiring amplification</td>
<td>1 (1.0)</td>
<td>3 (3.0)</td>
<td>.37†</td>
<td></td>
</tr>
<tr>
<td>Seizure disorder, n (%)</td>
<td>4 (3.4)</td>
<td>4 (3.7)</td>
<td>1.0†</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus with shunt, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any neurodevelopmental impairment, n (%)</td>
<td>34 (27.9)</td>
<td>28 (24.6)</td>
<td>.56*</td>
<td>-14.5, 8.0</td>
</tr>
</tbody>
</table>

*By the $\chi^2$ test.
†By Fisher’s exact test.
‡By Wilcoxon’s test.
§CIs are for difference in medians for these variables.
DISCUSSION

The early introduction of iNO therapy for term and near-term infants with moderate respiratory failure (OI 15 to 25) improved oxygenation and decreased the progression to more severe respiratory failure. However, early initiation of iNO therapy did not reduce the use of ECMO/mortality in this study. The study infants were followed prospectively to age 18 to 24 months to determine whether this intervention had any effect on long-term neurodevelopmental outcome. Although the study was not powered to detect a prespecified difference in neurodevelopmental outcome between these two groups, a secondary hypothesis of the study was that early iNO would not increase the incidence of neurodevelopmental impairments at age 18 to 24 months. Our data show that the early iNO control groups did not differ significantly in terms of most long-term neurodevelopmental outcome variables. Although the proportion of infants with medical problems, such as the need for home medications, oxygen, and ventilator support and abnormal neurologic assessment findings, appears to be higher in the early iNO group, the 95% CIs show that these differences are not significant. The clinically significant neurodevelopmental impairments, such as moderate to severe CP, Bailey MDI and PDI scores < 70, blindness, and hearing loss, show equivalent outcomes with P ≥ 0.5 and the 95% CI for difference distributed well on both sides of 0.

Three randomized trials of iNO therapy included neurodevelopmental follow-up at age 18 to 24 months. In these studies, which included a placebo control group for comparison with iNO treatment, no differences in the neurodevelopmental impairments were noted between the control and treatment groups. The early iNO trial enrolled infants with less severe respiratory failure compared with the previous trial conducted by our group, and in the present trial the overall incidence of abnormal neurologic findings was 12.8%, compared with 21.5% in our previous trial. The prevalence of moderate to severe CP was 3.8% in the present trial, compared with 7.6% in our previous trial.

Although our trial enrolled infants with less severe respiratory failure, we found a high use of supportive therapies, such as volume expanders and vasopressors (in >80%) and sedation and analgesia (in 96%). In addition, >60% of the study infants received surfactant therapy, 44% received high-frequency ventilation, 56% underwent skeletal muscle paralysis, and 43% were given postnatal steroids. An association between the use of these therapies and an elevated incidence of neurodevelopmental impairments and hearing loss was suggested in previous follow-up studies. In the present study we found no association between the use of skeletal muscle relaxants and postnatal steroids and neurodevelopmental impairments, in contrast to previous studies reporting worse long-term outcome with these therapies.

As part of the study protocol, we performed a complete audiologic assessment in the study infants. The overall incidence of hearing loss (24%) was similar to what we observed in the follow-up of infants in the NINOS trial. Although we found no difference in the prevalence of hearing loss in the early iNO and control groups in our study, a relatively high incidence of hearing loss persisted in this cohort of less sick infants. Whether this high rate of hearing loss is related to respiratory failure or to the use of adjunctive therapies, such as alkalinosis, analgesia, and neuromuscular blocking agents, remains unknown.

Bayley MDI scores were similar in the 2 groups, but PDI scores differed. This difference in PDI scores persisted even after the exclusion of infants with moderate to severe CP. The MDI and PDI scores showed significant variability, with a standard deviation of 18 to 21 points. In addition, the data were subjected to multiple comparisons, which could increase the probability of a type 1 error for the observed difference. However, a possible adverse effect of early iNO in term and near-term neonates with respiratory failure cannot be excluded. We observed lower PDI scores at the follow-up of the NINOS trial for the iNO group compared with the control group, though the difference was not statistically significant. Comparing the PDI scores for the infants who progressed to standard iNO therapy in both treatment groups in the early iNO trial showed that the difference was not significant, indicating that early initiation of iNO therapy did not have an adverse effect on outcome in infants who experienced progressive respiratory failure. In addition, iNO therapy itself and ECMO support did not affect neurodevelopmental outcome. Note, however, that our samples of infants who did not receive iNO therapy (56 infants) and those who received ECMO support (24 infants) are small.

Our early iNO and control groups were similar in terms of all measured socioeconomic variables. The 2 groups had similar postdischarge medical needs, including rates of hospital readmission, need for home oxygen, tube feedings, and other medications. Therefore, the neurodevelopmental outcomes in our study subjects were unlikely to be influenced by differences in health status or socioeconomic factors.

In conclusion, our findings indicate that early iNO therapy was not associated with an increase in medical, neurodevelopmental, or hearing abnormalities at age 18 to 24 months compared with standard iNO therapy in a population of term or near-term infants with hypoxic respiratory failure. Even though early iNO therapy decreased the progression of respiratory failure in these infants, this apparent benefit was not associated with a decrease in long-term morbidity. Survivors of neonatal hypoxic respiratory failure remain at a significant risk for neurodevelopmental and hearing deficits and need close monitoring and follow-up. Whether these abnormalities are related to underlying disease process or to the postnatal interventions used in these infants remains unknown and requires further investigation.

REFERENCES


APPENDIX

The Neonatal Inhaled Nitric Oxide Study was a collaboration of the National Institute of Child and Health and Human Development Neonatal Research Network and the Canadian Inhaled Nitric Oxide Study Group. The following institutions and investigators participated in the trial. Members of the Executive Committee are indicated by asterisks.

NINOS Follow-Up Principal Investigators

Case Western Reserve University, Cleveland: D. Wilson; University of Texas, Dallas: S. Broyles; Wayne State University, Detroit: V.D. Black, Y. Johnson; University of Toronto, Toronto: A. James; University of Tennessee, Memphis: K. Yolton; University of Miami, Miami: C. Bauer; University of New Mexico, Albuquerque: G. Laadt; University of Cincinnati, Cincinnati: J. Steichen; Indiana University, Indianapolis: A. Dusick; Yale University, New Haven, CT: L. Mayes; Women and Infants’ Hospital, Providence, RI: B. Vohr; Stanford University, Palo Alto, CA: B. Fleisher; University of Alabama, Birmingham: K. Nelson; Harvard University, Boston: K. Lee; University of Texas, Houston: B. Morris; University of Alberta, Edmonton: C. Robertson; University of Calgary, Calgary: R. Sauve; University of British Columbia, Vancouver: M. Whitfield; Baylor College of Medicine, Houston: A. Reynolds; McGill University, Montreal: P. Riley; University of Ottawa, Ottawa: M. Blayney; McMaster University, Hamilton, Ontario: S. Saigal; University of Manitoba, Winnipeg: O. Casiro.

NICHD Neonatal Research Network


Canadian Inhaled Nitric Oxide Study Group


Data Safety and Monitoring Committee


Data Coordination Center

Aspiration of Gastric Contents in Sudden Infant Death Syndrome without Cardiopulmonary Resuscitation

HENRY F. KROUS, MD, HOMEYRA MASOUMI, MD, ELISABETH A. HAAS, MPH, AMY E. CHADWICK, BA, CHRISTINA STANLEY, MD, AND BRADLEY T. THACH, MD

Objectives  (1) To compare demographic profiles among sudden infant death syndrome (SIDS) infants with or without gastric aspiration, for whom cardiopulmonary resuscitation (CPR) had not been attempted; (2) to review the severity and potential significance of aspiration in those SIDS cases; and (3) to assess the risk of supine sleep position with regard to gastric aspiration.

Study design  Retrospective review of records and microscopic slides for all postneonatal SIDS cases (29 to 365 days of age) accessioned by the San Diego County Medical Examiner from 1991 to 2004.

Results  Ten (14%) of 69 cases of SIDS infants who had not undergone CPR before autopsy revealed microscopic evidence of gastric aspiration into the distal lung; this group was not otherwise clinically or pathologically different from cases of SIDS infants without aspiration. Similar proportions of infants were found supine or prone, regardless of gastric aspiration.

Conclusions  Gastric aspiration is not uncommon in infants dying of SIDS, and supine sleep position does not increase its risk. Gastric aspiration may be a terminal event that some infants, representing a subset of SIDS cases, cannot overcome. (J Pediatr 2007;150:241-6)

Gastric contents are present in the lungs of 30% to 40% of infants whose deaths are attributed to sudden infant death syndrome (SIDS). Studies in adults indicate that intrapulmonary migration of gastric contents can occur postmortem as a result of cardiopulmonary resuscitation (CPR) or transport of the body. Accordingly, the majority of pediatric pathologists have dismissed aspiration of gastric contents (henceforth referred to as “gastric aspiration”) as a cause of death, believing it to be a postmortem artifact. The pathology literature addressing gastric aspiration in SIDS is not only limited, but, most importantly, none of the studies has controlled for the potential role of CPR in forcing gastric contents from the oral cavity and/or pharynx into the distal lung. Therefore, the aims of our study are to: (1) compare the demographic characteristics and findings from the death scene and autopsy in SIDS infants with or without gastric aspiration who had no CPR attempted before autopsy; (2) review the degree and significance of aspiration in this subset of SIDS cases; and (3) assess the risk of supine sleep position relative to gastric aspiration.

METHODS

The Rady Children's Hospital-Health Center Institutional Review Board approved this study. A search of the records of all postneonatal infants (29-365 days of age) dying suddenly and unexpectedly who were autopsied at the Medical Examiner's Office in San Diego County, California, between January 1, 1991 and December 31, 2004 and accessioned into the San Diego SIDS Research Project database at Children's Hospital-San Diego revealed 69 cases of infants who had a diagnosis of SIDS and had not undergone CPR before autopsy.

Case data were selected from the medical history, death scene, investigative and autopsy reports, and from two standardized data protocols for the death scene investigation and autopsy. In 1989, a California statute mandated use of standardized scene investigation and autopsy protocols (developed by a multidisciplinary expert committee) for cases of sudden, unexpected infant death without external evidence of inflicted injuries. Trained, experienced investigators from the Medical Examiners Office are charged with collecting this information within 30 hours of an infant's death. The data are not complete for every case.

| ALTEs | Apparent life-threatening events |
| CPR   | Cardiopulmonary resuscitation   |
| GER   | Gastroesophageal reflux         |
| SIDS  | Sudden infant death syndrome    |

From the Department of Pathology, Rady Children's Hospital, San Diego, California (H.F.K., H.M., E.A.H., A.E.C.); the Department of Pathology, University of California, San Diego School of Medicine, La Jolla, California (H.F.K.); Office of the Medical Examiner, County of San Diego, California (C.S.); and the Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri (B.T.T.).

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Figure. Aspirated gastric contents distend a distal bronchiole (dashed arrow) and extend into adjacent alveoli (solid arrow) of the lung of this 3-month-old male found prone with his face to the side. Hematoxylin and eosin, ×100.

A diagnosis of SIDS was made when criteria from the recent definition proposed in 2004 were fulfilled. For analytical purposes, the cases were divided into two groups: Group I, SIDS cases with gastric aspiration, and Group II, SIDS cases without gastric aspiration.

Microscopic lung sections stained with hematoxylin and eosin were available in all cases; the mean numbers of sections for Group I cases with aspiration and Group II without aspiration were 4.9 ± 2.2 and 4.3 ± 1.2, respectively; the ranges for the two groups were 1 to 10 and 1 to 6, respectively. Two pathologists (HFK and HM) reviewed the slides. Inter- and intra-observer reproducibility (κ) testing was calculated; inter-observer κ-value was 0.82, intra-observer results ranged from 0.82 to 1.00. Gastric contents were identified by the presence of amorphous and finely granular and/or faintly basophilic eosinophilic material. Isolated clumps of bacterial colonies were not interpreted as gastric aspiration (see discussion). The severity of gastric aspiration (defined as gastric contents identifiable in distal bronchioles [Figure], with or without extension into the intra-alveolar spaces) was assessed semiquantitatively according to the following scale: 0 = absent, 1 = very mild, 2 = mild, 3 = moderate, and 4 = severe.

Data Analysis

Categorical variables were analyzed using the χ² or Fisher’s exact test, along with odds ratios. Continuous data were analyzed with two-sample t tests and are summarized using means ± standard deviations. Calculations were performed with Epi Info v. 3.3, Statacalc v. 6 (Centers for Disease Control and Prevention, Atlanta, GA), or Statistical Package for the Social Sciences v. 11.5 (SPSS Inc., Chicago, IL). A P value < .05 was considered significant.

RESULTS

Group I (SIDS cases with aspiration) includes 10 (14%) of the 69 cases. No demographic findings were significantly different between the two groups (Table I). The majority of infants in both groups were male, born term, delivered vaginally, and fed formula as their last meal. None of the infants who were breast-fed for their last meal had evidence of gastric aspiration. Clinically documented gastroesophageal reflux (GER) was more common in cases with aspiration (20% vs 2%); a history of apnea or apparent life-threatening events (ALTEs) was uncommon in both groups. Approximately one quarter of the infants in both groups was bed-sharing when they died. The interval from time of last feeding to time of discovery was similar between the two groups as was the postmortem interval. Only one of the Group I cases had grade 4 aspiration.

No significant differences in the death scene and postmortem findings between groups were identified, including the positions the infant was placed for sleep or found, the position of the face when found, gastric contents in the tracheobronchial lumen, and intrathoracic petechiae (Table II). Seventy percent of the Group I cases had very mild to mild gastric aspiration;
moderate or severe gastric aspiration was present in less than one third of the cases. There was no association between age and the severity of gastric aspiration.

Details of the 10 Group I infants with gastric aspiration are given in Table III. Eight of 9 (89%) for which body position was known were discovered prone. Face position when found was known in 8 cases; 7 (88%) were face down or to the side. None had a history of ALTE, 2 (20%) had previously documented GER, and 9 (90%) had intrathoracic petechiae at autopsy. Three infants, one of which was the only infant with grade 4 aspiration, had evidence of vomitus when discovered lifeless. The Figure is from Case F (Table III) and shows a bronchiole distended with gastric contents.

**DISCUSSION**

Prone sleep position has been long recognized as one of the most important risk factors for SIDS.6–10 Adoption of the supine sleep position as recommended in the Back to Sleep campaign and other similar public education programs has

<table>
<thead>
<tr>
<th>Position body placed</th>
<th>Group I with gastric aspiration (N = 10)</th>
<th>Group II without gastric aspiration (N = 59)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>N = 6</td>
<td>N = 37</td>
<td>NS</td>
</tr>
<tr>
<td>Side</td>
<td>1 (17%)</td>
<td>11 (30%)</td>
<td></td>
</tr>
<tr>
<td>Prone</td>
<td>5 (83%)</td>
<td>21 (57%)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Position body found</th>
<th>Group I with gastric aspiration (N = 10)</th>
<th>Group II without gastric aspiration (N = 59)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>N = 9</td>
<td>N = 53</td>
<td>NS</td>
</tr>
<tr>
<td>Side</td>
<td>1 (11%)</td>
<td>13 (25%)</td>
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</tr>
<tr>
<td>Prone</td>
<td>8 (89%)</td>
<td>36 (68%)</td>
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</table>

<table>
<thead>
<tr>
<th>Position face found</th>
<th>Group I with gastric aspiration (N = 10)</th>
<th>Group II without gastric aspiration (N = 59)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up</td>
<td>N = 8</td>
<td>N = 43</td>
<td>NS</td>
</tr>
<tr>
<td>Side</td>
<td>1 (13%)</td>
<td>6 (14%)</td>
<td></td>
</tr>
<tr>
<td>Down</td>
<td>5 (63%)</td>
<td>18 (42%)</td>
<td></td>
</tr>
<tr>
<td>Prone</td>
<td>2 (25%)</td>
<td>19 (44%)</td>
<td></td>
</tr>
<tr>
<td>Tracheobronchial</td>
<td>2 (20%)</td>
<td>2 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>gastric contents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at autopsy</td>
<td></td>
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<td></td>
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</tbody>
</table>

| Intrathoracic         | 9 (90%)                                | 51 (86%)                                 | NS|
| petechiae             |                                        |                                          |   |

| Vomitus when found*   | 3 (30%)                                | 3 (5%)                                   | .04|

| Gastric aspiration    | 0                                       | 59 (100%)                                |   |
| score†                | 1                                       | 4 (40%)                                  |   |
| 2                     | 3 (30%)                                |                                          |   |
| 3                     | 2 (20%)                                |                                          |   |
| 4                     | 1 (10%)                                |                                          |   |

NS, Not significant.
*Descriptions include: vomit, dried formula, thick white purge.
†Gastric aspiration semiquantitative score: 0 = absent, 1 = very mild, 2 = mild, 3 = moderate, and 4 = severe.

Table II. Death scene and postmortem findings in SIDS cases without CPR by presence or absence of gastric aspiration

<table>
<thead>
<tr>
<th>Stomach contents aspiration† (mL)</th>
<th>Group I with gastric aspiration (N = 10)</th>
<th>Group II without gastric aspiration (N = 59)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
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<tr>
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<td>Z</td>
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</table>

Fed interval* elapsed time between the last feed and when found unresponsive.
†Tracheobronchial aspiration noted at gross autopsy.

**Table III. Clinical and pathologic findings in SIDS cases with gastric aspiration**

<table>
<thead>
<tr>
<th>Gastric aspiration score</th>
<th>Group I with gastric aspiration (N = 10)</th>
<th>Group II without gastric aspiration (N = 59)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>59 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4 (40%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3 (30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 (10%)</td>
<td></td>
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</tbody>
</table>
resulted in a dramatic reduction in the incidence of SIDS.\textsuperscript{9,11,12} However, some segments of the population have not followed the supine sleep recommendation, causing disparities in the decreasing rates of SIDS.\textsuperscript{13-16} Fear of gastric aspiration leading to death is among the variety of reasons that supine sleep position has not been adopted,\textsuperscript{16} although epidemiological and postmortem evidence to support this fear has not been forthcoming from studies in Australia, the United Kingdom, and the United States.\textsuperscript{10,17,18} In fact, a report from the Infant Care Practice Study provides data to indicate the safety of supine sleeping with regard to a number of health outcomes, including GER and vomiting.\textsuperscript{19}

Although our study does not identify significant differences between the groups with and without gastric aspiration, there are several noteworthy findings: (1) all but one of the nine case infants with gastric aspiration for whom body position was known were found prone; (2) the majority of infants (>85%) in both groups were found with their faces down or to the side; (3) approximately one quarter of each group was bed-sharing at the time of their deaths; and (4) none of the infants who were last breast-fed had evidence of gastric aspiration.

In contrast to previous studies of gastric aspiration in sudden infant death,\textsuperscript{1,2,20} the principal and unique strength of our study is inclusion of only SIDS infants who had not undergone CPR before autopsy. We were, therefore, able to eliminate CPR as a cause of gastric contents in the distal parts of the lung. Consequently, we found gastric aspiration in 14% of our SIDS cases, a proportion somewhat less than that observed by other investigators in cases of sudden infant death.\textsuperscript{1,20,21}

Two previous studies have analyzed cases or subsets of infant death cases limited to SIDS.\textsuperscript{1,20} Their analyses are confounded, however, by inclusion of cases of infants who had undergone CPR before autopsy. Bajanowski et al did not identify “deep aspiration,” defined as the presence of gastric contents in bronchioles and alveoli, in any of 131 cases of SIDS infants whether found prone, supine, or on their side.\textsuperscript{1} In contrast, Alex et al identified aspirated gastric contents in 37% of 99 SIDS cases. The degree of aspiration was never severe nor considered a cause of death.\textsuperscript{20} These investigators included the presence of milk in typical form with or without clumps of bacteria, clumps of bacteria having a similar distribution but without other airway contents identifiable as milk, and other food particles as evidence of aspirated gastric contents. We did not accept isolated bacterial clumps as evidence of gastric aspiration in our study, and we agree with others that CPR even after death can account for this finding.\textsuperscript{1,2,22} Alex et al also found that the risk of gastric aspiration was significantly increased in association with being found supine or having the autopsy performed on the day after death or later. In contrast, we found no association between sleep position or the duration of the postmortem interval and gastric aspiration in our study.

Other epidemiological and pathological studies that combined SIDS cases with cases of infants who died of other causes into a single group have shown that supine sleep position did not increase the risk of gastric aspiration. After reviewing vital statistics for the United States for the years 1991, 1995, and 1996, Malloy determined that gastric aspiration had not accounted for any increase in postneonatal mortality.\textsuperscript{10} This finding is important given that the prevalence of prone positioning for infant sleep decreased from 70% in 1992 to 14% in 2000 (<http://www.nichd.nih.gov/publications/pubs/BTS_Q_A_Healthproviders.cfm>) and supine positioning increased from 13% to 35%.\textsuperscript{15} During the same interval, Malloy determined that postneonatal aspiration-related deaths dropped from 1.39 per 100,000 live births in 1991 to 0.93 in 1996.\textsuperscript{30} In their review of 196 cases of infant and early childhood death, Byard and Beal identified the cases of three infants with severe gastric aspiration into airways and alveoli, all of whom were discovered prone and one with the face in a pool of vomitus, and concluded that supine positioning did not increase the risk of aspiration.\textsuperscript{2} In this regard, it is worth noting again that 8 of the 9 cases of infants positive for gastric aspiration for whom the data were available were found prone (Table III).

Considerable evidence indicates that young infants are susceptible to numerous conditions that cause episodes of severe hypoxemia resulting in loss of consciousness. The vast majority of these infants autoresuscitate, as a result of hypoxic gasping. In such cases brainstem centers initiate the autoresuscitation reflex mechanisms. This is the last chance for survival after arousal or other protective responses have failed.\textsuperscript{24} Terminal gasping has been recorded in infants being monitored at the time of their deaths, suggesting that at least a subset of SIDS cases may represent a failure of autoresuscitation.\textsuperscript{25,26} In a mouse model using saline infused into the pharynx during hypoxic gasping, reflexive swallowing facilitates successful autoresuscitation.\textsuperscript{27} In cases where swallowing does not occur, resuscitation fails, presumably because of intrapulmonary aspiration. This is supported by Stevens’ observations of human infants who died rapidly of unknown causes; he witnessed repeated successful autoresuscitations in the absence of regurgitation; however autoresuscitation eventually failed when vomitus appeared in the upper airway.\textsuperscript{28} Considering these and other observations, Gardner suggested that agonal aspiration may be the coup de grace leading to death in some.\textsuperscript{4} It is therefore reasonable to speculate that when a hypoxic comatose infant regurgitates and fails to swallow, then pulmonary aspiration can prevent autoresuscitation. In such cases, failure to swallow might be enhanced by abnormalities in brainstem centers regulating respiratory functions during hypoxic coma.\textsuperscript{29-32}

Regardless of the association between gastric aspiration and infant positioning, important questions remain regarding the pathophysiological significance of aspiration. For example, why should gastric aspiration not be considered the immediate cause of death, especially in those cases with considerable aspiration into distal bronchioles and alveoli? There were three (4%) such cases in our study diagnosed as SIDS by the medical examiner. Vomitus was present at the scene where one of these infants was found lifeless. Gastric contents were present in the tracheobronchial lumen of the other two at the time of autopsy, possibly the result of postmortem manipulation of the...
We agree with others that gastric contents in the distal bronchioles and alveoli must be a consequence of terminal gasping during attempts at autoresuscitation, especially when the possibility of forced entry into these sites by CPR has been excluded. Gastric contents in the distal lung, in the absence of such material in the trachea and larger bronchi, effectively rules out postmortem migration. Furthermore, postmortem manipulation of an infant’s body may result in changes at a much lower pressure than that of gasping and would likely be insufficient to cause migration of gastric contents into the intra-alveolar spaces. For migration of gastric contents to occur, gastric contents would have to be in the pharynx before death. Reflexive apnea as a result of regurgitation could have precipitated hypoxia just before hypoxic gasping. The observation that none of the infants whose last feed consisted exclusively of breast milk had evidence of gastric aspiration, although not statistically significant, deserves comment. Rates of gastric emptying are faster in breast-fed versus formula-fed infants. Given that infants with severe GER may be more likely to have significantly delayed gastric emptying, it may be that breast-fed infants are less likely to have GER than formula-fed infants. With less GER, it follows hypoxic gasping.

For migration of gastric contents to occur, gastric contents would have to be seen at postmortem examination. Furthermore, postmortem manipulation of the body. We agree with others that gastric contents in the distal bronchioles and alveoli must be a consequence of terminal gasping during attempts at autoresuscitation, especially when the possibility of forced entry into these sites by CPR has been excluded. Gastric contents in the distal lung, in the absence of such material in the trachea and larger bronchi, effectively rules out postmortem migration. Furthermore, postmortem manipulation of an infant’s body may result in changes at a much lower pressure than that of gasping and would likely be insufficient to cause migration of gastric contents into the intra-alveolar spaces. For migration of gastric contents to occur, gastric contents would have to be in the pharynx before death. Reflexive apnea as a result of regurgitation could have precipitated hypoxia just before hypoxic gasping.

The observation that none of the infants whose last feed consisted exclusively of breast milk had evidence of gastric aspiration, although not statistically significant, deserves comment. Rates of gastric emptying are faster in breast-fed versus formula-fed infants. Given that infants with severe GER may be more likely to have significantly delayed gastric emptying, it may be that breast-fed infants are less likely to have GER than formula-fed infants. With less GER, it follows that there is less risk of gastric aspiration. Large, prospective studies are required to clarify the relationship between breast-feeding and the risk of aspiration.

Our data do not suggest that bed-sharing increases the risk of gastric aspiration, given that roughly one quarter of cases in both groups (Table I) were bed-sharing. Similarly, there were no significant differences between the two groups with respect to either histories of ALTEs or mean interval between the time last fed and the time of their pronounced deaths. Proportional differences in history of GER, though striking, were not statistically significant in our small sample. Our study is unable to address a potentially lethal role of gastric aspiration in cases in which gastric contents were not observed in the pharynx at postmortem examination. It is tempting to dismiss any role when this material is not seen, but the pharynx is not always carefully inspected during postmortem examination. Experiments with mice have shown that considerable adverse physiological consequences can follow the introduction of even small volumes of irritant solutions into the pharynx.

In conclusion, our data describe the presence of gastric contents in the distal lung fields in 14% of SIDS cases for which CPR was not attempted. Approximately two thirds of infants with or without pulmonary gastric aspiration were found prone, suggesting that sleep position does not affect the risk of aspiration. Our findings also suggest that gastric aspiration may be a terminal event that some infants, representing a subset of SIDS cases, cannot overcome. Therefore, gastric aspiration may be a potentially more important causal factor in a subset of SIDS cases than previously thought and should be a renewed focus for future research.

**REFERENCES**


Fifty Years Ago in The Journal of Pediatrics

EDITOR’S COLUMN: THE STORY OF ASPIRIN
Hoehwalt C. J Pediatrics 1957;50:394-6

Exhilarated by the remarkable history of aspirin, in 1957 the editors of The Journal of Pediatrics published the full text of a talk on this subject by Carroll Hoehwalt, vice president of research and development of the Monsanto Chemical Company. Her remarks concluded with:

“There still is so much to be learned . . . of [aspirin’s] mechanisms of action. How does it do what it does for the rheumatic and arthritic suffers? . . . reduce abnormal body temperature while having no effect upon normal temperatures? . . . moderating pain? The answers . . . are sure to come in time . . . and with them more important applications for this . . . genuine ‘wonder’ drug.”

Who in 1957 could have imagined the cascade of knowledge that would ensue about aspirin’s mechanism of action? The discoveries leading to our understanding of aspirin’s inhibitory effect on prostaglandin production by cyclooxygenase (COX) provided a unifying explanation for both its therapeutic actions (reduction of inflammation, swelling, pain, and fever) and its adverse effects (gastrointestinal irritation and impaired kidney function and platelet aggregation). This understanding lead to investigation of new uses for aspirin, including prevention of stroke and myocardial infarction, with research exploring its role in the prevention of colon cancer, Alzheimer’s disease, and premature labor. Numerous additional non-steroidal anti-inflammatory agents have been developed, and our understanding of the COX system has expanded, including the discovery of COX genes and three COX isoenzymes.

At the same time, the field of pediatrics could not in 1957 have envisioned the agony associated with the use of aspirin and its role in the epidemic of Reye’s syndrome. First described in 1963, the incidence of Reye’s syndrome climbed in the next 15 years, peaking in the United States in 1980 with 658 cases. The first of a series of controlled studies confirming a relationship between aspirin and Reye’s syndrome was published in 1981 and prompted warnings from the Centers for Disease Control and Prevention, Institute of Medicine, and Federal Drug Administration against the use of aspirin in children and adolescents with a flu-like syndrome. Although the controversy in the medical literature continued through the subsequent decade (and to some, continues still), the rapid decline in the use of aspirin for flu-like symptoms in children was associated with a corresponding plummet in the incidence of Reye’s Syndrome.

As much as we have learned about the mechanism of aspirin, its potential uses, and its hazards since 1957, we may anticipate that we still have much more to learn.

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Pediatrician-in-Chief
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Wayne State University School of Medicine
Detroit, Michigan
10.1016/j.jpeds.2006.09.035
Association between Brachial-Ankle Pulse Wave Velocity and Cardiovascular Risk Factors in Healthy Adolescents

JEE-AEE IM, PhD, JI-WON LEE, MD, JAE-YONG SHIM, MD, PhD, HYE-REE LEE, MD, PhD, AND DUK-CHUL LEE, MD, PhD

Objective  To investigate the associations between cardiovascular risk factors and arterial stiffness, measured as brachial-ankle pulse wave velocity (baPWV), in healthy adolescents.

Study design  In this cross-sectional study, 178 male and 84 female adolescents, aged 12 to 18 years, were recruited. Total homocysteine levels, serum lipid profiles, high-sensitivity C-reactive protein (hs-CRP) levels, fasting glucose levels, fasting insulin levels, and baPWV were measured.

Results  baPWV was significantly higher in male adolescents than in female adolescents. In both sex groups, baPWV was positively correlated with body mass index (BMI), waist circumference, waist-hip ratio, systolic and diastolic blood pressures, fasting insulin levels, homeostatic model assessment of insulin resistance, triglyceride levels, hs-CRP levels, and total homocysteine levels. In male adolescents, age, total cholesterol level, low-density lipoprotein cholesterol levels, and white blood cell counts were positively correlated with baPWV, and, in female adolescents, high-density lipoprotein cholesterol levels were negatively correlated with baPWV. In multivariate analysis, sex, mean blood pressure, BMI, and total homocysteine levels were found to be independent factors associated with baPWV.

Conclusion  Blood pressure, BMI, sex, and total homocysteine levels were independently associated with arterial stiffness, measured as baPWV, in healthy adolescents, suggesting that these risk factors may be associated with an increased risk of atherosclerosis in adolescents. (J Pediatr 2007;150:247-51)

Although the clinical end-point of atherosclerosis mainly occurs in middle age or later in life, observations in pathology studies revealed that atherosclerotic lesions begin during childhood. In addition, some of the traditional cardiovascular (CV) risk factors, which include hypercholesterolemia, hypertension, cigarette smoking, and obesity, may have an association with the development of atherosclerosis in adolescents or young adults. Recent studies have consistently shown that CV risk factors identified in childhood predict the carotid intima-media thickness (IMT) in adulthood. These observations suggest that early detection of modifiable CV risk factors in this population may have an impact on health in later life.

Hyperhomocysteinemia may affect small vessels with time, beginning in childhood. Several studies have reported that the total homocysteine level has an association with atherosclerotic risk factors in groups of children with obesity, stroke, familial hypercholesterolemia, or arterial hypertension with type 1 diabetes mellitus. However, it is unclear whether the total homocysteine level is associated with preclinical atherosclerosis in a healthy population.

Increasing arterial stiffness is one of the pathological symptoms of vascular damage and is closely associated with atherosclerotic cardiovascular diseases. Pulse wave velocity (PWV) is known to be an indicator of arterial stiffness and a marker of vascular damage. The aim of this study was to determine the associations between arterial stiffness, measured as brachial-ankle pulse wave velocity (baPWV), and total homocysteine levels and other cardiovascular risk factors in apparently healthy adolescents.

<table>
<thead>
<tr>
<th>baPWV</th>
<th>Brachial-ankle pulse wave velocity</th>
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<tbody>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<td>CV</td>
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<td>HDL-C</td>
<td>High-density lipoprotein cholesterol</td>
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<tr>
<td>HOMA-IR</td>
<td>Homeostatic model assessment of insulin resistance</td>
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<tr>
<td>hs-CRP</td>
<td>High-sensitivity C-reactive protein</td>
</tr>
<tr>
<td>IMT</td>
<td>Intima-media thickness</td>
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<tr>
<td>LDL-C</td>
<td>Low-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>PWV</td>
<td>Pulse wave velocity</td>
</tr>
<tr>
<td>WHR</td>
<td>Waist-hip ratio</td>
</tr>
</tbody>
</table>

See editorial, p 219
METHODS

All participants signed a consent form approved by the ethics committee of Yong-dong Severance Hospital (Seoul, Korea). Healthy volunteers were recruited from junior high schools or high schools via a public advertisement. A total of 178 male adolescents and 84 female adolescents, 12 to 18 years old, were surveyed for this study. Exclusion criteria included a medical history or evidence with physical examination of cardiovascular disease, diabetes mellitus, hypertension (resting blood pressure > 140/90 mm Hg), a body weight fluctuation >5 kg in the previous 6 months, endocrine disorders, or medication that could affect cardiovascular function or metabolism. Participants completed a questionnaire to assess past and current medical illnesses and lifestyle choices such as alcohol ingestion and cigarette smoking. Alcohol ingestion was defined as the ingestion of alcohol >1 time per week. Smoking was defined as current cigarette smoking.

Anthropometric measurements were taken with the participants in light clothing and without shoes. Height to the nearest 0.1 cm and weight to the nearest 0.1 kg were measured with an automatic height-weight scale. Body mass index (BMI) was calculated as the participants’ weight divided by their height squared. Waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest. Hip circumference was measured at the widest part of the hip region, and thigh circumference was measured 10 cm proximal to the superior patella border. To reduce variation in measurements, 1 person measured all anthropometric parameters throughout the study.

baPWV was measured with a volume-plethysmographic apparatus (PWV/ABI, Colin Co., Komaki, Japan) as previously described.20,21 This device simultaneously records the phonocardiogram, electrocardiogram, volume waveform, and arterial blood pressure at both the left and right brachia and ankles. Subjects were examined in the supine position. Electrodes were placed on both wrists to obtain an electrocardiogram. A microphone for a phonocardiogram was placed on the left margin of sternum to detect heart sounds. Occlusion cuffs, which were connected to a plethysmographic sensor that determined the pulse volume waveform and an oscillometric pressure sensor that measured blood pressure on each extremity, were applied to both arms and ankles of subjects. The time interval between arm and ankle (ΔTa) was defined by the pulse transit time between the brachial and tibial arterial pressure waveforms. The distance between the right arm and ankle was estimated automatically on the basis of the subject’s height.22 The distance from suprapcrtanal notch to elbow (ΔDa) and from suprapcrtanal notch to ankle (ΔDb) were expressed with this equation:

\[ Da = 0.2195 \times \text{height of subject (cm)} - 2.0734, \]

and

\[ Db = 0.8129 \times \text{height of subject (cm)} + 12.328. \]

The baPWV was calculated with this equation:

\[ \text{baPWV} = (Db - Da) / Ta. \]

An earlier study reported that in healthy subjects, the coefficient of variation for interobserver reproducibility (n = 15) was 2.4%, and intraobserver reproducibility (n = 17) was 5.8%.21 Because there was a significant correlation between the right PWV and left PWV \((r = 0.90, P < .001)\), the mean PWV value was used for analysis.23 After an 8-hour overnight fast, blood samples were obtained from each participant from an antecubital vein and placed into a plain and an EDTA tube. The total homocysteine level was measured with a competitive immunoassay using an Immulite 2000 (DPC, Pacific Concource, LA), and the inter- and intra-assay variations were 6.8% ± 2.8% and 4.9% ± 1.7%, respectively. Levels of high sensitivity C-reactive protein (hs-CRP), fasting glucose, total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) were measured with an ADVIA 1650 Chemistry system (Bayer, Tarrytown, NY), and levels of low-density lipoprotein cholesterol (LDL-C) were calculated from the Friedewald equation.24 Fasting insulin levels were measured with an electrochemiluminescence immunoassay (Roche, Indianapolis, IN). Insulin resistance was estimated with the homeostatic model assessment of insulin resistance (HOMA-IR); the calculations were:

\[ \text{HOMA-IR} = \frac{(\text{insulin (}\mu\text{IU} / \text{mL})) \times \text{Fasting blood glucose (mg/dl)} \div 18}{22.5}. \]

White blood cell (WBC) counts were assayed with an ADVIA 2120 Hematology System (Bayer, Tarrytown, NY). Data are expressed as means ± SD. Variables such as baPWV, hs-CRP levels, total homocysteine levels, triglyceride levels, fasting insulin levels, and HOMA-IR were logarithmically transformed before statistical analysis to improve normality. Clinical and metabolic characteristics between sexes of the study population were compared with the \(t\) test for continuous variables and the chi-square (χ²) test or Fisher exact test for categorical variables. Pearson (for continuous variables) or Spearman rank (for categorical variables) correlation analyses were used to assess the relationship of baPWV to clinical variables by sex. To determine independent association between arterial stiffness, measured as baPWV (dependent variables), and CV risk factors (explanatory variables) in this study, multivariate regression analysis was used. Data from 247 subjects (165 male adolescents and 82 female adolescents) who completed the questionnaire for lifestyle were used in multivariate analysis; 15 subjects (13 male adolescents and 2 female adolescents) did not respond to the questions about smoking habits or alcohol ingestion. Explanatory variables included in the multiple linear regression model were age, sex, mean blood pressure, fasting glucose level, total cholesterol level, HDL-C, triglyceride level, hs-CRP level, BMI, HOMA-IR, total homocysteine level, a current history of smoking (no = 0, yes = 1), and alcohol ingestion (no = 0, yes = 1). Significance was defined at the level of \(P = .05\). All calculations were performed with SAS software version 8.01 (SAS Institute, Cary, NC).
Association between Brachial-Ankle Pulse Wave Velocity and Cardiovascular Risk Factors in Healthy Adolescents

### RESULTS

The clinical characteristics are shown in Table I. There was no significant difference in mean age, BMI, diastolic blood pressure, total cholesterol levels, triglyceride levels, HDL-C levels, LDL-C levels, and hs-CRP levels between sexes. In addition, there were no differences in health behaviors, such as smoking habits and alcohol ingestion, in the 2 groups. In contrast, waist circumference, waist-hip ratio (WHR), systolic blood pressure, baPWV, total homocysteine level (P < .001), fasting glucose level, fasting insulin level, and HOMA-IR (P < .05), were significantly lower in female subjects. The WBC count (P < .05) was significantly higher in female subjects compared with male subjects.

In both sex groups, baPWV was positively correlated with BMI, waist circumference, WHR, systolic blood pressure, diastolic blood pressure, fasting insulin level, HOMA-IR, triglyceride level, hs-CRP level, and total homocysteine level. In male subjects, age, total cholesterol level, LDL-C level, and WBC were positively correlated with baPWV, and in female subjects, HDL-C level was negatively correlated with baPWV, as shown in Table II.

### SEX, MEAN BLOOD PRESSURE, BMI, AND TOTAL HOMOCYSTEINE LEVEL

Sex, mean blood pressure, BMI, and total homocysteine level were found to be independent factors significantly associated with arterial stiffness in the multivariate analysis, as shown in Table III. Other clinical variables, such as age, fasting glucose level, total cholesterol level, HDL-C level, triglyceride level, hs-CRP level, HOMA-IR, a current history of smoking, and alcohol ingestion, which were included in a multiple regression model, were not significantly associated with baPWV.

