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Depression in parents following the diagnosis of cystic fibrosis

Parents of 45 children recently diagnosed with cystic fibrosis (CF) were tested with the Beck Depression Inventory at two time points by Glasscoe et al at the University of Liverpool. Overall, there was no difference in the rates of depression between parents of children affected by CF and matched control couples. However, when the data were stratified by age, the parents of children diagnosed with CF who were less than 9 months old at the time of the initial study had an increased rate of mild depression compared to controls and to the parents of older children with CF. These symptoms of depression were still present, although less common, on follow-up 9 months later. Medical providers caring for young infants diagnosed with cystic fibrosis, for example, through newborn screening programs, should carefully assess the mood of the parents as they are vulnerable to developing depression.

—Robert W. Wilmott, MD

Evaluating neonates with congenital cytomegalovirus infection

Although options for treating infants with congenital cytomegalovirus (CMV) expand, they are difficult. Accurate prediction of outcome if untreated would be very helpful. Ancora et al in this issue of The Journal offer up evidence for a new tool – cranial ultrasonography (US). In 57 neonates with congenital CMV infection, investigators performed neonatal and follow-up US at birth, with repeated study up to 3 months of age if normal and to 6 months of age if abnormal. They prospectively evaluated neurodevelopment and hearing through 24 months and school age, respectively (mean follow-up 42 months). All 10 of 18 infants with symptomatic CMV infection who had an abnormal neonatal US had at least one sequela, whereas none of the 8 symptomatic infants with normal US had long term sequelae (P < .001). In 37 asymptotically infected neonates, 3 of 37 with normal US developed sensorineural hearing loss and one of two neonates with abnormal US developed serious neurologic sequelae.

The investigators have shown that in neonates with symptomatic congenital CMV infection, US is a valuable screening tool to predict outcome – comparable with other imaging modalities, less costly, available at the bedside, and with no radiation. Their data also give reason to believe that further study might prove the value of US in asymptotically-infected infants as well.

— Sarah S. Long, M.D.

Lipids and diabetes

Cardiovascular disease is an important adverse occurrence in patients with diabetes. Dyslipidemia is an important risk factor for cardiovascular disease. There have been few longitudinal studies of lipid abnormalities in young patients with Type 1 diabetes. In this issue, Maahs et al report on a study in which they evaluated lipid abnormalities in patients with Type 1 diabetes. They found that non-HDL cholesterol was persistently above 130 mg/dL in 28%, ≥ 160 mg/dL in 10.6% and ≥ 190 mg/dL in 3.3%. Medications to lower LDL-cholesterol had been started in only 23/360 patients. These results suggest that although lipid abnormalities are common, treatment is not common in children and adolescents with Type 1 diabetes.

—Stephen R. Daniels, MD, PhD

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Outcomes for young adults with fetal alcohol syndrome

Fetal alcohol syndrome (FAS) is diagnosed by maternal history and physical findings in infants and early childhood. Some children have the incomplete findings called the fetal alcohol syndrome spectrum disorder (FASD). Spohr, Willms, and Steinhausen report the 20-year outcomes of 37 individuals with FAS and FASD that they followed from early childhood. Although the physical findings become less apparent, the intellectual and behavioral problems persist and prevent most of the individuals from successfully working or living independently. This report highlights the dismal outcomes resulting from fetal alcohol embryopathy.

—Alan H. Jobe, MD, PhD

A “beta” way to treat hypertension

As we have learned more about the pathophysiology of hypertension, a host of new drug classes have been developed to target these various mechanisms. Many of these agents have much less in the way of side effects than earlier drugs; angiotensin converting enzyme (ACE) inhibitors and angiotensin 2 receptor antagonists, to cite two examples, are now widely used in children.

These drugs have displaced other categories of agents which, although effective, often had unacceptable side effects in children. Beta blockers such as propranolol, for example, have been less frequently employed because of troublesome features such as a sedating effect. Recently, however, new classes of beta blockers, with a more cardioselective profile and greater tolerability, have been used widely in adults. There has been a paucity of data upon which to base pediatric use of these agents.

In the current issue of The Journal, Batisky et al report an exceptionally well-designed trial of an extended release formulation of the beta 1 selective blocker metoprolol. The trial was powerful for a number of reasons, not the least of which was the presence of a placebo arm. Although some eyebrows might be raised by this, in reality, the risk to children with asymptomatic hypertension of the degree in this trial posed by a few weeks without treatment is close to nonexistent. On the other hand, the presence of this group makes the results of the trial even more meaningful. The drug proved safe and effective, with a very favorable side effect profile. An accompanying editorial by Chesney puts this trial into perspective. Currently, beta blockers are chosen as first-line agents by pediatric nephrologists less than 10% of the time; in contrast, the drugs are quite popular in adult medicine. The study of Batisky et al may set the stage for a major change in this approach.

—Thomas R. Welch, M.D.

2A February 2007 The Journal of Pediatrics
Cortisol levels as preterms age

Cortisol is a potent developmental regulator that is normally very low in the fetus until just prior to term. Following preterm birth, the newborn must increase plasma cortisol to support multiple physiologic and metabolic adaptations. Cortisol then remains elevated relative to fetal levels until term equivalence. In animal models, fetal corticosteroid exposures can result in altered neuroendocrine regulation and behavior as the newborn grows to become an adult. Grunau et al report the developmental trajectory of salivary cortisol in large cohorts of 23-28 weeks, 28-32 weeks, and term infants at 3, 6, 8, and 18 months corrected age. The preterms have low cortisol levels at 3 months, but high levels at 8 and 18 months, indicating dysregulation of cortisol homeostasis relative to term infants. The multiple effects of cortisol on developing systems suggest that these altered cortisol levels as preterms age may contribute to collateral changes in physiologic and metabolic responses that may be long lasting.