### DISCUSSION

This study shows that baPWV in healthy adolescents has a significant association with a number of CV risk factors, including systolic and diastolic blood pressure, adiposity, insulin resistance, lipid profiles, and total homocysteine levels. This suggests that arterial stiffness can be affected by CV risk factors as early as the second decade of life. Furthermore, vascular changes in this population may not be confined to high-risk groups. These findings are consistent with earlier, community-based reports, showing inverse associations between arterial stiffness measured with a non-invasive ultrasound scanning...
positively correlated with baPWV in our study, in accordance with other studies.\(^ \text{36,37} \) CRP induces complement activation, enhances infiltrations of monocytes, and stimulates monocytes to produce tissue factor, a potent stimulus for thrombosis, thus enhancing the risk of thrombosis and the generation of atherosclerosis lesions.\(^ \text{38,39} \)

Carotid IMT,\(^ \text{40} \) flow-mediated dilatation,\(^ \text{41} \) and PWV\(^ \text{18,19} \) have all been shown to reflect early atherosclerosis or future risk of CV disease. Among these surrogate markers, measurement of baPWV may have an advantage in its use in the primary care setting or large population studies because this simple method does not require specialized skills and is easy, time saving, and relatively free from operator bias compared with other assessments.\(^ \text{21,42,43} \) Although the value of carotid IMT for CV risk prediction has been studied most extensively and supported by a large number of clinical trials,\(^ \text{44} \) this technique must be performed by trained personnel and may have substantial variation in reproducibility because of differences in technical protocols.\(^ \text{44} \) Further, flow-mediated dilatation is of limited use because of large inter-individual variation.\(^ \text{44,45} \)

To our knowledge, there are few studies of baPWV in healthy children. Niboshi et al\(^ \text{36} \) reported in a study with a large sample size of Japanese children that baPWV in children is largely influenced by age and sex. Collins et al\(^ \text{37} \) measured baPWV of African-American and Caucasian children in a pilot study with a small sample size and suggested racial differences of baPWV compared with the measurements in age-matched Chinese children.\(^ \text{38} \) Further studies are needed to clarify this issue.

### REFERENCES


### Table III. Multiple regression analysis to assess independent relationships between baPWV and clinical variables (N = 247)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Parameter estimate</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender†</td>
<td>0.051</td>
<td>0.012</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MBP</td>
<td>0.004</td>
<td>0.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.006</td>
<td>0.002</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>0.042</td>
<td>0.018</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Variables significantly associated with baPWV (P < 0.05) are shown in the table. Waist circumference was also a significant correlates of baPWV when entered into the model instead of BMI.

*Data from a total of 247 subjects who completed the questionnaire for the lifestyle were used in multivariate analysis, including age, gender, mean blood pressure, homocysteine, BMI, fasting glucose, total cholesterol, HDL cholesterol, Triglyceride, hs-CRP, HOMA-IR, and current history of smoking and alcohol ingestion as independent variables. (R^2; 0.46, F-value; 18.09, P < .001).

†Male:1 Female:0.

technique and CV risk factors, such as cholesterol levels\(^ \text{3} \) and adiposity with its associated metabolic disturbances,\(^ \text{25} \) in children and adolescents. Because arterial stiffness is a marker of future CV risk and mortality in adults and the elderly,\(^ \text{26-28} \) therapeutic modification of CV risk factors in adolescents may help to prevent atherosclerosis and CV disease in adults.

We found that the total homocysteine level has an independent association with arterial stiffness in adolescents. Although it is well-established that hyperhomocysteinemia is an independent predictor for CV disease in the adult population,\(^ \text{29} \) there have been only a few studies to clarify this association in children or young adults. Zhu et al\(^ \text{30} \) reported that homocysteine levels in obese female children were significantly correlated with carotid intima thickness and flow-mediated dilatation. Martos et al\(^ \text{31} \) reported that increased homocysteine levels may be involved in the pathogenesis of atherosclerosis. However, other observational studies in healthy young Northern Irish adults,\(^ \text{15} \) obese non-atherosclerotic patients,\(^ \text{32} \) and middle-aged volunteers\(^ \text{16} \) did not find any association between total homocysteine levels and PWV.

The association between baPWV and blood pressure in this study is in concordance with earlier studies showing an inverse association between arterial distensibility and blood pressure in adolescents\(^ \text{25} \) and healthy young adults.\(^ \text{24} \) In addition, Li et al reported that childhood blood pressure predicts arterial stiffness measured as baPWV in young adults.\(^ \text{33} \) They found that 1 single measurement of systolic blood pressure in childhood, regardless of its variation, was associated with baPWV in young adults.\(^ \text{33} \) Mean IMT was higher in men than in women. Men also demonstrated a higher mean PWV and prevalence of plaque.\(^ \text{16} \)

In this study, the baPWV of adolescents was significantly related to BMI, WHR, and hs-CRP level, suggesting a link between obesity and inflammation and atherogenic changes. Obese children showed a significantly increased IMT, compared with a normal-weight control group,\(^ \text{8,34} \) and the common carotid artery stiffness of obese children is associated with obesity and insulin resistance.\(^ \text{35} \) hs-CRP level was positively correlated with baPWV in our study, in accordance with other studies.\(^ \text{36,37} \) CRP induces complement activation, enhances infiltrations of monocytes, and stimulates monocytes to produce tissue factor, a potent stimulus for thrombosis, thus enhancing the risk of thrombosis and the generation of atherosclerosis lesions.\(^ \text{38,39} \)

To our knowledge, there are few studies of baPWV in healthy children. Niboshi et al\(^ \text{36} \) reported in a study with a large sample size of Japanese children that baPWV in children is largely influenced by age and sex. Collins et al\(^ \text{37} \) measured baPWV of African-American and Caucasian children in a pilot study with a small sample size and suggested racial differences of baPWV compared with the measurements in age-matched Chinese children.\(^ \text{38} \) Further studies are needed to clarify this issue.


The Influence of Timing of Elective Cesarean Section on Risk of Neonatal Pneumothorax

VINCENTO ZANARDO, MD, EZIO PADOVANI, MD, CARLA PITTINI, MD, NICOLETTA DOGLIONI, MD, ANNA FERRANTE, MD, AND DANIELE TREVISANUTO, MD

Objectives To determine whether the timing of elective cesarean delivery at term influences the risk of neonatal pneumothorax.

Study Design Chart reviews confirmed gestational age, delivery modalities, and diagnosis of pneumothorax of 66,961 term infants delivered in the Veneto region of northern Italy. Of these neonates, 17,783 (26.5%) were delivered by cesarean section, including 9988 elective (56.1%) and 7795 emergency (43.8%).

Results In 5498 (55.0%) of neonates, an elective cesarean section was performed before 39 completed weeks. Fifty-nine neonates had pneumothorax diagnosed (0.88/1000 births). Neonates delivered by elective cesarean section had an increased incidence of pneumothorax (2.90/1000 births), in comparison with neonates delivered by emergency cesarean (1.53/1000 births; OR 4.21; 95% CI 2.02-8.74) or vaginally delivered (0.39/1000 births; OR 7.95; 95% CI 4.41-14.32). In elective cesarean sections there was a significant progressive reduction in the incidence of pneumothorax from week 37 0/7 to 37 6/7 onward (P < .01).

Conclusions The timing of elective cesarean section influences the pneumothorax risk. A reduction in neonatal iatrogenic pneumothorax would result if elective deliveries were performed after the 39 completed weeks of pregnancy.

Over the past 30 years, the rates of cesarean deliveries have increased in the Western world. In particular, there has been an increase in the incidence of elective cesarean delivery at term, as a result mainly of the management of previous cesarean sections. Elective cesarean delivery is believed to be less distressing for the fetus, but it has negative effects on the physiological responses to birth, resulting in an increased risk of iatrogenic respiratory distress syndrome (RDS) when performed at 37 or 38 weeks rather than 39 or 40 weeks of gestation. The American College of Obstetricians and Gynecologists Committee on Obstetrics: Maternal and Fetal Medicine currently recommends that delivery by elective cesarean section at 39 weeks be based on accurate assessment of fetal maturity.

Respiratory morbidity in infants with iatrogenic RDS is remarkably severe, and our previous studies suggested an increased risk because of the need for resuscitation and respiratory disorders after elective cesarean section. The initial reports found pneumothorax in 10.3% to 34.0% of infants with iatrogenic RDS. More recently, pneumothorax, severe persistent pulmonary hypertension, or both conditions have been noted in infants delivered by elective cesarean section. These studies, however, have been biased by being limited only to infants admitted to neonatal intensive care units (NICUs) and were not large enough to allow differentiation between method of delivery and each week of pregnancy at term. The diagnosis of neonatal pneumothorax in infants born after an elective cesarean section remained less well characterized. This is relevant, considering that iatrogenic pneumothorax represents a life-threatening condition, one that needs a prompt recognition and therapy, and requires specialized care offered generally at tertiary referral centers. We determined the incidence of pneumothorax in infants who were electively delivered at term and who were then transferred to the two Level-III referral NICUs of the Veneto region of Italy, to correlate their incidence with the vaginal or cesarean method of delivery, and to examine the risk during each week of gestation between week 37 0/7 and 41 6/7.
METHODS

Study Design and Population
All patients with pneumothorax transported to the Veneto region in northeastern Italy, from January 1, 2002 through December 31, 2003 by two dedicated neonatal transport teams of the Pediatric Departments of the Universities of Padua and Verona, respectively, were eligible for inclusion in the study. Inborn neonates with pneumothorax cared for at the Level-III reference centers and those registered in four Level-II hospitals also were included. The transport teams, which include a neonatologist and a nurse, provide ground ambulance transport of neonatal critical care for all of the Veneto region, with a total population referral base of 4.3 million people with a radius of approximately 250 km. There are approximately 35,000 to 40,000 births per year in 42 delivery units. Of these units, 36 are classed as Level I (care for normal near-term and term infants), 4 as Level II (full resources for neonatal intensive care = intermediate care), and 2 as Level III (Padua and Verona educational hospitals with resources for obstetrics and complete neonatal intensive care).

Questions and outcome variables, as well as methods of analysis and exclusion criteria, were determined prospectively. Data for method of delivery, gestational age, birth weight, Apgar scores, need of resuscitation at birth, mode of respiratory support, postnatal age at diagnosis, management, underlying primary lung disease, presence of major congenital malformations, length of hospital stay, and mortality were recorded for all the patients. Deliveries were classified as spontaneous if the woman presented in spontaneous labor, emergency if a maternal or fetal obstetric or medical condition prompted delivery, and elective when the patient did not present in labor and no maternal or fetal condition warranting delivery was noted in the Maternal Fetal Medicine database or on review of the obstetric chart. Vaginal-delivered women with conditions that might influence the likelihood of an adverse neonatal outcome (breech presentation, twinning) were not excluded from the low risk population. Complications that occurred during or after delivery were not utilized in determining the criteria for inclusion because only factors that could be identified prenatally were considered to reflect the information available to the obstetrician when planning delivery. Resuscitation in the delivery room was done according to the International Guidelines for Neonatal Resuscitation.12

Statistical Analysis
For initial analysis, the obstetric population targeted was searched for those women whose pregnancy was at term between 37 0/7 and 41 6/7 weeks gestation (estimated by last menstrual cycle period or, if uncertain, by the use of sonography).13 Subsequently, the women were classified into two groups: (1) those women with vaginal delivery; and (2) those women with deliveries by cesarean section. Following initial analysis, the cesarean section group was further narrowed to identify the group of women who underwent elective cesarean sections.

The diagnosis of neonatal pneumothorax was established on the basis of characteristic clinical signs and the radiographic findings.14 All neonatal diagnoses were made at the time of the baby’s discharge by an experienced neonatologist. The mode of delivery at term and the timing of births in each week from 37 0/7 to 41 6/7 in the Veneto region during the 2 year were computed from the Regional Register Database Certificate of Assistance to the birth. The study was approved by the Institutional Review Board of the involved hospitals.

The incidence of pneumothorax, OR, and the 95% CI with mode of delivery and for each week of gestation at term were calculated using the Confidence Interval Analysis: Microcomputer Program.15 Testing for comparison across multiple proportions was performed using the Cochram-Armitage trend test. A P value of <.05 was regarded as significant.

RESULTS
During the 2-year study period, 87,418 infants were delivered and 66,961 (82.5%) were infants born at term. Of these neonates, 17,783 were delivered by cesarean section (26.5%), including 9988 (56.1%) delivered by elective cesarean and 7795 (43.8%) by emergency cesarean section, and 49,178 (68.0%) vaginally delivered. Fifty-nine neonates had pneumothorax diagnosed (0.8/1000 births) and all were treated with thoracostomy. Neonates delivered by elective cesarean section showed an increased incidence of pneumothorax (2.90/1000), in comparison with neonates delivered by emergency cesarean (1.53/1000) or vaginally delivered (0.39/1000). Elective cesarean delivery was associated with an increased risk of pneumothorax with respect to both vaginal delivery (OR 7.95; 95% CI 4.41-14.32) and emergency cesarean delivery (OR 4.21; 95% CI 2.04-8.74). Also emergency cesarean delivery showed an increased pneumothorax relative risk with respect to vaginal delivery (relative risk 1.26; 95% CI 1.03-1.53) (Table I).

The numbers of infants born at each week of gestation by mode of delivery are shown in Table II. In 5498 (55.0%) neonates elective cesarean section was performed before 39 0/7 weeks. For the elective cesarean section there was a significant progressive reduction in the incidence of pneumothorax from the week 37 0/7 to 37 6/7 onward (P < .01; linear slope $-2.48 \times 10^{-3}$). A similar but less significant trend was also evident for vaginal delivery (P < .01; linear slope $-4.95 \times 10^{-3}$). For the group of babies born by emergency cesarean section there was no difference in the incidence of neonatal pneumothorax occurrence on testing across week 37 0/7 to 37 6/7 onward. In addition, in the group of babies born by elective cesarean section, the notable feature was the association with risk, in particular at 37 0/7 to 38 6/7 and 38 0/7 to 38 6/7 weeks.

No mortality occurred among vaginally and electively or emergency cesarean delivered neonates with pneumothorax. Nevertheless, pulmonary hypertension appeared to complicate...
the course of some of the neonates with pneumothorax born after an elective cesarean section (13.7%) and was the cause for the need to utilize high-frequency oscillatory ventilation and inhaled nitric oxide therapy.

### DISCUSSION

Respiratory morbidity in infants with iatrogenic RDS can be remarkably severe, despite awareness for over a quarter century, and guidelines to minimize its occurrence.\(^9,16-20\) In this study, we evaluated the contributing of elective cesarean delivery to pneumothorax risk in term neonates delivered in the Veneto region, an industrialized area of northern Italy, during a 2-year period. We found that for term infants elective cesarean delivery resulted in a significantly greater risk of neonatal pneumothorax compared with both vaginal and cesarean emergency deliveries. However, what seems novel, and what has not been fully appreciated, is that in elective cesarean section there was a significant progressive reduction in the incidence of pneumothorax from week 37 0/7 to 37 6/7 onward.

The availability of precise dating, accurate documentation of pneumothorax in tertiary referral centers, and the database for mode of delivery during each week of gestation between week 37 0/7 and 41 6/7 of all the Veneto region has allowed this detailed analysis of pneumothorax risk and the influence of timing of elective cesarean delivery. The overall incidence of pneumothorax at term was 0.88 per 1000 deliveries, and it was 2.90 per 1000 in elective cesarean, 1.53 per 1000 in emergency cesarean, and 0.39 per 1000 in vaginal delivery. These figures extend the findings of previous reports. Radiological surveys demonstrated an incidence of 1.0% to 2.0% of all live births.\(^21\) Symptomatic pneumothorax, however, was diagnosed in only 0.05% to 0.07% of live births.\(^11,16,22\) In the recent study by Wax et al,\(^9\) pneumotho-

### Table I. Number of term infants with pneumothorax by mode of delivery

<table>
<thead>
<tr>
<th>Mode of delivery</th>
<th>No. (%) of deliveries</th>
<th>No. with pneumothorax</th>
<th>Pneumothorax per 1000</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>66,961 (76.56)</td>
<td>59</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>CS elective</td>
<td>9,988 (13.6)</td>
<td>29</td>
<td>2.90</td>
<td>7.95 (4.41-14.32)</td>
</tr>
<tr>
<td>CS emergency</td>
<td>7,795 (11.6)</td>
<td>12</td>
<td>1.53</td>
<td>4.21 (2.02-8.74)</td>
</tr>
<tr>
<td>Vaginal</td>
<td>49,178 (73.4)</td>
<td>18</td>
<td>0.39</td>
<td></td>
</tr>
</tbody>
</table>

Odds ratios are given comparing the risk of pneumothorax with the incidence after vaginal delivery.

CS, Cesarean section.

### Table II. Risk of pneumothorax with advancing gestation by mode of delivery from the week of gestation 37 0/6 to 37 6/7

<table>
<thead>
<tr>
<th>No. (%) of deliveries</th>
<th>No. with pneumothorax</th>
<th>Respiratory morbidity per 1000</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>37 0/6-37 6/6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS elective</td>
<td>1492 (16.8)</td>
<td>14</td>
<td>9.38</td>
</tr>
<tr>
<td>CS emergency</td>
<td>691</td>
<td>1</td>
<td>1.44</td>
</tr>
<tr>
<td>Vaginal</td>
<td>2628</td>
<td>5</td>
<td>1.90</td>
</tr>
<tr>
<td>Total</td>
<td>4811</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38 0/6-38 6/6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS elective</td>
<td>4006 (42.4)</td>
<td>10</td>
<td>2.49</td>
</tr>
<tr>
<td>CS emergency</td>
<td>1105</td>
<td>4</td>
<td>3.6</td>
</tr>
<tr>
<td>Vaginal</td>
<td>6961</td>
<td>6</td>
<td>0.85</td>
</tr>
<tr>
<td>Total</td>
<td>12072</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39 0/6-39 6/6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS elective</td>
<td>2490 (26.3)</td>
<td>5</td>
<td>2.00</td>
</tr>
<tr>
<td>CS emergency</td>
<td>1733</td>
<td>3</td>
<td>1.73</td>
</tr>
<tr>
<td>Vaginal</td>
<td>13614</td>
<td>4</td>
<td>0.29</td>
</tr>
<tr>
<td>Total</td>
<td>17837</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 0/6-41 6/6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS elective</td>
<td>2000 (21.1)</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>CS emergency</td>
<td>4266</td>
<td>4</td>
<td>0.93</td>
</tr>
<tr>
<td>Vaginal</td>
<td>25975</td>
<td>3</td>
<td>0.11</td>
</tr>
<tr>
<td>Total</td>
<td>32241</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>

Odds ratios are given comparing the risk of pneumothorax with the incidence after vaginal delivery at comparable gestational age.

CS, Cesarean section.
rnx occurrence in term infants with iatrogenic RDS requiring mechanical ventilation was remarkably high. Two-thirds of newborns’ courses were complicated by a pulmonary air leak, pulmonary hypertension, or both conditions. Half of electively delivered newborns suffered these sequelae. As expected, in our study, vaginally delivered infants showed the lowest incidence rates of respiratory morbidity, and cesarean delivery in the absence of labor increased iatrogenic pneumothorax incidence.

Calculations made on the basis of the incidence of pneumothorax after elective cesarean section at term from week 37 0/7 to 37 6/7 onward estimate that widespread adoption of careful planning of elective cesarean section after week 39 0/7 could mean substantial cost saving with the avoidance of separating the baby from his or her parents, which causes considerable anxiety to the family. Even if mortality from respiratory disease in the infants reported was zero, the babies were subjected to painful procedures with the risk of complications and of additional morbidity. Conceivably, adhering to recommended guidelines or performing amniocentesis may have avoided most, if not all, of the morbidity in the elective cesarean patient group.

One limitation of this study is the absence of information on fetal and maternal indications and various confounding variables governing the exact week of gestation in which emergency and scheduled cesarean sections were carried out. Nevertheless, there are major implications for the timing of elective cesarean section at term as the incidence of air leak could be almost halved for each week of prolongation of pregnancy. It should be noted, in addition, that this study excluded air leaks without evidence of respiratory decompensation. Gestational age at delivery is thus key to interpretation of the iatrogenic pneumothorax risk and interhospital neonatal care. Given the neonatal problems resulting by this high rate of elective cesarean deliveries before 39 0/7 weeks, it is equally important when offering a woman delivery options to discuss such neonatal respiratory risk that prompts admission to the NICU or interhospital transport.

In conclusion, elective cesarean delivery at term remains associated with increased risk of pneumothorax to the neonate compared with emergency and vaginal delivery. Our data, from a cohort of 9998 elective term cesarean deliveries and 59 newborns with pneumothorax, indicate that there is a definite benefit on neonatal respiratory outcome to be obtained by better selection of mothers and by waiting until week 39 0/7 before performing elective cesarean section. Information should be readily available to all pregnant women and their attendants concerning the iatrogenic pneumothorax risk to the baby in delivery before 39 weeks.

REFERENCES

Respiratory Health in Prematurely Born Preschool Children with and without Bronchopulmonary Dysplasia

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Objective To investigate the respiratory health of preterm infants with bronchopulmonary dysplasia (BPD) at preschool age and to determine whether lung function (measured by forced oscillation technique (FOT) and interruption technique (Rint)) is affected by BPD in preterm infants compared with preterm infants without BPD.

Study design Participants: 3 to 5 years of age born preterm with BPD (N = 40, mean gestational age 28 weeks, mean birth weight 1051 g), and without BPD (N = 36, mean gestational age 29 weeks, mean birth weight 1179 g). Outcome variables: prevalence of symptoms determined by European Community Respiratory Health Survey and lung function measured by FOT and Rint.

Results A large percentage of infants in both preterm groups reported respiratory symptoms during the last 12 months. Lung function measurements showed higher resonant frequency (Hz) in BPD compared with non-BPD (mean 26.8 vs 22.7, \( P < .001 \)) and lower mean reactance \( X_{\text{rs}} \) (–0.30 vs –1.9, \( P = .005 \)). No differences were found in respiratory resistance between the groups, although the mean values of both groups were increased compared with reference values.

Conclusion Preterm birth affects respiratory health at 3 to 5 years of age. Children with BPD could be distinguished from children without BPD based on a higher resonant frequency and a lower mean reactance. (J Pediatr 2007;150:256-61)

Current neonatal intensive care, including the use of antenatal steroids and postnatal surfactant therapy, has made the classic presentation of bronchopulmonary dysplasia (BPD), originally described by Northway, less common. However, small premature infants with a mild initial respiratory course, requiring mechanical ventilation with low pressures and oxygen concentration, seem to acquire another form of BPD, which has been referred to as “new BPD.” One of the major problems of new BPD is the disturbance of alveolarization and vascularization of the alveoli. In preterm infants requiring prolonged assisted ventilation this problem is sometimes accompanied by a heterogeneous pattern of atelectasis and emphysema in the different zones of the lung as described in classic BPD. Remodeling of both lung tissue and airway wall can lead to alterations in elasticity of the lung and decrease lung compliance. In prematurely born children, pulmonary function tests are important in the evaluation of the disease severity and the individual response to treatment.

Current pediatric lung function testing techniques include the forced oscillation technique (FOT), interruption technique (resistance by interruption, or Rint), tidal breathing measurements, lung volume measurements, and forced expiratory maneuvers such as spirometry. Because conventional lung function measurements require either sedation or considerable patient cooperation, the lung function of prematurely born children usually is assessed either during the first year under sedation or during school age with cooperative patients. FOT and Rint have minimum demand for cooperation, which makes this method particularly suitable for use in young nonsedated preschool children.

FOT determines the respiratory resistance (\( R_{\text{rs}} \)) and reactance (\( X_{\text{rs}} \)) of the total respiratory system, Rint measures airway resistance.

Studies on long-term outcome of neonatal lung injury and BPD indicate that during later life some children have lung function abnormalities including airway obstruction, hyperinflation of the lungs, and bronchial hyperreactivity. Lung function studies in...
nonsedated preschool children with BPD are limited. FOT does not measure volumes, but it is able to measure resistance and reactance. The latter can provide information on alterations in elasticity and compliance of the respiratory system. The aim of the study was to investigate the respiratory health of preschool-age prematurely born children with and without BPD.

METHODS

Study Groups

Children with a history of BPD, born prematurely between 1998 and 2001 and treated in the neonatal intensive care unit of the Beatrix Children’s Hospital, were invited to participate in this study. BPD was defined as the need for continuous supplemental oxygen at 28 days of age combined with radiographic manifestations. These abnormalities include hyperinflation and nonhomogeneity of pulmonary tissues, with diffuse haziness, or fine or coarser densities extending to the periphery. According to the refined definition of the National Institute of Child Health and Human Development/National Heart, Lung, and Blood Institute/Office of Rare Diseases workshop, we differentiated mild (no oxygen dependency at 36 weeks), moderate (>21% but <30% oxygen at 36 weeks), and severe (>30% oxygen at 36 weeks) BPD.9 Children without BPD matched for gestational age and birth weight were also invited to participate. Lung function data from both groups were compared with age-matched term healthy controls. This reference group was derived from two nursery and three primary schools in the North of the Netherlands. The study was approved by the Medical Ethical Committee of University Medical Center, Groningen.

Study Design

Parents of the participating children completed a questionnaire (based on the European Community Respiratory Health Survey [ECRHS]) on (airway) symptoms, use of medication, smoking habits of the parents, and family history of asthma or eczema. Additionally, questions were included on respiratory syncytial virus (RSV) and admissions to hospital. Baseline lung function measurements were obtained in all children. Reversibility of airway obstruction was tested by administration of a bronchodilator (400μg of salbutamol) with a metered-dose inhaler and spacer device. Postbronschodilator response was measured after 15 minutes.

Lung Function Tests

FORCED OSCILATION TECHNIQUE. With FOT the Rrs and Xrs of the total respiratory system is determined. The i2m® device (Chess Medical, Gent, Belgium) measures these values over a frequency spectrum of 4 to 48 Hz, within 8 seconds during quiet, spontaneous breathing. FOT has been described in detail elsewhere.10 The Rrs is not equivalent but similar to airway resistance as measured by bodybox and yields consistent information.11 The Xrs is mainly dependent on the compliance of the chest-lung system and on the inertial forces of lung tissue, chest wall, and air within the airways. With increasing frequency, Xrs undergoes the transition from negative values (when the elastic reactance dominates) to positive values (when the inertial reactance dominates). The frequency point at which elastic and inertial reactance magnitudes are equal is associated with zero Xrs. This point is known as resonance frequency (fres). As Rrs values are simultaneously measured over a frequency spectrum of 4 to 26 Hz, the so-called frequency dependence of Rrs can be calculated. Frequency dependence of Rrs is defined by the mean slope of Rrs versus frequency curve calculated over the 4 to 26 Hz frequency spectrum. Negative frequency dependence of oscillatory Rrs is a sensitive index of airway obstruction in older children and adults, but it is a normal finding in children <5 years of age because of upper airway motion.4,12

During the FOT procedure the child sat behind the apparatus in an upright position, wearing a nose clip. Cheeks and submandibular area were controlled by the hands of the investigator to diminish upper airway shunting. The child breathed quietly through the mouthpiece, which was connected to the i2m®, for 40 seconds (5 consecutive measurements). A pseudo-random noise pressure signal, containing all harmonics of 4 to 48Hz was applied at the mouth by means of a loudspeaker. Mouth pressure and flow signals were fed into the analyzer, which calculated the resistance and reactance at several frequencies using fast Fourier transforms to convert the time domain to the frequency domain. The mean of 5 measurements was used. Measurements showing glottic closure, swallowing, or episodes of irregular breathing were discarded. These events can be detected from the flow signal, which is displayed on the screen during the measurements. Only data with a coherence function >0.95 were retained. The accuracy of the measurements was checked daily by means of several reference impedances. As reference values, results of healthy Dutch preschool children were used. These reference data are consistent with previous reports but are based on larger numbers and the novel instrumentation (i2m®).4

INTERRUPTION TECHNIQUE (RINT). The portable device MicroRint (Micro Medical Ltd., Rochester, UK) was used to determine airway resistance by measuring the flow at the mouth using a pneumotachograph, and it has been described before.13 After a period of quiet breathing, a single interruption was triggered at peak tidal expiratory flow during 100 milliseconds. For the MicroRint examination, participants sat in an upright position and used a disposable mouthpiece and a nose clip. The hands of the investigator restrained the cheeks and mouth floor. In each subject 10 occlusions were performed and the mean of 5 or more technically satisfactory readings was taken as a valid measurement. Measurements were rejected when the computer (displaying results and waveforms) indicated a leakage of air, when children used their vocal cords, or when an overflow had occurred.14 All children were examined using FOT first, followed by Rint.
Of the 122 eligible prematurely born patients (64 children with BPD and 58 matched prematurely born children without BPD), 77 (63%: 41 BPD and 36 no BPD) agreed to participate in this study (Table I). No differences were found between the (77) participants and (45) “nonparticipants” with regard to gestational age or birth weight. From the nonparticipants, 8 children had moved, 1 child was not able to participate because of a tracheotomy, 5 parents refused to give permission, and 31 parents did not respond. Thirty-four of 41 participating children with BPD had the need for continuous supplemental oxygen not only at 28 days of age but also at the postconceptual age of 36 weeks. Several differences were found between the characteristics of our study groups. Although we tried to match for birth weight and gestational age, the responding children with BPD had a shorter gestational age compared with the children without BPD. Children with BPD were more often male, their weight at follow-up was significantly lower, and risk factors for development of BPD such as patent ductus arteriosus and infection were found more often compared with children without BPD. All children with BPD were treated with either assisted ventilation or continuous positive airway pressure. The reference population consisted of 73 healthy term children in the same age category.

**RESULTS**

**Participants**

The raw data for $R_{rel}$ was log-transformed to obtain a normal distribution, before $Z$ scores could be calculated. We studied the independent effects of height, age, sex, weight, RSV infection, and BPD on lung function measurements using a multiple linear regression model. We studied the independent effects of sex, height, weight, prematurity with or without BPD, and admission because of RSV on respiratory symptoms using multiple logistical regression. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, Ill.). $P$ values $<.05$ were considered to be statistically significant (tested 2-sided).

**Statistical Analyses**

Normality of data distribution was checked using normal p-plots. The significance of differences among the two study groups was tested using unpaired $t$ test, $\chi^2$ test, or Fisher’s test. For nonparametric analyses, we used the Mann-Whitney $U$ test. $Z$ scores or standardized deviation scores $(\text{observed value} – \text{predicted value})/\text{RSD}$, where RSD is the residual standard deviation in the reference population. The reference population consisted of healthy children according to European Respiratory Society and American Thoracic Society guidelines.15,16 The raw data for $R_{rel}$ was log-transformed to obtain a normal distribution, before $Z$ scores could be calculated. We studied the independent effects of height, age, sex, weight, RSV infection, and BPD on lung function measurements using a multiple linear regression model. We studied the independent effects of sex, height, weight, prematurity with or without BPD, and admission because of RSV on respiratory symptoms using multiple logistical regression. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, Ill.). $P$ values $<.05$ were considered to be statistically significant (tested 2-sided).

**Table I. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>BPD N = 41</th>
<th>No BPD N = 36</th>
<th>Controls N = 73</th>
<th>P BPD-no BPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>29 (71)</td>
<td>12 (33)</td>
<td>40 (55)</td>
<td>.001</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1051 ± 536</td>
<td>1179 ± 408</td>
<td>&gt;2500</td>
<td>.246</td>
</tr>
<tr>
<td>Gestation (wk)</td>
<td>28 ± 2</td>
<td>29 ± 2</td>
<td>&gt;37</td>
<td>.03</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>106.5 ± 6.6</td>
<td>108.6 ± 6.2</td>
<td>111 ± 6.5</td>
<td>.153</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>16.6 ± 2.9</td>
<td>18.3 ± 3.2</td>
<td>19.7 ± 2.8</td>
<td>.02</td>
</tr>
<tr>
<td>Age (mo)</td>
<td>56 ± 9</td>
<td>58 ± 9</td>
<td>57 ± 9</td>
<td>.325</td>
</tr>
<tr>
<td>Antenatal steroids (Celestone)</td>
<td>25 (61)</td>
<td>25 (70)</td>
<td>0</td>
<td>.418</td>
</tr>
<tr>
<td>Surfactant (%)</td>
<td>36 (88)</td>
<td>15 (42)</td>
<td>0</td>
<td>.000</td>
</tr>
<tr>
<td>Assisted ventilation (d)§</td>
<td>19 (0-64)</td>
<td>2 (0-17)</td>
<td>0</td>
<td>.000</td>
</tr>
<tr>
<td>CPAP (d)¶</td>
<td>17 (0-55)</td>
<td>2 (0-48)</td>
<td>0</td>
<td>.000</td>
</tr>
<tr>
<td>Oxygen (d)§</td>
<td>76 (28-1095)</td>
<td>6 (0-63)</td>
<td>0</td>
<td>.000</td>
</tr>
<tr>
<td>PDA¶</td>
<td>25 (61)</td>
<td>7 (19)</td>
<td>0</td>
<td>.000</td>
</tr>
<tr>
<td>Infection¥</td>
<td>30 (73)</td>
<td>13 (36)</td>
<td>0</td>
<td>.012</td>
</tr>
<tr>
<td>Postnatal steroids (Dexamethasone)¥</td>
<td>31 (76)</td>
<td>1 (3)</td>
<td>0</td>
<td>.000</td>
</tr>
<tr>
<td>RS monoclonal antibody†</td>
<td>15 (37)</td>
<td>7 (19)</td>
<td>0</td>
<td>0.131</td>
</tr>
</tbody>
</table>

**BPD:** Bronchopulmonary dysplasia. Bold $P$ values refer to statistically significant results.

*Completed days of either intermittent positive pressure ventilation or high frequency oscillation.

†$15 \text{ mg/kg/month intramuscular (October-March).}$

‡$\text{Mean } \pm \text{ SD (t test).}$

§$\text{Median (range) (Mann-Whitney U).}$

∥$\text{Continuous positive airway pressure.}$

¶$\text{Patent ductus arteriosus.}$

¥$\text{0.5 mg/kg/day tapered down until 0 in 7-40 days.}$

†$\text{Highly suspected or proven infection, sepsis, or meningitis.}$
nose in the last 12 months? Yes (%) 18 (44) 13 (36) .487
Did your child wheeze in the last
12 months? Yes (%) 13 (32) 14 (39) .510
Did your child cough in the last
12 months? Yes (%) 39 (95) 35 (97) .635
Does your child have allergy? Yes (%) 0 (0) 7 (19) .004
Does your child have eczema? Yes (%) 4 (10) 6 (17) .501
Was your child admitted during
first 3 years? Yes (%) 22 (54) 5 (14) .000
Admissions during first 3 years/
person* 1 (0-20) 0 (0-4) .000
Was your child admitted because
of RSV? Yes (%) 17 (42) 1 (3) .035
Is your child troubled by shortness
of breath when hurrying on level
ground? Yes (%) 11 (27) 9 (25) .912
Did your child use β-agonist in the
last 12 months? Yes (%) 16 (39) 18 (50) .146
Did your child use inhaled
corticosteroids in the last
12 months? Yes (%) 15 (37) 11 (31) .484

χ² test was used.
Bold P values refer to statistically significant results.
*Median (range) (Mann-Whitney U).

DISCUSSION

Premature birth, particularly when complicated by the subsequent development of BPD, has been associated with respiratory morbidity in early childhood. This study shows that children with BPD do not report having more respiratory symptoms, but they do have lung function abnormalities (i.e. a lower mean reactance and a higher resonance frequency), indicating decreased compliance, compared with premature children without BPD. Another important finding is that FOT is able to discriminate between prematurely born children (with or without BPD) and healthy controls. Rint is able to differentiate between the total prematurely born group and the healthy controls, but not between the children with and without BPD.

Most differences found between the characteristics of our study groups were in accordance with previous studies. Children with BPD are more often male and risk factors for development of BPD—such as patent ductus arteriosus and infection—were found more often compared with children without BPD. Corticosteroid use in the neonatal phase was limited to exceptional clinical circumstances, such as ventilator-dependency after the second week of life without the possibility to wean or worsening condition of the patient. Therefore the percentage of patients treated with dexamethasone, is far higher in the BPD group compared with the children without BPD. The weight of children with BPD at follow-up was significantly lower in the current study. In previous studies, some reported that height and weight in patients with BPD at school age were not different from either a term control group or a matched preterm group without BPD.17-19 Other studies reported impaired growth and body composition in infants with BPD.20

Prematurity and low birth weight appear to be risk factors for respiratory problems at follow-up.21,22 Approximately one-third of the patients reported symptoms such as wheeze or dyspnea, which could be because of increased bronchial hyperreactivity or disturbed patency of small airways.17,23-25 Bronchodilator response did not differ between children with and without BPD in our study. Therefore we speculate that small airways could be the main factor. Children with BPD are often like children with asthma, with recurrent wheeze, shortness of breath, and airflow limitation, and they are treated with β2-agonists and inhaled corticosteroids (ICS).26

An unexpected finding was the high use of ICS in both study groups. There is increasing evidence that inflammation plays an important role in the pathogenesis of BPD. However, although early inhaled corticosteroid therapy does not prevent BPD, some beneficial effects have been demonstrated including earlier extubation, improved ventilator settings, and
a reduction in airway resistance. To our knowledge, no prospective studies have been carried out to measure the potential value of ICS on mid- and long-term respiratory outcome of BPD. Indications for ICS are based on clinical symptoms, frequency and severity of wheezing, the need for rescue β2-agonists, and frequency of hospitalization. Also in our study population almost all the patients with symptoms such as wheeze or dyspnea used β2-agonists (as needed) and ICS (on daily basis). However, although BPD and asthma share some clinical features, pathophysiologic pathways are different. Baraldi et al showed that, in contrast to asthma, airflow limitation is not associated with an increase in exhaled nitric oxide. In future research, it will be necessary to objectify the long-term effects and the risks of ICS treatment.

Children with BPD more often reported admissions because of RSV. Some authors have the opinion that infants with BPD are predisposed to respiratory failure as a result of RSV because of increases in pulmonary vascular reactivity and pulmonary edema formation. Compared with reference values, $R_{56}$, $f_{res}$, and frequency dependence of $R_s$ are increased and $X_s$ is decreased in children with BPD in this study. Duiverman et al reported negative frequency dependence of $R_s$ in children with BPD, but no significant difference in $R_{56}$ compared with healthy controls. The decreased $X_s$ and higher $f_{res}$ in children with BPD (compared with prematurely born children without BPD) are in agreement with the oscillometric lung function study performed by Malmberg et al. They had similar findings in (older) school-age children with BPD. Other lung function studies are all performed in younger or in older children. The studies in neonates and infants with BPD were recently reviewed and show low compliance and high resistance compared with term children. The studies in older children with BPD show mild to severe flow limitation. In prematurely born school children without BPD, Cano et al found lower forced expiratory volumes and higher airway resistance (measured by plethysmography).

Theoretically, $X_s$ is mainly determined by elastic and mass-inertial properties of the respiratory system; at lower frequencies the elastic properties predominate and $X_s$ varies in relation to dynamic compliance. At low frequencies a more negative $X_s$ is indicative of decreased compliance. Dynamic compliance of the lung is decreased in both peripheral airway obstruction and in disorders causing stiffness of the lungs. The increased resonant frequency and decreased reactance measured by FOT in BPD may reflect impaired elastic and inertial properties of the lungs, possibly caused by disturbed recovery and repair after neonatal damage. The negative frequency dependence of $R_s$ may reflect not only upper airway obstruction and in disorders causing stiffness of the lungs.

| Table III. Lung function parameters by forced oscillation technique and Rint |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | BPD (N = 41)    | No BPD (N = 36) | Controls (N = 73) | BPD-no BPD | BPD-controls | No BPD-controls |
| $R_{56}$ (hPa s/l)              | 9.9 ± 2.5       | 9.3 ± 2.9       | 7.6 ± 2.4        | .301       | <.001        | .003           |
| $R_{56}$ (% predicted)          | 129.4 ± 32.0    | 127.3 ± 51.2    | 100 ± 22.6       | .809       | <.001        | .003           |
| Z score Ln$R_{56}$              | 0.9 ± 0.7       | 0.7 ± 1.0       | 0 ± 1           | .183       | <.001        | .001           |
| $R_{5-24}$ (hPa s/l)            | 7.3 ± 2.0       | 7.1 ± 1.7       | 6.2 ± 1.9       | .724       | <.009        | .020           |
| $X_{5-24}$ (hPa s/l)            | −3.0 ± 1.5      | −1.95 ± 1.6     | −1.25 ± 0.9     | .008       | <.001        | .020           |
| $f_{res}$ (Hz)                  | 26.8 ± 5.9      | 22.7 ± 4.0      | 22.7 ± 5        | .001       | .923         | .001           |
| $f_{res}$ (% predicted)         | 119.3 ± 26.9    | 102.6 ± 23.6    | 100 ± 16.8      | .007       | <.001        | .484           |
| Z score $f_{res}$               | 0.8 ± 1.2       | 0.1 ± 0.8       | 0 ± 1           | .001       | .001         | .923           |
| Z score $f_{RS}$                | −0.23 ± 0.11    | −0.19 ± 0.09    | −0.12 ± 0.07    | .099       | <.001        | <.001          |
| Bronchodilator response (%) $R_{56}$ | −1.6 ± 1.5      | −1.0 ± 1.4      | 0 ± 1           | .090       | <.001        | <.001          |
| Rint (kPa s/l)                  | 1.06 ± 0.37     | 0.91 ± 0.28     | 0.70 ± 0.21     | .080       | <.001        | .001           |
| Rint (% predicted)              | 139.0 ± 41.7    | 120.6 ± 34.7    | 100 ± 26        | .078       | <.001        | .002           |
| Z score Rint                    | 1.7 ± 1.9       | 1.0 ± 1.5       | 0 ± 1.0         | .080       | <.001        | <.001          |
| Bronchodilator response (%) Rint| 24.5 ± 18       | 23 ± 13         | N/A             | .775       | N/A          | N/A            |

Mean ± SD (r test).

$fdRres$, frequency dependence of respiratory resistance (mean slope of $R_s$ vs frequency curve calculated over the 4-26 Hz frequency spectrum); $fres$, resonance frequency; N/A, not applicable; Rint, interrupter respiratory resistance technique; $R_{56}$, resistance measured at oscillation frequency of 6 Hz; $X_{56}$, reactance of the respiratory system. Bold P values refer to statistically significant results.
not only very premature but also needed prolonged mechanical ventilation and supplemental oxygen.

REFERENCES


Characteristics of Children Receiving Proton Pump Inhibitors Continuously for Up to 11 Years Duration

ERIC HASSALL, MBCHB, FRCP, WENDY KERR, RN, BSN, AND HASHEM B. EL-SERAG, MD, MPH

Objective To characterize those pediatric patients who receive long-term proton pump inhibitors (PPIs) and to determine the safety of long-term use of PPIs in this population.

Study design Patient databases were screened for long-term PPI use, defined as more than 9 months of continuous prescription, between 1989 and 2004.

Results The median duration of PPI use in the 166 patients in the study group was 3 years (range, 0.75 to 11.25 years). A total of 80 patients used PPIs for 3 to 11 years duration; 35 of these for more than 5 years, and 15 for more than 8 years. Mean age at initial prescription was 7.8 years. At least 1 gastroesophageal reflux disease (GERD)-predisposing disorder was present in 79% of the patients; the major disorders were neuromotor (in 66%) and esophageal atresia (in 14.5%). No GERD-predisposing disorder was present in 35 patients (21%). Endoscopic findings included hiatal hernia in 39% and histologically proven Barrett’s esophagus in 4.8%. Omeprazole was used in 90% of the patients; lansoprazole, in 7%. Six adverse reactions seen in 4 patients were potentially related to PPI (nausea and diarrhea, skin rash, agitation, and irritability).

Conclusions Children with underlying GERD-predisposing disorders compose the majority of long-term PPI users. Few adverse reactions to these drugs occur, and discontinuation of the drug is seldom indicated. These preliminary data suggest that PPIs may be efficacious and safe for continuous use for up to 11 years’ duration in children. (J Pediatr 2007;150:262-7)

Until recently, antireflux surgery was the mainstay of treatment for children with severe gastroesophageal reflux disease (GERD), whereas histamine-2-receptor antagonists (H2RAs) were widely used for milder disease. However, both of these modalities have significant shortcomings. In children, surgery carries high rates of early failure and other morbidities, whereas H2RAs are often ineffective in treating severe reflux, and their effect diminishes over time, often within just a few weeks of therapy. Proton pump inhibitors (PPIs) have the advantages of higher and faster rates of healing of esophagitis compared with H2RA and do not cause tachyphylaxis.

As in adults, in children PPIs are highly efficacious and safe for treating GERD-related signs and symptoms, including the most severe degrees of reflux esophagitis, with rates of symptom relief and cure of esophagitis exceeding 90%. Thus it is not surprising that in children, as in adults, PPIs are increasingly being used not only in the short term for healing, but also for long-term maintenance of remission of GERD. However, whereas the safety of omeprazole has been shown in adults for up to 11 years’ continuous use, safety data for prolonged use in children are not yet available. Studies have shown the efficacy and safety of omeprazole or lansoprazole therapy of up to 3 months’ duration in children. However, the longest period for which detailed PPI safety and efficacy data are available in children is for up to 2 years’ continuous use of omeprazole. In addition, there are few data indicating which children require long-term PPI therapy.

Consequently, we aimed to characterize pediatric patients who receive long-term treatment at our institution, and to examine the safety of long-term use of PPI in those children.

ALT Alanine aminotransferase
AST Aspartate aminotransferase
BCCH British Columbia Children’s Hospital
GERD Gastroesophageal reflux disease
GI Gastrointestinal
H2Ra Histamine-2-receptor antagonist
IQR Interquartile range
PPI Proton pump inhibitor
METHODS

In this retrospective cohort study, patient databases from British Columbia Children’s Hospital (BCCH) were screened for long-term PPI use, defined as more than 9 months of continuous prescription in patients with follow-up at BCCH. “Index date” was the date on which a PPI was first prescribed, marking the start of data collection. Potential PPI-related adverse drug reactions were identified and recorded. The final encounter for the purposes of data collection was the last recorded visit in the patient’s chart up to August 2004.

To identify and characterize a cohort of pediatric patients who had received long-term PPI therapy at BCCH, clinical databases from January 1989 through August 2004 were screened for the diagnosis of GERD and PPI use. These included a database of gastrointestinal (GI) endoscopies performed, GI Division outpatient records, and BCCH inpatient charts, as well as databases of PPI users from previous clinical studies. The primary inclusion criterion was long-term PPI use, defined as continuous prescription of drug for 9 months or more.

From these patient records, data were extracted and manually entered into a standardized purpose-designed 38-page data acquisition form. The data collected included patient demographics, associated medical disorders, signs and symptoms of GERD at presentation and at the latest encounter, laboratory values, and adverse drug reactions. Associated medical disorders were categorized as those predisposing to GERD (specifically neurologic impairment, congenital esophageal abnormalities, previous esophageal surgery, cystic fibrosis, and other chronic pulmonary disorders), and those not predisposing to GERD (eg, disorders of the liver, heart, and kidney and Helicobacter pylori status).

Details of PPI prescription included drug dose and the start and end dates for each PPI course, referred to as an “episode.” A “PPI episode” referred to a new start of drug (including the first), a change of dose, or a change of drug. “Exposure” to PPI was defined as the duration for which the patient was prescribed the drug in a continuous fashion, that is, total number of episodes or total number of days. For the same drug, a new PPI episode referred to each new start of drug separated by at least 7 days from the previous episode. Adverse drug reaction information included the occurrence of new signs or symptoms deemed to be possibly due to PPI and not to an intercurrent illness. Specifically, these were nausea, headache, diarrhea, vomiting, skin rash, abnormal hepatic transaminase values, and abnormal serum urea or creatinine levels.

The data acquisition form was designed using Teleform, an electronic data capture/management system pilot-tested for the purpose of this study. An experienced research associate (W.K.) and the senior investigator (E.H.) extracted patient data from source documentation and completed and submitted the forms. The data collection forms were subsequently scanned into an Access database designed for the study. SAS (version 9.1, SAS Institute, Cary, NC) datasets were used for the statistical analyses. Descriptive statistics were generated. Comparisons between variables were conducted using $\chi^2$ tests for categorical variables and $t$-tests and Mann-Whitney tests for continuous variables. Each patient was identified on the form by a unique study number, and confidentiality was maintained.

The study design was approved by the Clinical Research Ethics Board of the University of British Columbia and the Clinical Ethics Board of BCCH.

RESULTS

Patients

A total of 166 patients had a prescription for a PPI for more than 9 months. The mean age of these patients at the time of the index PPI prescription on record was 7.8 years (standard deviation [SD], 4.9) with a range of 4 weeks to 17 years (Table I). Approximately 1/3 of the patients were age 5 years or younger, 1/3 were age 6 to 10 years, and the remaining 1/3 were age 11 to 17 years.

GERD-Predisposing and Non–GERD-Predisposing Disorders

At least 1 GERD-predisposing disorder was present in 131 of the 166 patients (79%). These GERD-predisposing disorders included neuromotor impairment in 66% (with cerebral palsy in 48 (29%)) and other neurologic disorders or syndromes, with a major motor component in 62 patients (37%) (Table II; available at www.jpeds.com); esophageal atresia (with or without fistula) in 24 (14.5%); esophageal duplication cyst in 1 (0.6%); and chronic lung disorders in 38 (22.9%), including cystic fibrosis in 7 (4.2%) and other chronic pulmonary disorders in 31 (18.7%). Several patients had multiple disorders from those mentioned above. Non–GERD-predisposing disorders were present in 107 patients and included diabetes, chronic liver disease, Asperger’s syndrome, and cardiac and renal disorders. The group of 131 patients with at least 1 GERD-predisposing disorder and the 35 patients without any GERD-predisposing disorders are compared in Table III.

Endoscopic Findings

Approximately 74.7% of the patients (124/166) underwent an upper GI endoscopy on or before their PPI index date; the rest underwent endoscopy at a later date. The
findings included erosive esophagitis in 81 patients (65.3%), histological esophagitis in 20 (16.1%), and normal endoscopy and histology in 23 (18.6%). Esophageal stricture was present in 15 patients (12.1%). Twelve patients (9.7%) had suspected Barrett’s esophagus, which was confirmed histologically in 8 patients (4.8%) by the presence of goblet cell metaplasia with acid mucin. As shown in Table III, there were no significant differences in the prevalence of these findings between the 2 groups with and without GERD-predisposing disorders. All but 1 of these 8 patients was age 11 years or older. During upper GI endoscopy, the locations of the major esophagogastric landmarks are routinely documented, and hiatal hernia is considered present if the tops of the gastric folds are proximal to the diaphragmatic pinchock. By this criterion, hiatal hernia was present in 28% of the patients with GERD-predisposing disorders and in 11% of those without such disorders. There were no significant differences in these findings between the groups with and without GERD-predisposing disorders (Table III). Only 7 patients (4.2%) exhibited evidence of _H. pylori_ at index PPI prescription, all diagnosed by gastric biopsy.

### Presenting Symptoms

Most of the patients (149; 90.9%) had more than 1 presenting symptom (Table III). In the group with GERD-predisposing disorders, significantly greater proportions of patients had vomiting, abdominal pain, failure to thrive, and irritability. In general, symptoms were more frequent in those patients with underlying GERD-predisposing disorders (Table III).

Approximately 76% of the patients (n = 126) reported at least 1 GERD symptom at their last visit; 24% had no symptoms. However, the median number of symptoms sig-

### Table III. Comparison of several demographic, clinical, and PPI prescription features between pediatric patients with and without GERD-predisposing disorders

<table>
<thead>
<tr>
<th>GERD-predisposing disorders, n = 131 (79%)</th>
<th>None, n = 35 (21%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (IQR)</td>
<td>8 (4 to 12)</td>
<td>8 (3 to 12)</td>
</tr>
<tr>
<td>Fundoplication before PPI index, n (%)</td>
<td>21/29 (72.4%)</td>
<td>2 (66.7%)</td>
</tr>
<tr>
<td>Fundoplication after PPI index, n (%)</td>
<td>8/29 (27.6%)</td>
<td>1 (33.3%)</td>
</tr>
<tr>
<td>Median number of presenting symptoms (IQR)</td>
<td>3 (3 to 4)</td>
<td>3 (2 to 4)</td>
</tr>
<tr>
<td>Respiratory symptoms, n (%)</td>
<td>75 (57.3%)</td>
<td>12 (34.3%)</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
<td>95 (72.5%)</td>
<td>18 (51.4%)</td>
</tr>
<tr>
<td>Regurgitation, n (%)</td>
<td>39 (29.8%)</td>
<td>13 (37.1%)</td>
</tr>
<tr>
<td>Dysphagia, n (%)</td>
<td>28 (21.4%)</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>Nausea, n (%)</td>
<td>3 (2.3%)</td>
<td>9 (25.7%)</td>
</tr>
<tr>
<td>Gagging/retching, n (%)</td>
<td>27 (20.6%)</td>
<td>3 (8.6%)</td>
</tr>
<tr>
<td>Abdominal pain, n (%)</td>
<td>42 (32.1%)</td>
<td>19 (54.3%)</td>
</tr>
<tr>
<td>Irritability, n (%)</td>
<td>31 (23.7%)</td>
<td>2 (5.7%)</td>
</tr>
<tr>
<td>Failure to thrive, n (%)</td>
<td>48 (36.6%)</td>
<td>3 (8.6%)</td>
</tr>
<tr>
<td>Anemia, n (%)</td>
<td>16 (12.2%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>EGD before PPI use, n (%)</td>
<td>99 (75.6%)</td>
<td>25 (71.4%)</td>
</tr>
<tr>
<td>EGD findings (before PPI use)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erosive esophagitis, n (%)</td>
<td>66/99 (66.7%)</td>
<td>15/25 (60%)</td>
</tr>
<tr>
<td>Histological esophagitis, n (%)</td>
<td>14/99 (14.1%)</td>
<td>6/25 (24%)</td>
</tr>
<tr>
<td>Strictures, n (%)</td>
<td>14/99 (14.1%)</td>
<td>1/25 (4%)</td>
</tr>
<tr>
<td>Hiatal hernia, n (%)</td>
<td>22 (28.2%)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>Proven histological Barrett’s esophagus, n (%)</td>
<td>6/99 (6%)</td>
<td>2/25 (8%)</td>
</tr>
<tr>
<td>PPI prescription</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of follow-up, median (IQR)</td>
<td>1146 (676 to 1918)</td>
<td>677 (469 to 1309)</td>
</tr>
<tr>
<td>Duration of PPI exposure, median (IQR)</td>
<td>1085 (564 to 1680)</td>
<td>512 (402 to 826)</td>
</tr>
<tr>
<td>Dose of PPI, median (IQR)</td>
<td>20 (20 to 40)</td>
<td>20 (15 to 40)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table IV. Duration of continuous-use exposure to PPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on PPI, n (%)</td>
</tr>
<tr>
<td>Years on PPI</td>
</tr>
<tr>
<td>&lt; 2</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Median daily dose was 20 mg (range, 4 to 90 mg); median total dose-exposure per patient was 22 g (range, 2.2 to 178 g).
significantly declined from 3 (interquartile range [IQR], 2) recorded on the initial presentation to 1 (IQR, 1) recorded on the last presentation.

Antireflux Surgery

A total of 32 patients (19.3%) underwent fundoplication, 23 before the PPI index date and 9 during follow-up. For the 9 patients who underwent fundoplication after the PPI index date, the median time from that date to the surgery was 368 days (range, 97 to 1141 days). In those 9 patients, the stated or inferred reasons for fundoplication were poor response to PPI therapy in 6 and patient request in 3. Two of the 9 patients returned to PPI therapy during follow-up.

PPI Prescription

The duration of continuous exposure to PPI is shown in Table IV. The median duration of follow-up (between the presentation date and date of last encounter) was 3.0 years. The patients had PPI exposure for most of this time (median, 2.75 years). PPI prescription during the follow-up period was continuous in 21 patients (13%), at least 65% of the time in 104 patients (63%), and 50% of the time in 31 patients (19%).

Most of the patients (141; 85%) used omeprazole only. Seven patients (4.2%) used lansoprazole only; 1 used another PPI only; 10 used omeprazole and lansoprazole (not concurrently); 5 used omeprazole and another PPI; and 2 used omeprazole, lansoprazole, and another PPI. The 166 patients had a total of 452 PPI episodes, of which 423 (93.6%) were of more than 30 days’ duration. Omeprazole was prescribed in 405 of these episodes (89.6%), lansoprazole in 32 (7.1%), and other PPIs in 15 (3.3%).

A total of 136 patients (81.9%) had no gaps between PPI episodes; that is, for the periods that they were prescribed medication, they took it continuously. In the remaining patients, the median duration of gaps in PPI episodes was 108 days (IQR, 290 days). The median number of PPI episodes per patient was 2 (range, 1 to 8). The median duration of PPI prescription per patient was 916 days, approximately 2.5 years (IQR, 923 days). The minimum was 273 days, and the maximum was 4103 days (11.24 years). The daily dose ranged from 4 to 90 mg; the median daily dose was 20 mg (IQR, 20 mg). Only 2 patients received 90 mg, and 11 received 80 mg. The duration of follow-up and hence the duration of PPI exposure was significantly longer in patients with GERD-predisposing disorders; however, there were no differences in the dose of PPI between the groups with and without GERD-predisposing disorders (Table III).

For omeprazole, the median number of episodes was 2 (IQR, 3 episodes). The median duration was 897 days (IQR, 934 days). The median dose was 1.1 mg/kg (IQR, 0.9 mg/kg), and the total daily dose was 20 mg (IQR, 20.0 mg). The median absolute daily dose was 20 mg (range, 4 to 90 mg).

For lansoprazole, the median number of episodes of use per patient was 1 (IQR, 1), with a minimum of 1 and maximum of 3. The median duration of use per patient was 915 days (IQR, 930 days), with a minimum of 80 days and a maximum of 4108 days. The median dose was 1.4 mg/kg (IQR, 1.7 mg/kg), with a minimum of 0.4 and a maximum of 3.7 mg/kg. The median absolute daily dose was 30 mg (IQR, 45.0 mg), with a minimum of 7.5 and a maximum of 90 mg.

Adverse Drug Reactions

Only 6 signs or symptoms possibly related to PPI use were seen in 4 patients (2.4%). The details of these events and their outcomes are given in Table V.

Table VI (available at www.jpeds.com) shows the distribution of biochemical test values in the patients who underwent more than 1 test. For example, of the 112 patients who had more than 1 aspartate aminotransferase (AST) measurement, 80 (71.4%) were normal and 9 (8%) were “always abnormal.” Of those 9, none had values greater than twice the upper limit of normal, and all were taking other medications concurrently with a PPI. Tests for hepatitis B and C were negative in the 5 patients tested. Three patients had AST levels that went from normal at the first measurement to abnormal at the last measurement, 3 had alanine aminotransferase (ALT) levels that did the same, and 1 had AST and ALT levels that did the same. Again, no patient had an

<table>
<thead>
<tr>
<th>Patient number</th>
<th>PPI</th>
<th>Possible adverse reaction</th>
<th>Outcome</th>
<th>Associated disorders</th>
<th>Age, years</th>
<th>Time of onset after index date, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lansoprazole</td>
<td>Nausea</td>
<td>Discontinued PPI</td>
<td>Cerebral palsy</td>
<td>12</td>
<td>188</td>
</tr>
<tr>
<td>2</td>
<td>Lansoprazole</td>
<td>Diarrhea</td>
<td>Discontinued PPI</td>
<td>Motor disorder</td>
<td>14</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>Lansoprazole</td>
<td>Skin rash</td>
<td>Discontinued PPI and fundoplication performed</td>
<td></td>
<td></td>
<td>133</td>
</tr>
<tr>
<td>4</td>
<td>Omeprazole</td>
<td>Agitation, irritability</td>
<td>Resolved with decrease in dose</td>
<td>Chronic pulmonary</td>
<td>16</td>
<td>128</td>
</tr>
<tr>
<td>5</td>
<td>Omeprazole</td>
<td>Nausea, vomiting</td>
<td>Resolved spontaneously</td>
<td>Chronic cardiac</td>
<td>15</td>
<td>25</td>
</tr>
</tbody>
</table>
enzyme level higher than twice the upper limit of normal, and tests for hepatitis B and C were negative in all 3 of the 7 patients tested. Use of other medications concurrently with a PPI was common in this cohort; these medications included anticonvulsant agents known to affect hepatic transaminase values. In the 2 patients in whom creatinine levels went from normal to abnormal, the abnormal levels were only negligibly elevated (by < 5% above the upper limit of normal), and in the 2 patients in whom creatinine levels were “always abnormal,” primary renal disease was present. There were no significant differences among the patients with abnormalities in creatinine, AST, or ALT in PPI type, dose, or duration, or in the presence or type of comorbid disorders.

**DISCUSSION**

Some have alleged that long-term PPI therapy is overused in adults. For example, in various series, reported indications for PPI therapy were nonulcer dyspepsia in 6% to 21%, uninvestigated dyspepsia in 7% to 33%, and use of nonsteroidal anti-inflammatory drugs (mostly uninvestigated) in 5% to 42%; in 1 series, only 27% of the patients on long-term PPI therapy had undergone endoscopy. Although it is possible that the same trends might also apply to children, there are no data supporting this. In the present series, all children had GERD documented by investigation, including endoscopy. Therefore, our series focuses only on the severe end of the spectrum of GERD, those needing treatment with PPIs or surgery.

In this study, we identified and characterized a cohort of 166 children with GERD who were prescribed a PPI continuously for a long duration. As is well recognized, certain disorders predispose persons to the most severe and chronic GERD through various mechanisms, and it is these children—who often respond poorly to antireflux surgery—who stand to especially benefit from long-term PPI therapy. Most patients in this study had GERD-predisposing disorders and exhibited significantly more symptoms at presentation, a higher prevalence of failure to thrive, and a lower prevalence of nausea than those without underlying disorders (Table III). This profile is consistent with the nature of many of the underlying disorders themselves; children with neurologic impairment and syndromes often are unable to report symptoms. Thus in this group, there should be a high degree of suspicion for GERD based on observed physical signs as well as reported symptoms. Although only 21% of all our patients had no major underlying disorder, this study provides new information on the safety of PPI use in this group of patients, which is becoming increasingly more recognized and treated.

There is no standard definition of what constitutes “long-term” PPI use. We adopted an arbitrary definition of at least 9 months of continuous prescription to avoid capturing data on patients taking short courses of PPIs. Although our methodology does not allow us to determine compliance, our patients attended regularly for follow-up and prescription renewal, were severely affected with GERD, and had somatic responses to PPI, and thus it is likely that most took the medications on a regular basis.

Of the 166 patients, 48% took a PPI for 3 to 11 years; most (66%) were started on the drug at age 6 years or older. Although this reflects our approach over the period analyzed (January 1989 through August 2004), it does not necessarily reflect our current practice; with more data and experience, we have become increasingly comfortable starting PPI therapy in younger children, and not only for failures of H2RA. In the present study, 14 patients were started on a PPI before age 1 year, but most of these patients were referred to us while already receiving a PPI. This age group is under study for PPI pharmacokinetic and safety parameters. Nevertheless, under 1 year of age, we prescribe PPIs in only very carefully selected patients, as there are relatively few indications for PPI use in this age group.

Although 76% of patients took a PPI for at least 2/3 of the time monitored, the patients with GERD-predisposing disorders had a significantly greater degree of exposure to PPIs, indicating that they were less likely or able to withdraw from PPI therapy. Most of the documented experience in this study is with omeprazole. This is partly for historical reasons, because we started using it in children in 1989 and it was the first PPI for which efficacy, dosing, and safety data were available for children. The other PPI for which considerable pediatric data are now available is lansoprazole; the considerable shorter-term data available suggest that efficacy and safety rates for this drug are similar to those for omeprazole.

That PPIs are efficacious in even the most severely affected children is confirmed by symptom resolution or significant decrease in symptom frequency from presentation to final visit. This was previously shown in shorter follow-up studies. Along the same lines, it is not surprising that the cohort maintained on PPI included a significant proportion (14%) who had failed at least 1 antireflux procedure. The high failure rates of open and laparoscopic antireflux surgery in children are well recognized, and in our center, the number of new antireflux surgery procedures has fallen from approximately 50 per year to 5 per year today. In our series, 9 patients (5%) on long-term PPI therapy were referred for surgery at the physician’s or patient’s instigation, but 2 of these returned to PPI therapy during follow-up.

The endoscopic findings are of particular interest. Hiatal hernia was found on at least 1 endoscopy in 39% of the patients; this is a higher prevalence than reported previously. That most hernias were seen in the GERD-predisposing patients is not surprising—children with neurologic disorders, repaired esophageal atresia, and chronic lung disease have many reasons to develop hernias. But even in the absence of these disorders, hernias tend to be present in children with severe GERD.

Of the 12 patients (15%) with suspected Barrett’s esophagus on endoscopy, 8 (5%) were documented. This is a higher percentage than reported previously and suggests in...
children with severe GERD, Barrett’s esophagus may be more prevalent than previously considered. However, this group of patients with severe GERD is highly selected, and thus the findings may not be generalizable to other settings.

The adverse drug reactions considered associated with PPI therapy were nausea, vomiting, diarrhea, skin rash, and irritability. These occurred in only 4 patients. Although the incidence of reactions was very low (6/528 patient-years), our retrospective analysis likely underestimates their true incidence. Nevertheless, it does appear that no serious reactions occurred, and that those that possibly may be attributable to PPIs were of sufficient discomfort or inconvenience so as to cause permanent discontinuation of the drug in only 3 of the 166 patients. No significant effect on liver or renal function was seen.

In conclusion, in the present study, most of the children on long-term PPI therapy had an underlying systemic disorder that predisposed them to severe reflux. These children had more symptoms than those without such GERD-predisposing conditions, but both groups experienced significant symptomatic improvement from long-term PPI therapy. There were no serious adverse drug reactions, and it was very seldom necessary to discontinue PPI therapy because of an adverse reaction. Although prospective studies are needed to determine the true prevalence of PPI-attributable reactions, this preliminary study suggests that in children, long-term use of PPIs is efficacious and may be safe for periods up to 11 years. Although these findings should provide some reassurance to pediatric prescribers and families, an important caveat is that gastric acid has many important physiological functions, and the goal in healing should not be to make patients achlorhydric. Further analysis of other parameters over time is needed, such as gastric histology, vitamin $B_{12}$ levels, and other nutritional indices.

REFERENCES

**Table II. Underlying neuromotor impairments**

**Syndromes with a major motor component***
- Angelman’s syndrome
- Autonomic dysfunction NYD
- Banyan-Riley-Ruvalcaba syndrome
- Cerebral dysgenesis
- CHARGE syndrome
- Chromosomal abnormality unknown
- Chromosome 4p monosomy
- Chromosome 9 short-arm deletion
- Chromosome 22 deletion
- Chromosome 4 abnormality
- Cornelia de Lange syndrome
- Cri du chat syndrome
- Dandy-Walker syndrome
- Down syndrome
- Duchenne muscular dystrophy
- Glutaric aciduria type I
- Goldenhaar syndrome
- Leigh syndrome
- Metachromatic leukodystrophy
- Microcephaly
- Mitochondrial disorder
- Rett syndrome
- Trisomy 21
- VACTERL association
- X-linked mental retardation

**Neurologic disorders without syndromes†**
- Autism with motor component
- Brainstem dysfunction NYD
- Cerebral palsy, etiology unknown
- Central nervous system lupus
- Global delay NYD
- Perinatal hypoxia
- Postencephalitis
- Posttraumatic
- Prematurity

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*Some disorders were present in more than 1 patient; for example, 2 patients had Down syndrome, and 3 had mitochondrial disorder.
†Many of these diagnoses were present in more than 1 patient; for example, several had cerebral palsy—etiology unknown, and 3 had neuromotor impairment postencephalitis.
The Contribution of the DLG5 113A Variant in Early-Onset Inflammatory Bowel Disease

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Objective To assess the contribution of the 113 G→A missense mutation within the discs, large homolog 5 (DLG5) gene in childhood-onset inflammatory bowel disease (IBD) in Scotland.

Study design Two-hundred and ninety-six children with IBD were studied. Parental DNA was also collected for transmission disequilibrium testing (TDT) analysis. Genotyping was performed by TaqMan®. Genotype-phenotype analysis was also undertaken. Socioeconomic status was assigned using a deprivation category (DepCat) score 1 through 7 (1 = most affluent).

Results TDT analysis demonstrated a significant association with IBD (P = .045). On unifactorial analysis, 113A carriage was associated with: (1) higher social class (DepCat 1 compared with 2-7, and 1-2 compared with 3-7) (66.7% vs 22.6%, P = .0005, OR 6.84 [1.99-23.55] and 37.2% vs 22.2%, P = .03, OR 2.08 [1.04-4.17], respectively); (2) higher height centile (>75th centile vs <75th centile) (42.9% vs 23.1%, P = .01, OR 2.50 [1.18-5.28]); and (3) male sex in Crohn’s disease (CD) (29.3% vs 16.9%, P = .04, OR 2.04 [1.01-4.11]). Multifactorial analysis demonstrated that higher social class (DepCat 1) was independently associated with carriage of variants of 113A (P = .001, OR=6.92 [2.24-21.33]).

Conclusions DLG5 113A is associated with increased susceptibility to IBD in Scottish children. The effect may be most marked for those children living in relative affluence. (J Pediatr 2007;150:268-73)

A strong genetic basis for inflammatory bowel disease (IBD) has been suggested by evidence from twin studies, and family studies,¹ and has been supported by the identification of several genes associated with increased susceptibility to IBD: CARD15,²,³ DLG5,⁴ SLC22A4/5,⁵ MDR1,⁶ and CARD4.⁷ The disease model that has evolved is that ulcerative colitis (UC) and Crohn’s disease (CD) are related polygenic diseases sharing some but not all susceptibility genes.⁸

We have demonstrated a rising incidence of childhood-onset IBD in Scotland⁹,¹⁰ and within the Scottish population we have demonstrated association between susceptibility to early-onset CD both with northern latitudes and with relative affluence.¹¹ In a study of 580 incident IBD cases over the period 1981 to 1995, the relative risk of developing IBD and CD was significantly increased in areas of relative affluence, compared with areas of socioeconomic deprivation (P = .02 and P = .03, respectively).

Over the last decade, genome-wide scanning in IBD has been remarkably successful, leading to the identification of several susceptibility loci, satisfying rigorous criteria for definite linkage.¹² We have shown that IBD1 and IBD5 both contain determinants of susceptibility and disease severity in early-onset IBD in Scotland, but these loci alone do not account for the majority of the genetic risk in our population.¹³,¹⁴

A European genome-wide scan in 353 IBD sibling pairs (including UK patients) identified an area on chromosome 10 that achieved criteria for “suggestive linkage” in patients with CD.¹²,¹⁵ Fine mapping of this region identified variants of the discs, large homolog 5 (Drosophila) (DLG5) gene situated within this locus that may be associated with increased susceptibility to IBD.⁴ The 113 G→A variant (a missense mutation in...
69% of cases).

To be performed (DNA from both parents was available in available to allow transmission disequilibrium testing (TDT)

These persons were recruited from pediatric gastroenterology centers across Scotland and from the Western General Hos-

cial, Edinburgh. Parental DNA was also collected where

In a retrospective case note review and personal interview. The

Comprehensive clinical phenotypic data were obtained using

Disease Phenotyping and Data Collection

The diagnosis of IBD was based on standard criteria.24 The complete set of phenotypic variables collected in this cohort has been described previously and includes growth measurements and socioeconomic data assessing relative affluence/deprivation.13 The anthropometric information collected was weight and height of patients with a body mass index (BMI) calculated thereafter. The data were plotted on a standard UK centile chart of the UK 1990 population data (© Child Growth Foundation 1996) and an appropriate centile band was allocated. The Vienna classification together with a more extensive phenotypic description for each patient were used to describe the phenotype of patients with CD.13,25

**Deprivation Status**

Socioeconomic status of the patient’s postcode was allocated using the Carstairs score. This score is a measure of socioeconomic deprivation derived from levels of male unemployment, head of the household’s social class, the level of overcrowding in households, and car ownership generated from census data.26 Data used to calculate the scores for this study were based on the UK 2001 census data (www.
gros.com). The Carstairs score was then assigned a numerical deprivation category (DepCat score) based on the postcode (scored 1–7; 1 = no deprivation and 7 = maximum deprivation). The data for the DepCat score were not calculated by us as part of this study; we simply matched the DepCat scores with the patient postcode (the DepCat scores and matching postcodes were obtained from the Edinburgh University data library). In cases where a patient’s postcode fell between two different DepCat categories, no score was allocated. Thus, this score is derived from a person’s postcode and reflects the socioeconomic status of the area in which a patient lives rather than an individual case-specific score. The Carstairs score has been widely used to study the association between socioeconomic conditions and disease.

The methodology used to define North and South Scotland was based on patients’ postcodes.11 Written informed consent from all patients and controls was obtained. All relevant Research Ethics Committees approved the study protocol.

**Genotyping**

Genomic DNA was extracted from peripheral venous blood in all patients by a modified salting-out technique,27 and it was re-suspended in 1xTE (10 mM Tris [pH 8.0], 1 mM EDTA [pH 8.0]) at a final concentration of 100 ng/μL. The SNP 113G/A (rs1248696) was typed using the TaqMan® sys-

tem (Applied Biosystems, Foster City, CA) in the Wellcome Trust Clinical Research Facility, Western General Hospital in January 2005 by personnel blinded to the project aims. The genotyping methods used for the three CARD15 mutations (Gly908Arg, Arg702Trp, and Leu1007fsinsC) have been de-
scribed previously.28

| Table I. Demographics of inflammatory bowel disease patients at diagnosis |
|-----------------------------|------------------|
| Sex (M/F)                   | 161/135          |
| Median age at diagnosis (y) | 11.00 (IQR 8.42-12.92) |
| Current smoker              | 7/295 (2.4%)     |
| Family history of IBD       | 98/292 (33.5%)   |
| Caucasian (%)               | 288 (97.3%)      |
| Extrainestinal manifestations|                  |
| Joint                       | 23/282 (8.2%)    |
| Erythema nodosum            | 26/282 (9.2%)    |
| Location according to the Vienna classification† |
| Terminal ileum (L1)         | 9 (4.6%)         |
| Colon (L2)                  | 48 (24.3%)       |
| Ileocolonic (L3)            | 38 (19.3%)       |
| Upper gastrointestinal (L4) | 93 (47.2%)       |
| None*                      | 9 (4.6%)         |
| Behavior according to the Vienna classification† |
| Inflammatory (B1)           | 163 (82.7%)      |
| Stricture (B2)              | 7 (3.6%)         |
| Penetrating (B3)            | 27 (13.7%)       |
| Ulcerative colitis disease extent |
| Extensive colitis**         | 52 (71.2%)       |
| Anthropometric centiles†    |
| Weight (75-91st)            | 22/288 (7.6%)    |
| Height (75-91st)            | 28/272 (11.1%)   |
| BMI (75-91st)               | 27/270 (10.0%)   |

The phenotypic data at diagnosis represent 296 patients with IBD (including 197 CD and 73 UC) unless otherwise stated.

*These patients fulfilled diagnostic criteria for Crohn’s disease, but their disease location did not fit into the Vienna classification.

†Based on centile plotted on UK Growth Chart © Child Growth Foundation 1996.

**Inflammation proximal to the splenic flexure.

exon 30) encoding for the amino acid substitution R30Q was associated with susceptibility to IBD and CD.4 Further stud-

ies have yielded inconsistent results.16-23 Thus the effect appears inconsistent, relatively weak, and population-specific. We have rigorously assessed the contribution of the DLG5 113G/A mutation with respect to IBD susceptibility and phenotype in the high incidence Scottish population.

**METHODS**

Patients diagnosed with IBD younger than 16 years of age were studied (197 CD, 73 UC, and 26 indeterminate colitis [IC]). There were 161 males and 135 females (Table I). These persons were recruited from pediatric gastroenterology centers across Scotland and from the Western General Hospital, Edinburgh. Parental DNA was also collected where available to allow transmission disequilibrium testing (TDT) to be performed (DNA from both parents was available in 69% of cases).

The phenotypic data at diagnosis represent 296 patients with IBD (including 197 CD and 73 UC) unless otherwise stated.

*These patients fulfilled diagnostic criteria for Crohn’s disease, but their disease location did not fit into the Vienna classification.

†Based on centile plotted on UK Growth Chart © Child Growth Foundation 1996.

**Inflammation proximal to the splenic flexure.

**Anthropometric centiles†**

| Weight (75-91st) | 22/288 (7.6%) |
| Height (75-91st) | 28/272 (11.1%) |
| BMI (75-91st)    | 27/270 (10.0%) |

The phenotypic data at diagnosis represent 296 patients with IBD (including 197 CD and 73 UC) unless otherwise stated.

*These patients fulfilled diagnostic criteria for Crohn’s disease, but their disease location did not fit into the Vienna classification.

†Based on centile plotted on UK Growth Chart © Child Growth Foundation 1996.

**Inflammation proximal to the splenic flexure.

<table>
<thead>
<tr>
<th>Location according to the Vienna classification†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal ileum (L1)</td>
</tr>
<tr>
<td>Colon (L2)</td>
</tr>
<tr>
<td>Ileocolonic (L3)</td>
</tr>
<tr>
<td>Upper gastrointestinal (L4)</td>
</tr>
<tr>
<td>None*</td>
</tr>
</tbody>
</table>

Disease Phenotyping and Data Collection

The diagnosis of IBD was based on standard criteria.24 Comprehensive clinical phenotypic data were obtained using retrospective case note review and personal interview. The complete set of phenotypic variables collected in this cohort has been described previously and includes growth measurements and socioeconomic data assessing relative affluence/deprivation.13 The anthropometric information collected was weight and height of patients with a body mass index (BMI) calculated thereafter. The data were plotted on a standard UK centile chart of the UK 1990 population data (© Child Growth Foundation 1996) and an appropriate centile band was allocated. The Vienna classification together with a more extensive phenotypic description for each patient were used to describe the phenotype of patients with CD.13,25

**Deprivation Status**

Socioeconomic status of the patient’s postcode was allocated using the Carstairs score. This score is a measure of socioeconomic deprivation derived from levels of male unemployment, head of the household’s social class, the level of overcrowding in households, and car ownership generated from census data.26 Data used to calculate the scores for this study were based on the UK 2001 census data (www.
gros.com). The Carstairs score was then assigned a numerical deprivation category (DepCat score) based on the postcode (scored 1–7; 1 = no deprivation and 7 = maximum deprivation). The data for the DepCat score were not calculated by us as part of this study; we simply matched the DepCat scores with the patient postcode (the DepCat scores and matching postcodes were obtained from the Edinburgh University data library). In cases where a patient’s postcode fell between two different DepCat categories, no score was allocated. Thus, this score is derived from a person’s postcode and reflects the socioeconomic status of the area in which a patient lives rather than an individual case-specific score. The Carstairs score has been widely used to study the association between socioeconomic conditions and disease.

The methodology used to define North and South Scotland was based on patients’ postcodes.11 Written informed consent from all patients and controls was obtained. All relevant Research Ethics Committees approved the study protocol.

**Genotyping**

Genomic DNA was extracted from peripheral venous blood in all patients by a modified salting-out technique,27 and it was re-suspended in 1xTE (10 mM Tris [pH 8.0], 1 mM EDTA [pH 8.0]) at a final concentration of 100 ng/μL. The SNP 113G/A (rs1248696) was typed using the TaqMan® system (Applied Biosystems, Foster City, CA) in the Wellcome Trust Clinical Research Facility, Western General Hospital in January 2005 by personnel blinded to the project aims. The genotyping methods used for the three CARD15 mutations (Gly908Arg, Arg702Trp, and Leu1007fsinsC) have been described previously.28
Statistical Analysis

TDT was performed in IBD trios using TRANSMIT. This method makes full use of the data available using inferred genotypes if data from both parents are not available. The PedCheck software program (Department of Human Genetics, University of Pittsburgh, Pittsburgh, PA) was used to exclude any potential cases of nonpaternity or genotyping error. Genotype-phenotype associations were analyzed by χ² test, or Fisher's exact test where appropriate, using the Minitab statistical software package (Minitab Ltd., Coventry, UK). To identify significant independent variables associated with genotype, unifactorial and multifactorial logistic regression analyses were carried out.

RESULTS

Transmission Disequilibrium Testing Analysis

In total, 97% of samples were successfully genotyped. TDT analysis based on 270 families demonstrated an association of allelic variants of the 113A allele with IBD only (χ² = 4.01, P = .045) (Table II).