—Alan H. Jobe, MD, PhD

Rocky Mountain Spotted Fever: Missed opportunities for early treatment

Buckingham et al from six institutions in the southeastern and south-central United States pooled 92 hospitalized cases of Rocky Mountain Spotted Fever (RMSF) to permit re-assessment of the disease, management, and outcome 30 years after the last large case series. Although this retrospective series has limitations of undoubtedly low case ascertainment and probable low symptom/sign ascertainment, the major findings stand alone. The infection and potential for morbid or fatal outcome of RMSF has not changed, and physicians continue to miss opportunities for early diagnosis. Although 86% of patients in the series had been taken for medical care prior to hospitalization, RMSF had not been suspected or treated in most patients. Treatment of RMSF should be begun empirically on the basis of clinical suspicion. The challenge for physicians is consideration of the diagnosis. Buckingham et al report an incomplete classic constellation of symptoms in most patients at first outpatient evaluation (median of 2 days of illness), as well as in 58% of patients at the time of hospitalization and first anti-rickettsial antimicrobial therapy (median of 7 days of illness). The finding in this study that a medical outpatient visit early in the course of illness was significantly associated with delay in therapy reminds us that barring another diagnosis, patients with febrile illnesses have diseases and diagnoses “in-progress” (rather than diagnoses of viral illnesses) requiring continuous re-thinking as the course evolves.

—Sarah S. Long, MD
NOTES FROM THE ASSOCIATION OF MEDICAL SCHOOL PEDIATRIC DEPARTMENT CHAIRS, INC.

Factors Influencing Community Pediatrics Training in Residency
Cynthia S. Minkovitz, MD, MPP, Anita Chandra, DrPH, Barry S. Solomon, MD, MPH, Lee M. Sanders, MD, MPH, Holly A. Grason, MA, and Carol Carraccio, MD, Baltimore, Maryland, Arlington, Virginia, and Miami, Florida

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PET Scanning for Infants with HHI: A Small Step for Affected Infants, A Giant Leap for the Field
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Functional Echocardiography: An Emerging Clinical Tool for the Neonatologist
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Linda A. Althouse, PhD, and James A. Stockman III, MD, Chapel Hill, North Carolina

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Comparative Efficacy and Cost of Asthma Care in Children with Asthma Treated with Fluticasone Propionate and Montelukast
David A. Stempel, MD, Denise T. Kruzikas, PhD, and Ranjani Manjunath, MSPH, Bellevue and Seattle, Washington, Phoenix, Arizona, and Research Triangle Park, North Carolina

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Fetal Alcohol Spectrum Disorders in Young Adulthood
Hans-Ludwig Spohr, MD, Judith Willms, MD, and Hans-Christoph Steinhausen, MD, PhD, Berlin, Germany, and Zurich, Switzerland

Clinical and Laboratory Features, Hospital Course, and Outcome of Rocky Mountain Spotted Fever in Children
Steven C. Buckingham, MD, Gary S. Marshall, MD, Gordon E. Schutze, MD, Charles R. Woods, MD, MS, Mary Anne Jackson, MD, Lori E. R. Patterson, MD, and Richard F. Jacobs, MD, as the Tick-borne Infections in Children Study Group, Memphis and Knoxville, Tennessee, Louisville, Kentucky, Little Rock, Arkansas, Winston-Salem, North Carolina, and Kansas City, Missouri

Parental Depression Following the Early Diagnosis of Cystic Fibrosis: A Matched, Prospective Study
Claire Glasscoe, PhD, Gillian A. Lancaster, PhD, Rosalind L. Smyth, MD, and Jonathan Hill, FRCPsych, Liverpool, United Kingdom

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Albert M. Li, MB, Shatin, Hong Kong

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Daniela Baumgartner, MD, Sabine Scholl-Bürgi, MD, Jörn Oliver Sass, Dr. rer. nat., Wolfgang Sperl, MD, PhD, Ulrich Schweigmann, MD, Jürg-Ingolf Stein, MD, and Daniela Karall, MD, Innsbruck and Salzburg, Austria, and Freiburg, Germany

50 Years Ago in The Journal of Pediatrics—Spontaneous Pneumothorax in the First Ten Days of Life

James M. Greenberg, MD, Cincinnati, Ohio

GRAND ROUNDS

A Newborn Infant with Protracted Diarrhea and Metabolic Acidosis

Amir Bar, MD, Arieh Riskin, MD, Theodore Iancu, MD, Irena Manov, PhD, Ayala Arad, MD, and Ron Shaoul, MD, Haifa, Israel

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Recipient Twin Limb Ischemia with Postnatal Onset

Roland Spencer Broadbent, MB, ChB, Dunedin, New Zealand

Congenital Patent Ductus Venosus: An Association with the Hyper IgE Syndrome

Keren Sagiv-Friedgut, MD, Michaela Witzling, MD, Ilan Dalal, MD, Chana Vinkler, MD, Eli Someh, MD, and Arie Levine, MD, Holon and Tel Aviv, Israel

50 Years Ago in The Journal of Pediatrics—Classification and Etiological Factors in Mental Retardation

Pasquale J. Accardo, MD, Richmond, Virginia

LETTERS

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

Erythromycin for Treatment of Feeding Intolerance in Preterm Infants

Bai-Horng Su, MD, and Hung-Chih Lin, MD, Taichung, Taiwan

Sandra Mascarenhas, MRCPCH, and Mithilesh Lal, MRCPCH, Middlesborough, United Kingdom