Association with Affluence

A higher rate of carriage of the 113A variant was present in the patients with DepCat score 1 (n = 12) compared with those with DepCat score 2 through 7 (n = 252) (66.7% vs 22.6%, P = .0005, OR 6.84 [1.99-23.55]) and in comparing allele frequency between the two groups (33.3% vs 13.3%, P = .006, OR 3.26 [1.34-7.92]) (Table III). Higher carriage of 113A variants was also demonstrated if patients with DepCat scores 1 and 2 were analysed together (n = 43) and compared with patients with DepCat scores 3 through 7 (n = 221) (37.2% vs 22.2%, P = .03, OR 2.08 [1.04-4.17], respectively). There was no significant difference between northern (n = 35) and southern latitudes (n = 259) in carriage of variant 113A alleles (34.4% vs 23.9%, P = .20, respectively).

Multifactorial Analysis

Binary logistic regression analysis combining family history of IBD, sex, weight, height, BMI centile (as either 75th-91st or other), and social class (as either DepCat score 1 or 2-7) together with joint disease in all patients with IBD was performed.

Carriage of the 113A variant was associated with DepCat score 1 taking into account all of the above factors (P = .001, OR = 6.92 [2.24-21.33]). If the same model was run combining DepCat 1 and 2 together compared with 3 through 7 and with all other factors, the association between higher socioeconomic class and 113A carriage was confirmed (P = .02, OR = 2.49 [1.13-5.47]).

Genotype-Phenotype Analysis: Unifactorial Analysis

GROWTH CENTILES. On unifactorial analysis, carriage of the 113A allele was associated with the higher height centiles

Table II. Transmission disequilibrium testing results for the DLG5-113 mutant allele

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>DLG5 carriage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed Expected</td>
<td>(O-E) χ² value P value</td>
</tr>
<tr>
<td>IBD 68 58.543 22.272 4.01 .045</td>
<td></td>
</tr>
<tr>
<td>CD 48 42.453 15.991 1.92 .178</td>
<td></td>
</tr>
<tr>
<td>UC 20 16.09 6.4409 2.37 .105</td>
<td></td>
</tr>
</tbody>
</table>

The result of transmission disequilibrium testing for the 113 G→A in 270 families demonstrates association with IBD but not Crohn’s disease or ulcerative colitis.

Table III. DepCat scores in patients with IBD together with DLG5 113A carriage rates

<table>
<thead>
<tr>
<th>DepCat score</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Unclassified</td>
<td>32</td>
</tr>
</tbody>
</table>

There is a significant difference in DLG 113A variant carriage in patients in DepCat score 1 vs 2-7 as well as 1 and 2 combined compared with scores 3-7 (P = .001, OR = 6.92 [2.24-21.33], and P = .02, OR = 2.49 [1.13-5.47], respectively). All patients in DepCat 1 were Caucasian (7 males and 5 females).

A validated scoring system of deprivation based on data from the 2001 UK census (1 = no deprivation, 7 = maximum deprivation). The deprivation score is a measure of socioeconomic deprivation derived from demographic factors that relate to a person’s postcode.

Sex

In CD, the carriage rate of 113A variant alleles was higher in males than in females (29.3% vs 16.9%, P = .04, OR 2.04 [1.01-4.11]). Allele frequency showed a similar trend (male 15.1% vs female 9.0%, P = .07, OR 1.79 [0.94-3.40]), but this difference was not statistically significant. There was no sex-related difference between allele frequency and carriage rates of 113A variants in patients with UC or IBD.

Extra-intestinal Manifestations. The carriage of 113A variant alleles was uncommon in patients with joint disease or symptoms but did not reach statistical significance (13.0% vs 25.9%, P = .21, OR 0.42 [0.12-1.49], respectively).

Age at Diagnosis. There was no difference in the median ages at diagnosis of carriers of 113A variant alleles versus
noncarriers for patients with CD at 11.4 years versus 11.2 years ($P = .91$) and with IBD at 11.3 years versus 10.9 years ($P = .73$).

**Disease Location and Behavior**

There was no difference in allele frequency or carriage rates of this 113A DLG5 variant in disease location or behavior in patients with either CD or UC at diagnosis.

**DLG5-CARD15 interaction.** There was no difference in carriage of the DLG5 113A variant when patients were stratified based on carriage of at least one of the three common CARD15 variants (Gly908Arg, Arg702Trp, and Leu1007Ile). The carriage of CARD15 variant alleles compared with noncarriage in patients with IBD or CD was 14.0% versus 20.5% ($P = .01$, OR 0.63 [0.26-1.53]) and 14.7% versus 20.5% ($P = .43$, OR 0.66 [0.23-1.88]), respectively.

**DISCUSSION**

Our data suggest that the penetrance of the DLG5 genetic variants, and thus genetic associations with disease, may be influenced by environmental factors present in affluent families in Scotland. Thus although the overall association of the DLG5 113 variant alleles with early-onset IBD in the Scottish population appears modest, the association with children living in affluence is strong. These findings suggest a potentially novel insight into gene-environmental interactions in IBD.

We have previously demonstrated an association between higher social class (DepCat 1) and early-onset IBD in Scotland by Poisson regression analysis in a study of 580 patients with IBD; these data clearly demonstrated that the relative risk of IBD and CD is highest in the most affluent families. The association of CD with affluence has also been demonstrated in other childhood IBD populations. Our findings complement previous UK data, suggesting that the presence of a hot water tap and a separate bathroom increase the risk of developing CD. The reason for these associations is not entirely clear, but the role of water quality, diet (cold-chain hypothesis), hygiene, and infection rates are potentially plausible.

We now present evidence suggesting that the most susceptible persons within these affluent regions may also possess a risk genotype, supporting a gene-environment interaction as an explanation for the association with affluence. The association with the most affluent appears robust in the present study—the relationship is present when DLG5 113A carriage rate is compared between patients with DepCat score 1 and DepCat 2 through 7; moreover, the association holds on multifactorial analysis notwithstanding the small number of patients in DepCat 1.

The potential mechanisms whereby DepCat 1 children should differ from children with other DepCat scores and how this influences the development of IBD remain uncertain and a matter for investigation, but it is interesting to note some of the differences highlighted from published studies. Children from lower DepCat scores have higher rates of dental caries, are more likely to be colonized with yeasts, and have higher rates of Helicobacter pylori infection. Breast-feeding incidence and duration are highest in DepCat 1 and 2 together in one study, and they are higher in DepCat 1 compared with 2 and other categories in a second study. These data highlight the fact that the early exposure to microbes in each DepCat category is likely to be different and present a possible mechanism of how DepCat score, environment, and genotype interact.

Growth and development are critical aspects of childhood-onset IBD. Growth failure is a severe manifestation of CD that we have recently shown to be strongly linked to carriage of disease associated variants from within the IBD5 locus. However, in the present study the association of DLG5 variants is with higher height and weight centiles leading to the hypothesis that this variant may act in the opposite manner to IBD5 variants and confers a protective effect against growth failure. A similar protective role has been previously suggested for the −238 tumor necrosis factor-α variant in a pediatric CD population. These data therefore also provide indirect support for the concept that this growth variant leads to disease expression in children lacking socioeconomic deprivation.

The 113A variant was commoner in male compared with female children with CD in our study. It has been previously reported that the DLG5 variants are more common in males. It is entirely plausible that DLG5 studies in early-onset populations are more likely to give positive results because of the male predominance in childhood-onset CD (contrasting with the female predominance in adult populations).

What then of the overall contribution of this DLG5 variant to disease susceptibility? Our TDT analysis ($P = .045$) reveals data similar to those of Stoll et al and subsequent publications, which have suggested a weak overall association of variant alleles of DLG5 113A with IBD. Daly et al reported TDT data in two further IBD populations, one demonstrating significant association ($P = .02$) but the second showing no association. In the Flemish population, contrasting results to those of Stoll and colleagues are reported with significant undertransmission of 113A variants.

Case-control studies have yielded inconsistent results, with heterogeneity among controls more than cases providing the differences between study populations. This heterogeneity between different study populations matches data in the Scottish population for CARD15 and TLR4.

Our positive TDT results and the conflicting data from other series are nonetheless consistent with the hypothesis.
that DLG5 may represent a gene of relatively modest effect in IBD. The population differences can be explained by a combination of factors—heterogeneity between geographically and ethnically distinct populations and, heterogeneity within subgroups of IBD patients with specific differences in the sex and age of patients. It is interesting to note that in our own Scottish population using TDT analysis, a method that protects against the problems of population stratification, we have shown a positive association when a case-control study in a Scottish adult population has been negative. An adequately powered case-control study to prove beyond doubt a definite role for DLG5 variants in IBD etiology may necessitate studies of greater size than any yet carried out in CD or UC, requiring several thousand patients and controls. This strategy is similar to that applied to many other polygenic diseases, in which genetic determinants of low genotype relative risk have been identified.

In summary, we provide preliminary evidence that suggests that a novel environmental modifier, affluence, may affect gene penetrance and disease expression in early-onset IBD. We suggest deprivation status represents a potentially important confounding variable that needs to be investigated in studies of the genetics of IBD and perhaps other common immune-mediated illnesses.

The authors would like to acknowledge the help of all patients and parents who participated in the study together with the specialist nurses, dieticians, and secretaries in each of the teaching hospitals as well as the pediatricians, practice nurses, and GPs throughout Scotland whose support for the study was invaluable. We thank Robin Rice in the University of Edinburgh data library for supplying the DepCat data and matching postcodes. We would also like to thank the staff at the Wellcome Trust Clinical Research Facility Edinburgh.

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EXPLOSION OF NURSING BOTTLES
Burnham, P. J. Pediatr 1957;50:371

How prophetic was this title? During the next 3 decades, beginning in the United States and Europe and subsequently across the globe, the use of formula feeding rather than breast-milk-feeding of infants did indeed explode. The health consequences of bottle-feeding described in this report are undoubtedly rare and increasingly so with the advent of disposable bottles and liners. However, the relative adverse health consequences to both the infant and mother ensuing from bottle-feeding compared with breast-feeding are altogether too well known. And the list increases annually. Among its virtues, breast-feeding, compared with bottle-feeding, reduces a wide range of infections (most notably gastrointestinal infections, pneumonia, and neonatal sepsis), atopy, obesity, and both child and maternal cancer.1

Although nearly universal at the turn of the 20th century in the United States, by the 1950s when this report was written, breastfeeding rates were declining, and they reached their nadir in the 1970s, with only approximately one quarter of mothers initiating it in the hospital and one twentieth continuing it at 6 months. Concern about the use of bottle-feeding compared with breast-feeding was not noted in this article; indeed, there was little awareness of the trend or of the consequences of this trend at that time. Fortunately, in recent years, the rate of breast-feeding has increased substantially, with approximately two thirds of mothers initiating breast-feeding and nearly one quarter sustaining breast-feeding at 6 months at the turn of the 21st century.

However, the good news ends here. In the United States, breastfeeding rates are lowest among those at greatest risk: the poor, the undereducated, and infants with a birth weight <2500 g.2,3 Recovery from the decreases in breast-feeding seen globally in the last half-century has been slow and has required an enormous investment of resources from multinational organizations, foundations, and ministries of health. Exclusive breast-feeding during the first 6 months of life is recognized as a key intervention for reducing infant and childhood deaths. However, to date, only 39% of infants in the 42 countries that account for 90% of childhood mortality worldwide are exclusively breastfed.4

Indeed, the explosion of nursing bottles was a national and global calamity from which we have still not recovered.

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10.1016/j.jpeds.2006.09.005

REFERENCES

Characteristics of Children with Vomiting after Minor Head Trauma: A Case-Control Study

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Objective  To study selected factors associated with vomiting after minor head trauma in children.

Study design  During a 1-year study, 1097 children with a minor head injury were consecutively discharged from the pediatric emergency department; 162 had associated vomiting. A case-control study was conducted, with each subject matched with 2 children of the same age group with a minor head injury who did not have associated vomiting. Final analysis was conducted in 148 case subjects and 296 matched control subjects.

Results  With univariate analysis, a personal history of recurrent headache (6.1% versus 2.4%), motion sickness (27% versus 11.8%), and recurrent vomiting (6.1% versus 0.7%) were significantly more common in the vomiting group, as was a family history of recurrent headache in parents (45.9% versus 27%) or motion sickness in parents (26.4% versus 15.2%) or siblings (14.2% versus 3.7%). The strongest predictors of vomiting were a personal history of recurrent vomiting (odds ratio, 5.90; 95% CI, 1.18-29.47), motion sickness (odds ratio, 2.34; 95% CI, 1.32-4.10), headache at the time of the injury (odds ratio, 4.37; 95% CI, 2.23-8.57), and a strong family history of the same recurrent problems (odds ratio, 1.66; 95% CI, 1.29-2.13).

Conclusions  Post-traumatic vomiting is significantly related to personal or familial predisposition to vomit rather than to the presence of intracranial lesions. (J Pediatr 2007;150:274-8)

Head trauma is a common reason for medical evaluation in an emergency department (ED). In Italy, we estimate that approximately 300,000 children each year seek medical care for traumatic brain injuries, which is currently the leading cause of death and disabilities in children aged 1 to 18 years in Italy and in other developed countries. However, most children with head injuries seen in the ED have minor blunt head trauma and recover without sequelae. Because of the lack of clear predictors of intracranial hemorrhage, there is great variation in medical practice patterns for the examination and treatment of these patients.

Vomiting is the most common presenting complaint of children after a head trauma, and many studies indicate that it may be a feature of possible intracranial injury. Controversy exists about the etiology of this symptom, and clear evidence that it is an independent predictor of intracranial lesion is still lacking. Two previous studies found an association between posttraumatic vomiting and a personal or family history of migraine or other recurrent symptoms associated with childhood migraine (ie, periodic syndrome). Moreover, a more recent meta-analysis on the predictive effect of various clinical signs and symptoms concluded that vomiting is not an independent factor for predicting intracranial lesion. Despite these findings, a history of post-traumatic vomiting is often a basis for obtaining a computed tomography in children admitted to the ED after head trauma.

This study evaluates the factors associated with vomiting after minor head injury to delineate its value in management decisions.

METHODS

Setting  The study was conducted in the pediatric emergency department (PED) of the Children’s Hospital of the University of Padova, a tertiary children’s hospital providing primary and secondary care for a metropolitan area of 350,000 people (45,000 younger than 15 years) and tertiary care for a regional and extraregional population. A total of
been reported. After discharge from the PED, all patients (depressed, or open fracture. A temporary loss of consciousness to home either directly mission between the attacks. Parents were also asked about remarkable physical examination, followed by complete remission between the attacks. Parents were also asked about the subsequent health state of their child to further exclude late complications related to trauma.

Statistical Analysis

The 1248 children younger than 15 years were consecutively admitted to the PED after a blunt head trauma of any severity. For each child, clinical data were prospectively recorded on a standardized data sheet and included mechanism of injury, loss of consciousness, vomiting, headache, seizures or other associated symptoms, level of consciousness at presentation, physical and neurological examination, and final diagnosis.

Of the 1248 patients, 1097 children with a minor head injury were discharged from the PED to home either directly or after observation (Figure). Children were included in this category when they were previously healthy and had normal results on their initial and subsequent examinations, including a normal mental status and no physical evidence of basilar, depressed, or open fracture. A temporary loss of consciousness (<1 minute) or immediate post-traumatic seizure may have been reported. After discharge from the PED, all patients received a follow-up visit or telephone interview within 10 days of their traumatic event to rule out subsequent complications caused by the trauma. In addition, we regularly checked data on the admissions to the ED and related wards, for as long as 1 month after the conclusion of the study. No patient reported symptoms of traumatic brain injury at the follow-up visit or telephone interview or had subsequent admissions for a brain injury related to the trauma.

The remaining 151 patients with more severe signs or symptoms were, after the first examination and stabilization in the PED, admitted to the inpatient units (Figure).

Case-Control Study Design

Of the 1248 patients initially enrolled, 170 reported vomiting before arrival or during the ED examination period. This included 8 children who were hospitalized and 162 who were discharged to home. These 162 patients (case subjects) were the focus of this study and were subsequently included in a case-control study, each matched with 2 children (control subjects) of the same age group (0-5 years, 6-10 years, >11 years) with minor head injuries who did not vomit and were discharged from the PED immediately before or after each case. A structured questionnaire was developed and used in a telephone interview with parents of both case subjects and control subjects. Of the 486 eligible patients, 14 could not be contacted by phone; for this reason, 14 triplets of children (42 patients) were excluded from the study, and the final analysis was conducted on 148 case subjects and 296 matched control subjects (Figure).

Telephone Interview Questionnaire

The questionnaire focused on a personal and family history (parents and sibling) of recurrent vomiting, motion sickness, recurrent headache, and on the child’s personal history of recurrent abdominal or limb pain. These diagnostic criteria were used: for recurrent vomiting, recurrent explosive bouts of vomiting, at least 3 attacks in 1 year, lasting hours to a few days, precipitated by stress, fatigue, or infection inter- spersed with normal periods; for motion sickness, ≥3 episodes of nausea, malaise, or vomiting during the period of motion (car, boat, air plain, train); for recurrent headache, at least 1 episode monthly during the last 6 months; for recurrent abdominal pain, recurrent stereotypic episodes of paroxysmal abdominal pain with nausea or vomiting, at least monthly for 3 consecutive months, a history of wellness between episodes, and no identifiable underlying disease; for recurrent limb pain, history of recurrent, self-limited short episodes of pain localized deeply in the arms or the legs, with at least 2 episodes in a 1-year period, severe enough to interfere with normal daily activities, associated with an unremarkable physical examination, followed by complete remission between the attacks. Parents were also asked about the subsequent health state of their child to further exclude late complications related to trauma.

The telephone interviews were carried out by the same interviewer (M.G.), approximately 1 to 6 months after the traumatic event. Informed consent was obtained from the parents.

Statistical Analysis

The χ² test (or Fisher exact test when appropriate) was used to test the significance of the univariate association for categorical variables. The Mann-Whitney test was used to compare the only continuous variable, age. P values < .05 were considered to be significant.

Multivariate analysis was used to determine the presence and strength of the association between post-traumatic vomiting and multiple clinical features: mechanism of injury; symptoms at the time of the injury; personal and family history of recurrent headache, recurrent vomiting, and motion sickness; total number of recurrent problems in the whole

Figure. Sample selection process.

22,000 children are admitted annually, in a setting with 4 beds for acute evaluation and 6 beds for children requiring treatment longer than 2 hours.

Study Population

During the 1-year study, 1248 children younger than 15 years were consecutively admitted to the PED after a blunt head trauma of any severity. For each child, clinical data were prospectively recorded on a standardized data sheet and included mechanism of injury, loss of consciousness, vomiting, headache, seizures or other associated symptoms, level of consciousness at presentation, physical and neurological examination, and final diagnosis.

Of the 1248 patients, 1097 children with a minor head injury were discharged from the PED to home either directly or after observation (Figure). Children were included in this category when they were previously healthy and had normal results on their initial and subsequent examinations, including a normal mental status and no physical evidence of basilar, depressed, or open fracture. A temporary loss of consciousness (<1 minute) or immediate post-traumatic seizure may have been reported. After discharge from the PED, all patients received a follow-up visit or telephone interview within 10 days of their traumatic event to rule out subsequent complications caused by the trauma. In addition, we regularly checked data on the admissions to the ED and related wards, for as long as 1 month after the conclusion of the study. No patient reported symptoms of traumatic brain injury at the follow-up visit or telephone interview or had subsequent admissions for a brain injury related to the trauma.

The remaining 151 patients with more severe signs or symptoms were, after the first examination and stabilization in the PED, admitted to the inpatient units (Figure).
Table I. Main features at admission of case and control subjects

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Case subjects (n = 148)</th>
<th>Control subjects (n = 296)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>76/72</td>
<td>178/1118</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>2.9 (1-6)</td>
<td>2.8 (0.9-5.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Mechanism of injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>121 (81.8%)</td>
<td>190 (64.2%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Impact (direct trauma)</td>
<td>12 (8.1%)</td>
<td>69 (23.3%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Road traffic</td>
<td>12 (8.1%)</td>
<td>33 (11.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Symptoms and signs at arrival†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>7 (4.7%)</td>
<td>6 (2.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Headache</td>
<td>31 (20.9%)</td>
<td>20 (6.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Seizure</td>
<td>4 (2.7%)</td>
<td>3 (1.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Others‡</td>
<td>22 (14.9%)</td>
<td>30 (10.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Skull fracture</td>
<td>21 (14.2%)</td>
<td>42 (14.2%)</td>
<td>NS</td>
</tr>
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</table>

Table II. Results of telephone interview questionnaire of case and control subjects

<table>
<thead>
<tr>
<th>Personal history</th>
<th>Case subjects (n = 148)</th>
<th>Control subjects (n = 296)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent vomiting</td>
<td>9 (6.1%)</td>
<td>2 (0.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Recurrent headache</td>
<td>9 (6.1%)</td>
<td>7 (2.4%)</td>
<td>.047</td>
</tr>
<tr>
<td>Motion sickness</td>
<td>40 (27.0%)</td>
<td>35 (11.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Recurrent limb pain</td>
<td>13 (8.8%)</td>
<td>24 (8.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (8.1%)</td>
<td>24 (8.1%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Family history

At least 1 parent with

| Recurrent vomiting | 1 (0.7%) | 1 (0.3%) | NS |
| Recurrent headache | 68 (45.9%) | 80 (27.0%) | <.001 |
| Motion sickness    | 39 (26.4%) | 45 (15.2%) | .005 |

At least 1 sibling with

| Recurrent vomiting | 3 (2.0%) | 1 (0.3%) | NS |
| Recurrent headache | 10 (6.8%) | 12 (4.1%) | NS |
| Motion sickness    | 21 (14.2%) | 11 (3.7%) | <.001 |

Notes:
- NS, Not significant.
- *Data presented as median (interquartile range).
- †Excluding vomiting.
- ‡Drowsiness, amnesia, dizziness.

A stepwise logistic regression analysis was performed with an entry criteria of $P < .3$. Variables that retained an association with post-traumatic vomiting with a $P$ value $< .05$ were considered to be independent predictors. The commercial statistical software package used was SAS, version 8.2.

RESULTS

Population Characteristics

Of the 1248 children admitted to our PED after a blunt head trauma during the study period, 8 had a final diagnosis of an intracranial injury: 4 cases of cerebral edema, 2 cases of epidural hematoma, 1 case of subdural hematoma, and 1 case of cerebral hemorrhage.

When comparing children with and without intracranial lesions, children with lesions were older (median age, 10.0 years versus 2.9 years), more likely to be victims of traffic accidents (75.0% versus 14.6%), and more commonly sustained a loss of consciousness (50.0% versus 2.7%), seizures (25.0% versus 1.1%), vomiting (25.0% versus 13.5%), Glasgow Coma Scale <13 (75% versus 0%), focal neurological signs (25% versus 0%), or signs of skull fracture (50.0% versus 14.3%). In the group of children without lesions, falls were the most common mechanism of injury (67%) and vomiting was the most common reported symptom (13.5%), although it was relatively less frequent than in children with lesions. Of the 170 children with vomiting, an intracranial lesion developed in only 2 (1%).

Predictors of Vomiting

A total of 444 structured telephone interviews were completed with either the child’s mother or father. Table I and II report the main features of case and control subjects at the time of admission and subsequent interview. The 2 groups were comparable for demographic and clinical characteristics at the time of the injury except for the higher prevalence of falls as the mechanism of trauma (81.8% versus 64.2%) and headache as an associated symptom (20.9% versus 6.8%) in the vomiting group (Table I). Analysis of the telephone interview questionnaire showed that a personal history of recurrent headache (6.1% versus 2.4%), motion sickness (27% versus 11.8%), and recurrent vomiting (6.1% versus 0.7%) were significantly more common in the vomiting group (Table II). Moreover, a family history of parental headache (45.9% versus 27.0%) and motion sickness in parents (26.4% versus 15.2%) and siblings (14.2% versus 3.7%) was reported more frequently in the vomiting group. A family history of sibling headache (6.8% versus 4.1%) tended to be more frequent in patients who vomited than in control subjects, but this difference was not statistically significant.

Table III outlines the predictors of vomiting at the multivariate analysis. The likelihood of vomiting was increased in children with a personal history of recurrent vomiting (odds ratio [OR], 5.90; 95% CI, 1.18-29.47), motion sickness (OR, 2.34; 95% CI, 1.32-4.10), headache at the time of the injury (OR, 4.37; 95% CI, 2.23-8.57), or when there was a strong family history of the same recurrent problems (OR, 1.66; 95% CI, 1.29-2.13).

DISCUSSION

The use of a case-control design provided us the opportunity to explore the possible association between vomiting in children who sustained a head injury and other clinical data. Few patients were found with intracranial injury (ICI) in this prospective study, because the patients selected for this study were at low risk. All children admitted to the ED after head trauma were included; in Italy, it is common to bring
Characteristics of Children with Vomiting after Minor Head Trauma: A Case-Control Study

Table III. Independent predictors of posttraumatic vomiting from multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal history of recurrent vomiting</td>
<td>5.90</td>
<td>1.18-29.47</td>
</tr>
<tr>
<td>Headache at the time of injury</td>
<td>4.37</td>
<td>2.23-8.57</td>
</tr>
<tr>
<td>Personal history of motion sickness</td>
<td>2.34</td>
<td>1.32-4.10</td>
</tr>
<tr>
<td>Number of recurrent problems in the family</td>
<td>1.66</td>
<td>1.29-2.13</td>
</tr>
<tr>
<td>whole family</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Children to the ED for trivial problems, including trivial trauma. Our results supplement previous observations that vomiting is a common symptom after head trauma in the pediatric age, occurring in approximately 1 of every 6 patients and that it is unrelated to the severity of the head injury.14,15,23,24 This symptom was more common in children with intracranial lesions, but the contrary was not true; most children who vomited (99%) had no demonstrable anatomic abnormalities.

Our goal was to study the significance of vomiting that was not associated with anatomical lesions. Our case-control analysis focused on children with minor head trauma. We identified an association of vomiting after mild head injury with a family or personal history of recurrent headache and other periodic symptoms. A history of recurrent vomiting, motion sickness, or both in the affected child resulted in strong individual predictors of vomiting after trauma, both with the univariate and multivariate analyses. In children with vomiting, a striking predominance of recurrent headache in parents and of motion sickness in parents and siblings were also noted in the univariate analysis. At the multivariate analysis, the strongest familiar predictors was the “intensity” of periodic symptoms in the family: when many family members had ≥1 periodic symptoms, the likelihood of vomiting was higher.

Our results reinforce the conclusions of 2 previous studies that suggested that familiar and personal intrinsic factors can predispose children to vomit after a head trauma.13,14 The first study was conducted in a small group of children admitted to an observation unit of a PED after a minor head trauma. The second was a larger, but unselected, group of children seen in a PED for head injury of different severity. Both these studies identified a personal or family history of motion sickness or recurrent vomiting or migraine headache as risk factors for vomiting after head trauma.

The precise mechanism of post-traumatic vomiting is unknown, but it has been hypothesized that forces applied to the head as a consequence of trauma can cause shearing and compressive strain within the brain stem, causing stimulation of the vomiting center in the reticular formation of the lateral medulla and the adjacent chemoreceptor trigger zone of the area postrema.10 The brain stem auditory evoked potentials are markedly different in children with mild brain injury with vomiting compared with those in children with mild brain injury who do not vomit.25 It is possible that all individuals have the potential to sustain vomiting after a head trauma, and the mechanism is set into motion when a physiologic threshold is exceeded. Cyclic vomiting syndrome and motion sickness are examples of abnormal activation of the vomiting center; the threshold of the vomiting center might be lower in these affected patients. In children with cyclic vomiting, trauma has been reported as a precipitating factor of attacks, with stress and intercurrent infections.26

Similarities between recurrent vomiting and other recurrent symptoms, such as motion sickness and migraine headache, have been described, on the basis of parallel temporal patterns, associated symptoms, positive family history of migraine, and the strong association of these symptoms or the progression from 1 to another within the same individuals.27,28 We found a strong association between subsequent vomiting and headache at the time of injury. Headache is the second most common symptom after a minor head injury, and, as with vomiting, it is not an independent predictor of ICI.15 In adults, trauma may aggravate headache in those with a pre-existing history of migraine or may facilitate de novo onset of migraine after minor trauma.29,30 Our study does not support a personal history of recurrent headache as an independent predictor of post-traumatic vomiting, but recurrent headaches are an uncommon clinical entity in young children31 and long-term follow-up was not planned to determine whether our patients developed headaches in subsequent years. However, a family history of recurrent headaches in parents or siblings was more common in the vomiting group, and, with multivariate analysis, the prediction of vomiting was more powerful when many members of the family were affected by headache or other recurrent problems.

Our study did also observe an increased likelihood of vomiting after falls from heights, although the results did not reach significance. This supports speculation of direct stimulus on the area postrema being contributory to post-traumatic vomiting.10

There are some limitations of our study. First, few children included in the case-control study (6% of case subjects and 4% control subjects; data not shown) underwent brain computed tomography because our policy is to prefer observation for most minor head injured patients.3,4 Follow-up supports that no clinically significant lesions were missed.2,3-32 Second, the telephone interviewer was not blinded to the patient type, but the structured questionnaire may have minimized observer bias. Third, most of the diagnostic criteria we used for childhood periodic symptoms at the time of the study have only recently been better defined.33 However, identical criteria were used for both the study groups, minimizing a potential impact on our study. In addition in children who did not vomit, we found an incidence of recurrent problems quite similar to the general pediatric population.19 Fourth, we did not distinguish between single or repetitive vomiting. In a recent paper, the absence of repetitive vomiting has been reported as a sensitive criteria in excluding an intracranial lesion, but the specificity of this symptom in predicting an intracranial lesion was low, especially in children who are younger than 3 years.34
In conclusion, our results suggest that post-traumatic vomiting is not an independent predictor of intracranial injury and that this symptom is more related to the predisposition of the host to vomiting than to the presence of lesions. In patients with minor head trauma, vomiting alone is not a symptom of relevance in decisions about further investigations. Additional studies are needed to better understand the biological factors contributing to post-traumatic vomiting.

REFERENCES

Temporal Trends in the Treatment of Pediatric Type 1 Diabetes and Impact on Acute Outcomes

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Objective To evaluate temporal trends in pediatric type 1 diabetes (T1DM) management and resultant effects on outcomes.

Study design Two pediatric T1DM cohorts were followed prospectively for 2 years and compared; Cohort 1 (N = 299) was enrolled in 1997 and Cohort 2 (N = 152) was enrolled in 2002. In both cohorts, eligible participants were identified and sequentially approached at regularly scheduled clinic visits until the target number of participants was reached. Main outcome measures were hemoglobin A1c (A1c), body mass index Z score (Z-BMI), and incidence rate (IR; per 100 patient-years) of hypoglycemia, hospitalizations, and emergency room (ER) visits.

Results At baseline, Cohort 2 monitored blood glucose more frequently than Cohort 1 (≥4 times/day: 72% vs 39%, P < .001) and was prescribed more intensive therapy than Cohort 1 (≥3 injections/day or pump: 85% vs 68%, P < .001). A1c was lower in Cohort 2 than Cohort 1 at baseline (8.4% vs 8.7%, P = .03) and study’s end (8.7% vs 9.0%, P = .04). The cohorts did not differ in Z-BMI (0.83 vs 0.79, P = .57) or IR of hospitalizations (11.2 vs 12.9, P = .38). Cohort 2 had lower IR of total severe hypoglycemic events (29.4 vs 55.4, P < .001) and ER visits (22.0 vs 29.3, P = .02).

Conclusions T1DM management intensified during the 5 years between cohorts and was accompanied by improved A1c and stable Z-BMI. Along with improved control, IR of severe hypoglycemia and ER visits decreased by almost 50% and 25%, respectively. (J Pediatr 2007;150:279-85)

The Diabetes Control and Complications Trial (DCCT) demonstrated that optimal glycemic control in type 1 diabetes mellitus (T1DM) delays the onset and slows the progression of microvascular complications.1 Current recommendations therefore mandate that youth with T1DM should be treated with intensive therapy to normalize glycemic control as early as possible.2 Intensive therapy involves multiple daily injections (MDI) of insulin or insulin pump therapy (continuous subcutaneous insulin infusion, CSII), as well as other essential components of diabetes care, such as self-monitoring of blood glucose (SMBG).3-5

It has long been acknowledged that the treatment of T1DM in children and adolescents is difficult. The combination of severe insulin deficiency and the physical and psychosocial changes that accompany normal growth and development present unique challenges to pediatric healthcare professionals.6-9 In the DCCT, the 195 adolescents, 13 to 17 years of age at entry, had significantly higher A1c values compared with their adult counterparts, and the investigators anticipated that worldwide translation of treatment recommendations for youth would be especially challenging.10 Recent data, however, suggest that clinicians have gained success in implementing DCCT standards in pediatric practice. Advances in technology, such as improved methods of SMBG, modern insulin infusion pumps, and new short- and long-acting insulin analogs, as well as innovative behavioral and educational approaches, have contributed to this success.11-14

Maintenance of near-euglycemia, however, is not the only goal of intensive diabetes management. The prevention of excessive weight gain, previously associated with intensive therapy,2-5 has contributed to this success.11-14
sification of diabetes therapy, \textsuperscript{15-17} is desirable. In addition, acute diabetes-related complications (e.g., episodes of severe hypoglycemia, hospitalizations, and emergency room [ER] visits) should be minimized. Although early evidence from the DCCT showed that intensively treated adolescents had a greater risk of severe hypoglycemia, more recent data suggest that hypoglycemia does not inevitably accompany improved metabolic control. \textsuperscript{18-20}

Data regarding the impact of intensification of therapy on the occurrence of hospitalizations and ER utilization are limited. The purpose of this study was to examine whether intensive management and outcomes of diabetes care, as reflected by glycemic control, body mass index Z score (Z-BMI), and acute complication rates have changed in the pediatric population in recent years.

**METHODS**

**Participants**

Two cohorts of youth with T1DM were followed longitudinally for 2 years and acute adverse event rates of the two groups were compared. Eligibility criteria for both cohorts included: age 8 to 16 years, duration of T1DM >6 months, stable living environment, no major psychiatric problems, and intention for routine follow-up care at the clinic. All youth had received insulin since diagnosis and had insulin requirements \(\geq 0.5\) U/kg/day at enrollment. The Committee on Human Studies of the Joslin Diabetes Center approved the study protocols.

Enrollment of Cohort 1 occurred between 1997 and 1998 (4 years post-DCCT). Enrollment of Cohort 2 occurred between 2002 and 2003 (9 years post-DCCT). The two time intervals allow for an examination of gradual trends in clinical care.

For Cohort 1, 413 eligible participants were identified and sequentially approached until the target number of 299 was reached. During enrollment, 35 families declined participation. Nonparticipants had a mean (SD) age of 13.0 (2.7) years, mean diabetes duration of 7.0 (3.7) years, and mean A1c of 9.0 (1.3)\%.

Nonparticipants were slightly older and had slightly longer diabetes duration than participants, but they did not differ from participants with respect to glycemic control.

For Cohort 2, 462 eligible participants were identified and sequentially approached until the target number of 154 was reached. Two patients were subsequently removed from data analyses because of the occurrence of significant psychiatric problems in one patient and a revision of diagnosis from T1DM to maturity-onset diabetes of the young in the other patient. During enrollment, 20 families declined participation. Nonparticipants had a mean age of 13.2 (1.8) years, mean diabetes duration of 6.5 (3.2) years, and mean A1c of 8.5 (1.6)\%.

The target number of participants in each cohort was in part determined by the availability of research staff to follow patients prospectively over a 2-year period. Each research assistant (RA) followed between 70 and 75 patients. Fewer RAs were available in 2002, resulting in Cohort 2 being half the size of Cohort 1. More than 90\% of patients in both cohorts were first seen, and subsequently followed at our center, within 1.5 years of diagnosis and thus represent a community-based sample. Thirty-five patients were enrolled in both Cohort 1 and Cohort 2.

**Procedures**

Eligible families were enrolled at their regularly scheduled visits. RAs obtained written, informed consent from the parent and assent from the child.

During the 2 years of follow-up, families were encouraged by their medical providers to visit the clinic every 3 months. At each clinic visit, an RA conducted a 5- to 10-minute structured, joint child-parent interview to gather data pertaining to family demographics, diabetes management, and frequency and severity of recent hypoglycemia, hospitalizations, and ER utilization. The RA also extracted data, based on the interval history and physical examination performed by the medical provider, from the patient’s medical record. These data included measurements of height, weight, and blood pressure, as well as staging of sexual development by the method of Tanner. The inter-rater reliability of data extraction by chart review exhibited >94\% concordance in both studies. Medical providers (not RAs) formulated and implemented all management plans.

**Measures of Outcomes of Care**

We assessed outcomes of diabetes care using four separate measures: glycemic control (measured as A1c), Z-BMI, frequency of hypoglycemia, and hospitalizations/ER utilization. A1c was measured at each visit using high-performance liquid chromatography standardized to the DCCT assay (reference range: 4%-6%; Tosoh Medics, Inc., Foster City, Calif.). BMI was calculated from weight and height at each visit. Because normative values of BMI for children vary by sex and age, we calculated an age- and sex-adjusted BMI (Z-BMI), which represents the number of SDs above or below the mean.

Severe hypoglycemia was defined, as in the DCCT, as any hypoglycemic event in which the patient required assistance from another person to recover. \textsuperscript{21} These events were divided into two mutually exclusive categories: (1) events requiring the help of another person for oral treatment; and (2) events, such as coma or seizure, requiring emergency medical response or treatment with glucagon and/or intravenous dextrose. The frequency of these events was ascertained by patient/family interviews, chart reviews, and interval questionnaires.

ER visits and hospitalizations included assessments and admissions for diabetic ketoacidosis, severe hypoglycemia, other diabetes-related problems (e.g., major treatment adjustments), and problems not directly related to, but complicated by, diabetes. As with hypoglycemic events, the frequency of
these events was ascertained by patient/family interviews, chart reviews, and interval questionnaires.

Statistical Analysis

Statistical analysis of the data was performed with SAS, Version 8.2, for Windows (SAS Institute, Cary, NC). Means (SD) are presented unless otherwise indicated. Analyses included t tests, $\chi^2$ tests, and incidence rate (IR) calculations and comparisons. The numbers of months for which each patient contributed data were summed, and clinical outcomes were calculated as the number of events per 100 patient-years. An integrated A1c value was calculated for each patient by averaging all A1c values obtained during follow-up. Integrated A1c and outcome data were compared with previously published findings from the DCCT. An $\alpha$ level of .05 was used to determine statistical significance.

RESULTS

Patient Characteristics

The Table displays baseline characteristics for each cohort. The mean number of clinic visits per patient per year was 3.8 (1.7) in Cohort 1 and 4.1 (0.8) in Cohort 2 ($P = .03$).

<table>
<thead>
<tr>
<th>Table. Baseline patient characteristics</th>
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<tbody>
<tr>
<td>N = 299</td>
</tr>
<tr>
<td>Age at entry (y)</td>
</tr>
<tr>
<td>Sex (% male)</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
</tr>
<tr>
<td>Developmental stage (%)</td>
</tr>
<tr>
<td>Prepubertal (Tanner stage I)</td>
</tr>
<tr>
<td>Pubertal (Tanner stage II-IV)</td>
</tr>
<tr>
<td>Postpubertal (Tanner stage V)</td>
</tr>
<tr>
<td>Socioeconomic status (%)*</td>
</tr>
<tr>
<td>Major professional</td>
</tr>
<tr>
<td>Minor professional/skilled worker</td>
</tr>
<tr>
<td>Semi-skilled worker</td>
</tr>
<tr>
<td>Unskilled/employed/retired/student</td>
</tr>
<tr>
<td>Family structure (% two-parent family)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Z-BMI</td>
</tr>
<tr>
<td>Duration of T1DM (y)</td>
</tr>
<tr>
<td>Insulin analog usage (%)</td>
</tr>
<tr>
<td>A1c (%)</td>
</tr>
<tr>
<td>A1c ≤8% (% of patients)</td>
</tr>
</tbody>
</table>

Data reported as mean (SD) or percent.
*Major professional = physician, lawyer, etc.; minor professional = nurse, teacher, etc.; skilled worker = administrative personnel, etc.; semi-skilled worker = data entry personnel, etc.; unskilled worker = truck driver, etc.

At study entry, only 39% of patients in Cohort 1 were performing SMBG ≥4 times/day, compared with 72% of Cohort 2 ($\chi^2 = 48.0, df = 3, P < .0001$) (Figure 1A). Cohort 2 had a significantly higher mean frequency of SMBG than Cohort 1 at both baseline and after 2 years of follow-up (3.8 [0.9] vs 3.1 [1.0], $P < .0001$, Figure 1B). At study’s end, 94% of Cohort 2 were prescribed intensive therapy (59% MDI, 35% CSII), compared with 75% of Cohort 1 (73% MDI, 2% CSII) ($\chi^2 = 90.2, df = 3, P < .0001$, Figure 1B). At study’s end, 94% of Cohort 2 were prescribed intensive therapy (59% MDI, 35% CSII), compared with 75% of Cohort 1 (73% MDI, 2% CSII) ($\chi^2 = 132.5, df = 3, P < .0001$). Both cohorts transitioned to intensive therapy during follow-up at similar rates, with 14% of Cohort 1 and 12% of Cohort 2 changing to a more intense mode of therapy (i.e., ≤2 injections/day to MDI or CSII) ($\chi^2 = 2.1, df = 2, P = .34$).

The type of insulin used at study entry was also examined. In Cohort 1, 133 patients (45%) used a rapid-acting
insulin analog as part of their injection regimen. In Cohort 2, 125 patients (89 injections, 36 CSII; 82%) used a rapid-acting analog as part of their regimen at baseline.

**Glycemic Control**

After 2 years of follow-up, the mean A1c was 9.0 (1.5)% in Cohort 1 and 8.7 (1.4)% in Cohort 2 \((P = .04)\). Thirty-five percent of Cohort 2 had an A1c ≤ 8.0% at study’s end, compared with 25% of Cohort 1 \((P = .02)\). There were no significant differences between Cohorts 1 and 2 with regard to increase in A1c \((0.3 \pm 1.3)% vs 0.3 \pm 1.1)%, \(P = 1.0)\) or proportion of youth maintaining/improving their level of glycemic control \((45% vs 40%, P = .39)\) over the course of the study. The integrated mean A1c values for Cohorts 1 and 2 over the 2 years of follow-up were 8.9 (1.2)% and 8.6 (1.3)%, respectively \((P = .03)\).

**Z-BMI**

After 2 years of follow-up, mean Z-BMI was 0.79 (0.72) in Cohort 1, an increase of 0.08 (0.43) from baseline, and 0.83 (0.69) in Cohort 2, an increase of 0.06 (0.42) from baseline. Neither follow-up \(Z\)-BMI \((P = .57)\) nor change in \(Z\)-BMI \((P = .64)\) differed significantly between cohorts.

**Frequency of Severe Hypoglycemia**

The IR of severe hypoglycemic events requiring the help of another person for oral treatment was 47.1 per 100 patient-years in Cohort 1 and 18.5 per 100 patient-years in Cohort 2 \((P < .001)\). The IR of severe hypoglycemic events requiring emergency medical response or treatment with glucagon and/or intravenous dextrose was 8.4 per 100 patient-years in Cohort 1 and 10.9 per 100 patient-years in Cohort 2 \((P = .24)\). The IR of total severe hypoglycemic events was 55.4 per 100 patient-years in Cohort 1 and 29.4 per 100 patient-years in Cohort 2 \((P < .001)\). Hence, the annual IR for any severe hypoglycemic event in Cohort 2 was almost half that of Cohort 1 (Figure 2A).

**Frequency of Hospitalizations and ER Utilization**

The IR of hospitalizations was 12.9 per 100 patient-years in Cohort 1 and 11.2 per 100 patient-years in Cohort 2 \((P = .38)\). The IR of ER visits was 29.3 per 100 patient-years in Cohort 1 and 22.0 per 100 patient-years in Cohort 2 \((P = .02)\). Thus, the IR of ER visits was 24% lower in Cohort 2 than Cohort 1.

**Comparison with Adolescent Cohort of the DCCT**

The integrated mean A1c values of the conventionally \((N = 103)\) and intensively \((N = 92)\) treated adolescents in the DCCT were 9.8 (1.2)% and 8.1 (1.2)% respectively. Both Cohorts 1 and 2 had significantly lower A1c values compared with the conventionally treated adolescent DCCT cohort \((P < .001)\) but significantly higher A1c values compared to the intensively treated adolescent DCCT cohort \((P < .001)\). The IR of total severe hypoglycemia for the conventionally and intensively treated adolescent DCCT groups were 27.8 per 100 patient-years and 85.7 per 100 patient-years, respectively. Cohorts 1 and 2 had significantly lower IR of total severe hypoglycemia than the intensively treated adolescent DCCT cohort \((P < .001)\), whereas no difference was observed between Cohort 2 and the conventionally treated adolescent DCCT cohort \((P = .99)\) (Figure 2A).

**DISCUSSION**

By comparing two pediatric cohorts with T1DM followed at the same center and separated in time by 5 years, we...
found that intensive insulin therapy and frequency of SMBG increased significantly in the post-DCCT era. A significant improvement in glycemic control coincided with these changes in treatment practices. Although the results are somewhat encouraging, the integrated mean A1c for the cohort enrolled in 2002 remained 0.5% higher than the intensively treated adolescent group in the DCCT.

Our A1c results are consistent with previous studies, including the large multicenter Hvidore study conducted in 17 European countries between 1995 and 1998, which documented the difficulty in improving individual clinic hemoglobin A1c values. Only 40% of our 2002 cohort maintained or improved their level of glycemic control over the course of the study. This finding suggests that significant opportunities for improving blood glucose levels in youth remain. Unfortunately, although we currently have more tools (e.g., insulin analogs) than did the DCCT investigators, available resources, such as personnel required to perform monthly visits and weekly phone calls, remain fewer.

Although less frequent than the DCCT, the mean number of clinic visits per year in both cohorts was in keeping with current practice recommendations. However, patients in Cohort 2 had significantly more visits per year on average than patients in Cohort 1 (4.1 vs 3.8). Previous reports have shown that patients with more frequent clinic visits demonstrate improved glycemic control. It is unclear, however, if increased exposure to care is the true mediator of improved glycemic control, or if increased exposure to care is better viewed as a marker of implementation of intensive diabetes management, which is the true mediator of improved glycemic outcomes.

Perhaps more important than the number of clinic visits in improving glycemic control, however, was the increased frequency of SMBG performed by Cohort 2. Previous studies have shown that more frequent SMBG is associated with lower HbA1c levels.

Both cohorts experienced equivalent deterioration in glycemic control during the 2 years of follow-up. Although disappointing, this finding was not entirely unexpected. At study entry, the mean age of participants in Cohorts 1 and 2 were 11.9 and 12.9 years, respectively. Numerous studies have shown that the transition to adolescence for children with T1DM is commonly associated with decreased adherence to diabetes management tasks leading to worse metabolic control. Clearly, the design, implementation, and evaluation of affordable, efficacious, and transferrable interventions aimed at improving glycemic control among adolescents with T1DM are still needed. The introduction of continuous glucose monitoring technologies into clinical practice could prove particularly useful in this patient population.

We did not find a significant difference in mean Z-BMI between the two cohorts at baseline or after 2 years of follow-up. These results are encouraging because intensive insulin therapy has previously been associated with significant weight gain. Although concerns about weight gain should not deter intensive insulin therapy, forms of therapy that improve glycemic control without causing weight gain are desirable.

Hypoglycemia is the most frequent acute complication of T1DM. We observed a substantial decrease in the annual incidence of total severe hypoglycemic events between our two cohorts. Interestingly, this decrease occurred despite the fact that the 2002 cohort had diabetes of longer duration, a known risk factor for hypoglycemia. We speculate that the cause of this declining incidence was multifactorial and likely a result of more physiologic insulin replacement with MDI, CSII, and analog use. Previous reports evaluating pump therapy in children have shown significant reduction in risk of severe hypoglycemia despite improvements in A1c. Furthermore, other reports have suggested that severe hypoglycemia may be less common with insulin analog therapy. Although the relationship has not been as strong in pediatric studies, the fact that nearly twice as many patients were using insulin analogs as part of their treatment regimens in 2002 than in 1997 likely contributed to the decreased incidence of severe hypoglycemia in this cohort.

We also observed that the 2002 cohort experienced nearly 25% fewer ER visits than the 1997 cohort. Unfortunately, a similar trend was not observed in the rate of hospitalizations. When considering the direct and indirect costs of diabetes care in the US, it is well established that inpatient hospital care is a major cost driver, amounting to 30% of the total costs. Therefore, the fact that we did not observe a decrease in the rate of hospitalizations for Cohort 2 at first glance suggests that intensification of therapy would not result in cost-savings for this population. One limitation of this study, however, is that duration of hospital stay was not evaluated. Recent studies involving pediatric patients have suggested that the mean length of hospital stay for admissions unrelated to diabetic ketoacidosis, as well as those related to diabetic ketoacidosis, is decreasing. If the same holds true for our patients, cost-savings may have been realized. The decrease in IR of ER visits likely translated into fewer missed school/work days for patients and family members. In addition, the better glycemic control that we observed would translate into cost-savings associated with the prevention or postponement of long-term complications and decreased inpatient hospital care in the future. Of course, these savings would be partially offset by increased outpatient charges and the increased cost of supplies needed for intensive diabetes management (e.g., insulin pump supplies). The lack of cost data is a weakness of this study; future studies addressing this issue are needed.

A few additional cautions must be made in discussing the results of this study. Although the prospective nature of data collection was designed to minimize underreporting of adverse events, it is possible that underreporting by parents and physicians resulted in underestimations of IR in all categories. However, such underreporting would likely have occurred to the same extent in both cohorts, so that...
the differences observed between the cohorts would remain unchanged at a minimum. Next, these studies were conducted at a single tertiary care facility. Similar studies conducted at other centers involving different pediatric populations are needed. Nonetheless, these data are informative in showing that as we continue to pursue the goal of near-normal metabolic control in youth with diabetes, an increase in acute adverse events is not a necessary outcome.

We acknowledge contributions of the Pediatric Team at the Joslin Diabetes Center: Joan Mansfield, MD; Alyne Ricker, MD; Cindy Pasqualetto, RN, BSN, CDE; Kathleen Walsh, RN, CDE; Deborah Holtorf, MPH, MSN, PNP; Kelly Reilly, BSN, RN; Kerry Milaszewski, BSN, RN, CDE; Louise Crescenzi; and the pediatric endocrine fellows. We also acknowledge the research assistance of Samantha Huestis and Allison Maher.

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Loffler’s pneumonia associated with hypogammaglobulinemia
Aziza C, Lapin JH. J Pediatr 1957;50:296-303

Aziza and Lapin describe an infant with recurrent pneumonia, which began when the patient was 7.5 months old. The gammaglobulin level was 5.43% (reference range for age, 8.8% ± 1.2%) with the Tiselius method (electrophoresis assay). Specific antibodies were anti-B 1:64, but the Schick test for measuring neutralizing antibody titer to diphtheria was not performed because the patient was not fully immunized. Intramuscular gammaglobulin (5-15mL) was administered every 2 weeks (1.7-5 g monthly). The gamma globulin level rose to 6.22% when the patient was 2.5 years old, and the level was 10.4% when the patient was 3 years old. The authors concluded that the child had, per “... the recent review by Good and Zak (1956)... transient hypogammaglobulinemia of infancy.” What amazingly astute physicians! In the intervening years, the advances in understanding, examining, and treating immunodeficiencies of what Robert A. Good called in his report “Experiments of Nature” have exploded. Quantitative levels of immunoglobulin (Ig) G (and 4 IgG subclasses), IgA (and 2 IgA subclasses), IgM, IgE, and IgD have been identified. Immunological responses of T cell and B cell responses to protein, polysaccharide, and lipid antigens is appreciated. Identification and function of T cells, T cell subpopulations, B cells, B cell subpopulations, and natural killer studies is routine. The authors measured properdin of the complement pathway; 3 complement pathways have since been described (classical, alternate, and mannose binding lectin). Molecules of the innate immune system have been described and are routinely examined, so-called pathogen associated molecular pattern molecules. The World Health Organization–International Union of Immunologic Societies has categorized primary immunodeficiency diseases into 8 categories.1 Twenty separate B cell immunodeficiency disorders have been described, with the genetic defect identified in many. Transient hypogammaglobulinemia of infancy is still a recognized primary B cell immunodeficiency.

The treatment of hypogammaglobulinemia has also evolved. Intramuscular gammaglobulin was the standard treatment until intravenous gamma globulin was licensed for use in the early 1980s.2 This allowed for the first time an increase in the dosage of gamma globulin used to control the infections. The current recommended dosage is 300 to 600 mg/kg/month, which is approximately what I estimate that this patient received at the high end. It is fascinating, however, that investigators led by Melvin Berger began administrating intramuscular gammaglobulin subcutaneously. In 2006, there is a licensed subcutaneous gammaglobulin preparation (Vivaglobulin) available for the treatment of patients with B-cell immunodeficiencies.
Objective  To compare quantitative ultrasound (QUS) measurements in adolescents with anorexia nervosa (AN) with that in healthy control subjects and to determine the utility of QUS as a tool to evaluate skeletal status in these patients.

Study design  Female adolescents with AN (n = 41) and healthy control subjects (n = 105) were recruited. Speed of sound (SOS) was measured at the radius and tibia. Participants with AN also had hip and spinal areal bone mineral density measurements by dual-energy x-ray absorptiometry (DXA); bone mineral apparent density (BMAD) was calculated.

Results  Subjects with AN had higher mean radial SOS (4044 ± 99 m/s) than did control subjects (3947 ± 116 m/s; P < .0001). These results were replicated at the tibia (AN, 3918 ± 55 m/s vs control subjects, 3827 ± 106 m/s; P < .0001). Neither DXA measures of areal bone mineral density nor BMAD were correlated with SOS. Weight and body mass index were negative predictors of tibial but not radial SOS. AN status remained a significant predictor of SOS after controlling for body mass index, age, and race.

Conclusions  Subjects with AN had higher mean tibial and radial SOS than did control subjects. QUS variables did not correlate with DXA measures, calculated BMAD, or anthropometric variables. QUS measurements of SOS do not appear to be appropriate for bone density screening in patients with AN. (J Pediatr 2007;150:286-90)

Bone loss is a well-established complication of anorexia nervosa (AN).1-4 Given that adolescence is the crucial time for establishment of peak bone mass, this loss is clinically significant and may place these young women at higher risk for fracture.5 Dual-energy x-ray absorptiometry (DXA) has been the most widely used tool for assessment of bone mass in this patient population. DXA measures bone in two dimensions and allows for calculation of areal bone mineral density (aBMD, g/cm²). The greatest challenge in the interpretation of aBMD in the adolescent age group is that it is highly influenced by bone and body size.6-8 Additionally, although DXA measures are highly correlated with bone strength, strength depends on skeletal properties such as geometry, elasticity, and internal architecture, which are not reflected directly in DXA measurements.9,10

Quantitative ultrasound (QUS) is an attractive alternative method for the evaluation of skeletal status. QUS assesses peripheral bone by measuring the speed of sound (SOS) of an ultrasound wave as it is propagated along the bone. The speed of propagation along bone is influenced by bone density, elasticity modulus, and the microarchitecture of bone.7 Studies have shown that QUS can predict fracture risk in older women, independent of aBMD, and monitor skeletal responses to exercise with good sensitivity.11-14 The use of QUS is appealing because of its portability, speed, low cost, and lack of ionizing radiation. QUS could also be used as a screening tool for low bone mass or provide information beyond that obtained by current bone density measurement techniques. However, to our knowledge, this modality has not been investigated in young women with AN at peripheral sites other than the calcaneus.15-17

The aim of the current study was to compare QUS measurements in patients with AN with that in healthy control subjects and to determine the utility of QUS as a tool to evaluate skeletal status in this patient population.
METHODS

Subjects

Female adolescents and young women ages 13 to 26 years with a diagnosis of AN (n = 41) were recruited from the Eating Disorders Program at an adolescent medicine clinic for participation in a randomized, controlled trial. Entry criteria included having a diagnosis of AN by Diagnostic and Statistical Manual IV (DSM-IV) criteria and amenorrhea for at least 3 months. All patients with AN were at least 2 years postmenarche. Patients were excluded who had a chronic disease in addition to the eating disorder or if they were receiving medications known to have skeletal effects.

Healthy female adolescents (n = 105) within the same age range were recruited as control subjects from the same adolescent clinic. All control subjects had a body mass index (BMI, kg/m²) between the 5th and 95th percentiles for age, based on Centers for Disease Control growth charts published in 2000. Subjects were excluded if they were taking medications known to affect bone health, such as contraceptive hormones (oral contraceptive pills, depot medroxyprogesterone), glucocorticoids, or anticonvulsants during the 3 months before study enrollment. We also excluded potential participants who were premenarchal, pregnant, lactating, or had other medical conditions known to affect aBMD.

All study procedures were reviewed and approved by the local institutional review board. Informed consent was obtained from all subjects or their parents. Minor subjects provided assent for participation.

Data Collection

All participants completed a semistructured interview for demographic information and health history, including information about medication use, menstrual history, smoking, and family history of osteoporosis. Height (cm) was measured with the use of a wall-mounted stadiometer. Weight (kg) was measured after voiding, with subjects wearing a hospital gown. The same stadiometer and calibrated scale were used for all measurements. BMI was calculated, and BMI percentile was determined with the use of standard percentile tables.

Bone Density Evaluation

The SOS through bone is a ratio of the distance traveled to transit time and is expressed as meters per second. The SOS measurement records the shortest time between pulse transmission and the first reception of a signal. The axial technique was used, with one transducer both transmitting and receiving the signal. SOS was measured on the nondominant limb at the distal one third of the radius and the mid-shaft of the tibia, using the Omnisense 7000P QUS (Sunlight Medical Ltd, Tel-Aviv, Israel). The dominant limb was determined by asking patients to report their hand preference. All measurements were performed by two highly trained researchers. The percent coefficient of variation at the tibia was 0.55% between technicians and 0.82% at the radius. No inter-rater differences were noted at either site.

AN subjects also had aBMD (g/cm²) measured by DXA, using the QDR-4500 with Delphi upgrade (Hologic, Inc, Waltham, Mass). Measurements were performed at the left total proximal hip and lumbar spine (L1-L4). Hip, spine, and total body measurements were compared with age- and sex-matched control subjects. For participants younger than 20 years of age, pediatric normative data were used.

To correct for the influence of body size on the measured areal BMD, we performed a volumetric estimation of BMD by using DXA data. Using the method published by Carter et al, we calculated bone mineral apparent density (BMAD, g/cm³), using the equation BMAD = BMC/Áp, where Ap is the projected area (cm²) of interest.

Statistical Analysis

Student t tests were used to compare anthropometric characteristics, age, and SOS between groups. Differences in categoric demographic variables (race, family history of osteoporosis) were evaluated through the use of χ² tests. Pearson correlation analyses were used to evaluate relations among the DXA variables and SOS. Multiple regression was used to determine predictors of SOS while controlling for potential confounding variables. The analysis was performed separately for the radius and tibia. Statistical analyses were performed with SAS (SAS Institute, Inc, Cary, NC). The level of significance was set at a value of P < .05.

RESULTS

We studied 41 adolescents and young women with AN and 105 healthy control subjects (Table I). Mean age of all participants was 17.5 ± 2.8 years; subjects with AN were slightly older than the control group (P = .01). As expected, based on the underlying disease of interest, the two groups differed significantly with respect to weight, height, BMI, and

| Table I. Anthropometric measures and demographic characteristics of healthy female adolescents and adolescents with anorexia nervosa |
|-----------------|-----------------|-----------------|
|                  | Control subjects (n = 105) | AN subjects (n = 41) | P value |
| Age (y)          | 17.1 ± 2.7       | 18.4 ± 2.9       | .01     |
| Height (cm)      | 161.3 ± 6.3      | 164.9 ± 7.0      | .01     |
| Weight (kg)      | 59.2 ± 9.3       | 49.0 ± 6.1       | <.0001  |
| BMI (kg/m²)      | 22.8 ± 3.3       | 17.9 ± 1.7       | <.0001  |
| Duration of AN (mo) | 24.9 ± 29.9      | 12.3 ± 13.6      |         |
| Positive family history of osteoporosis (%) | 14.9 | 34.3 | .01 |

AN, Anorexia nervosa; BMI, body mass index. Data are presented as mean ± SD.
Table II. Demographic characteristics and anthropometric measures of white healthy female adolescents and adolescents with anorexia nervosa

<table>
<thead>
<tr>
<th></th>
<th>Control subjects (n = 20)</th>
<th>AN subjects (n = 40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>17.4 ± 3.1</td>
<td>18.4 ± 2.9</td>
<td>.22</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.2 ± 6.4</td>
<td>164.7 ± 7.0</td>
<td>.82</td>
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<tr>
<td>Weight (kg)</td>
<td>62.5 ± 7.9</td>
<td>49.2 ± 6.1</td>
<td>&lt;.0001</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>22.9 ± 2.7</td>
<td>18.1 ± 1.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Positive family history of osteoporosis (%)</td>
<td>30.0</td>
<td>35.3</td>
<td>.69</td>
</tr>
</tbody>
</table>

BMI, Body mass index.
Data are presented as mean ± SD.

Figure 1. Speed of sound at the radius and tibia in subjects with anorexia nervosa compared with healthy control subjects. *Boxes represent the median speed of sound (SOS, m/s) and quartile limits. Normal nonwhite indicates healthy, nonwhite control subjects; normal white indicates healthy, white control subjects; AN, subjects with anorexia nervosa.

*Difference between subjects with AN and control subjects was significant, P < .0001 at both anatomic sites.

Race. There were also group differences noted with respect to family history, with control subjects less likely to report a positive family history of osteoporosis (Table I).

We also completed a subgroup analysis, limiting the analysis to only control subjects who reported white race (n = 20). When white control subjects and subjects with AN were compared, the two groups were significantly different only in terms of weight and BMI (Table II).

QUS measurements were significantly different between the two groups (Figure 1). Subjects with AN had a higher SOS at the radius than control subjects (P < .0001). These results were replicated at the tibia (P < .0001). The group differences remained significant at both sites when the control group was restricted to white subjects and were even more pronounced at the tibia (P < .0001). There was no difference in SOS at the radius or the tibia between white and nonwhite control subjects.

Bone density as measured by DXA was low (aBMD Z-score ≤ −1.0 SD) in the subjects with AN. The mean hip aBMD by DXA in the patients with AN was 0.874 ± 0.109 g/cm². The mean aBMD Z-score was −0.45 ± 0.92, with a range of −2.1 to 1.6. Total hip aBMD Z-scores were between −1.0 and −2.0 SD in 34% of patients and ≤ −2.0 SD in 3% of patients. The mean hip BMAD was 0.153 ± 0.019 g/cm³. At the lumbar spine, mean aBMD in the subjects with AN was 0.872 ± 0.089 g/cm³. The mean Z-score was −1.12 ± 0.90, with a range of −3.1 to 0.5. Spinal BMD Z-scores were between −1.0 and −2.0 SD in 59% of patients, and ≤ −2.0 SD in 18% of patients. The mean spine BMAD was 0.115 ± 0.011 g/cm³.

In participants with AN, neither hip nor spinal aBMD by DXA was significantly correlated with QUS measurements of SOS at either the radius or tibia (Figure 2). The relationship between BMAD (at the hip and spine) and SOS measures (at the radius and tibia) followed an almost identical trend (Figure 2); no significant associations were found between BMAD and SOS (P = .30 to .68). No association was found between severity of AN (expressed as duration of illness or duration of amenorrhea) and SOS measures. Moderate correlations were observed between subject age and SOS results at both the radius and tibia (r = 0.36 and r = 0.37, respectively; P = .02). In patients with AN, anthropometric measures did not correlate with SOS at either anatomic site.

Regression analyses of SOS at the radius and tibia were carried out (Table III; available at www.jpeds.com). In univariate analyses of the entire sample, weight and BMI were significant negative predictors of SOS at the tibia but not at the radius. Age and height positively predicted SOS at both sites. Neither race nor family history of osteoporosis was a significant predictor of SOS. In the final multivariate regression model, AN status remained a significant predictor of SOS at the radius even after controlling for baseline group differences in BMI, race, and age. Neither BMI nor race remained important predictors of SOS in the final model. At the tibia, age and BMI remained significant predictors of SOS, although AN status was borderline-significant (P = .056) after controlling for these variables and race.

DISCUSSION

In this study, we have evaluated quantitative ultrasound as a tool to measure bone density in adolescents and young women with AN. Although measurements of aBMD by DXA were low, replicating results from our and others’ previous studies in this patient population, we found a paradoxically higher SOS at both the radius and the tibia in young women with AN compared with healthy control sub-
projects. This unexpected result was contrary to our hypothesis that SOS would be reduced in AN patients.

In the group with AN, 37% of subjects had a total hip aBMD Z-score more than 1 SD below the mean, and 77% had a lumbar spine aBMD Z-score more than 1 SD below the mean of age- and sex-matched reference data. Unexpectedly, there were no significant correlations between ultrasound measurements of SOS and either aBMD or BMAD. In other patient populations, including children with rheumatologic disease or celiac disease, QUS end points have been highly correlated with site-matched aBMD values. As DXA is a well-established methodology for the evaluation of skeletal status in young women with AN, and our results confirm the low bone mass frequently demonstrated in this population, it appears that SOS measures are problematic in this group.

Previous studies have used QUS to evaluate bone mass at the calcaneus in patients with AN. Milos et al measured SOS at the calcaneus in 36 adult women with AN and 30 healthy adult female control subjects. Their group found no significant difference in SOS between the two subject cohorts. Similarly, Kutilek et al measured SOS at the calcaneus in 26 adolescents with AN. They found that SOS values were significantly higher than reference data obtained from healthy girls of similar age. In contrast, broadband ultrasound attenuation (BUA) measurements by QUS in patients with AN were lower than in the healthy subjects. The BUA results at the calcaneus were replicated by Resch et al, who additionally demonstrated significant correlations between BUA and BMD of the femoral neck and lumbar spine. No significant relations were found between BUA and peripheral quantitative computed tomography values of the distal radius. That study did not compare SOS measurements between groups. The Omnisense 7000P QUS used in the current study does not have the capability to measure BUA; thus, this information could not be obtained in the current participants.

This study used QUS to evaluate the tibia and radius in subjects with AN. As the tibia is a weight-bearing site and a common site for stress fracture in patients with AN who frequently participate in excessive exercise, bone ultrasound measurements at this site would have provided a convenient screening tool for clinicians in the outpatient setting. However, our data suggest that the accuracy of the SOS measurements at the tibia and radius are compromised. This is potentially due to the minimal soft tissue in these malnourished young women that may violate underlying operating assumptions of this methodology. In our analysis, BMI was a significant predictor of SOS at the tibia, but in a negative direction. The direction of the association indicates that SOS decreases as BMI increased, the opposite of what has been demonstrated with aBMD measurements by DXA. Although unexpected, our results replicate findings from other patient populations. Littner et al studied bone SOS at the tibia in small for gestational age infants, a group that also exhibits minimal body fat. The small for gestational age infants studied had higher bone SOS than the predicted SOS of appropriate for gestational age infants. These results corroborate with literature that has shown an inverse correlation between tibial SOS and measures of adiposity (percentage of body fat and sum of skinfold measurements). At the opposite extreme, Eliakim et al found low QUS values in obese children. Future studies are needed in which body composition data are obtained as well as bone assessments by ultrasound to answer more definitively why SOS measurements are higher in malnourished young women with AN.

Another explanation for the higher SOS measures in AN patients may be related to an internal lack of fat. With axial measurement of SOS by QUS, the “fastest” signal will be detected by the receiver. The signal pathway traverses cortical bone and also penetrates the trabecular portion or bone marrow cavity. Thus, if the marrow cavity decreases (like AN patients who may have either a hypoplastic bone marrow or possess decreased marrow fat), the inner course will also decrease, leading to an increased transmission speed. These hypotheses are speculative and merit future research.

It is also possible that the higher SOS measures seen at this weight-bearing site in patients with AN were related to the high levels of physical activity often reported by these young women. A significant association between level of physical activity and bone SOS has been reported in healthy young female athletes. However, aBMD by DXA was low in our subjects. If the patients with AN were engaging in protective physical activity, it would have been anticipated that aBMD would be normal or high.

The role of bone size in measurements of SOS has been disputed. For axial measurements by QUS, the ultrasound wave is passing within a small layer underneath the surface of the cortical bone. In one previous study, it was reported that body height and therefore bone size influenced SOS measured at the thumb and patella in healthy children, teenagers, and adults. The authors concluded that as a result of an increase in bone size, cortical thickness increases. Sound waves thus propagate at a longer distance through the cortical bone in larger skeletal elements, resulting in a dependence of SOS on growth measures. However, this hypothesis has been refuted by larger studies that have found that QUS variables were not affected by body size in healthy adolescents and athletes. In our patient sample, however, AN subjects were significantly taller than control subjects. If the results were influenced by bone size, the measured SOS in AN subjects should have been lower than that observed in the control subjects. We also demonstrated that there was no association between SOS measures and both aBMD and BMAD, the latter calculated in an attempt to account for differences in bone size.

Matching patients with control subjects on the basis of stage of maturation is critical in the evaluation of bone density. Because all study subjects were postmenarchal, pubertal stage was not a contributing factor to the differences noted between groups. We elected to include all control participants despite the racial diversity of the control group and recognize this as a study limitation. However, although the two study
populations differed in terms of race, the differences between groups were only more pronounced when white control subjects alone were included in the analysis. The family history differences align with the racial make-up of the two groups (as white individuals are more likely to have a low bone mass and are at higher risk for osteoporosis). However, family history of osteoporosis was not a significant predictor of SOS at the tibia or the radius. Although BMI, race, and age were important contributing factors to the SOS results, AN status remained a significant predictor, even when these variables were included in the multivariate analyses.

In conclusion, we found that subjects with AN had a higher SOS as measured by QUS at the radius and tibia than healthy control subjects. SOS values did not correlate with aBMD measures by DXA or calculated BMD or anthropometric variables in adolescents and young women with AN. Based on these results, QUS measurements of SOS at the radius or tibia do not appear to be appropriate for carrying out bone density evaluations in patients with AN.

REFERENCES

Table III. Regression analyses of speed of sound at the radius and tibia

<table>
<thead>
<tr>
<th>Models/predictors</th>
<th>Δ SOS radius (m/s) AN vs control</th>
<th>P value</th>
<th>Δ SOS tibia (m/s) AN vs control</th>
<th>P value</th>
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<tbody>
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<td>AN</td>
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<td>.005</td>
<td>109.7 (26.7)</td>
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<td>AN, white subjects only</td>
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<td>119.4 (25.2)</td>
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<td>AN, adjusted for BMI, race, age</td>
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<td>Family history of osteoporosis</td>
<td>43.7 (24.4)</td>
<td>.08</td>
<td>15.5 (22.8)</td>
<td>.51</td>
</tr>
</tbody>
</table>

SOS, Speed of sound; AN, anorexia nervosa status (yes/no); BMI, body mass index.
Data are presented as parameter estimate (β), standard error in parentheses, and indicate the change in SOS (m/s) per unit change of the covariate.
Prospective Study of Infantile Hemangiomas: Demographic, Prenatal, and Perinatal Characteristics

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Objectives To characterize demographic, prenatal, and perinatal features of patients with infantile hemangiomas and to determine the importance of these factors in predicting rates of complication and treatment.

Study design We conducted a prospective study at 7 U.S. pediatric dermatology clinics. A consecutive sample of 1058 children, aged 12 years and younger, with infantile hemangiomas was enrolled between September 2002 and October 2003. A standardized questionnaire was used to collect demographic, prenatal, perinatal, and hemangioma-specific data. National Vital Statistic System Data (NVSS) was used to compare demographic variables and relevant rates of prenatal events.

Results In comparison with the 2002 United States National Vital Statistics System birth data, we found that infants with hemangiomas were more likely to be female, white non-Hispanic, premature ($P < .0001$) and the product of a multiple gestation (10.6% versus 3.1%; $P < .001$). Maternal age was significantly higher ($P < .0001$), and placenta previa (3.1%) and pre-eclampsia (11.8%) were more common.

Conclusions Infants with hemangiomas are more likely to be female, white non-Hispanic, premature, and products of multiple gestations. Prenatal associations include older maternal age, placenta previa, and pre-eclampsia. No demographic, prenatal, and perinatal factors predicted higher rates of complications or need for treatment. (J Pediatr 2007;150:291-4)

Infantile hemangiomas are the most common tumors of childhood, estimated to occur in 3% to 10% of Caucasian infants. Previous case series and retrospective studies have suggested that female sex, prematurity, fair skin and history of chorionic villus sampling may all be risk factors for the development of infantile hemangiomas. Demographic, prenatal, and perinatal factors in patients with hemangiomas may provide clues to pathogenesis. For example, the increased incidence of hemangiomas in premature infants has been hypothesized to be related to an early withdrawal of placental antianangiogenic factors. Other prenatal and perinatal risk factors, such as alcohol, tobacco, or other drug use, have not been investigated previously, in part because hemangiomas are not present at birth and thus do not lend themselves to conventional birth defect registries. Our study was undertaken to better characterize these factors in patients with infantile hemangiomas and to determine whether specific patient characteristics predisposed patients to complications, the need for treatment, or both.

METHODS

Study Design

A prospective study of patients with infantile hemangiomas was initiated in September 2002 by members of the Hemangioma Investigator Group (HIG) at 7 U.S. academic pediatric dermatology clinics. One additional site in Spain enrolled patients, but data from that site was not used in the analysis of demographic features because U.S. National Vital Statistics System (NVSS) birth data was used for comparison. The

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**Hig** | Hemangioma Investigator Group
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**NVSS** | U.S. National Vital Statistics System

**PIGF** | Platelet growth factor

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The demographic data were compared to the NVSS birth registry. Data was sent to the National Outcomes Center, an independent data management and statistical group, where digital images were scanned into a computer database. Information was manually verified. The database was managed in Microsoft Access and SAS software programs. Digital images were identified with study code numbers and stored securely to protect patient confidentiality. Follow-up visits were scheduled according to clinical need.

Investigator Training
A manual outlining study procedures was distributed to all study investigators before patient enrollment commenced. The investigators attended 2 training sessions (in New Orleans, LA, in March 2002, and in Annapolis, MD, in May 2002), where study procedures and data collection forms were reviewed and terminology and hemangioma subtype classification criteria were defined.

Patients
Study investigators offered participation in the study to eligible patients in their pediatric dermatology clinics. To be eligible, patients had to be 12 years or younger at the time of enrollment and have had ≥1 infantile hemangiomas in any stage of evolution. Patients with other vascular malformations in the absence of infantile hemangiomas were excluded. A consecutive sample was enrolled by each investigator. A total of 1096 patients, of whom 1058 were U.S. patients, were enrolled in a 13-month period from September 2002 to October 2003. Clinical follow-up continued until June 2004.

Main Outcome Measures
Using standardized computer-scannable forms, investigators collected information about patient sex, ethnicity, prematurity, birth weight, maternal/paternal age, prenatal testing procedures and infertility treatments, placental abnormalities, maternal smoking and drug use, and family history. Clinical features of each hemangioma were recorded, and treatment and complications incurred before and during the study period were noted. The study period extended for a minimum of 8 months and as long as 23 months after enrollment to maximally capture morbidities during hemangioma proliferation. In addition, a digital photograph of each patient was obtained at the time of enrollment. Each patient’s intake forms and digital images were identified with study code number and stored securely to protect patient confidentiality. Follow-up visits were scheduled according to clinical need.

Statistical Analysis
Data was sent to the National Outcomes Center, an independent data management and statistical group, where forms were scanned into a computer database. Information was manually verified. The database was managed in Microsoft Access and SAS software programs. Digital images were coded and sent to the University of California, San Francisco, for storage. Data analysis was performed in conjunction with the National Outcomes Center and the University of California, San Francisco biostatistics department. The demographic data were compared to the NVSS birth data for the year 2002.

RESULTS

Group Characteristics
A total of 1058 U.S. patients were enrolled in a 1-year period. Most (68%) of our patients were younger than 1 year. Ninety percent of patients were 2 years or younger. A total of 750 patients (71%) were female, and 308 patients (29%) were male. White, non-Hispanic patients comprised 68.9% of patients. African-American and Hispanic patients comprised 2.8% and 14.4% of patients, respectively. Data on gestational age were available on 1047 patients, 214 (20.4%) of whom were born prematurely (defined as younger than 37 weeks gestational age), and 60 (5.7%) of whom were born very prematurely (defined as younger than 32 weeks of age). The mean birth weight was 3.1 kg (SD = 0.8), and the median birth weight was 3.2 kg. Of the 1058 patients in the group, 55 (5.2%) were very low birth weight (defined as <1500 g), 141 (13.3%) were low birth weight (defined as 1500-2499 g), and 862 (81.5%) were normal birth weight (defined as ≥ 2500 g).

One hundred twelve infants (10.6%) were products of multiple gestations. Most of these patients (99/112) were twins; 13 were products of triplet gestation. Sixty-two infants (54.8%) of multiple gestation were dizygotic, 23 infants (20.4%) were monozygotic, 5 (4.4%) were mixed, and 22 (19.6%) were of unknown zygosity. A positive family history of vascular anomalies in first-degree relatives (parents or siblings) was reported in 348 patients (32.9%). These anomalies included hemangiomas, port wine stains, medial telangiectatic nevi, venous malformations, cutis marmorata telangiectatica congenita, and arterial-venous malformations. Hemangiomas were present in first-degree relatives of 130 patients (12.3%).

The maternal age of patients ranged from 14 to 49 years, with a mean maternal age of 29.9 years (SD = 6.1) and a median age of 30.0 years. The average maternal age for infants who were the first-born was 28.2 years (95% CI, 27.7–28.8; SD, 6.3). Prenatal and perinatal data revealed a higher than expected incidence of placenta previa and pre-eclampsia. Placenta previa was reported in 35 patients (3.3%), and pre-eclampsia was reported in 122 patients (11.8%).

Chorionic villus sampling was performed in 37 patients (3.5%) with normal results in all patients except 1. A history of amniocentesis was obtained in 129 patients (12.4%), all who had normal results.

No maternal chronic or prenatal illness was over-represented in our study population. Alcohol and tobacco use were not increased compared with NVSS data. There was no increased usage of other drugs, including prescription drugs and illicit drugs.

Complications were noted in 299 patients (28.3%) before enrollment; 255 patients (24.1%) experienced complications during the study period. During the study period, ulceration was the most common complication, noted in 168 patients (16.0%); threat to vision (59, 5.6%), airway obstruction (40, 1.4%), auditory canal obstruction (6, 0.6%), and cardiac compromise (4, 0.4%) were seen less commonly.
TREATMENT

Treatment was administered in 269 patients (25%) before enrollment, and 402 (38%) during the study period. During the study period, patients received systemic steroids (130, 12.3%), intraliesional steroids (43, 4.1%), topical steroids (103, 9.8%), wound care for ulceration (145, 13.7%), oral antibiotics (21, 2.0%), pulsed dye laser (84, 8.0%), and excisional surgery (60, 5.7%). Rarely, interferon (1 patient) and vincristine (3 patients) were used. Some patients received >1 mode of therapy.

National Vital Statistic Comparison

Sex, ethnicity, gestational age, birth weight, maternal age, twinning, and rate of placenta previa were compared with NVSS data from 2002. These data, which are taken from birth certificates, are a comprehensive data base that captures vital statistics on virtually all births in the United States each year and are reported by the National Center for Health Statistics (http://www.cdc.gov/nchs/nvss.htm).