Reply

Pracha Nuntnarumit, MD, Pakaphan Kiatchoosakun, MD, Wacharee Tantiprapa, MD, and Suppawat Boonkasidecha, MD, Bangkok, Khon Kaen, and Chiang Mai, Thailand

Cardiovascular Support in the Preterm: Treatments in Search of Indications

Istvan Seri, MD, PhD, Los Angeles, California

Reply

Keith J. Barrington, MD, Montreal, Quebec, Canada
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.ppgcpip.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 Symposium Medicus. For more information, contact Symposium Medicus; phone: 925-969-1789, 800-327-3161; E-mail: info@symposiumedicus.org; Website: www.symposiumedicus.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

111 Silver Cedar Court, Chapel Hill, NC 27514-1513 telephone: 919-929-0461 fax: 919-918-7114 or 919-929-9255 Website: www.abp.org

All applicants for certifying examinations must complete applications online during the registration period. The final month of each registration requires payment of a late fee. The requirements for online applications may be found on the ABP Website (www.abp.org) or may be obtained by contacting the ABP. Additional information including eligibility requirements and registration dates may be found on the ABP Website.
Factors Influencing Community Pediatrics Training in Residency

CYNTHIA S. MINKOVITZ, MD, MPP, ANITA CHANDRA, DRPH, BARRY S. SOLOMON, MD, MPH, LEE M. SANDERS, MD, MPH, HOLLY A. GRASON, MA, AND CAROL CARRACCIO, MD

Increasingly, pediatricians are expected to work collaboratively within their communities to address the complex environmental and social issues affecting children's well-being. The American Academy of Pediatrics identifies community pediatrics as “an integral part of the professional role and duty of the pediatrician.” Residency training is perceived as an opportune time in which to equip pediatricians with the necessary skills to advocate effectively for children in their communities. Since 1997, pediatric residency programs have been required to provide structured educational opportunities, both didactic and experiential, in the areas of community pediatrics and child advocacy.

Most pediatric residency programs do provide community experiences for residents, with more than two thirds of programs in 2002 requiring involvement in four or more community settings as well as teaching about issues such as cultural competency, and the mental health and social service systems. Nonetheless, there is considerable variability in curricular offerings. Prior reports have suggested that resident interest, faculty involvement, and the commitments of academic and community organizations are instrumental in implementing community pediatrics curricula in residency training programs. Yet, there has been no systematic assessment of the factors that influence the ability of residency programs to implement community training.

METHODS

To address these issues, we conducted a Web-based survey of pediatric residency program directors between May and July 2005. The American Medical Association’s Fellowship and Residency Electronic Interactive Database provided contact information. The 11-item survey asked about program identification, designation of having a primary care track, and continuity clinic settings. Respondents indicated required or elective resident involvement in 15 community settings (eg, Head Start program) and whether their programs provided education regarding 14 community health topics (as didactic or practical instruction). Respondents also reported the level of resident involvement (4-point Likert scale, 1 “not at all” to 4 “heavily”) in five additional activities: communicating with elected officials; providing legislative testimony; participating in longitudinal community projects; conducting research in the community; and addressing parents, teachers, or other community groups. Using a similar Likert scale, respondents reported on the degree to which the program emphasized resources and training related to 11 content areas (eg, child advocacy) in marketing the program to prospective residents.

We developed a community orientation scale using responses to a question asking “In the last 3 years, to what degree have the following factors influenced your ability to offer residency training experiences in community child health?” The scale included eight factors: community interest, faculty expertise and interest, departmental priorities, resident interest, institutional initiatives, implementation of a competency-based curriculum, and resources and money (Table I). For each program, the community orientation score was calculated as the mean rating for all eight factors, with higher scores indicating a more positive orientation to community pediatrics.

Data analysis was conducted using the Statistical Package for the Social Sciences version 11.5 (SPSS, Inc., Chicago, Ill) using non-parametric tests to allow for non-normal distribution of responses. Mean scores are reported for ease of interpretation. The Johns Hopkins Committee on Human Research approved the study.

RESULTS

Of the 203 accredited programs, 161 program directors or their designees completed the survey (response rate = 79%). All but 12 respondents completed the question regarding factors influencing community pediatrics training with a resulting analytic sample of 149. The degree to which selected factors positively influence a program’s ability to offer residency training experiences in community child health (“community orientation”) varied, with work...
Table I. Factors influencing community pediatrics (n = 149)*

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<td>Resident interest</td>
<td>3.72</td>
<td>1.07</td>
</tr>
<tr>
<td>Institutional initiatives</td>
<td>3.54</td>
<td>0.90</td>
</tr>
<tr>
<td>Implementing a competency-based curriculum</td>
<td>3.47</td>
<td>0.96</td>
</tr>
<tr>
<td>Resources and money</td>
<td>2.49</td>
<td>1.19</td>
</tr>
<tr>
<td>Work hours restrictions†</td>
<td>2.41</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Note: A community-orientation score was created for each program using the sum of responses from the 8 factors/total number of items (higher score = more positive orientation to community pediatrics). The Cronbach a reliability coefficient for the 8-item community-orientation scale (sum of items/8) was 0.83, indicating high internal consistency. The scale range was 1.75 to 4.88 with a mean score of 3.61 (SD 0.69).

*Respondents identified the degree of influence (Likert scale, 1 "very negative" to 5 "very positive").

†Excluded in 8-item scale. All other factors were highly correlated (P < .05).

These findings suggest that multiple factors influence the ability of pediatric residency programs to offer training experiences related to community child health and that many of these factors are mutable. Across all programs, both resources and money and work hours restrictions negatively impacted training, whereas all other factors exerted a positive influence. However, among programs receiving significant financial support for community pediatrics training, resources and money were viewed positively; such resources can be used to support training provided by community partners, faculty development, and coordinators responsible for scheduling resident activities in community settings.

Although work hours restrictions influenced programs’ abilities to offer community health training, these restrictions did not correlate with the other factors that describe community orientation. It is likely that respondents perceived the impact of work hours restrictions for community child health training to be comparable to its impact on other training opportunities, and not unique to community pediatrics. In a separate question asking respondents about the influence of work hours on their ability to offer training experiences related to the care of hospitalized patients, scores for the impact of work hours restrictions were comparable to those for community pediatrics.

This brief report offers a glimpse into the factors that influence the ability of programs to offer community pediatrics training experiences. Clearly, more work is needed to understand the role of other factors that may be important and to understand the full scope and quality of these experiences. However, this study does demonstrate a positive orientation to community pediatrics training when there is institutional support as well as community, faculty, and resident interest. Pediatrics departments that are interested in revising curricular opportunities related to community pediatrics should assess the varied factors that likely influence their programs’ abilities to support these efforts. This information also may be important in informing the Residency Review and Redesign Project of the American Board of Pediatrics as it looks to how the future of pediatric residency training should be structured to meet the evolving healthcare needs of children.

We gratefully acknowledge participation of the program directors and generous support from The Dyson Foundation. The Dyson Initiative National Evaluation Advisory Committee reviewed survey content and provided critical input regarding preliminary findings. References available at www.jpeds.com.

DISCUSSION

hours restrictions having the lowest score (2.41) and community interest having the highest (3.95) (Table I).

Using scaled scores, there were no differences in community orientation by program size or presence of a primary care track. However, those programs offering community health centers as one of the possible continuity clinic sites reported greater community orientation (mean 3.77 vs 3.45, P = .004). Among sites receiving support from the Dyson Community Pediatrics Training Initiative ($500,000/year for each of 5 years to support training in community pediatrics), mean scores regarding the importance of resources and money were substantially higher than for their counterparts without Dyson support (3.83 vs 2.37, P < .001), as were overall scores on community orientation (4.31 vs 3.55, P < .001).

Greater community orientation was reported by programs with more required community settings, with scores of 3.38 for programs requiring fewer than four settings, 3.67 for four to six settings, and 3.80 for programs requiring seven or more settings (P = .006). Greater community orientation also was associated with more didactic training in 5 of the 14 topics and more practical experiences in 3 of the 14 topics (Table II; available at www.jpeds.com). Greater community orientation was reported by programs with more involvement of residents in the five selected community activities (Table III; available at www.jpeds.com).

Community orientation also was associated with how programs market themselves to prospective residents. In particular, higher community orientation scores were reported by programs that emphasized their resources and training related to primary care, behavior and development, community pediatrics, and advocacy but not to other areas such as breadth of specialty services, clinical and lab research, or intensive care.
Table II. Community orientation and health system topics, mean (SD) (n = 149)*

<table>
<thead>
<tr>
<th>Community health system topic</th>
<th>Didactic training</th>
<th>Practical experience</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Social service system</td>
<td>3.66 (0.69)</td>
<td>3.42 (0.66)</td>
</tr>
<tr>
<td>Welfare system</td>
<td>3.76 (0.64)</td>
<td>3.44 (0.70)</td>
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<tr>
<td>Foster care system</td>
<td>3.74 (0.61)</td>
<td>3.46 (0.74)</td>
</tr>
<tr>
<td>Public education system</td>
<td>3.70 (0.69)</td>
<td>3.52 (0.68)</td>
</tr>
<tr>
<td>Juvenile justice system</td>
<td>3.68 (0.68)</td>
<td>3.55 (0.69)</td>
</tr>
<tr>
<td>Mental health system for children/adolescents</td>
<td>3.65 (0.67)</td>
<td>3.29 (0.80)</td>
</tr>
<tr>
<td>Substance abuse treatment</td>
<td>3.63 (0.66)</td>
<td>3.51 (0.82)</td>
</tr>
<tr>
<td>Managed care</td>
<td>3.63 (0.69)</td>
<td>3.54 (0.68)</td>
</tr>
<tr>
<td>Healthcare financing</td>
<td>3.66 (0.69)</td>
<td>3.38 (0.63)</td>
</tr>
<tr>
<td>Cultural competency</td>
<td>3.69 (0.65)</td>
<td>3.17 (0.74)</td>
</tr>
<tr>
<td>Legislative advocacy</td>
<td>3.75 (0.62)</td>
<td>3.33 (0.75)</td>
</tr>
<tr>
<td>Migrant healthcare</td>
<td>3.96 (0.66)</td>
<td>3.56 (0.68)</td>
</tr>
<tr>
<td>Indian Health Service</td>
<td>3.80 (0.63)</td>
<td>3.59 (0.69)</td>
</tr>
<tr>
<td>Children with special healthcare needs</td>
<td>3.63 (0.67)</td>
<td>3.32 (0.92)</td>
</tr>
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</table>

*Higher community-orientation scores reflect greater community orientation. Significance testing reported using Mann-Whitney tests.