Seven hundred fifty patients (71%) were female and 308 (29%) were male, which was significantly different than NVSS population data ($P < .0001$). Distribution among ethnic groups differed significantly from NVSS population data ($P < .0001$); there was a higher proportion of white, non-Hispanic patients and a lower proportion of African-American and Hispanic patients in our group. Study patients were more likely to be preterm (<37 weeks) and very preterm (<32 weeks; $P < .0001$). They were also more likely to be of low birth weight or very low birth weight ($P < .0001$). The mean maternal age for first-born infants in the study group (28.2 years) was significantly higher than the mean maternal age for first-born children in the NVSS data (25.1 years; $P < .0001$). Similarly, overall maternal age differed significantly from the general population, with a higher proportion of mothers who were 30 years and older; 55.1% of our group had mothers who were 30 years old or older, compared with 37.5% of the general population ($P < .0001$). One hundred twelve infants (10.6%) were products of multiple gestations, compared with 3.1% in the NVSS report ($P < .001$). Placenta previa was reported in 35 patients (3.1%) in the study group, compared with 0.41% in the NVSS population data.

The role of demographic, prenatal, and perinatal factors in predicting complications and the need for treatment was examined by using regression analysis. Neither sex nor ethnicity predisposed patients to experience complications or receive treatment. Fifty percent of Hispanic patients received some form of treatment, compared with 46.9% of white non-Hispanic patients and 41.4% of African-American patients, reflecting a marginally significant difference ($P = .05$). Subanalysis by type of treatment revealed that 32.3% and 31.1% of Hispanic and white non-Hispanic patients, respectively, received systemic therapy, compared with only 24.1% of African-American patients, but the small number of African-American infants precludes robust analysis of this trend. No correlation between patient birthweight and the presence of complications or need for treatment was seen. Premature gestational age, multiple gestation, placenta previa, and preeclampsia were not predictive of a higher likelihood of experiencing complications or receiving treatment.

DISCUSSION

Identifying patient characteristics associated with the development of a birth defect or “birthmark” has traditionally been performed by using formal birth defect registries. Birth defect registries are tools used to identify demographic, prenatal, and perinatal characteristics and potential risk factors that can have both clinical and scientific implications. Unfortunately, hemangiomas, though considered a type of “birthmark” have not been included in such registries because their presence at birth is subtle at best, with diagnostic clinical characteristics usually appearing within the first few days to weeks of life. In this large group, we systematically collected demographic, prenatal, perinatal, and clinical data on infants with hemangiomas to identify important trends.

Demographic Factors

Previously recognized risk factors for the development of infantile hemangiomas, including female sex and fair skin, were confirmed in our study. The female-to-male ratio was 2.4:1.0, which is similar to previously published ratios that ranged from 1.4:1.0 to 3:1.4,5 The reason for female predominance is unclear. Kindred studies have suggested a subset of hemangiomas may be heritable and linked to genes on chromosome 56; no genetic mutations on the X chromosome have been reported. Historically, some have argued that parents perceive hemangiomas to pose a greater cosmetic concern when females are affected, and therefore they are over-represented in dermatology clinics.

The racial/ethnic distribution is significantly different in our study group compared with the general population data. There was a higher proportion of white non-Hispanic patients and a lower proportion of black and Hispanic patients. We recognize a limitation of our study is that our data was obtained through parental recall, introducing the potential for some recall bias. Twenty percent of infants were premature (defined as younger than 37 weeks gestational age) and 6% of patients were very premature (defined as younger than 32 weeks of age). It is unclear whether the presence of hemangioma places infants at risk for prematurity or vice versa. It is possible that an imbalance of angiogenic control mechanisms may result from prematurely removing a developing fetus from maternal and placental influences.

Prenatal and Perinatal Factors

Prematurity and low birth weight were significantly more common in our study group compared with NVSS data. Our data was obtained through parental recall, introducing the potential for some recall bias. Twenty percent of infants were premature (defined as younger than 37 weeks gestational age) and 6% of patients were very premature (defined as younger than 32 weeks of age). It is unclear whether the presence of hemangioma places infants at risk for prematurity or vice versa. It is possible that an imbalance of angiogenic control mechanisms may result from prematurely removing a developing fetus from maternal and placental influences.
Chorionic villus sampling during pregnancy has also been suggested to result in a higher risk of hemangioma development. A history of chorionic villus sampling was found in only a small minority (3.5%) of our patients. On the basis of our study, chorionic villus sampling does not appear to play a significant role in the formation of most hemangiomas.

Advanced maternal age was found more frequently in our group compared with the general population data. The rate of pre-eclampsia (11.6%) was surprisingly high as well. Because advanced maternal age and multiple gestation are associated with a higher incidence of pregnancy complications including preterm birth, low birth weight, and pre-eclampsia, we recognize these as possible confounding factors. The pathogenesis of pre-eclampsia is incompletely understood, but certain placental growth factors may play a role in its development. Alterations in platelet growth factor (PlGF) and soluble fms-like tyrosine kinase 1 are more pronounced in patients with pre-eclampsia. PlGF is significantly lower at 13 to 16 weeks gestational age in patients in whom pre-eclampsia later develops. PlGF was recently shown by means of immunohistochemical staining to be expressed in involuting hemangiomas, giving further support to the notion that hemangiomas and placenta are under similar angiogenic control mechanisms. Levels of placental proteins, such as human placental lactogen, differ in multiple gestation pregnancies compared to singleton pregnancies. Our group had a disproportionate number of infants of multiple gestation (10.6%). Placental abnormalities were not diagnosed in most of our patients. Further studies are needed to understand the role of angiogenic growth factors in relation to hemangioma and placental vessels.

Family History

Rigorous studies of family histories in patients with hemangiomas have not been previously reported. One third of the patients in our group had a first-degree relative with a vascular anomaly, and 12% had a first-degree relative with a hemangioma. The percent of patients with a family history of hemangiomas is only slightly higher than the cited incidence in the general population (3%-12%), but some of the studies used to cite the incidence of hemangiomas include other vascular birthmarks such as vascular malformations and nevus simplex in their reports of “hemangiomas”. Other studies have relied on parental recall and primary care physicians for diagnosis, which may have contributed to inaccuracies. A study of 3 kindreds with familial hemangioma revealed linkage to chromosome 5q31-33, with various vascular growth factors suspected to be responsible. Although this likely represents only a small percentage of patients with hemangiomas, the role of genetics as a co-factor increasing the expression of hemangiomas deserves further study.

On the basis of the results of this study, a profile for patients with infantile hemangiomas can be constructed. Hemangiomas more commonly occur in fair-skinned, premature, female infants who are more likely to be born as a product of multiple gestation. Compared with the general population, their mothers are of higher maternal age, have a higher incidence of pre-eclampsia and placenta previa, and are more likely to have had multiple gestation pregnancies. Additional controlled studies are needed to further define risk factors for hemangiomas and to understand the relationship between potentially confounding factors.

The authors gratefully acknowledge our colleagues and staff in the Vascular Anomalies Centers at each institution for their hard work and caring for our patients, and Alan Bostrom, Charles McCulloch, and the National Outcomes Center for their database and statistical expertise. We would like to acknowledge Dr Nancy Esterly for all her support and guidance.

REFERENCES

Developmental Outcomes of Cryptogenic West Syndrome

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Objective To elucidate factors affecting the developmental outcome of cryptogenic West syndrome.

Study design Medical records of 32 patients, who were followed-up regularly for more than 1 year, were reviewed for clinical features: treatment lag, electroencephalography findings, and seizure evolution. Those features were compared between the normal outcome group (12 patients) and the delayed outcome group (20 patients). The outcomes were determined at the average age of 8.6 ± 4.7 years.

Results The duration from onset to any treatment of the delayed group was longer than that of the normal group ($P < .05$). Evolution of electroencephalographic findings showed that paroxysmal discharges reappeared in frontal regions more frequently in the delayed group than in the normal group ($P < .05$). In the delayed group, other types of seizure except for spasms occurred more commonly than in the normal group ($P < .05$). More patients of the delayed group evolved to focal epilepsy than those of the normal group ($P < .05$).

Conclusions Shorter treatment lag might be associated with a favorable outcome in cryptogenic West syndrome. Reappearance of paroxysmal discharges in the frontal regions and evolution to other types of seizure may be associated with undetectable lesions in the frontal regions. (J Pediatr 2007;150:295-9)

West syndrome is an intractable epileptic syndrome, characterized by epileptic spasms and hypsarrhythmia. It is frequently associated with developmental arrest and even regression. Other types of epilepsy develop in many patients with West syndrome, and many have severe psychomotor retardation.1,2 West syndrome is usually classified into cryptogenic and symptomatic groups. Symptomatic West syndrome includes various underlying (preexisting) pathologies, and it is difficult to reach any conclusion about the effects of treatment on developmental outcomes in these children. Outcomes in the cryptogenic group are usually more favorable than those of the symptomatic group.2-7 However, even in patients with cryptogenic West syndrome, almost half have moderate to severe mental retardation.2,3,6 Cryptogenic West syndrome is also considered to be “probably symptomatic,” more precisely, to be suspected of being symptomatic but to have unidentified underlying biochemical or structural causes, although some researchers recognize the existence of idiopathic cases that are usually included in the cryptogenic group.8

We investigated 32 patients with cryptogenic West syndrome to elucidate factors affecting developmental outcome.

METHODS

We investigated 32 patients (16 boys and 16 girls) in whom cryptogenic West syndrome was diagnosed, who were referred to Saitama Children’s Medical Center, Saitama, Japan, and who were examined regularly for more than 1 year by pediatric neurologists. Cryptogenic West syndrome was defined according to the following criteria: (1) clusters of epileptic spasms with onset <3 years, (2) hypsarrhythmia on electroencephalography (EEG), (3) normal pregnancy, normal development and no eventful history (including no other type of seizures before onset of spasms), (4) no focal abnormality on neurologic examinations, (5) normal brain images on CT and/or MRI.

We also performed the following studies on every patient to detect a symptomatic cause: neurologic examination, ophthalmologic examination, biochemical and metabolic tests (including urine amino acids and organic acids), and chromosomal analysis. Follow-up examinations (neurologic, developmental, and EEG) were performed on each patient.
patient, and information on seizure patterns was obtained from parents every 6 months at least before patients were 7 years old and at least annually thereafter.

The average onset age of epileptic spasms of the 32 infants was 5.8 ± 3.0 (average ± SD) months, ranging from 2.8 to 19.7 months. The mean follow-up was 96.4 ± 54.6 months, ranging from 12.6 to 221.7 months; the outcomes were determined at the age of 8.6 ± 4.7 (average ± SD) years, ranging from 2.0 to 19.1 years old. Developmental status was evaluated by using tests appropriate for each developmental state (Tsumori-Inage developmental questionnaire, Kinder infant development scale, Tanaka-Binet Intelligence Scale, Japanese Wechsler intelligence scale for children-revised, Japanese Wechsler intelligence scale for children III). Thirty-two patients were divided into two groups: the normal outcome group (IQ ≥ 75) and the delayed outcome group (IQ < 75) to compare onset age, treatment lag from onset to any treatment, effective treatment, evolution of EEG findings, and seizures.

Initial effective treatment was considered to which first caused cessation of spasms. Cessation of spasms was defined as no clinical spasms having been witnessed from a time commencing within 14 days of treatment and for ≥28 consecutive days from the time of the last witnessed spasms. Information on the frequency of spasms was obtained from the parents and from nursing staff when in the hospital.

Twenty-one of the 32 patients, who could not achieve cessation of spasms by prior administrations of sodium valproate and/or pyridoxine and/or clonazepam (before June 1994) or pyridoxine and intravenous gamma globulin (after July 1994), were treated with adrenocorticotropic hormone (ACTH) therapy according to the following protocol. To 14 infants (before June 1994), synthetic ACTH, zinc hydroxide suspension of tetracosactide acetate (Cortrosyn Z, N.V. Organon, Oss, the Netherlands), was given intramuscularly at 0.02 mg/kg per day for 2 weeks, then gradually tapered off to once every other day for 2 weeks, twice weekly for 2 weeks, and then weekly for 2 weeks (the total amount of ACTH was 0.52 mg/kg in 8 weeks). While the patients were receiving ACTH, previous medications were continued. The other 7 patients (after July 1994) were treated with a lower dose of ACTH therapy. Synthetic ACTH was given intramuscularly at 0.015 mg/kg per day for 2 weeks to one patient and at 0.0125 mg/kg per day for 2 weeks to 6 patients, then the amounts were tapered off to every other day for 1 week, twice weekly for 1 week. (Total amounts of ACTH were 0.285 mg/kg, 0.2375 mg/kg, respectively, in 4 weeks.) While these 7 patients were receiving ACTH, the preceding medications were also stopped. If none of the above treatments controlled the spasms, various drugs, including zonisamide, valproate, clonazepam, and thyrotropin-releasing hormone were administered.

EEG was performed before treatment and after cessation of spasms, and then on each patient every 6 months at least before they were 7 years old and annually at least after then. EEG findings were evaluated, focusing on when and where paroxysmal discharges reappeared for the first time in the course of consecutive EEG follow-up after cessation of spasms and resolution of hypsarrhythmia and focusing on evolutionary changes of topographic distributions of paroxysmal discharges. These changes were classified into six types: no paroxysmal discharges in the follow-up EEGs, transient focal discharges, persistent focal discharges, migrating and/or multiple focal discharges, migrating and/or multiple focal discharges with transient generalized discharges, and generalized discharges.

The Mann-Whitney U test, the χ² test, or the Fisher exact probability test was used for statistical analysis. Differences were considered significant at a value of P ≤ .05.

RESULTS

Thirty-two patients were divided into two groups: 12 patients in the normal outcome group and 20 in the delayed outcome group (Table I). The delayed outcome group consisted of 5 patients with mild mental retardation (IQ ≥ 50 and < 75), 8 with moderate (IQ ≥ 25 and < 50), and 7 with severe (IQ < 25). There was no statistical difference in the onset age of spasms and the follow-up duration. The duration from onset of spasms to any treatment of the delayed outcome group was longer than that of the normal outcome group (Table II. P < .05). The average duration from onset to cessation of spasms in the delayed outcome group was longer than that of the normal outcome group, but there was no statistical difference between them. Cessation of spasms for ≥28 days accompanied with resolution of hypsarrhythmia was achieved in all 32 patients, once at least, including one patient in whom spasms disappeared after exanthema subitum without any treatment. ACTH therapy ceased spasms for ≥28 days in 8 of 9 patients in the normal outcome group and in 12 of 12 in the delayed outcome group (Table II). The duration from the commencing of ACTH therapy to the disappearance of spasms of both groups was not statistically different.

Relapses of spasms occurred more frequently in the delayed outcome group than in the normal outcome group; relapses of spasms occurred in 7 patients of 20 of the delayed outcome group and in none of the normal outcome group (P < .05). Six of 7 patients who had relapses also had other types of seizures after relapses of epileptic spasms (Table III).

<table>
<thead>
<tr>
<th>Table I. Onset age and follow-up durations</th>
</tr>
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<tbody>
<tr>
<td>Normal outcome group</td>
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<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Boy: Girl</td>
</tr>
<tr>
<td>Onset age of spasms (m)</td>
</tr>
<tr>
<td>(range)</td>
</tr>
<tr>
<td>Follow-up duration (y)</td>
</tr>
<tr>
<td>(range)</td>
</tr>
</tbody>
</table>

NS, Not significant.
The average duration from cessation to relapse of spasms was 2.8 ± 1.6 months, ranging from 1.1 to 5.0 months.

Evolution of EEG findings and seizures during follow-up is summarized in Table III. The average age at which paroxysmal discharges reappeared for the first time during follow-up of the delayed outcome group was statistically later than that of the normal outcome group (P < 0.05). Reappearance of paroxysmal discharges was observed in four patients in the normal outcome group from 8 months old to 18 months old; in the delayed outcome group, this was observed in 11 patients younger than 24 months old, in 3 during ages 24 and 36 months old, and in 3 after 72 months old. Topographic distributions of paroxysmal discharges that reappeared for the first time during follow-up showed that paroxysmal discharges reappeared in frontopolar and frontal regions more frequently in the delayed outcome group than in the normal outcome group (P < 0.05). Eight patients of 12 in the normal outcome group were classified into the no paroxysmal discharges group, and more frequently than in the delayed outcome group (P < 0.05). The patterns of persistent focal discharges, migrating and/or multifocal discharges, and generalized discharges with/without migrating and/or multiple focal discharges were observed more frequently in the delayed outcome group, although there were no statistical differences between the two groups. Transient focal discharges in two patients of the normal outcome group appeared in parieto-occipital region or central region, respectively. Their transient focal discharges disappeared when they were 13 months old and 16 months old, respectively. Transient focal discharges in two of the delayed outcome group observed in parieto-occipital region and in one in frontopolar-frontal region. Their transient focal discharges disappeared when they were 11 months old and 20 months old, respectively. Persistent focal discharges appeared in the temporal region in one patient of the normal outcome group. Persistent focal discharges appeared in the central region in one patient of the delayed outcome group, in the parieto-occipital region in one and in the frontopolar-frontal region in two, respectively. In one patient of the normal outcome group, paroxysmal discharges migrated from the parieto-occipital to the central region and then to the parieto-occipital region again. Paroxysmal discharges migrated from the parieto-occipital region to the temporal region in three patients of the delayed outcome group. In one patient of the delayed outcome group, independent focal discharges reappeared in both the frontopolar-frontal region and the temporal region, and then focal discharges migrated from the parietal region to the frontopolar-frontal region again. Four patients in the delayed outcome

<table>
<thead>
<tr>
<th>Table II. Response to therapy of both groups</th>
<th>Normal outcome group</th>
<th>Delayed outcome group</th>
<th>P &lt; .05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration from onset to any treatment (d)</td>
<td>40.8 ± 59.3 (3-198)</td>
<td>104.5 ± 112.2 (3-480)</td>
<td></td>
</tr>
<tr>
<td>Duration from onset to cessation of spasms (d)</td>
<td>77.0 ± 76.2 (12-264)</td>
<td>139.8 ± 152.4 (31-558)</td>
<td>NS</td>
</tr>
<tr>
<td>Initial effective therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>8</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>VPA</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gamma globulin</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>TRH</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vitamin B₆</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>ZNS</td>
<td>0</td>
<td>1</td>
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</tr>
<tr>
<td>VPA + Vitamin B₆</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>1*</td>
<td></td>
</tr>
<tr>
<td>ACTH therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients treated with ACTH therapy</td>
<td>9</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>No. of responders (seizure free ≥28 days)</td>
<td>8</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Duration from the commencing of ACTH therapy to disappearance of spasms (d)</td>
<td>2.8 ± 1.4 (1-5)</td>
<td>3.6 ± 3.4 (1-11)</td>
<td>NS</td>
</tr>
<tr>
<td>Relapse of spasms</td>
<td></td>
<td></td>
<td>P &lt; .05</td>
</tr>
<tr>
<td>No. of patients with relapse</td>
<td>0</td>
<td>7†</td>
<td></td>
</tr>
<tr>
<td>Duration from cessation to relapse of spasms (m)</td>
<td>2.8 ± 1.6 (1.1-5.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACTH, Adrenocorticotropin hormone; NS, not significant; TRH, thyrotropin-releasing hormone; VPA, valproate; ZNS, zonisamide.

*Spasms disappeared after exanthema subitum without any treatment in one patient.
†Six of seven patients also had other types of seizures after relapses of epileptic spasms during follow-up periods (shown in Table III).
The evolution of EEG findings and seizures

<table>
<thead>
<tr>
<th>Ages at which focal paroxysmal discharges reappeared for the first time during follow-up</th>
<th>Normal outcome group</th>
<th>Delayed outcome group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age ± SD (m) (range)</td>
<td>10.8 ± 4.9 (8.4-18.0)</td>
<td>29.2 ± 28.2 (8.2-89.1)</td>
</tr>
<tr>
<td>≤ 12 months</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12 months, &lt; 12 months</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>≤ 24 months, &lt; 36 months</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>≤ 36 months, &lt; 72 months</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≤ 72 months</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Topographic distributions of paroxysmal discharges that reappeared for the first time during follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontopolar-frontal</td>
<td>0</td>
<td>7*</td>
</tr>
<tr>
<td>Central</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Temporal</td>
<td>1</td>
<td>1*</td>
</tr>
<tr>
<td>Parieto-occipital</td>
<td>2</td>
<td>8*†</td>
</tr>
<tr>
<td>Generalized</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Evolutional changes of topographic distributions of paroxysmal discharges</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No paroxysmal discharges</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Transient focal discharges</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Persistent focal discharges</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Migrating and/or multiple focal discharges</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Migrating and/or multiple focal discharges with transient generalized discharges</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Generalized discharges</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Evolution of seizures except spasms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occurrence of other types of seizures</td>
<td>0</td>
<td>11‡</td>
</tr>
<tr>
<td>Average age of onset ± SD (m) (range)</td>
<td>38.2 ± 46.1 (8.4-151.2)</td>
<td></td>
</tr>
<tr>
<td>Seizure types</td>
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<tr>
<td>Focal motor seizures</td>
<td>0</td>
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<tr>
<td>Complex partial seizures</td>
<td>0</td>
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<tr>
<td>Generalized seizures</td>
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<td>4§</td>
</tr>
<tr>
<td>Evolution to focal epilepsy</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

NS, Not significant.

*One patient had multifocal spikes in frontal and occipital regions and one had multifocal spikes in frontal and midtemporal regions. They were counted in both frontopolar-frontal regions and parieto-occipital regions and in both frontopolar-frontal regions and temporal regions, respectively.

†Two of eight had diffuse spike and wave in addition to parieto-occipital focal discharges.

‡Six of 11 had development of other types of seizure after relapse of epileptic spasms, and the other five had other types of seizure without relapse of epileptic spasms.

§One patient of four had brief tonic seizures only; one had brief tonic seizures and generalized tonic clonic seizures; two had tonic seizures, atypical absences, and myoclonic seizures.

Group were classified into the pattern of migrating and/or multiple focal discharges with transient generalized discharges, and these focal discharges were observed in the frontopolar-frontal and/or parieto-occipital region as independent multiple focal discharges or as migrating focal discharges. In these four patients, generalized discharges appeared at the age of 12 months, 14 months, 16 months, and 23 months, respectively. Generalized discharges appeared at the age of 14 months and 28 months in two patients of the pattern of generalized discharges without focal discharges.

Eleven patients had other types of seizure during follow-up. Six developed other types of seizure after relapse of spasms, and the other five had them without epileptic spasm relapse. Other types of seizure occurred in the delayed outcome group only (P < .05). The other types of seizure included focal motor seizures (version, tonic posturing) in four patients, complex partial seizures with or without automatism in three, and generalized seizures in four. Concerning generalized seizures, one patient of four had brief tonic seizures only; one had brief tonic seizures and generalized tonic clonic seizures; two had tonic seizures, atypical absences, and myoclonic seizures. More patients of the delayed group had development of focal epilepsies than those of the normal group (P < .05).

DISCUSSION

Our study revealed two significant points regarding the outcome of cryptogenic West syndrome. First, the duration from onset of spasms to any treatment of the delayed outcome group was longer than that of the normal outcome group. Thus, a shorter treatment lag may be associated with a favorable outcome in cryptogenic West syndrome. This result...
implies the importance of early treatment, which coincides with numerous previous reports.3,6,9-13 Kivity et al9 mentioned that once major developmental regression lasts for 1 month or more, the prognosis for normal cognitive outcome was poor and that early treatment might be important to prevent irreversible cognitive decline.

The second point is that the some of the patients with cryptogenic West syndrome may be associated with potential lesions in frontal region and that they would evolve to focal epilepsy. More patients in the delayed group had other types of seizures after cessation of spasms and developed focal epilepsy than those in the normal group. Evolution of EEG findings showed that paroxysmal discharges in frontopolar and frontal regions reappeared more frequently in the delayed group than in the normal group. In patients with reappearance of frontal paroxysmal discharges, there may be undetectable underlying lesions in the frontal regions, which would be associated with developmental delay. Another possibility to consider regarding frontal abnormality of EEG in the delayed group would be the influence of the persistence of hypsarrhythmia. Persistence of hypsarrhythmia may lead to subsequent cognitive impairment.3,11,13 Our study did not evaluate duration of hypsarrhythmia; however, longer duration from onset of spasms to any treatment or cessation of spasms is probably in proportion to persistence of hypsarrhythmia. Chugani et al14 proposed that raphe-cortical projections could mediate the hypsarrhythmic changes on EEG. The prominent raphe-striatal pathway in humans has strong connections between raphe neurons and the putamen, which may influence frontal lobe function through the putamen. The frontal regions mature more slowly than the other cortical regions.15-19 Persistence of hypsarrhythmia would affect immature cerebral regions, or the frontal regions may have vulnerability for the condition of persistence of hypsarrhythmia. This possibility may influence frontal lobe function, and that may result in paroxysmal discharge in frontal regions and cognitive developmental delay. That is, to prevent cognitive developmental delay and evolution after seizures, improvement of hypsarrhythmia might be important. Early treatment would be valuable for the improvement of cognitive outcomes in cryptogenic West syndrome.

We appreciate the editing of this paper, provided by Prof Eric Johnson (Jichi Medical University). We also thank Ms Etsuko Hamano for her constant encouragement and helpful advice.

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Increased Prevalence of Thyroid Autoimmunity and Hypothyroidism in Patients with Glycogen Storage Disease Type I

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Objective To investigate the hypothalamus-pituitary-thyroid axis in patients with glycogen storage disease type 1 (GSD1).

Study design Ten patients with GSD1a, 7 patients with GSD1b, and 34 sex- and age-matched healthy control subjects were enrolled in the study.

Results The levels of serum-free thyroxine (FT4) were significantly lower in patients with GSD1a and GSD1b (P < .05), whereas thyrotropin was significantly higher compared with control subjects only in patients with GSD1b (P < .005). Thyroglobulin and thyroperoxidase auto-antibodies were significantly higher in patients with GSD1b than in patients with GSD1a and control subjects (P < .005). After thyrotropin-releasing hormone stimulation, an enhanced thyrotropin response was found in patients with GSD1a and patients with GSD1b (P < .0005) compared with control subjects. The presence of a subclinical or overt hypothyroidism was found in 4 of 7 patients with GSD1b and in no patient with GSD1a (χ² = 7.47, P < .005) or control subject (χ² = 27.2, P < .0001).

Conclusions Patients with GSD1b have an increased prevalence of thyroid autoimmunity and hypothyroidism, although patients with GSD1a have little evidence of thyroid abnormalities. Concomitant damage at the level of the hypothalamus or pituitary gland might be hypothesized on the basis of the slightly elevated thyrotropin levels, even in patients with overt hypothyroidism. (J Pediatr 2007;150:300-5)

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axis in patients with GSD1; 2) to correlate its function to the main clinical and biochemical features of patients affected by GSD1; and 3) to compare the results in patients with the 2 different forms of GSD1.

METHODS

Patients and Control Subjects

Patients with GSD1 (10 with GSD1a and 7 with GSD1b; 6 male, 11 female) and 34 sex- and age-matched healthy control subjects (12 male, 22 female) entered the study after informed consent had been obtained from either them or their parents. All the patients had negative results at the neonatal screening for hypothyroidism. Seven patients with GSD1a and 3 patients with GSD1b were pre-pubertal, 1 patient with GSD1b (female) was in puberty, and 3 patients with GSD1a and 3 patients with GSD1b were adults; among control subjects, 20 were pre-pubertal, 2 (female) were in puberty, and 12 were adults.

The length of follow-up for patients ranged from 5.8 to 23.2 years (median follow-up duration, 11.7 years). GSD1a was diagnosed with enzyme studies that showed the combination of deficient glucose-6-phosphatase activity in intact and disrupted microsomes, with mutation analysis of the glucose-6-phosphatase gene, or both. GSD1b was diagnosed with enzyme studies that showed the combination of deficient glucose-6-phosphatase activity in intact microsomes and (sub)normal glucose-6-phosphatase activity in disrupted microsomes, with mutation analysis of the glucose-6-phosphate transporter gene, or both (Table I; available at www.jpeds.com).

All patients with GSD1b received granulocyte-colony-stimulating factor (G-CSF) treatment for neutropenia at the time of study entry, with the exception of 1 patient (#17) who had stopped the therapy 6 months before the study of hypothalamic-thyroid-axis was performed. Ileocolonoscopy was performed in all patients with GSD1b to search for bowel involvement. A diagnosis of a severe Crohn-like ileocolitis was made in 2 patients (#11, #12), and moderate colitis was detected in 2 other patients (#6, #7). At the time of the study, 1 patient (#11) was receiving mesalamine treatment.

Study Design

This prospective study protocol was in accordance with the Helsinki Doctrine for Human Experimentation and was approved by the local ethics committee. The hypothalamic-pituitary-thyroid-axis was evaluated in patients with GSD1 and control subjects by measuring baseline thyrotropin, thyroid hormone, and thyroid auto-antibodies levels and thyrotropin response to thyrotropin challenge. The morphology of the thyroid gland was also evaluated with thyroid ultrasound scanning in patients and control subjects. In patients with GSD1, the results of the examinations were correlated with the clinical and biochemical features classically associated with thyroid dysfunction or associated with GSD1 and reflecting the metabolic control of the disease.

Clinical and Biochemical Features

The evaluation of the clinical and biochemical features of GSD1 included height SDS score, body mass index, serum glucose, triglyceride, cholesterol, lactic and uric acid levels, and liver size. The biochemical features were measured at 7:30 a.m.; because of poor tolerance, the fasting period varied between 3 and 4 hours only. Pubertal age was recorded in adult patients and control subjects.

Hypothalamus-pituitary-thyroid Axis

The evaluation of the hypothalamic-pituitary-thyroid axis included the measurement of baseline total free thyroxine (FT4), free triiodothyronine (FT3), thyroxine binding globulin (TBG), thyroglobulin (Tg), thyroperoxidase (TPO), and Tg auto-antibodies. Serum thyrotopin, FT4, FT3, Anti-Tg, and Anti-TPO levels were measured with an immunoassay by using an electrochemiluminescence system. TBG levels were measured with an immunoassay by using a solid phase chemiluminescent enzyme system. The sensitivity of FT4 assay was 0.023 ng/dL. The intra-assay and interassay CV were 1.9% and 3.7%, respectively.

A thyrotropin releasing hormone (TRH) stimulation test was performed measuring thyrotopin levels at baseline and every 15 minutes for 2 hours after intravenous injection of 200 μg of TRH. Subclinical hypothyroidism was defined on the basis of an increased baseline serum thyrotopin concentration (>5.0 μU/mL in children and >4.5 μU/mL in adults) with normal FT4 values, on the basis of an exaggerated response (>20 μU/mL for children and adults) of plasma thyrotopin to TRH stimulation, or both. Patients were considered to be affected by overt hypothyroidism when increased serum thyrotopin levels were associated with a decreased FT4 levels. Subclinical hyperthyroidism was defined on the basis of a decreased baseline serum thyrotopin concentration (<0.3 μU/mL for children and <0.4 μU/mL for adults) with normal FT4 values, on the basis of a depressed response (<2.5 μU/mL for children and adults) of plasma thyrotopin to TRH stimulation, or both.

Thyroid Ultrasound Scanning

Thyroid ultrasound scanning was performed with a real-time scanner, by using a 7.5-MHz linear transducer. The ultrasound scanning structural characteristics, the volume of the thyroid gland, and the presence, number, and characteristics of the nodules were evaluated in all patients and control subjects.

Statistical Analysis

Data are expressed as means ± SE. Statistical analysis was performed with Statistical Package for Social Science software (SPSS 10 for Windows Update, SPSS, Chicago, IL). The comparisons between numerical variables were performed with Kruskal-Wallis and Mann-Whitney tests. The comparison between categorical variables or associations between different features were performed using χ2 test cor-
rected for the Fisher exact test. The possible correlation between the values of hypothalamus-pituitary-thyroid axis hormones or the patterns of thyroid ultrasound scanning and possible risk factors associated with GSD1 (disease duration, features of metabolic control and frequency of admission for hypoglycemia) was studied with regression analysis calculating the Spearman rank correlation coefficient. Significance was set at 5%.

RESULTS

Clinical and Biochemical Features

Clinical and biochemical features of patients and control subjects are shown in Table II. Height SDS was lower and pubertal age was delayed in both patients with GSD1a and GSD1b than in controls. Serum uric acid ($P < .05$) and lactic acid levels ($P < .005$) were significantly higher, whereas serum bicarbonate ($P < .05$) levels were significantly lower in both patients with GSD1a and patients with GSD1b than in control subjects. In patients with GSD1a, serum triglyceride and cholesterol levels were significantly higher than in control subjects ($P < .005$). In patients with GSD1b, serum cholesterol levels were significantly lower ($P < .005$) and glucose levels were higher ($P < .005$) than in control subjects. Serum triglyceride ($P < .005$), cholesterol ($P < .005$), and bicarbonate ($P < .05$) levels were significantly lower and glucose levels were higher ($P < .005$) in patients with GSD1b than in patients with GSD1a.

Hypothalamus-pituitary-thyroid Axis and Thyroid Ultrasound Scanning

Table III summarizes the results of the baseline evaluation of hypothalamus-pituitary-thyroid axis.

GSD1a

At the baseline evaluation, serum FT4 levels were significantly lower ($P < .05$), Tg serum levels were significantly higher ($P < .05$), and thyrotropin levels were slightly higher ($P = .02$) in patients than in control subjects (Figures 1 and 2); after TRH challenge, a significantly enhanced thyrotropin response was found in patients compared with control subjects, either when thyrotropin peak ($13.4 \pm 0.8$ versus $8.3 \pm 0.5$, $P < .001$) or area under the curve ($701 \pm 45$ versus $410 \pm 30$, $P < .005$) were considered. FT4 serum levels significantly correlated with height SDS ($r = 0.7$, $P = .01$) and inversely with disease duration ($r = -0.7$, $P = .01$). Thyroid volume was similar in patients and control subjects ($8.3 \pm 1.6$ versus $6.7 \pm 0.5$). A dishomogeneous pattern of the thyroid gland was ob-

Table II. Clinical and biochemical features of patients with glycogen storage disease type 1 and control subjects

<table>
<thead>
<tr>
<th>Features</th>
<th>Patients with GSD1a</th>
<th>Patients with GSD1b</th>
<th>Control subjects</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SE</td>
<td>Mean SE</td>
<td>Mean SE</td>
<td>Ia vs C</td>
</tr>
<tr>
<td>Age (years)</td>
<td>12.1 1.5</td>
<td>14.9 2.2</td>
<td>13.6 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index</td>
<td>22.9 1.3</td>
<td>25.8 2.1</td>
<td>23.8 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Height-SDS</td>
<td>-1 0.3</td>
<td>-1 0.5</td>
<td>0.8 0.09</td>
<td>0</td>
</tr>
<tr>
<td>Pubertal age (years)</td>
<td>14 1.5</td>
<td>15.3 0.3</td>
<td>10.8 0.3</td>
<td>.03</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>81.5 3.3</td>
<td>110.5 8.6</td>
<td>88.1 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>379.1 55.6</td>
<td>116.4 28.2</td>
<td>96.3 6.3</td>
<td>.001</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>191 11.1</td>
<td>104.5 5.6</td>
<td>145 4.6</td>
<td>.001</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>5.1 0.3</td>
<td>6.2 0.5</td>
<td>3.8 0.1</td>
<td>.001</td>
</tr>
<tr>
<td>Lactic acid (mg/dL)</td>
<td>2 0.1</td>
<td>3.8 0.8</td>
<td>1.3 0.03</td>
<td>0</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>22.4 0.7</td>
<td>19.8 0.4</td>
<td>25.5 0.3</td>
<td>0</td>
</tr>
</tbody>
</table>

NS, not significant.

Table III. Biochemical features of thyroid function of patients with glycogen storage disease type 1 and control subjects

<table>
<thead>
<tr>
<th>Features</th>
<th>Patients with GSD1a</th>
<th>Patients with GSD1b</th>
<th>Control subjects</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SE</td>
<td>Mean SE</td>
<td>Mean SE</td>
<td>Ia vs C</td>
</tr>
<tr>
<td>Thyrotropin (µU/mL)</td>
<td>2.2 0.3</td>
<td>3.8 0.7</td>
<td>1.6 0.1</td>
<td>.06</td>
</tr>
<tr>
<td>FT3 (pg/mL)</td>
<td>3.4 0.1</td>
<td>2.8 0.6</td>
<td>3.2 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>FT4 (ng/dL)</td>
<td>10.4 0.4</td>
<td>8.3 1.4</td>
<td>12 0.4</td>
<td>.02</td>
</tr>
<tr>
<td>Tg (ng/mL)</td>
<td>20.6 4.3</td>
<td>14 2.5</td>
<td>11.7 1.1</td>
<td>.01</td>
</tr>
<tr>
<td>TBG (µg/mL)</td>
<td>20.3 1.3</td>
<td>24.8 1</td>
<td>25 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Ab α TPO (UI/mL)</td>
<td>8.2 0.9</td>
<td>35 4.9</td>
<td>14.7 1.08</td>
<td>.001</td>
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<tr>
<td>Ab α Tg (UI/mL)</td>
<td>16.8 0.7</td>
<td>45.5 13.8</td>
<td>14.8 0.7</td>
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</table>
Increased Prevalence of Thyroid Autoimmunity and Hypothyroidism in Patients with Glycogen Storage Disease Type I

**DISCUSSION**

The results of this study demonstrate that GSD1 is associated to an impairment of hypothalamus-pituitary-thyroid axis, characterized by a decrease of FT4 levels, an increase of baseline thyrotropin levels, and an enhanced thyrotropin response to TRH challenge. This impairment is severe in GSD1b, which is associated with an increased prevalence of thyroid autoimmunity and hypothyroidism, whereas patients with GSD1a showed little evidence of thyroid abnor-

**Table IV. Biochemical features of thyroid function of patients with glycogen storage disease type 1 and thyroid disease**

<table>
<thead>
<tr>
<th>Patients</th>
<th>#6</th>
<th>#7</th>
<th>#16</th>
<th>#17</th>
</tr>
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<tbody>
<tr>
<td>Thyrotropin (μU/mL)</td>
<td>2.4</td>
<td>5.3</td>
<td>5.4</td>
<td>6.2</td>
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<tr>
<td>FT3 (pg/mL)</td>
<td>3.9</td>
<td>3.5</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>FT4 (ng/dL)</td>
<td>11</td>
<td>10.8</td>
<td>6.7</td>
<td>6</td>
</tr>
<tr>
<td>Peak value</td>
<td>23</td>
<td>26</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Tg (ng/mL)</td>
<td>9</td>
<td>9</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>TBG (μg/mL)</td>
<td>21</td>
<td>25</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Ab α TPO (UI/mL)</td>
<td>78</td>
<td>57</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>Ab α Tg (UI/mL)</td>
<td>49</td>
<td>121</td>
<td>18</td>
<td>37</td>
</tr>
</tbody>
</table>

Reference values (children; adults): Thyrotropin (3-12; 2-10 μU/mL), FT3 (1.6-3.7 ng/mL), FT4 (7-14.8 ng/dL), Tg (0-50 ng/mL), TBG (25-46; 15-34 μg/mL), Ab α TPO and Ab α Tg (<40 UI/mL).

**GSD1b**

At the baseline evaluation, serum FT4 levels were significantly lower ($P < .01$), and thyrotropin (Figures 1 and 2) and thyroid auto-antibodies levels were significantly higher ($P < .005$) in patients than in control subjects. Positive antibody titre was found in 3 patients (42.8%) and 1 control subject (2.9%; $\chi^2 = 5.2, P < .05$). After TRH challenge, a significantly enhanced thyrotropin response was found in patients compared with control subjects, either when thyrotropin peak (17.7 ± 2.5 versus 8.3 ± 0.5, $P < .001$) or area under the curve (972 ± 145 versus 410 ± 30, $P < .005$) were considered. In detail, an overt hypothyroidism was found in 2 patients (#16,#17; 11.7%), whereas a subclinical hypothyroidism was detected in 2 additional patients (#6,#7; 11.7%; Table IV). Therefore, the presence of a subclinical or overt hypothyroidism was found in 57.1% of patients with GSD1b and in none of the control subjects ($\chi^2 = 27.2, P < .0001$). At statistical analysis, baseline thyrotropin levels inversely correlated with serum bicarbonate levels ($r = -0.7, P = .05$); the thyrotropin level peak after TRH challenge correlated with the lactic acid serum levels ($r = 0.7, P = .05$). Moreover, in patients with hypothyroidism, lactic acid (5.6 ± 0.5 versus 1.5 ± 0.2, $P < .05$) and uric acid serum levels (7.1 ± 0.5 versus 5.1 ± 0.7, $P = .08$) were higher than in patients with GSD1b without thyroid disease. No association was detected between the presence of thyroid disease and both the diagnosis of Crohn-like colitis and G-CSF treatment; also, no association was found among the presence of pathological levels of thyroid autoantibody and the severity of neutropenia and neutrophil dysfunction, G-CSF treatment, non steroidal anti-inflammatory drug therapy, and Crohn-like colitis. Also, no correlation was detected among thyroid autoantibody levels and neutrophil mean count, duration of neutropenia, and duration of G-CSF treatment.