REFERENCES
<table>
<thead>
<tr>
<th>Activity</th>
<th>Degree of involvement</th>
<th></th>
<th></th>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communicated with elected officials to advocate on behalf of children's concerns</td>
<td>3.36 (0.77)</td>
<td>3.62 (0.62)</td>
<td>3.98 (0.55)</td>
<td>3.75 (0.83)</td>
<td>.004</td>
</tr>
<tr>
<td>Provided legislative testimony</td>
<td>3.49 (0.72)</td>
<td>3.92 (0.46)</td>
<td>3.84 (0.78)</td>
<td>4.0 (—)</td>
<td>.01</td>
</tr>
<tr>
<td>Participated on a longitudinal project providing services in the community</td>
<td>3.31 (0.78)</td>
<td>3.41 (0.64)</td>
<td>3.88 (0.56)</td>
<td>4.00 (0.55)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Conducted research in the community</td>
<td>3.23 (0.78)</td>
<td>3.57 (0.61)</td>
<td>4.00 (0.55)</td>
<td>4.19 (0.55)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Address parents, teachers, or other community groups</td>
<td>3.30 (0.99)</td>
<td>3.40 (0.69)</td>
<td>3.69 (0.58)</td>
<td>4.14 (0.40)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Higher community-orientation scores reflect greater community orientation. Significance testing reported using Kruskall-Wallis tests.*
Is There a Role for β-Adrenergic Blockers in Treating Hypertension in Children?

Over the past decade, it has been recognized that hypertension exists in children and adolescents, that pediatricians should screen for and evaluate it, and that the ideal goal is to prevent the long-term cardiovascular consequences of elevated blood pressure. Two parallel developments have influenced the choice of antihypertensive agent for children with persistent elevated blood pressure. The first development is the concept that drug testing is needed to ensure the efficacy and safety of any drug in children. A mechanism to accomplish this goal is patent extension to induce a company marketing a drug under a patent to support development is the recommendations emanating from a report on the diagnosis, evaluation, and treatment of hypertension in children and adolescents recommending that certain classes of antihypertensive agents be used as therapy.

In this issue of The Journal, Batisky et al evaluate a class of antihypertensive drugs recommended by that report: the cardioselective β-blocker metoprolol. The importance of this study lies in the fact that it is well designed; previously, few well-conducted trials of β-blockers had been performed in children.

The study evaluates metoprolol extended-release tablets, which can be given once daily. The findings are from a 4-week double-blind dose-range study and a 52-week open-label extension study. Children age 6 to 16 years were evaluated.

The report provides evidence that extended-release metoprolol significantly reduced systolic blood pressure at 1.0 and 2.0 mg/kg compared with placebo. Only the 2.0 mg/kg dose significantly reduced diastolic blood pressure. The drug was well tolerated in the 52-week trial, and only 5% of study participants had to drop out due to adverse events. The response rate increased significantly, from 41% at the beginning of the study to 64% at week 52.

The principal value of this study lies in the assessment of the safety and efficacy of a β-blocker in a short-term trial. This assessment is important because this class of agents has not been extensively evaluated. From these 2 studies, it appears that this agent is generally safe. However, a majority of subjects in each trial did not achieve target blood pressure control (55% and 59%, respectively) over the short term. The open-label study found that many more patients achieved the target blood pressure.

A limitation of this study is that it fails to define precisely the circumstances in which a β-blocker would be chosen. All patients with hypertension secondary to coarctation of the aorta, pheochromocytoma, hyperthyroidism, and Cushing syndrome were excluded, and most patients in both trials had essential hypertension. Patients with other forms of hypertension were not generally evaluated.

The studies by Batisky and Sorof et al are placebo-controlled trials. Although the drug caused a greater drop in both systolic and diastolic pressure than placebo, there was a substantial placebo effect. This effect could be explained by 2 factors: the Hawthorne effect and the oft-made observation that hypertensive children may improve over time. The Hawthorne effect is a well-established phenomenon wherein the very fact of entering a study has an effect on patient behavior and may influence the symptoms or findings in a patient. Moreover, the data from these 2 trials and other studies indicate that children with mild primary hypertension followed over time may experience normalization of blood pressure without treatment. A clear implication is that such patients may need several months of observation before initiation of pharmaceutical intervention.

The use of a placebo arm in childhood hypertension trials is controversial. Many hypertensive trials in both children and adults do not have a placebo arm so as to avoid the well-established consequences of untreated hypertension. The International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline E10 concluded that “when a new treatment is tested for a condition for which no effective treatment is known, there is usually no ethical problem with a study comparing the new treatment to placebo.” The situation in antihypertensive trials falls outside this guideline, especially because so many effective agents are available.

Batisky et al have made the argument that a placebo control can be justified if the hypertension is mild, if the subjects do not have hypertension-related target organ damage, and if the study duration is short.

In the study by Batisky et al, adverse effects were uncommon, and even in the long-term open label component of the study, only 5 children dropped
out because of side effects. This represents just 5% of the 100 patients in this phase of the trial. Reported side effects included fatigue, nightmares, anxiety, dizziness, and asthma. Traditional contraindications to β-adrenergic inhibition, such as asthma and diabetes, also are relevant; however, a β receptor antagonist should largely affect the cardiogenic receptors. The present study does not comment on the use of β-blockers in competitive athletes or runners, in whom the need to raise the heart rate is pertinent.

A recent survey review of 438 North American pediatric nephrologists indicated that most used angiotension-converting enzyme inhibitors (ACEIs), followed by calcium-channel blockers (47% and 37%, respectively), in the first-line treatment of primary hypertension. β-blockers were used as a first-line agent by only 7% of respondents, but in second-line therapy by 17%. In children with hypertension associated with renal insufficiency, ACEIs were used by 84% of respondents in first-line therapy, and β-blockers were used only as second-line agents. The study of Batisky et al5 shows that the β-blocker metoprolol can be used safely in patients with primary hypertension, with the target pressure reached in approximately 70% of subjects. This is valuable new information.