Thyroid volume was similar in patients and control subjects (7.2 ± 1.0 versus 6.7 ± 0.5). A dishomogeneous pattern of the thyroid gland was observed in 4 patients (57.1%) and 2 control subjects (11.8%; $\chi^2 = 12.2, P < .005$), whereas a normal pattern was described in the remaining patients and control subjects. In particular, 2 of the 4 patients with GSD1b with a dishomogeneous pattern of the thyroid gland had subclinical hypothyroidism; the remaining 2 patients had no thyroid disease. Thyroid nodules were observed neither in patients nor in control subjects, with the exception of 2 pseudonodular areas in 1 patient.

**Figure 1.** Baseline thyrotropin values in patients with GSD1a (square), patients with GSD1b (triangle), and control subjects (upside down triangle).

**Figure 2.** Baseline FT4 values in patients with GSD1a (square), patients with GSD1b (triangle), and control subjects (upside down triangle).
malities. The increased prevalence of both thyroid autoimmunity and hypothyroidism in GSD1b is evident either when compared with that of control subjects included in this study or when compared with the normal population reported previously.20

The changes in the hormone profile of the hypothalamus-pituitary-thyroid axis found in patients with GSD1b suggest the presence of a predominant primitive damage of the thyroid gland. This usually induces an initial severe increase of thyrotropin levels and subsequently a decrease of thyroid hormone levels and clear-cut primitive hypothyroidism. GSD1b is associated to a similar change, although the decrease of thyroid hormone level is associated only with a slight increase in baseline thyrotropin levels, even in cases with an overt hypothyroidism, and therefore with FT4 levels, FT3 levels, or both lower than the reference range. This minimal elevation in thyrotropin levels suggest possible comcomitant damage at the level of the hypothalamus or pituitary beyond the thyroid gland. The hypothalamus-pituitary axis and thyroid damage in GSD1b might be caused by a glycogen accumulation or an impaired endogenous glucose production in these organs.6-9,21 A toxic effect of lactic acid excess on thyroid tissue might also be hypothesized,11-13 higher serum lactic acid levels were noted in patients with GSD1b with hypothyroidism.

The detection of an increased prevalence of thyroid autoimmunity in patients with GSD1b suggests that it could be the major cause of hypothyroidism and that these patients are at increased risk for autoimmune disorders. The reason why patients with GSD1b, but not those with GSD1a, show thyroid autoimmunity may be related to the documented evidence of neutropenia and neutrophil dysfunction only in patients with GSD1b.4 Indeed, neutropenia and neutrophil dysfunction are considered risk factors for the development of autoimmune disorders such as Crohn disease22 and have been found to correlate to the development of a Crohn-like colitis also in patients with GSD1b.4 However, we found no association between the neutropenia/neutrophil dysfunction and thyroid autoimmunity or hypothyroidism; therefore, according to our results, neutropenia does not seem to be responsible for the thyroid dysfunction associated with GSD1. We also excluded that the presence of a Crohn-like disease is responsible of the hypothyroidism23 because we found no association between the presence of Crohn-like colitis and thyroid autoimmunity.

Neutropenia and neutrophil dysfunction may place patients with GSD1b at risk for recurrent infections, requiring treatment with G-CSF. Frequent infections and the consequent chronic exposure to excessive antigenic stimulation may cause amyloidosis,24 which has been reported on thyroid biopsy specimens derived from patients with GSD1b.25 These findings suggest that thyroid amyloidosis might be a possible further cause of thyroid dysfunction. Conversely, published data exclude a causative effect of G-CSF treatment in the development of thyroid autoimmunity and hypothyroidism, although a concomitant role cannot completely be ruled out in patients with GSD1b.26,27

Frequent infections may also increase the production of cytokines, which are a risk factor responsible for the euthyroid sick syndrome.28 This phenomenon is mainly characterized by an early decrease in total triiodothyronine (TT3) and FT3 levels, normal total thyroxine (TT4) levels and normal or increased FT4 levels associated with normal or reduced baseline and stimulated thyrotropin levels and a late decrease of thyroid hormone levels associated with reduced thyrotropin secretion.29 The thyroid changes described in patients with GSD1, mainly characterized by a decrease of FT4, rather than FT3, associated with an increased baseline and stimulated thyrotropin secretion, seem to exclude that the GSD1-associated thyroid dysfunction resembles an euthyroid sick syndrome. However, the possible blunting effect of chronic illnesses associated with GSD1 on the hypothalamic-pituitary-thyroid axis cannot be excluded; this could explain the surprising findings of minimally elevated thyrotropin levels in contrast with the reduced thyroid hormone levels of patients with GSD1b.

Patients with hypothyroidism share clinical and biochemical features with patients with GSD1, such as short stature, delayed puberty, and dyslipidemia. Thus, a clinical diagnosis of thyroid disease could be missed in this particular group of patients. Although dyslipidemia is an important hallmark of GSD1, in this study serum triglyceride and cholesterol levels were lower in patients with GSD1b than in patients with GSD1a. In patients with GSD1b, serum triglyceride levels were similar to and serum cholesterol levels were even lower than those in control subjects. The different lipid profile of patients with GSD1a and patients with GSD1b might be explained by the different intracellular compartmentalization of G6P that would stimulate de novo lipogenesis in patients with GSD1a, but not in patients with GSD1b.30 Moreover, the documented presence of an inflammatory bowel disease, a Crohn-like colitis, or both in most cases could explain the normal or reduced lipid levels of patients with GSD1b.31,32 In this study, patients with lower lipid levels were those with inflammatory bowel disease. The patients with hypothyroidism, conversely, were those with relatively higher lipid levels, confirming a role of hypothyroidism in inducing a relative increase in lipid levels of patients with GSD1. Another possible explanation of the peculiar decreased cholesterol levels in patients with GSD1b could be related to G-CSF treatment, which has been demonstrated to induce a decrease in total cholesterol levels in monkeys.33

In conclusion, the results of this study demonstrated that patients with GSD1b (but not patients with GSD1a) have an increased prevalence of thyroid autoimmunity and hypothyroidism. Therefore, thyrotropin response to TRH challenge should be investigated in patients with GSD1b, especially in those with worsening metabolic control when this is not explained by a poor dietary compliance. Moreover, because hypothalamus-pituitary damage was hypothesized, it
is suggested that thyroxin supplementation therapy should be started even in patients with slightly elevated baseline thyrotropin serum levels.

REFERENCES

Table I. Patient profile

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Follow-up (years)</th>
<th>Diagnosis</th>
<th>Molecular diagnosis</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
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<td>GSD1a</td>
<td>R83C/R83C</td>
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<tr>
<td>2</td>
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<td>7.00</td>
<td>GSD1a</td>
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<tr>
<td>3</td>
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<td>GSD1b</td>
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<td>5</td>
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<td>8.00</td>
<td>GSD1a</td>
<td>R83C/W63R</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>10.50</td>
<td>10.00</td>
<td>GSD1b</td>
<td>G68R/------</td>
</tr>
<tr>
<td>7</td>
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<td>400X/400X</td>
</tr>
<tr>
<td>8</td>
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<td>11.30</td>
<td>GSD1a</td>
<td>R83C/R83C</td>
</tr>
<tr>
<td>9</td>
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<td>11.70</td>
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<tr>
<td>10</td>
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<tr>
<td>11</td>
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<td>13.00</td>
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<td>210X/------</td>
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<td>12</td>
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<td>13</td>
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<td>R83C/R83C</td>
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<tr>
<td>15</td>
<td>F</td>
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<td>18.90</td>
<td>GSD1a</td>
<td>W63R/------</td>
</tr>
<tr>
<td>16</td>
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<td>GSD1b</td>
<td>G68R/W248X</td>
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<tr>
<td>17</td>
<td>F</td>
<td>23.80</td>
<td>23.20</td>
<td>GSD1b</td>
<td>W248X/400X</td>
</tr>
</tbody>
</table>

M, male; F, female.
Neurologic Complications in Children Hospitalized with Influenza: Characteristics, Incidence, and Risk Factors

JASON G. NEWLAND, MD, V. MATT LAURICH, MD, ANNA W. ROSENQUIST, MD, KATERI HEYDON, MS, DANIEL J. LICHT, MD, RON KEREN, MD, MPH, THEOKLIS E. ZAOUTIS, MD, MSCE, BARBARA WATSON, MBCHB, RICHARD L. HODINNA, PhD, AND SUSAN E. COFFIN, MD, MPH

Objective To determine the characteristics, incidence, and risk factors for influenza-related neurologic complications (INC).

Study design A retrospective cohort study of INC in children hospitalized with laboratory-confirmed influenza infection (LCI) from June 2000 to May 2004 was conducted. Systematic chart review was performed to identify clinical characteristics and outcomes. A neighborhood cohort was constructed to estimate the incidence of INC. Logistic regression was used to identify independent risk factors for INC.

Results Of 842 patients with LCI, 72 patients had an INC: influenza-related encephalopathy (8), post-infectious influenza encephalopathy (2), seizures (56), and other (6). Febrile seizures were the most common type of seizures (27). No patient died from an INC. In our neighborhood cohort, the incidence of INC was 4 cases per 100,000 person-years. An age of 6 to 23 months (odds ratio [OR], 4.2; 95% CI, 1.4-12.5) or 2 to 4 years (OR, 6.3; 95% CI, 2.1-19.1) and an underlying neurologic or neuromuscular disease (OR, 5.6; 95% CI, 3.2-9.6) were independent risk factors for the development of INC.

Conclusion Seizures are the most common neurologic complication experienced by children hospitalized with influenza. In the United States, encephalopathy is uncommon. Young children and patients with neurologic or neuromuscular disease are at increased risk for INC. (J Pediatr 2007;150:306-10)

Influenza is a major cause of acute respiratory tract illnesses each winter. Additionally, influenza virus infection has been associated with a variety of neurologic complications including Reye syndrome, Guillian-Barré, transverse myelitis, encephalopathy, and seizures.1-3 Seizures are the most frequently reported neurologic complication, with most thought to be febrile seizures in young children.4,5 During the past decade, influenza encephalopathy has gained much attention in both Japan and the United States. Case reports and small case series suggest that the prevalence and epidemiology of influenza encephalopathy in the United States may differ from that reported from Japan.5-9

Few studies describe the epidemiology associated with influenza-related neurologic complications (INC) in a large group of patients with laboratory-confirmed influenza (LCI) infection. In this large cohort study, we examined the characteristics, incidence, and risk factors for neurologic complications among patients hospitalized with LCI in Philadelphia.

METHODS

Design/Setting/Patients

We conducted a retrospective cohort study of patients hospitalized with LCI from either influenza A or B during 4 consecutive seasons (June 2000 through May 2004). The study was conducted at The Children’s Hospital of Philadelphia (CHOP), an academic, tertiary-care hospital with 418 patient beds and approximately 24,000 hospital admissions.
each year. To facilitate the appropriate cohorting of patients, it is standard practice at CHOP for patients hospitalized with acute respiratory symptoms of unclear etiology to have a nasal wash specimen obtained for testing by respiratory viral pathogens. A detailed description of the assembly of the cohort has been previously reported. In brief, cases were identified by using the clinical virology laboratory records and admission or discharge codes (International Classification of Disease, 9th revision [ICD-9]) specific for influenza. When a patient was identified with an ICD-9 code, laboratory confirmation was required to be considered a case. This study was approved by the institutional review board at CHOP.

Case Finding

Hospital records of all patients with LCI were reviewed for evidence of neurological complications. Patients were selected to undergo detailed chart review when: 1) a lumbar puncture or neuroimaging study (computed tomography scan or magnetic resonance imaging) was performed; 2) a neurology consultation was obtained; 3) a seizure was documented in the admission or discharge note; or 4) a diagnostic code for seizure was present on the hospital bill.

Study Definitions

LABORATORY-CONFIRMED INFLUENZA. Influenza infection was defined as a positive determination for influenza A or B virus with rapid assay (immunoassay [IA] or direct fluorescent antibody testing [DFA]) or comprehensive viral culture. All specimens were initially tested with IA for respiratory syncytial virus and influenza (Binax; Portland, ME). DFA testing for adenovirus, influenza A and B, parainfluenza virus types 1, 2, and 3, and respiratory syncytial virus was performed on specimens that tested negative by using IA for respiratory syncytial virus and influenza. Comprehensive viral cultures were performed for all specimens with negative results for respiratory viruses by DFA.

CHRONIC MEDICAL CONDITIONS. To identify pre-existing chronic medical conditions that might predispose a child to serious influenza infection, we reviewed the hospital admission records for chronic medical conditions, including asthma, chronic pulmonary conditions, cardiac disease, immunodeficiency, hemoglobinopathy, diabetes mellitus, and metabolic or renal disease. Neurological or neuromuscular diseases (NNMD) were defined as diseases of the central nervous system (including seizure disorders) or myopathies. Detailed definitions of these conditions have been published. Neurological complications included:

1) Influenza-related encephalopathy (on the basis of definitions from the Centers for Disease Control)—patients who had altered mental status or personality change lasting >24 hours and occurring within 5 days of onset of an acute febrile respiratory illness that was proven subsequently to be LCI.

2) Post-infectious influenza encephalopathy—patients who had altered mental status or personality change lasting >24 hours and starting more than 5 days after the onset of respiratory symptoms.

3) Febrile seizures—patients with non-focal seizures in the setting of fever who were ≥6 months old and ≤6 years old with no underlying seizure disorder, brain pathology, or significant metabolic disturbance.

4) Seizure with fever—patients without an underlying seizure disorder, brain pathology, or significant metabolic disturbance who had a fever and suffered a focal seizure or were <6 months old or ≥6 years old.

5) Other seizures—patients with seizures with or without a fever who had an underlying neurologic disorder (static encephalopathy, developmental delay, hydrocephalus).

6) Other neurologic complications—patients with aseptic meningitis or cerebral infarction caused by hypotension.

Data Collection

Clinical data were retrieved with a systematic review of the medical record by using a structured data collection instrument. Demographic data were abstracted from hospital billing records and administrative data sets.

Clinical Data

A detailed chart review was performed by a research assistant (V.M.L.) using the electronic medical record to search for these clinical variables: 1) presence and duration of altered mental status; 2) seizure activity during or within 48 hours before hospitalization; 3) results of cerebrospinal fluid analysis; 4) findings of neuroimaging studies; and 5) clinical outcome. In patients determined to have an INC, it was confirmed by pediatric infectious diseases’ physicians (J.G.N., S.E.C.) and a pediatric neurologist (D.J.L.).

Patients were considered to have 1 of the aforementioned neurologic complications. When a child had both encephalopathy and seizures, the case was assigned only to the encephalopathy category.

Administrative Data

Demographic data collected included patient age, sex, and postal zip code of home residence.

Estimation of the Incidence

To estimate the incidence of neurological complications among patients hospitalized because of LCI, a population-based neighborhood cohort was defined. Administrative claims data from all acute care hospitals in Pennsylvania and New Jersey (Solutient Corporation, New Orleans, LA) was queried to identify zip code areas with documented preferential admission to the CHOP for acute asthma exacerbation (ICD-9 code 493.02 [extrinsic asthma, acute exacerbation]). Nine contiguous zip code areas were identified, from which >70% of asthma hospitalizations in children 18 years

Neurologic Complications in Children Hospitalized with Influenza: Characteristics, Incidence, and Risk Factors
and younger occurred at CHOP. These areas with documented preferential admission to CHOP defined the neighborhood cohort. Data from the United States Census 2000 were used to estimate the numbers of child-years of observation during the study period (July 2000 through June 2004) in these zip code areas.

Statistical Methods

Continuous variables were summarized with medians and interquartile range and categorical variables were summarized with frequencies. Categorical variables were compared with the \( \chi^2 \) test or the Fisher exact test, whereas continuous variables were compared with the Wilcoxon rank sum test. A 2-tailed \( P \) value <.05 was considered to be significant for all statistical tests.

Unadjusted and adjusted odds ratios and corresponding 95% CIs were derived to examine the risk factors for the development of an INC. We performed a multivariate analysis using a logistic regression model to examine the interaction between age, which was defined as a categorical variable, and NNMD. All statistical calculations were performed with standard programs in SAS software version 9.1 (SAS Corp., Cary, NC).

RESULTS

In our cohort of 842 patients hospitalized with LCI, we identified 72 patients who experienced an INC. The most frequent INC was seizures (n = 56). Other neurologic complications consisted of acute encephalopathy (n = 8), post-infectious encephalopathy (n = 2), cerebral infarction caused by hypotension (n = 4), and aseptic meningitis (n = 2; Table I). Among patients with seizures, 45% had an underlying seizure disorder (Table II). The median age for all patients with seizures was 1.4 years (range, 5 months-15 years; data not shown). The median time from onset of respiratory tract symptoms to the commencement of seizure activity was 1 day. Four patients had seizures as the initial symptom of influenza infection. Approximately half the patients with seizures had a simple febrile seizure (27/56, 48%), including 8 who had a history of febrile seizures. Eight previously healthy patients had seizures that did not fulfill the definition of simple febrile seizures: 2 were younger than 6 months, 2 were older than 5 years, and 4 had focal seizures. Recurrent seizures were observed in 4 patients. The results of all neuroimaging studies and CSF cytochemical analyses that were performed were normal. All previously healthy patients who experienced influenza-related seizures survived, and none had residual neurologic sequelae.

Acute influenza encephalopathy was observed in 8 patients. One patient had an underlying NNMD (Table II). Patients with encephalopathy ranged in age from 1 to 21 years, with a median age of 3.5 years. Six patients were infected with influenza A; influenza B was isolated from nasal wash specimens in the other 2 patients. The median time from the onset of respiratory tract symptoms to neurologic symptoms was 1.5 days (range, 0-3 days; data not shown).

Table I. Frequency of neurological complications in patients with laboratory-confirmed influenza (N = 72)

<table>
<thead>
<tr>
<th>Neurological complication</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>56</td>
</tr>
<tr>
<td>Febrile seizure</td>
<td>27</td>
</tr>
<tr>
<td>Seizure with fever</td>
<td>8</td>
</tr>
<tr>
<td>Other seizure</td>
<td>21</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>8</td>
</tr>
<tr>
<td>Post-infectious encephalopathy</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
</tr>
<tr>
<td>Stroke secondary to hypotension</td>
<td>4</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>2</td>
</tr>
</tbody>
</table>

Symptoms of encephalopathy included disorientation, lethargy, visual hallucinations, and speech abnormalities. A CSF specimen was obtained from 7 patients; cytochemical analysis results of 6 specimens were normal. Pleocytosis was noted in the specimen from 1 patient who had 14 white blood cells/mm\(^3\); the CSF protein and glucose concentrations were normal. Neuroimaging studies were performed at the time of admission on all patients with encephalopathy. Two patients had changes consistent with volume loss, 1 patient had prominent CSF spaces, and 1 patient had prominent vermian sulci. These findings did not correlate with the neurologic examination. In all other cases, neuroimaging results were normal or unchanged from baseline. The median length of stay was 3 days. At time of discharge from the hospital, 1 patient had neurologic sequelae that consisted of persistent nystagmus, dysmetria, and visual agnosia. No deaths occurred.

Two patients experienced the onset of neurologic symptoms longer than 5 days (6 and 14 days) after the onset of respiratory tract symptoms and were classified as having post-infectious influenza encephalopathy. One of these patients had static encephalopathy and an underlying seizure disorder (Table II). One patient was infected with influenza A and the other with influenza B. Both patients’ CSF cytochemical analysis and neuroimaging study results were normal. Neither patient sustained permanent neurologic sequelae or death.

An additional 6 patients experienced other neurologic complications: 4 patients sustained cerebral infarction after hypotension, and 2 patients were found to have aseptic meningitis. Among the 4 patients with cerebral infarction, 3 had a NNMD. Two of the patients were younger than 5 years, and 2 were infected with influenza A virus.

Two patients had aseptic meningitis. Their ages were 3 months and 2.5 months. Each patient had a mild mononuclear cell pleocytosis of 12 and 13 white blood cells, respectively. One patient was infected with influenza A virus and the other with influenza B virus.

INC occurred in 14 patients (12 with seizures, 2 with encephalopathy) in our neighborhood cohort. On the basis of a calculated 340,540 child-years of observation, we estimated that the incidence of INC was 4.1 cases per 100,000 child-years (95% CI, 2.3-6.9). To assess the impact of referral bias...
on this estimate, we also calculated the incidence of INC for a subgroup of patients who lived in 6 zip code areas with >90% admission to the study hospital. On the basis of a calculated 283,252 child-years of observation, the incidence of INC in this cohort was 4.6 per 100,000 child-years (95% CI, 2.4-7.8).

Possible risk factors for INC are shown in Table III. With univariate analysis, the risk for INC varied by age; patients aged 2 to 4 years were at greatest risk (OR, 10.0; 95% CI 3.4-29.2). Compared with previously healthy patients, an INC was more likely to develop in patients with a pre-existing NNMD (OR, 6.6; 95% CI, 3.9-11.1). Neither influenza type nor influenza season was a risk factor for INC. Multivariate analysis to determine the age-adjusted risk of INC is shown in Table III. After adjusting for age, the presence of a pre-existing NNMD was independently associated with the development of a neurologic complication (OR, 5.6; 95% CI, 3.2-9.6).

### DISCUSSION

In this report, we examine the characteristics, incidence, and risk factors for INC in a large cohort of children living in the United States. The incidence of INC was approximately 4 cases per 100,000 child-years. Patients between the ages of 2 and 4 years and patients with a pre-existing NNMD were at greatest risk for developing an INC. Seizures were the most common INC. Influenza encephalopathy occurred in a small proportion of patients hospitalized with LCI infections. In addition, we observed that cases of influenza encephalopathy were rare.

In this study, INC occurred in approximately 10% of children hospitalized with LCI. Seizures were the most common INC, and most were consistent with febrile seizures. Some investigators have speculated that influenza virus causes seizures directly, although a mechanism is unknown. Other investigators have reported that febrile seizures are common. We suspect that many influenza-related seizures are caused by the fever associated with the infection, particularly in patients with pre-existing NNMD and a lower seizure threshold.

Influenza encephalopathy has received much attention in the past decade because of the reports of severe and frequent disease observed by Japanese investigators. Our findings suggest that the incidence and characteristics of influenza encephalopathy in the United States might differ from that observed in Japan. In our study, influenza encephalopathy was observed in 1% of patients hospitalized with LCI, and only 1 patient experienced permanent neurologic sequelae. The mechanism by which influenza causes encephalopathy remains unclear. Although we did not observe abnormal findings on neuroimaging studies, case reports of influenza encephalopathy from the United States have observed cerebral edema and symmetric bilateral thalamic and cerebellar lesions in some patients. In Japan, neuroimaging results have been found to be abnormal in as many as 75% of cases; cerebral edema was observed most commonly. Similar to other studies, most of our patients had no evidence of inflammation with CSF analysis. It has been shown sporadically that influenza can be amplified from the CSF. Finally, none of the patients with influenza encephalopathy in our cohort died. In contrast, mortality rates have been reported to be as high as 25% to 37% in Japan. During the 2003-04 influenza season, 153 influenza-associated deaths occurred in children in the United States.
States, and 6% of these were attributed to encephalopathy. A case series from the same season observed no deaths in a group of patients with encephalopathy.

To our knowledge this report provides the first estimates of the incidence of INC in children hospitalized in the United States; each year, approximately 4 of 100,000 children will be hospitalized for influenza and experience a neurologic complication. Limiting our incidence calculations to a geographically defined cohort decreased the contribution of referral bias to the estimate of INC incidence. However, the zip code areas surrounding the hospital represent an urban population that is predominantly African American, and approximately one-quarter of the families have incomes below the poverty level, and so our findings may not be generalizable to the rest of the country. We did not calculate the incidence of influenza-associated encephalopathy because of its uncommon occurrence. Although the incidence of INC or influenza encephalopathy in children living in Japan is unknown, recent observations suggest that it might be much higher. Morishima and colleagues reported 148 cases of influenza-associated encephalopathy during a single season.

Risk factors associated with the development of INC have not been described previously. Patients between the ages of 6 months and 4 years were at increased risk for INC compared with patients in other age groups; the risk of INC was greatest in patients 2 to 4 years of age. Age-related risk of INC is partially attributable to the frequency of febrile seizures in this cohort. In addition, the presence of pre-existing NNMD was independently associated with the development of INC, a previously unrecognized association. This is not unexpected, because patients with NNMD, especially those with underlying seizure disorders, may have increased seizure activity during an acute illness. Our findings provide additional support to the recent recommendation that children with NNMD receive annual influenza vaccination.

Although this study provides useful information about INC, it has several limitations. First, we presume that some ascertainment bias influenced the assembly of our cohort. Morishima and colleagues observed that only 36% of children with acute encephalopathy had cough and 18% had rhinorrhea. Because influenza diagnostic testing is routinely performed on patients with acute respiratory tract symptoms, we might have failed to identify patients with INC who lacked associated respiratory tract symptoms. Second, we did not obtain CSF for the testing of influenza viral genome. Next, the definition of acute influenza-related encephalopathy is somewhat arbitrary and may both under- and over-identify patients with the acute onset of neurologic symptoms. However, we elected to use the Centers for Disease Control and Prevention case definition to facilitate comparison with other reports.

Additionally, this study reports from only 1 geographic location within the United States, and therefore the incidence and spectrum of disease could be different in other areas. Finally, we did not examine the potential effects that antiviral medications had on either the development of INC or the outcome of patients with INC.

REFERENCES


Pediatrics Workforce: A Look at Developmental-Behavioral Pediatrics Data from the American Board of Pediatrics

LINDA A. ALTHOUSE, PHD, AND JAMES A. STOCKMAN, III, MD

This report, which is part of a series discussing workforce trends for general pediatrics and related subspecialty areas, highlights the American Board of Pediatrics’ (ABP) workforce data for developmental-behavioral pediatrics. Readers are encouraged to read the initial report in the series, because it provides information about general pediatrics and summary information about other ABP subspecialties.

In 2002, developmental-behavioral pediatrics became the 13th ABP subboard to offer a certification examination, with the first examination yielding 300 board-certified developmental-behavioral pediatricians. Today, >400 pediatricians have been certified by the ABP in developmental-behavioral pediatrics. The focus of this report is to provide a snapshot of the current ABP workforce data for this subspecialty. The full ABP workforce data are available on the ABP Web site at www.abp.org.

METHODS

As described in the initial report, the ABP uses 3 primary methods to collect and maintain data about workforce numbers: tracking of residents and fellows, examination application surveys, and continual maintenance of the ABP master database as individuals become certified.

Tracking for first-year fellows began in 1995. By 1997-98, all subspecialty fellows in all training levels were tracked. Although tracking in developmental-behavioral pediatrics initially began in 2001-02, the tracking data (Table I) in this report will focus only on data from 2004-05, because earlier data were not complete; many programs were not yet being accredited, and there was crossover in training and, subsequently, tracking with neurodevelopmental pediatrics. Tracking data earlier than 2004-05 can be found on the ABP Web site, but should be used with caution.

In 2005, the ABP contacted all accredited training programs in developmental-behavioral pediatrics in the United States (n = 46) and Canada (n = 4) to obtain tracking information. All programs except 9 returned their tracking information, yielding a return rate of 82.4%.

RESULTS

Developmental-Behavioral Pediatrics Fellow Tracking

Table I provides the total number of fellows in training since the 2004 academic year, with a breakdown by sex and medical school. The number of fellows enrolled in developmental-behavioral pediatrics in the 2 tracking years was fairly consistent, with 75 trainees in 2004 and 76 trainees in 2005. The total percentage of women in developmental-behavioral pediatrics training is currently 77.6%, making it the second most selected subspecialty for women, behind adolescent medicine. The percentage of American Medical School Graduates (AMG) fellows is currently 82.9%.

Developmental-Behavioral Pediatrics Career Data

The ABP has 2 primary opportunities to gather information about career interest in developmental-behavioral pediatrics: a survey given to all first-time applicants for the general pediatrics certification examination and a survey given to all first-time applicants for the developmental-behavioral pediatric certification examination. This section highlights results from both the 2005 general pediatrics and 2004 developmental-behavioral pediatrics applications. (No developmental-behavioral pediatrics examination was administered in 2005).

Of the 2994 first-time candidates applying for the general pediatrics certification examination in 2005, 866 (29%) indicated an interest in 1 of the subspecialty areas in ABP American Board of Pediatrics
AMG American Medical School Graduates
FOPE II Future of Pediatric Education II From the American Board of Pediatrics. Submitted for publication Nov 22, 2006; accepted Nov 30, 2006. Correspondence: Linda A. Althouse, PhD, American Board of Pediatrics, 111 Silver Cedar Court, Chapel Hill, NC 27514. E-mail: laa@abpeds.org. J Pediatr 2007;150:311-2 0022-3476/$ - see front matter Copyright © 2007 Mosby Inc. All rights reserved. 10.1016/j.jpeds.2006.11.061

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which the ABP awards or jointly awards certificates. Developmental-behavioral pediatrics was selected by 1.8% of these 866 applicants, making it the 13th most selected pediatric subspecialty.

The developmental-behavioral pediatrics certifying examination is given every 2 years. In 2004, there were 114 first-time applicants. Of these applicants, 62.3% were women and 81.6% were AMG fellows. Approximately 38.6% of applicants planned to practice exclusively in developmental-behavioral pediatrics in an academic setting. An additional 19.3% of applicants planned to practice exclusively in developmental-behavioral pediatrics, but in a private practice or combined private practice and academic setting.

Certified Diplomates

As a pediatric subspecialty, developmental-behavioral pediatrics is one of the smallest disciplines, with approximately 427 certified practitioners (as of Dec 31, 2005) since the first exam in 2002. Only rheumatology and the 3 jointly administered subspecialties (neurodevelopmental diseases, sports medicine, and medical toxicology) have fewer pediatric specialists. The mean age of certified developmental-behavioral pediatricians is 50.6 years, with approximately 99% ranging in age from 31 to 65 years.

The ratio of current ABP-certified developmental-behavioral pediatricians-to-children younger than 18 years in each of the 50 states and the District of Columbia is shown in Table II (available at www.jpeds.com). The population of children listed in the table is based on the US Census Bureau Population Estimates and includes all children younger than 18 years. These numbers are based on a list of developmental-behavioral pediatricians with known addresses in 1 of the 50 states or the District of Columbia. Developmental-behavioral pediatricians older than the average retirement age of 65 years were excluded. On the basis of these adjustments, the total number of certified developmental-behavioral pediatricians categorized in Table II is 402.

Ten states have a pediatric developmental-behavioral pediatrician-to-child ratio of at least 1 per 100,000 children, with Rhode Island having the largest ratio (2.5), followed by Massachusetts (2.4). The remaining states have a ratio <1; no certified developmental-behavioral pediatricians practice in Alaska, Kentucky, New Hampshire, North Dakota, or Wyoming.

The 46 US developmental-behavioral pediatric training programs are distributed in 29 states and the District of Columbia, as noted by the asterisk in Table II. Five training programs are located in Canada. The number in parentheses denotes the number of training programs in the state that were tracked during the 2005-06 tracking period.

DISCUSSION

Although many studies have projected physician workforce needs, it was not until the Future of Pediatric Education II (FOPE II) task force report that a recent and detailed study focused exclusively on pediatrics, both at the generalist and subspecialty level.5,4

Although the data in Table II provide the developmental-behavioral pediatrician-to-child ratio, the data do not indicate which pediatricians are working full-time or part-time. General pediatrics research has shown an increasing trend toward part-time work, particularly with the increase in the number of women entering pediatrics.5,6 However, there are no current data to indicate that this is the case in developmental-behavioral pediatrics. Further research is needed. Studies have reported that women in subspecialties are equally likely to work full time and treat an equal number of patients as their male colleagues.5,7

Although it is important to have an adequate number of physicians, where these physicians practice is just as critical in determining whether appropriate care is available to all children. As aforementioned, currently 5 states do not have an ABP-certified developmental-behavioral pediatrician. In addition, the FOPE II survey results indicate that only 7% of developmental-behavioral pediatricians practice in rural areas.5,4

Also contributing to a growing need for developmental-behavioral pediatricians, the FOPE II survey results indicated that 36% developmental-behavioral pediatricians believe that the volume of the referrals has increased; 44% also believe that the referral complexity has increased. However, approximately 37% of developmental-behavioral pediatricians anticipated that their communities will not need additional subspecialists in the next 3 to 5 years.3,4

As Stoddard et al note, the FOPE II study provides the supply-side perspective.4 The ABP data in this report provide the same perspective. These data are useful not only to those studying workforce trends, but also to medical students and pediatric residents making career decisions. However, these data do not address or gauge the need for medical services.

Although workforce studies are not new, attention to workforce issues for pediatric subspecialties is relatively new. With developmental-behavioral pediatrics being a relatively new subspecialty, additional years of tracking will be needed before trends can be surmised. It is important that workforce research continues from both the supply and demand perspective. Only then can we be sure that the goal of providing all children with access to high-quality care be met.


Table I. Total number of developmental-behavioral fellows in training since 2004

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Female</th>
<th>Male</th>
<th>AMG</th>
<th>IMG</th>
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<tr>
<td>2004-05</td>
<td>75</td>
<td>72.0%</td>
<td>28.0%</td>
<td>76.0%</td>
<td>24.0%</td>
</tr>
<tr>
<td>2005-06</td>
<td>76</td>
<td>77.6%</td>
<td>22.4%</td>
<td>82.9%</td>
<td>17.1%</td>
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</tbody>
</table>

AMG, American medical school graduate; IMG, International medical school graduate.
REFERENCES


Table II. Number of American Board of Pediatrics-certified developmental-behavioral pediatric diplomates by state

<table>
<thead>
<tr>
<th>State</th>
<th>Number of ABP diplomates in developmental-behavioral pediatrics</th>
<th>Child population</th>
<th>Physician-to-child ratio (per 100,000 children)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alabama</td>
<td>2</td>
<td>1,094,533</td>
<td>0.2</td>
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<tr>
<td>Alaska</td>
<td>0</td>
<td>188,229</td>
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<tr>
<td>Arizona</td>
<td>5</td>
<td>1,547,260</td>
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<tr>
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<td>3</td>
<td>676,550</td>
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<tr>
<td>California*(7)</td>
<td>38</td>
<td>9,596,463</td>
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<td>3</td>
<td>1,178,889</td>
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<td>Connecticut*(1)</td>
<td>14</td>
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<td>Delaware</td>
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<td>193,506</td>
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<td>District of Columbia</td>
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<td>109,547</td>
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<td>4</td>
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<td>Kentucky*(1)</td>
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<td>Louisiana</td>
<td>3</td>
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<td>Maine</td>
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<td>Missouri*(1)</td>
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<td>1,384,542</td>
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<td>Montana</td>
<td>1</td>
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<td>Ohio*(3)</td>
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<td>Oregon*(1)</td>
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<td>Tennessee*(1)</td>
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<td>Texas*(1)</td>
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<td>740,114</td>
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<td>Vermont</td>
<td>3</td>
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<td>10</td>
<td>1,804,900</td>
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<td>Washington*(2)</td>
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<td>West Virginia</td>
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<td>Wisconsin*(1)</td>
<td>1</td>
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<tr>
<td>Wyoming</td>
<td>0</td>
<td>116,932</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>402</td>
<td>73,277,998</td>
<td>0.5</td>
</tr>
</tbody>
</table>

As of Dec 31, 2005.

*States with a developmental-behavioral pediatrics training program. The number in parentheses indicates the number of programs tracked in the 2005-06 academic year.
Neonatal Cholestatic Jaundice as the First Symptom of a Mutation in the Hepatocyte Nuclear Factor-1β gene (HNF-1β)

DOMINIQUE BECKERS, MD, CHRISTINE BELLANNE-CHANTELOT, PHARM.D, PH.D, AND MARC MAES, MD, PH.D

This report describes the phenotype of a novel de novo heterozygous frameshift mutation in the hepatocyte nuclear factor-1β gene (HNF-1β or TCF2) manifest as a neonatal paucity of intrahepatic bile ducts. HNF-1β mutations should be considered in neonates with cholestatic jaundice associated with renal malformation or diabetes mellitus. (J Pediatr 2007;150:313-4)

Maturity-onset diabetes of the young type 5 (MODY5) was first described in 1997.1 The clinical spectrum is broad,2-4 consisting of renal morphologic abnormalities and/or nondiabetic renal dysfunction and/or non-autoimmune diabetes mellitus that may be associated with pancreatic atrophy and exocrine deficiency, genital malformations, slightly elevated liver enzymes, and neonatal cholestasis.5 Until now, 50 heterozygous mutations in the hepatocyte nuclear factor-1β (HNF-1β) gene have been described in adults and young children, most frequently presenting insulin-dependent diabetes and renal morphologic or functional anomalies.2-4

CASE STUDY

This patient was originally described in 1996 by Devriendt et al6 as having atypical Alagille syndrome. The child is now 18 years of age, and an HNF-1β mutation has recently been established. The patient was a growth-retarded male infant (weight, 1520 g [−4.24 SDS]; length, 42 cm [−3.45 SDS]) born at 37 weeks of gestation from healthy parents of Sardinian origin. In the first weeks of life, he had progressive jaundice and a slightly enlarged liver (Table). The only abnormal finding was a hyperechogenicity of intrahepatic bile ducts.

Hepato-IDA scintigraphy, performed at 2 months of age, showed no passage of bile and the liver biopsy paucity of intrahepatic bile ducts with severe biliary stasis and slight periportal fibrosis. A second liver biopsy at the age of 21 months showed a less severe picture, with absence of biliary sludge, in agreement with the disappearance of the patient’s icterus and pruritus at 1 year of age. Because of the growth retardation, the cholestasis, the bilateral posterior embryotoxon, and a typical facies, a diagnostic of incomplete Alagille syndrome was reported in 1996.6 No mutation was found within the Jagged 1 gene responsible for at least 90% of the Alagille syndrome.7

Between 5 and 18 years, liver enzymes fluctuated up to 2 times the upper normal range. Between 12 and 15 years, the patient had 3 episodes of cholangitis. The hepato-IDA scintigraphy remained normal, but he still needed ursodesoxycholic acid treatment. In addition, high triglyceridemia (300 mg/dL) was present with a progressive and spontaneous normalization at 5 years of age. Agenesia of the left kidney and an enlarged and hyperechogenic right kidney were found during the neonatal period, but renal function was normal. Multiple cortical cysts appeared after a few months, with deterioration of renal function at 19 months. At 8 years, no renal cysts could be demonstrated on ultrasound. The renal function, based on glomerular filtration rate, progressively decreased from 79 to 58 mL/min per 1.73 m² (Table). During the neonatal period, a 48-hour intravenous insulin therapy was needed to control an episode of hyperglycemia occurring during parenteral feeding. At 5 years (body mass index, 13.4 kg/m² [−2 SD]), he presented a permanent non-autoimmune diabetes, without ketoacidosis, treated with 2 injections of rapid and long-acting insulin (1.26 Units/kg per day). Until now, metabolic control had been remarkably good, with a HBA1-C <7% (4% to 6%).

When diabetes was diagnosed, the pancreas was described as moderately atrophic on ultrasound. Three-day stool collection demonstrated a mild increase in fat excretion consistent with a mild exocrine pancreatic deficiency. At 16 years, the pancreas was

<table>
<thead>
<tr>
<th>HNF-1β</th>
<th>Hepatocyte nuclear factor-1β</th>
<th>MODYS</th>
<th>Maturity-onset diabetes of the young</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From the Department of Pediatrics, Division of Pediatric Endocrinology, Catholic University of Louvain, Yvoir, Belgium (D.B.); the Department of Cytogenetics, AP-HP Saint-Antoine, Université Pierre et Marie Curie-Paris, Paris, France (C.B.C.); and the Department of Pediatrics, Division of Pediatric Endocrinology, Catholic University of Louvain, Brussels, Belgium (M.M.).