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REFERENCES

PET Scanning for Infants with HHI: A Small Step for Affected Infants, A Giant Leap for the Field

A tempting to explain the pathophysiology of macrosomic infants with hypoglycemia has engaged physician/scientists for some 50 years. First came the era of careful observation and description suggesting a familial or genetic basis and similarities in the symptoms to an overdose of insulin.2,3 Next came the era of biochemistry, radioimmunoassay, and glucose kinetics by means of stable isotopes that defined hyperinsulinemic hypoglycemia of infancy (HHI) as the most common and potential neurologically devastating form of neonatal hypoglycemia.3,4 The exponential leap forward with remarkable progress occurred in the past decade, since the elucidation of the molecular mechanisms responsible for insulin secretion and its modulation through the adenosine triphosphate–regulated potassium channel (KATP).5 This channel converts the chemical energy of glucose or amino acid metabolism to electrical signals that trigger voltage-gated calcium channels leading to insulin secretion. Inactivating mutations in the actual channel pore (Kir 6.2), or its regulatory subunit (SUR1), prevent channel opening, resulting in prolonged membrane depolarization, with ongoing and unregulated insulin secretion causing hypoglycemia.5,6 Some of these mutations are familial, mostly inherited in an autosomal recessive manner. In the general population, most cases of HHI are sporadic.

See related article, p 140

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Functional Echocardiography: An Emerging Clinical Tool for the Neonatologist

MARTIN KLUCOW, FRACP, PHD, ISTVAN SERI, MD, PHD, AND NICK EVANS, DM, MRCPCH

Despite significant advances in our ability to monitor complex and clinically relevant hemodynamic variables,1-3 in most neonatal intensive care units (NICUs), cardiovascular function is assessed only by continuous heart rate, blood pressure monitoring or poorly validated clinical signs such as capillary refill time.4 The use of indirect measures for assessment of tissue perfusion is especially problematic in the very preterm neonate during the first postnatal days, when complex hemodynamic changes occur during the transition to postnatal life.1 Although clearly these measurements give important information, they provide only indirect and frequently limited insights into the complexities of cardiac function, changes in peripheral and pulmonary vascular resistance, intracardiac and extracardiac shunting, and the transitional circulation of the neonate. Indeed, the neonatologist is often faced with clinical dilemmas that are challenging to interpret and manage because of a lack of basic hemodynamic physiologic information. Recent publications have highlighted the current uncertainty as to the optimal management of hypotension in the newborn infant4,5 and patency of the ductus arteriosus.6 The emerging field of neonatal hemodynamics can offer a clearer understanding of the pathophysiology underlying these clinical presentations and help guide treatment choices.2,3,7,8

In the neonate, echocardiography is commonly used to assess the structure and function of the heart. Obtaining an echocardiogram is usually dependent on the availability of pediatric cardiologists or echocardiographic technicians. The pediatric cardiologist generally performs a single echocardiogram to rule out the presence of structural heart disease or global myocardial dysfunction. However, this snapshot view is inadequate for the assessment of ongoing changes in the hemodynamic status such as during the immediate postnatal transition or when cardiovascular compromise develops at a later stage during the neonate’s hospital course. Longitudinal studies demonstrate a wide range of hemodynamic findings, both between different babies with the same clinical scenario and in individual babies with time. These hemodynamic findings are often very different from what might be assumed clinically, using conventional thinking. We propose the term “functional echocardiography” to describe the bedside use of echocardiography to longitudinally assess myocardial function, systemic and pulmonary blood flow, intracardiac and extracardiac shunts, organ blood flow, and tissue perfusion. Functional echocardiography provides information about the underlying hemodynamic function in real time and the changes in the cardiovascular status in response to treatment. Functional echocardiography allows treatment to be targeted at actual rather than assumed functional status and for treatment effectiveness to be assessed over time.

Although the use of functional echocardiography has not yet been demonstrated to affect outcomes, its value for assessment of the rapidly changing hemodynamic status has been embraced by many neonatologists.9,10 In Australia and New Zealand, a recent survey showed 40% of NICUs had at least one neonatologist with functional echocardiographic skills,9 and several papers describe experience with neonatal functional echocardiography.7,9-12 The use of functional echocardiography is also widespread throughout Europe (personal communications) and a number of neonatal units in North America are developing the ability to provide point of care monitoring using functional echocardiography by appropriately trained neonatologists. More than 500 copies of a self-directed teaching program on echocardiography for the neonatologist using an interactive CD-ROM13 are available throughout the world, again suggesting a widespread interest in developing these skills.

Until recently, functional echocardiography was primarily used as a research tool to define the natural history of neonatal hemodynamics and relations to adverse outcomes.2,14-16 More recently, the hemodynamic effects of therapeutic interventions have been reported, but it remains to be shown whether the use of functional echocardiography can modify neonatal outcomes.17,18

| HDH | Congenital heart disease |
| NICU | Neonatal Intensive Care Unit |
| PDA | Patent ductus arteriosus |
| SBF | Systemic blood flow |

From the Departments of Neonatal Medicine, Royal North Shore Hospital and Royal Prince Alfred Mother’s and Babies, and University of Sydney, Sydney, Australia; and USC Division of Neonatal Medicine, Department of Pediatrics, Children’s Hospital Los Angeles and the Women’s and Children’s Hospital, LAC + USC Medical Center, Keck School of Medicine, University of Southern California, Los Angeles, California. Submitted for publication Jun 21, 2006; last revision received Aug 19, 2006; accepted Oct 12, 2006.

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CLINICAL USES OF FUNCTIONAL ECHOCARDIOGRAPHY

The range of methodologies and clinical uses of functional echocardiography have been reviewed.2,15,16,19 It should be highlighted that all ultrasound measures have an intrinsic error ranging from about 10% for intraobserver variability up to 15% to 20% for interobserver variability.16 This variance is similar to other noninvasive measures such as measurement of cardiac output using thermodilution.

The Very Preterm Infant During the Transitional Period

The first 24 postnatal hours after birth of the very preterm infant is a period of unique circulatory vulnerability. A significant number of babies develop not only hypotension but also low systemic blood flow (SBF).16 During this period, low SBF is often not recognized by measurement of blood pressure3 and has been associated with a range of adverse outcomes, both short and long term.20,21 The usual measurements of cardiac output used in older children and adults, such as the left ventricular output, are affected by the transitional circulation, so other measures of SBF such as measurement of superior vena cava flow have been developed.16,22 Low SBF also relates to larger ductal shunts, so assessment of the early constriction of the ductus arteriosus is important in early echocardiographic assessments. After the transitional first 24 hours, where low SBF predominates, hypotensive babies usually have normal or high SBF, indicating low peripheral vascular resistance that is probably due to abnormal regulation of vascular tone.23 This change from low to higher SBF has been implicated in the development of peri-intraventricular hemorrhage in the very preterm neonate.20

Assessment and Monitoring of the Ductus Arteriosus in the Preterm Infant

In some preterm infants, the ductus arteriosus effectively constricts within a few hours of birth, although others have a persisting large ductus arteriosus with no evidence of constriction. Many of the strategies for treating patent ductus arteriosus (PDA) are based on the incorrect assumption that early ductal shunting is of limited hemodynamic significance. The dominant direction of ductal shunting in the early postnatal period is left to right, and, in those ducts that fail to constrict, large volumes of blood move from the systemic to pulmonary circulation. The early left-to-right shunting results in consequences such as reduced systemic blood flow and blood pressure, increased ventilatory requirements, and pulmonary hemorrhagic edema.14,22,24 These hemodynamic effects may paradoxically be more important in the early hours after birth rather than later in the clinical course.25 These findings lend indirect support to the emerging suggestions regarding early prophylactic therapy of the PDA26 and subsequent tolerance of the PDA in older infants who do not have cardiac failure.6 Functional echocardiography to assess early ductal constriction in infants during circulatory transition allows prediction of the likely closure of the ductus arteriosus and potential targeting of early treatment of the ductus arteriosus (or targeted prophylaxis) rather than nonspecific prophylaxis.2 Functional echocardiography provides the clinician with further information to aid decision-making beyond just the presence or absence of the ductus arteriosus. Longitudinal assessment of changes with time allows a judgment regarding the likely closure of the ductus arteriosus. In addition, measurement of hemodynamic effects such as the direction of diastolic flow in the descending aorta and an estimate of the pulmonary blood flow give an indication of the impact of the ductus arteriosus on the cardiovascular status.14,23

The Infant With Suspected Circulatory Compromise (Often Hypotensive)

It is a common assumption in neonatology that normal blood pressure equates to normal SBF, and improving blood pressure means that blood flow must also have improved. However, in very preterm infants during the first postnatal days, mean blood pressure does not correlate well with the simultaneously measured left ventricular output.3,27 Consequently, the ability to repeatedly assess SBF at the bedside is of considerable importance. Hypotension in the neonate can be due to several underlying scenarios with variable hemodynamic physiology.28,29 Very preterm infants may initially have low SBF and/or a large PDA. Term infants may have poor myocardial function as the result of asphyxia, pathological vasodilation in septic shock or asphyxia, or, less frequently, hypovolemia with cardiac underfilling caused by fluid or blood loss. Each of these situations potentially results in low blood pressure. However, the appropriate management and logical choice of therapy in each varies.28,30 Echocardiography can be used to differentiate between these situations, combining measurement of cardiac output, assessment of cardiac filling, and myocardial function and even exclusion of life-threatening pathology, such as a pericardial effusion tamponade from an extravasation of a central line or from other causes. Finally, although detection of congenital heart disease (CHD) is not the primary goal of functional echocardiography, its use means that CHD can and will be diagnosed in some babies before it would have been suspected clinically.

Assessment and Response to Treatment of an Infant With High Oxygen Requirements

Babies with suspected persistent pulmonary hypertension present the neonatal intensivist with a range of respiratory and hemodynamic therapeutic challenges. As with the group of infants with hypotension, functional echocardiography reveals a broad range of pathology underlying the clinical presentation.31,32 These babies are often assumed to have pulmonary hypertension with right-to-left ductal shunting. In fact, such assumptions are often erroneous and can lead to inappropriate management. The ductus in such babies usually constricts early in the course and may close after the first 24
Table I. Principles of safe practice for neonatologists using neonatal functional echocardiography

- Neonatologists performing functional echocardiograms should receive appropriate training and participate in an audit process.
- Functional echocardiography should be used as an adjunct to, not a replacement for, the appropriate clinical assessment of the infant.
- A pediatric cardiologist should be consulted if any evidence of structural heart disease is found on functional echocardiography.
- If the primary question based on clinical signs or concerns is “has this baby got structural heart disease?,” this should be addressed to a pediatric cardiologist.
- A pediatric cardiologist should be consulted before any specific treatment or inter-hospital transfer for structural heart disease is instituted.

Functional Echocardiography: An Emerging Clinical Tool for the Neonatologist

Even in units experienced in the use of neonatal functional echocardiography, pediatric cardiologists will often add more detail to the initial screening echocardiographic findings made by the neonatologist.9,35 Although it is important to recognize that CHD can be missed by neonatologists, the presence of a structural cardiac abnormality is almost always detected, even if a full diagnosis is not made.7,10,11 Finally, neonatologists are not the only group of specialists using echocardiography that can miss CHD in neonates—much of the published data on such echocardiographic misdiagnosis relates to adult cardiologists and radiologists.35,36 Another issue that has been raised is that the neonate will have been deemed to have had a formal echocardiogram performed with high-level exclusion of CHD.37 This can be avoided by stressing to parents and other clinicians that the echocardiogram is “functional,” or screening in nature.