Submitted for publication May 17, 2006; last revision received Oct 5, 2006; accepted Dec 6, 2006.

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10.1016/j.jpeds.2006.12.006
months, he reached his final height (162.1 cm [−1.62 SD]), was identified in exon 2 of HNF-1α. This frame-shift change with Alanine 167 as the first affected amino acid is predicted to lead to a premature stop codon at position 193. The parents were not carriers of the mutation, and parental relationships were confirmed by genotyping microsatellite markers, suggesting that this event occurred spontaneously.

**DISCUSSION**

This is an unusual case description of a patient with HNF-1β mutation presenting as neonatal cholestasis with an 18-year-long follow-up. A similar case presentation has been recently reported with a shorter follow-up period. Both mutations are located in the POU-specific domain implicated in the DNA recognition. Coffinier et al described a decreased number of intrahepatic bile ducts in mice with liver-targeted deletion of HNF-1β resembling the hepatic phenotype of patients with Alagille syndrome. Therefore, it is not surprising that our patient was initially thought to be affected with Alagille syndrome. However, the coexistence of neonatal dystrophic kidney disease with the onset of insulin-dependent diabetes at 5 years of age led to the reconsideration of his diagnosis when the first series of these evolving features over time remain unexplained.

In conclusion, the presence of cholestasis caused by paucity of bile ducts associated with dysplastic kidney disease in an intrauterine, growth-retarded newborn infant and the later occurrence of insulin-dependent diabetes should raise the possibility of HNF-1β gene mutation. In addition, the evolving phenotype of these children, as in our patient, requires a long-term follow-up for optimal care.

<table>
<thead>
<tr>
<th>Table. Evolution of liver and renal function over time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver function</strong></td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
</tr>
<tr>
<td>Total/direct AST (IU/L)</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
</tr>
<tr>
<td>JGT (IU/L)</td>
</tr>
<tr>
<td>Bile acids (&lt;10 μmol/L)</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
</tr>
</tbody>
</table>

**Renal function**

- Blood urea nitrogen (mg/dL): 8/67/43/64/58
- Creatinine (mg/dL): 1.2/0.6/0.62/1.51/1.5
- GFR (mL/min per 1.73 m²): 79/58/58/58
- Microalbuminuria (μg/min): -

**REFERENCES**

5. Kitanaka S, Miki Y, Hayashi Y, Igarashi T. Promoter-specific repression of hepatocyte nuclear factor (HNF)-1β and HNF-1α transcriptional activity by an HNF-1β missense mutant associated with type 5 maturity-onset diabetes of the young with hepatic and biliary manifestations. J Clin Endocrinol Metab 2004;89:1369-78.
Transient Neonatal Hypothyroidism is Associated with Elevated Serum Anti-Thyroglobulin Antibody Levels in Newborns and Their Mothers

ARASH ORDOOKHANI, MD, PARVIN MIRMIRAN, PhD, PAUL G. WALFISH, CM, MD, AND FEREIDOUN AZIZI, MD

Transient congenital hypothyroidism (TCH) was detected in 6 of 35,067 newborns (1:5845 births) screened in Iran. Antithyroglobulin antibodies positivity was present in 4 of 6 (66.7%) of those with TCH and in 6 of 106 (5.7%) of those with "transient hyperthyrotropinemia and normal" diagnoses ($P = .0005$), but positivity was similar in newborns with transient hyperthyrotropinemia versus normal neonates ($P = .397$). (J Pediatr 2007;150:315-7)

METHODS

Screening for congenital hypothyroidism (CH) was initiated in 1998 in seven hospitals in different parts of Tehran and in the general hospital and the rural birth center of Damavand (a city north to Tehran with a population of 66,000) using TSH as the primary screening test. Until August 2002, cord dried blood spot samples were collected in all liveborn neonates and cord TSH ≥20 mIU/L were considered abnormal and were used as the criterion for infant recall. Upon recall, newborns with serum TSH >10 mIU/L and total thyroxine (T4) <84 nmol/L or TSH >30 mIU/L alone (regardless of T4 levels) were considered to have CH, and those with normal serum TSH and T4 values were considered to have transient hyperthyrotropinemia (THT). CH-affected neonates and their mothers were immediately recalled again, and neonatal serum TSH, T4, thyrotropin receptor autoantibodies (TRAb) and thyroid peroxidase antibodies (TPOAb), TgAb, and urinary iodine concentration (UIC) of spot urine samples and maternal serum TSH, free thyroxine, TRAb, TPOAb, TgAb, and spot UIC were assessed.

Levothyroxine replacement therapy (10-15 μg/kg/day) was initiated in hypothyroid neonates. At 3 years of age, Levothyroxine was withheld for 4 to 6 weeks in children in the CH-affected newborn group with orthothropic thyroid (diagnosed by thyroid 131I-technetium-pertechnetate scintigraphy and ultrasonography [US]), and normal serum TSH and T4 confirmed TCH. This schedule continued until September 2003. TCH diagnoses that were made before 2 years of age were reconfirmed, at least once, by serum TSH and T4 re-testing. Sixty-two mature infants with THT and 44 mature normal (i.e., cord TSH <20 mIU/L) newborns were randomly selected as control groups. The study protocol was approved by the appropriate Human Research Committee of Shaheed Beheshti University of Medical Sciences. Where required, informed written consent was obtained from the parents.

Laboratory Methods

Cord TSH (two-site immunoradiometric assay) was measured by NETRIA kits (RAW/6/003 Project, International Atomic Energy Agency) and serum TSH (immuno-
radiometric assay) and T4 (radioimmunoassay) by Spectria kits (Orion Diagnostica, Finland). Serum free thyroxine and TRAb (DRG Diagnostics, Marburg, Germany) and TPOAb and TgAb (RADIM, Italy) were assayed by the enzyme-linked immunosorbent assay method. TgAb was assayed using sera incubated in the polystyrene wells coated with purified human Tg. The absorbance of calibrators, controls, and samples were measured using a plate reader with wavelength set at 450 nm. Minimum detectable value was 11 IU/mL. Intraassay coefficient of variation at concentrations of 98.5 IU/mL, 307 IU/mL, and 976 IU/mL were 8.5%, 4.9%, and 4.4%, and interassay coefficient of variation at concentrations of 97 IU/mL, 296 IU/mL, and 962 IU/mL were 14.3%, 11.8%, and 13.4%, respectively. UIC was measured by Sandell-Kolthoff digestion method. Abnormal (positive) TPOAb and TgAb were 100 IU/mL and 150 IU/mL, respectively.

Mann-Whitney and Kruskal-Wallis tests were used for quantitative and Fisher’s exact test was used for categorical variables. Correlation between neonatal TPOAb and TgAb was assessed by Spearman’s rank correlation test. Statistical analyses were performed using the Statistical Package for the Social Sciences, version 9.05 software package (SPSS, Inc., Chicago, Ill). Significance was established at $P < .05$.

**RESULTS**

A total of 35,067 newborns (32,397 [92.4%] from Tehran and 2670 [7.6%] from Damavand) were screened by August 2002. Six (1:5845 births) neonates had TCH who were mature ($\geq$37 weeks’ gestation) and weighed between 2510 and 3950 g at birth.

Positive TPOAb and/or TgAb were present in 16 (14.3%) of 112 (6 TCH, 62 THT, and 44 normal) newborns. Positive TgAb frequency was significantly higher in TCH than in THT and normal neonates, whereas positive TPOAb frequency was similar among groups (Table I). A box-and-whisker plot of TgAb in newborns with TCH and THT, and in normal newborns is shown in the Figure. Follow-up of newborns with TCH showed serum TgAb was 20 to 64 IU/mL, 23 to 40 IU/mL, and 14 to 25 IU/mL between 3 and 5, 6 and 8, and 11 and 14 months of age, respectively.

**Table I. Frequency distribution of thyroid autoantibodies in newborns with TCH and THT, and in normal newborns**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>TPOAb Positive (≥100 IU/mL)</th>
<th>TPOAb Negative (&lt;100 IU/mL)</th>
<th>TgAb Positive* (≥150 IU/mL)</th>
<th>TgAb Negative* (&lt;150 IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCH</td>
<td>0 (0)†</td>
<td>6 (100)</td>
<td>4 (66.7)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>THT</td>
<td>8 (12.9)‡</td>
<td>54 (87.1)</td>
<td>5 (8.1)‡</td>
<td>57 (91.9)</td>
</tr>
<tr>
<td>Normal</td>
<td>3 (6.8)</td>
<td>41 (93.2)</td>
<td>1 (2.3)</td>
<td>43 (97.7)</td>
</tr>
<tr>
<td>Total</td>
<td>11 (9.8)</td>
<td>101 (90.2)</td>
<td>10 (8.9)</td>
<td>102 (91.1)</td>
</tr>
</tbody>
</table>

$^\dagger$Values in parentheses show percentage.

‡Five newborns had both positive TPOAb and TgAb and three had only positive TPOAb.

§TCH vs. THT and normal newborns.

$^*$Odds ratio (95% CI) of TgAb positivity was similar in THT vs. normal neonates ($P = .397$).

$^\dagger$Odds ratio (95% CI) in TCH vs. THT was 22.8 (3.32-156.75; $P = .002$) and in TCH vs. normal newborns was 86 (6.32-1169.47; $P = .0003$). TgAb positivity was similar in THT vs. normal neonates ($P = .303$).

$^\dagger$Values in parentheses show percentage.

$^\ddagger$Five newborns had both positive TPOAb and TgAb and three had only positive TPOAb.

$^\S$TCH vs. THT and normal newborns.

$^\S$TCH, transient congenital hypothyroidism; THT, transient hyperthyrotropinemia.

**Figure.** Box-and-whisker plot, showing 2.5, 25, 50, 75, and 97.5 cumulative relative frequencies (centiles) of TgAb in newborns with TCH ($n = 6$) and THT ($n = 57$), and in normal ($n = 44$) newborns (excluding 5 neonates with THT whose TgAb values were lower than the detection limit of the kit). “X” indicates Outliers. Median (range) TgAb values in newborns with TCH and THT, and in normal newborns were 274 (40-851) IU/mL, 30 (11-200) IU/mL, and 21.1 (12-179.5) IU/mL (Kruskal-Wallis test; $P < .0001$), respectively. Median TgAb was significantly different in TCH versus THT ($P = .0002$), in TCH versus normal ($P < .0001$), and in THT versus normal neonates ($P = .007$) using Mann-Whitney test. Excluding positives, median (range) TgAb values in newborns with TCH and THT, and in normal newborns were 274 (40-851) IU/mL, 30 (11-200) IU/mL, and 21.1 (12-179.5) IU/mL (Kruskal-Wallis test; $P < .0001$), respectively. Median TgAb was significantly different in TCH versus THT ($P = .0002$), in TCH versus normal ($P < .0001$), and in THT versus normal neonates ($P = .007$) using Mann-Whitney test. Excluding positives, median (range) TgAb values in newborns with THT ($n = 52$) was 27.5 (11-133) IU/mL and in normal newborns ($n = 43$) was 20.8 (12-57.7) IU/mL (Mann-Whitney test; $P = .021$). TCH, transient congenital hypothyroidism; THT, transient hyperthyrotropinemia.
Characteristics of newborns with TCH and their mothers are shown in detail in Table II (available at www.jpeds.com). History of maternal consumption of goitrogens and thyroid-affecting medications was negative, and TCH was not associated with low and excessive neonatal UIC.

**DISCUSSION**

Our study indicates that TCH is attributable to maternal autoimmune thyroid disease in an iodine-replete area. However, TRAb (although not bioassayed) did not seem to produce TCH because none of newborns had high TRAb levels. TPOAb and TgAb apparently have no pathogenetic effect on fetal and neonatal hypothyroidism.\(^5,6\) Antimicrobial antibodies were assessed in primary CH\(^7\) and in a significant number of (n = 78) neonates with TCH.\(^8\) Positive TPOAb were present in 17.5\% of 40 newborns with TCH in Italy.\(^9\)

Studies on TgAb and CH are less frequent. Lack of association between CH (not specifically TCH) and TgAb have been reported previously.\(^10\) The association between elevated TgAb and TCH occurrence in our population may be considered as new evidence in favor of the pathogenetic role of TgAb. Salt iodization in Iran may cause the 14.3\% prevalence of positive TPOAb and/or TgAb, but this would not explain the difference in frequency of TgAb positivity among groups.

Positive levels of thyroid hormone autoantibodies (THAb) coexist with positive TgAb values in 50\% of cases.\(^11\) High concentrations of THAb might cause hypothyroidism in a patient with no thyroid reserve, and THAb probably represents a subset of TgAb that interact with Tg epitopes containing the iodothyronines.\(^12\) TgAb or a subset of TgAb (e.g., THAb) may contribute to TCH in some neonates with little thyroid hormone reserve. Further studies on TgAb (and THAb) in newborns and infants with TCH are warranted.

The authors are indebted to the parents of the children for making the study possible. We are thankful to the staff of the laboratory of Endocrine Research Center, Shaheed Beheshti University of Medical Sciences.

**REFERENCES**

Table II. Characteristics of neonates with TCH and their mothers, 1998-2003*

<table>
<thead>
<tr>
<th>No.</th>
<th>Cord DBS TSH (mIU/L)</th>
<th>Serum TSH (mIU/L)</th>
<th>Serum T4† (nmol/L)</th>
<th>Serum TPOAb (IU/mL)</th>
<th>Serum TgAb (IU/mL)</th>
<th>Serum TRAb (IU/L)</th>
<th>Thyroid 99mTc (US)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>122</td>
<td>13‡ (1.8)</td>
<td>72‡ (18)</td>
<td>19 (15)</td>
<td>40 (35)</td>
<td>0.9 (0.9)</td>
<td>NG (—)</td>
</tr>
<tr>
<td>2</td>
<td>493</td>
<td>130 (1.2)</td>
<td>36 (12)</td>
<td>17 (18)</td>
<td>50 (47)</td>
<td>1.2 (1.2)</td>
<td>G (—)</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>31¶ (48)</td>
<td>81¶ (15)</td>
<td>4.0 (&lt;4.0)</td>
<td>228 (773)</td>
<td>2.2 (1.3)</td>
<td>NG (—)</td>
</tr>
<tr>
<td>4</td>
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<td>41 (2.0)</td>
<td>168 (27)</td>
<td>5.0 (4.0)</td>
<td>337 (521)</td>
<td>2.1 (0.8)</td>
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</tr>
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<td>5</td>
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<td>42 (32)</td>
<td>124 (3.9)</td>
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<td>320 (275)</td>
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<td>86 (—)</td>
<td>4.0 (—)</td>
<td>851 (—)</td>
<td>2.7 (—)</td>
<td>— (—)</td>
</tr>
<tr>
<td></td>
<td>n.v.</td>
<td>&lt;20</td>
<td>1.7-9.1§ (0.4-4.0)</td>
<td>106-221 (10-26)</td>
<td>&lt;100</td>
<td>&lt;150 (—)</td>
<td>±3.0</td>
</tr>
</tbody>
</table>

DBS, dried blood spot; G, goitrous; NG, non-goitrous; —, not done; n.v., normal value; "off-therapy," discontinuation of levothyroxine replacement therapy; 99mTc, Technetium pertechnetate thyroid scan; US, ultrasonography.

*All the values presented in the parentheses in the table display maternal values.
†Values are total T4 (nmol/L) of neonates and those in parentheses are free T4 (pmol/L) of their mothers.
‡Serum values of 30th day of life are shown.
¶Serum values of 38th day of life are shown.
§No blood samples were obtained from the mother of newborn 6 because of her severe injection phobia.
In infants and children 1-12 months and 1-5 years of age, normal serum TSH values are 0.8-8.2 mIU/L and 0.7-5.7 mIU/L and T4 values are 76-210 nmol/L and 94-193 nmol/L, respectively.*
<table>
<thead>
<tr>
<th>Serum TSH (mIU/L)</th>
<th>Serum T4† (nmol/L)</th>
<th>Serum TPOAb (IU/mL)</th>
<th>Serum TgAb (IU/mL)</th>
<th>Age (months)</th>
<th>Duration of “off-therapy” (months)</th>
<th>Serum TSH (mIU/L)</th>
<th>Serum T4 (nmol/L)</th>
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<td>1.4 (1.8)</td>
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<td>8.2 (29)</td>
<td>24 (32)</td>
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<td>7.3 (7.3)</td>
<td>25 (23)</td>
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<td>5</td>
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<td>147</td>
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<tr>
<td>2.4 (1.4)</td>
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<td>&lt;4.0 (&lt;4.0)</td>
<td>40 (774)</td>
<td>6</td>
<td>2.6</td>
<td>1.0</td>
<td>137</td>
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<tr>
<td>4.0 (4.4)</td>
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<td>&lt;4.0 (&lt;4.0)</td>
<td>22 (131)</td>
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<td>5</td>
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<td>&lt;4.0 (21)</td>
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<tr>
<td>0.8-8.2 (0.7-5.7)</td>
<td>76-210 (10-26)</td>
<td>&lt;100</td>
<td>&lt;150</td>
<td>—</td>
<td>0.8-8.2 (0.7-5.7)</td>
<td>76-210</td>
<td>—</td>
</tr>
</tbody>
</table>

Table II. Continued
Peer counselors may improve breastfeeding in the NICU


**Question** Among premature infants in an urban population, do peer counselors improve the duration of breastfeeding compared with standard care?

**Design** Randomized, controlled clinical trial.

**Setting** Neonatal Intensive Care Unit at Boston Medical Center, an inner-city teaching hospital with approximately 2000 births per year.

**Participants** 108 mother-infant pairs whose mother intended and was eligible to breastfeed per the 1997 guidelines from the American Academy of Pediatrics and whose infant was 26 to 37 weeks' gestational age and otherwise healthy.

**Intervention** Peer counseling with weekly visits for 6 weeks or standard of care.

**Outcomes** Any breast-milk feeding at 12 weeks postpartum.

**Main Results** Intervention and control groups were similar on all measured sociodemographic factors. The average gestational age of infants was 32 weeks (range, 26.3-37 weeks) with a mean birth weight of 1875 g (range, 682-3005 g). At 12 weeks postpartum, women with a peer counselor had odds of providing any amount of breast milk 181% greater than women without a peer counselor (odds ratio, 2.81 [95% confidence interval, 1.11-7.14]; \( P = .01 \)).

**Conclusions** Peer counselors increased breastfeeding duration among premature infants born in an inner-city hospital and admitted to the neonatal intensive care unit (NICU). Peer counseling programs can help to increase breastfeeding in this vulnerable population.

**Commentary** The benefits of breastfeeding are internationally recognized. Individuals and organizations have focused considerable effort and research to increase breastfeeding initiation and continuation, yet we remain below national goals. Merewood et al focus on a critically important, growing, and uniquely challenging population—preterm infants in NICUs. Their study provides compelling data that peer support may be beneficial; however, methodological limitations leave unanswered questions and clinical uncertainties. The strengths of the study include assembly of comparable groups at baseline, independent assessment of breastfeeding status, and explicit training and guidelines for counselors. Key limitations include limited outcome definition (“any” breastfeeding), short time-frame (12 weeks), differential loss to follow-up (72% intervention, 85% control), potential for subverting randomization (color-coded assignment), inability to examine or adjust for important factors (eg, gestational age), and lack of intention-to-treat analysis that particularly, given the differential loss to follow-up, may change the effect size. Despite these limitations, the study found that mothers who met weekly for 6 weeks with trained peer counselors were 181% more likely to be breastfeeding at 12 weeks compared with standard care.

A mother’s expectations of feeding and caring for her child (mothering) are shaken when her baby is admitted to the NICU. We do not know the extent to which a mother’s initial expectations and self-determination relate to breastfeeding, but it is likely they play an important role, particularly under adverse conditions. Peer counselors may serve as a bridge between the clinical necessities of caring for a NICU baby and the original dream a mother holds. Although further studies on breastfeeding outcomes (amount, duration, actualized health benefits) and costs are needed, this study is motivating for institutions to evaluate whether establishing and sustaining a peer counselor system is feasible.
Writing a wait-and-see prescription for the treatment of acute otitis media may decrease the use of antibiotics


**Question** Does giving a “wait-and-see-prescription” (WASP) in the emergency department (ED) for the treatment of acute otitis media (AOM) decrease antibiotic use compared with giving a standard prescription (SP)?

**Design** Randomized controlled trial.

**Setting** A pediatric emergency department.

**Participants** Children 6 months to 12 years of age, diagnosed with AOM in the ED.

**Intervention** Children were randomized to receive a WASP (to be filled in 48 hours if still symptomatic) or an SP, with instructions to fill immediately. All children were given ibuprofen and otic analgesic drops.

**Outcomes** Filling of the antibiotics prescription and clinical course of AOM.

**Main Results** Of the 283 patients enrolled in the study, 265 completed the phone interview 4 to 6 days after their visit to the ED. The groups were similar with regards to age, gender, race, symptoms, parental education level, and the percentage of participants receiving Medicaid insurance. Sixty-two percent of parents in the WASP group did not fill the prescription versus 13% in the SP group (P < .001, number needed to treat = 3). There was no statistical difference in frequency of fever, otalgia, or unscheduled medical visits between the groups. Fever (relative risk 2.95, confidence interval 1.75-4.99) and otalgia (RR 1.62, CI 1.75-4.99) were associated with filling the prescription in the WASP group.

**Conclusions** In an ED setting, writing a WASP for the treatment of AOM reduced the use of antibiotics when compared with writing a standard prescription.

**Commentary** AOM is the most common pediatric diagnosis for which antibiotics are given. It is well-documented that many cases of AOM will resolve without the use of antibiotics. In addition, bacterial resistance to antibiotics is a growing problem. Spiro et al present compelling evidence that the use of a WASP may decrease antibiotic use in AOM. When parents bring their children in for care, their primary goal is to help them feel better. In this study, the children whose parents filled their WASP were more likely to have fever and otalgia than children for whom the WASP was not filled. If the symptoms of AOM are relieved with adequate pain control and antipyretics, parents may be more willing to do without antibiotics.

Of 776 patients diagnosed with AOM during the enrollment period, 468 were eligible for inclusion. Exclusion criteria included “toxic” appearance, hospitalization, and antibiotic use within the preceding 7 days. These criteria appropriately excluded those patients with complicated AOM, for whom the use of a WASP may have been inappropriate. However, only 283 of 468 eligible patients were enrolled in this trial. One hundred and thirty-three were not enrolled because parents did not consent and 52 were withheld at “attending physician discretion.” It is unfortunate that >10% (52/468) of the eligible patients were not enrolled in the trial for unspecified reasons. This selection bias may affect the generalizability of the study results. There is one other important caveat to these results: many clinicians treat AOM in the hopes of preventing serious complications such as mastoiditis; this study was not powered to detect differences in such rare, but serious, outcomes.

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A preparticipation screening program can decrease the incidence of sudden cardiac death among young athletes


**Question** Among young competitive athletes, does a preparticipation screening program using electrocardiograms (ECGs) prevent sudden cardiovascular death?


**Setting** Veneto region of Italy.

**Outcomes** Incidence trends of total cardiovascular and cause-specific sudden death in screened athletes and unscreened non-athletes of the same age range over a 26-year period.

**Main Results** During the study period, 55 sudden cardiovascular deaths occurred in screened athletes (1.9 deaths/100,000 person-years) and 265 sudden deaths occurred in unscreened nonathletes (0.79 deaths/100,000 person-years). The annual incidence of sudden cardiovascular death in athletes decreased by 89% (from 3.6/100,000 person-years in 1979-1980 to 0.4/100,000 person-years in 2003-2004; P for trend < .001), whereas the incidence of sudden death among the unscreened nonathletic population did not change significantly. The mortality decline started after mandatory screening was implemented and persisted to the late screening period. Compared with the prescreening period (1979-1981), the relative risk of sudden cardiovascular death in athletes was 0.56 in the early screening period (95% CI, 0.29-1.15; P = .04) and 0.21 in the late screening period (95% CI, 0.09-0.48; P = .001). Most of the
Conclusions The incidence of sudden cardiovascular death in young competitive athletes substantially declined in the Veneto region of Italy following the introduction of a nationwide systematic screening. Mortality reduction was predominantly because of a lower incidence of sudden death from cardiomyopathies that paralleled the increasing identification of athletes with cardiomyopathies at preparticipation screening.

Commentary This study provides observational data regarding the implementation of preparticipation screening of athletes and a time-tested algorithm for how ECGs may be used in this screening. There are several important considerations when examining these results. First, in this population-based observational study, other changes over time could have contributed to the reduction in events. For example, enhanced awareness of exercise-related sudden death, prompted by the Italian screening requirement or by increased recognition of the problem, may have prompted physicians not involved in the screening process to restrict athletes or to evaluate symptomatic athletes or those with a strong family history more carefully. Second, this study did not compare routine use of ECGs to more limited screening using history and physical examination alone. Because ECGs were not examined independently, it is impossible to determine if the ECG added to the other components of the examination.

Third, the screening of Italian athletes was performed by specifically trained physicians, and other less well-trained clinicians may miss subtle ECG changes in at-risk persons, which may increase the rate of false-positive results and unnecessary disqualifications. The extraordinary disqualification rate for Italian athletes suggests that if applied broadly to a large population such as the United States, literally millions of young men and women would be disqualified from participation in competitive sports, many of them unnecessarily. Fourth, the annual death rate before the initiation of the mandatory screening program was 1 per year for 27,000 athletes, which is high compared with other studies. Although the death rate decreased progressively over time, this initial death rate accounts for much of the reduction during the study. And fifth, the lowest annual death rate achieved with screening was 0.4 deaths per 100,000 person-years, similar to the sudden death rate reported for high school and college athletes in the United States between 1983 and 1993. Despite these limitations, these results add important data to the debate on the role of screening (particularly aggressive workup and evaluation of symptomatic athletes) and its components, and insight into how to improve the screening process. For example, in a country such as the United States, all parents of young athletes could be offered voluntary ECG screening, either by their physicians or specialized referral centers, with appropriate follow-up as necessary. This strategy would allow families to understand and accept the risk of false-positive ECG findings, given the low specificity of the screening process. However, only studies involving direct comparison of different screening techniques will provide the type of data necessary to dictate public policy.

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REFERENCE

Swaddling young infants can decrease crying time

Question Among infants with excessive crying, does swaddling and stimulus reduction reduce crying compared with stimulus reduction alone?

Design Randomized, controlled trial.

Setting The Netherlands.

Participants 398 excessively crying infants up to 12 weeks of age.

Intervention Healthcare nurses coached parents for 3 months regarding behavioral modification. Intervention parents were also instructed on how and when to swaddle their infants.

Outcomes Crying, as measured by Barr’s 24-hour diary, and parental perception of crying.

Main Results Crying decreased by 42% in both groups after the first intervention week. Swaddling had no added benefit in the total group. Young infants (1-7 weeks of age at randomization) benefited significantly more from swaddling as shown by a larger decrease of crying over the total intervention period. Older infants (8-13 weeks of age at randomization) showed a significantly greater decrease in crying when offered the standardized approach without swaddling. The actual difference in crying time was 10 minutes.

Conclusions For older babies, swaddling did not bring any benefit when added to regularity and stimuli reduction in baby care, although swaddling was a beneficial supplementation in excessively crying infants <8 weeks of age.

Commentary This valid, randomized trial sought to evaluate the utility of behavior modification with and without swaddling in infants with parental or healthcare provider
report of excessive crying. The authors used the standard definition of excessive crying: crying greater than 3 hours/day for at least 3 days a week. In both groups, parents were taught baby care that supported regularity and stimuli reduction; the swaddling intervention group added swaddling at all sleep periods. Data were analyzed in blinded fashion and intention to treat was used. Overall, no difference in crying times was found between the two groups. In subgroup analyses, however, younger infants (those <7 weeks of age at time of randomization) benefited from swaddling, whereas older infants benefited only from behavior modification. There was a modest, but significant, decrease in crying time—on the order of 10 to 12 minutes per day. There was no mention as to whether the study was powered to detect a difference in crying time between the two intervention groups. As the authors point out, excessive crying may have significant implications for both infants and caretakers. To date, there is insufficient evidence for multiple other interventions that have been studied for excessive crying. These behavioral interventions appear to be well-received by parents, and swaddling may provide some further benefit in infants younger than 8 weeks of age.

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Rochester, NY

Immediate CT scan followed by early discharge may be appropriate management for selected patients with mild head injury


Question Among children and adults with mild head injury, how do immediate computed tomography (CT) during triage for admission and observation in the hospital compare with regards to outcomes and costs?

Design Pragmatic, non-inferiority randomized trial.

Setting 39 acute hospitals in Sweden.

Participants 2602 patients (≥6 years of age) with mild head injury.

Intervention Immediate CT or admission for observation.

Outcomes Dichotomized extended Glasgow outcome scale (1-7 vs 8). The non-inferiority margin was 5 percentage points.

Main Results At three months, 275 patients (21.4%) in the CT group had not recovered completely compared with 300 (24.2%) admitted for observation. The difference was −2.8 percentage points, nonsignificantly in favor of CT (95% confidence interval −6.1% to 0.6%). The worst outcomes (mortality and more severe loss of function) were similar between the groups. In the patients admitted for observation, there was a considerable delay in time to treatment in those who required surgery. None of the patients with normal findings on immediate CT had complications later. Patient satisfaction with the two strategies was similar.

Conclusions The use of CT in the management of patients with mild head injury is feasible and leads to similar clinical outcomes compared with observation in hospital.

Commentary What is the best strategy for managing mild traumatic brain injury (TBI)? Immediate head CT and rapid discharge if normal, or inpatient admission for observation? Geijerstam and colleagues, writing for the OCTOPUS study group, report on a multicenter, randomized, controlled trial comparing a course of immediate CT scan followed by early discharge for patients versus inpatient observation for mild TBI. Adults and children >6 years (n = 2602) whose mild TBI was defined strictly as a loss of consciousness or posttraumatic amnesia, but without focal neurological deficits and with a Glasgow Coma Scale (GCS) score of 15, were randomized to receive either early head CT and discharge to home if the study was normal, or admission to hospital for observation. Three months after injury, outcome was assessed by the validated, self-reported extended Glasgow outcome scale (GOS-E: 1 = death to 7 = lower, yet good recovery; and 8 = normal). Study compliance was excellent, few patients were lost to follow-up, and crossover was minimal (~8.5%). Analyzed by intention to treat, 3 months after injury 21.4% of patients in the CT group and 24.2% in the observation group had failed to make a complete recovery (ie, had GOS-E of 1 to 7 vs 8), with 95% confidence that the CT-based strategy was no more than 0.03% worse than observation. Outcomes of death and need for neurosurgery were very rare (<0.3%) and not different between the groups. Cost effectiveness was analyzed separately. The study included 920 children 6 to 15 years of age (35% of the study total), none of whom died or required operations. The authors comment that the equivalence between the strategies was maintained over all age groups in the study, but they do not provide age-specific outcome rates or confidence intervals. In BMJ's rapid response section, the authors comment that 3.8% of pediatric CT scans were abnormal, but none required neurosurgical intervention. Although the trial was well-conducted and reported, readers should consider the narrow definition of mild, closed head injury, and that the impact of radiation on young children was not considered in the outcome analysis. Given the low rate of CT findings and adverse outcomes in this population, additional studies in children to isolate the subset of patient who require neither CT nor admission would appear indicated.

Hugh Garton, MD
University of Michigan
Ann Arbor, MI

REFERENCES


The goal of this valid, randomized, controlled trial was to evaluate the immunogenicity of three vaccines (combined diphtheria, tetanus, whole cell pertussis; Haemophilus influenzae type b; and a serogroup C meningococcal glycoconjugate vaccine) and to assess the incidence of reactogenicity after each immunization dose using needles of varying lengths and gauges. The vaccines were administered using either a wide, long needle (23 gauge/0.6 mm diameter, 25 mm), a narrow, short needle (25 gauge/0.5 mm diameter, 16 mm), or a narrow, long needle (25 gauge, 25 mm). Local reactions to diphtheria, tetanus, whole cell pertussis, and H influenzae type b vaccinations decreased significantly with wide, long needles compared with narrow, short needles. The numbers needed to treat with the wide, long needles to prevent local reactions 1 to 3 days after vaccination are 6, 8, and 8 for the three doses. Non-inferiority of the immune response was shown using a wide, long needle rather than a narrow, short needle for serogroup C meningococcal glycoconjugate vaccine and for diphtheria, but not for H influenzae type b or tetanus, although no evidence was found of a decrease. Little difference was found between the two needles of the same length, but varying gauge in local reactions or immune responses. Thus, longer (25 mm) needles are recommended for administration of vaccines in infants.
In the article “Recombinant Human Insulin-Like Growth Factor I (rhIGF-I) and rhIGF-I/rhIGF-Binding-Protein-3: New Growth Treatment Options?” by Rosenbloom, AL, which appeared in the January 2007 issue of The Journal (J Pediatr 2007;150:7-11), the second sentence in the third paragraph (p. 7) that reads, “Intrauterine IGF-I synthesis, however, does not appear to be GH dependent because most patients with genetically determined severe IGF-I deficiency have normal or only minimally reduced intrauterine growth” should read, “Intrauterine IGF-I synthesis, however, does not appear to be GH dependent, because patients with genetically determined severe GH deficiency or GHRD have normal or only minimally reduced intrauterine growth.”

The article, “The Natural History of Euthyroid Hashimoto’s Thyroiditis in Children,” by Radetti et al, which appeared in the December 2006 issue of The Journal (J Pediatr 2006;149:827-32), did not include the following members of the Study Group for Thyroid Diseases of the Italian Society for Pediatric Endocrinology and Diabetes (SIEDP/ISPED):

Cecilia Volta, Parma
Maria Cristina Vigone, Milano
Malgorzata Wasniewska, Messina, Italy

In the article “Duration of Illness is an Important Variable for Untreated Children with Juvenile Dermatomyositis,” by Pachman et al, which appeared in the February 2006 issue of The Journal (J Pediatr 2006;148:247-53), $P$ should be less than ($) not greater than (>) as erroneously indicated in all 14 instances. It refers to the duration of the disease and the corrected copy should read “($P<$ . . .).” (Please note that “=” is correct whenever it appears.)

Also, the author affiliation of “Snyder Children’s Hospital/Long Island (New Hyde Park, New York) should instead read Schneider Children’s Hospital/Long Island.
Down syndrome and GATA1-related transient leukemia

To the Editor:

We read with keen interest the case report of an infant with trisomy 21 mosaicism restricted to the blast clone and transient leukemia.1 We recently cared for an infant with trisomy 21 mosaicism who developed transient leukemia harboring a GATA1 mutation.2 The transient leukemia resolved by 8 weeks of age. Two years after diagnosis, there was fluorescent in situ hybridization (FISH) evidence of trisomy 21 restricted to the hematopoietic organ, and at 2.5 years of age, FISH analysis was normal and there was no molecular evidence of mutated GATA1-positive blasts cells. In our review of the literature, 19% of infants with transient leukemia had acute leukemia 18.5 months after diagnosis.2 Our laboratory recently showed that GATA1 mutations can be exploited to diagnosis and detect minimal residual disease in transient leukemia and acute megakaryoblastic leukemia.3 We concur with the recommendation that all neonates with transient leukemia should be evaluated by standard cytogenetics and FISH for trisomy 21 mosaicism and GATA1 mutations. Moreover, if a GATA1 mutation is identified, this molecular marker can be used to supplement our clinical evaluations of these infants during remission. Infants with trisomy 21-mosaic, GATA1-mutated transient leukemia should be treated in the same fashion as infants with Down syndrome—related transient leukemia.

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REFERENCES

Nasal potential difference in cystic fibrosis diagnosis of very young children

To the Editor:

Neonatal screening may prevent malnutrition and minimize lung damage in infants with cystic fibrosis (CF). Sontag et al noted the diagnostic dilemma presented by children with persistent hypertrypsinemia, 1 or no identified mutation, and borderline sweat test results, or both, after neonatal screening. Three infants in whom CF was previously diagnosed with genotype and positive sweat test had typical CF results (basal PD = -46(SE=2) mV; Amiloride = 16(4) mV; ΔCl free-isoproterenol = -0.2 (SE=0.3) mV). Three other infants, in whom extensive genetic screening showed no CF-causing genotype, had nasal PD profiles similar to those in healthy children (basal PD = -16(SE=6) mV; ΔAmiloride = 7.6(SE=3) mV; ΔCl free-isoproterenol = -12 (-17 to -10) mV).

Among the 6 remaining children, 3 infants had no symptoms and had PD profiles within the reference range (basal PD = -21(5) mV; ΔAmiloride = 5.5(2) mV; ΔCl free-isoproterenol = -8.2 (2) mV). After genetic screening, these genotypes were identified: G622/-, 5T/5T, and F508del/R117H-7T. The 4 others had PD profiles showing little to no change after isoproterenol (basal PD = -30(6) mV; ΔAmiloride = 12(5) mV; ΔCl free-isoproterenol = -0.8(1.5) mV). They had symptomatic lung disease, recurrent bronchial infections, and Pseudomonas aeruginosa or Staphylococcus aureus colonization. Extensive genetic screening identified compound heterozygosity (F508del/R1070W, F508del/R933G, F508del/R11H-7T 12TG-10TG) and F508del/-.

An important issue of CF neonatal screening is the classification of children with persistent hypertrypsinemia, “borderline” sweat test results, and inconclusive CFTR genotypes, because CF may develop with fully expressed pulmonary involvement in some of these children.3 The identification of a subgroup of symptomatic children with CF-like NPD results suggests that disease may develop in these patients and urges extensive genetic screening. Three of the 4 patients with abnormal NPD investigated in our study eventually had 2 mutations identified. Patients with normal PD, borderline sweat test results, and no or only 1 identifiable CF mutation may have atypical CF or just simple heterozygosity. In our study, among the patients with a significant response to isoproterenol, 3 had no mutations identified, 1 was a simple

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heterozygote, and 2 had a mild mutation or the 5T polymorphism.

Children with questionable CF status after neonatal screening should be systematically investigated with NPD and monitored closely in specialized CF centers to clarify their diagnosis and the prognostic value of NPD testing.

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A 1-day-old male neonate developed dyspnea, tachycardia, pallor, feeding difficulty, and jaundice. He was born at term, with a 3.0 kg body weight, by vaginal delivery after an uncomplicated pregnancy. Prenatal diagnosis had not been done. He was noted to have heart murmur, cranial bruit, bounding pulse, and hepatomegaly. Transfontanellar cranial sonography showed vein of Galen aneurysmal malformation (VGAM). Arterial blood gas analysis revealed severe acidemia with pH 7.03 and base excess $-19.8$. Complications also included renal failure and disseminated intravascular coagulopathy. The patient was treated with intensive cardiopulmonary supports. We assessed therapeutic accommodation with a neonatal evaluation score, and coil embolization for the VGAM was warranted. At age 6 days, multislice spiral computed tomography (MSCT) (Aquilion™, Toshiba, Japan) was performed to evaluate the architecture of cerebral vessels before coil embolization. Contrast medium of 2 mL/kg was utilized. MSCT showed VGAM with multiple feeders and drainers (Figure 1; available at www.jpeds.com). At age 11 days and at age 19 days, transarterial coil embolization was performed in the right and left cerebral feeders, respectively, as heart failure progressed (Figure 2). Although shunt flow was effectively decreased, the patient developed multiple organ failure and unfortunately died at age 24 days.

VGAM is a rare neurovascular malformation with extremely poor morbidity and mortality. Recently, endovascular coil embolization has been established in the management of these patients. It is crucial to recognize the precise architecture of the VGAM before successful coil embolization because the malformation is very complicated and chaotic. Although magnetic resonance angiography before coil embolization is available, it takes longer time to complete the image processing than MSCT. MSCT is one of the useful imaging tools in the assessment of such a neonate with VGAM before endovascular intervention.

### REFERENCES


Figure 1. (Left) Frontal view of three-dimensional computed tomography images of VGAM. Entire cerebral vascular architecture of VGAM is shown in detail with dilated multiple feeders and drainage. (Right) Multiple feeder vessels predominantly consisting of right posterior cerebral artery, right anterolateral central artery, and right medial striate artery.

Figure 2. Frontal view of a fluoroscopic image after coil embolization of VGAM. Bilateral horizontal segments of posterior cerebral arteries are embolized effectively by 17 interlocking detachable coils and 7 tornade coils.