TRAINING AND ACCREDITATION

As clinicians realize the value of the hemodynamic information that functional echocardiography can provide in the neonate, the demand for access to functional echocardiographic data will increase. Already in Australia/New Zealand and many European countries, clinicians who are not formally trained as cardiologists or radiologists are using point-of-care clinical ultrasound to enhance their understanding of the hemodynamic physiology underlying the clinical circumstances they are managing.7,9 There is therefore a pressing need to proactively plan for the dissemination of these ultrasound skills by developing appropriate training and accreditation programs to limit the risks of untrained or unsupervised individuals using ultrasound in the NICU. In most countries, there are no recognized training and accreditation programs for neonatal ultrasound. This includes not only echocardiography but also cerebral ultrasound, which has been widely performed by neonatologists for many years.38

Neonatologists need to work in collaboration with the specialties that currently provide these imaging services on a consultative basis. For echocardiography, this is mainly pediatric cardiologists. It is our conviction that it is in the interest of pediatric cardiologists to encourage and support this emerging area to ensure appropriate use and limitations of echocardiography by neonatologists. There are a number of successful models of training and cooperation already operating in Europe, Australia, and New Zealand.10

The components of a formal structured training program should include both theoretical teaching and development of practical skills alongside experienced neonatal echocardiographers and/or interested pediatric cardiologists, a knowledge of ultrasound equipment and modalities available, and reinforcement of limitations with a close interaction between the neonatologist and pediatric cardiologist. Audit of performance and ongoing competency assessment are also important by use of logbooks and review of scans on video supervised by pediatric cardiologist(s) in collaboration with experienced neonatal echocardiographers.

Issues regarding supervision and monitoring will vary
from country to country and even between neonatal units, depending on the availability of skilled staff. There are a number of ways to maintain quality control with the introduction of functional echocardiography. One model being developed in Australia and New Zealand is through local training and accreditation programs administered by an experienced group of physicians. Other models used in North America allow for the cardiologist to “sign off” on functional studies within a certain time period after the echocardiogram has been performed. This model allows careful supervision of the introduction of echocardiographic skills to a wider group of individuals within the neonatal unit. In other units, echocardiographic technicians are utilized to provide timely hemodynamic monitoring.

Issues regarding appropriate training in a recognized center, certification of competence, and ongoing accreditation are all currently being addressed in Australia and New Zealand through the main ultrasound body, the Australasian Society of Ultrasound in Medicine (ASUM). This organization facilitates the provision of focused clinician-centered courses on point-of-care ultrasound, with ongoing accreditation and competence requirements. These courses are aimed at developing specific skills in particular clinician groups for whom ultrasound is an important skill but is not usually central to their training. Emergency physicians are able to learn skills of ultrasonic diagnosis of an abdominal aortic aneurysm, obstetricians learn to assess women with first-trimester bleeding by ultrasound and perform “screening” fetal ultrasound evaluations, and surgeons are taught to use ultrasound for diagnosis of the acute abdomen or scrotum.

Australian neonatologists are currently investigating development of a similar model of training, which, if successful, could be used as a model for other countries as well.

### Table II. Benefits, barriers, and risks of functional echocardiography

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Barriers and risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training and teaching</td>
<td>• Increased access to fECHO</td>
</tr>
<tr>
<td>Audit</td>
<td>• Important in maintenance of standards</td>
</tr>
<tr>
<td>Introduction of fECHO to the NICU</td>
<td>• Facilitates documentation of hemodynamic function in real time</td>
</tr>
<tr>
<td>Clinical use of fECHO in the NICU</td>
<td>• Assessment of need for treatment</td>
</tr>
<tr>
<td></td>
<td>• Assessment of response to treatment</td>
</tr>
<tr>
<td></td>
<td>• Longitudinal monitoring of hemodynamic changes</td>
</tr>
<tr>
<td></td>
<td>• Detection of structural heart disease</td>
</tr>
<tr>
<td></td>
<td>• Difficulties associated with recruiting experienced pediatric cardiologists interested in teaching fECHO</td>
</tr>
<tr>
<td></td>
<td>• Lack of appropriately trained, experienced neonatologists</td>
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<tr>
<td></td>
<td>• Lack of structured supervised training</td>
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<td></td>
<td>• Access to expensive equipment</td>
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<tr>
<td></td>
<td>• Reluctance of some pediatric cardiologists to participate</td>
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<tr>
<td></td>
<td>• Concerns about changes in income streams</td>
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<tr>
<td></td>
<td>• Possibility of excessive treatment or intervention as a result of the test</td>
</tr>
<tr>
<td></td>
<td>• Availability of staff and machine at the time they are needed</td>
</tr>
<tr>
<td></td>
<td>• Increased handling of the infant</td>
</tr>
<tr>
<td></td>
<td>• Risk of misdiagnosis</td>
</tr>
</tbody>
</table>

fECHO, Functional echocardiography.

### BARRIERS TO PROVISION OF FUNCTIONAL ECHOCARDIOGRAPHY WITHIN AN NICU

There are many practical barriers to the development of these skills, not the least of which is the access to an ultrasound machine, and creating opportunities for specialized and supervised training (Table II). These barriers are relatively straightforward in comparison to the political issues that emerge around access to ultrasound in the NICU by neonatologists. It is an uncomfortable truth that most of these barriers come from the consultative specialties that have traditionally provided these services. However, the extent of the barriers put up by the consultative specialties varies widely from country to country, and even between different centers in the same country. Each of the authors is indebted to local pediatric cardiologists who have supported us and our functional echocardiography programs. Without such collaboration the introduction of fECHO programs cannot safely occur. If the process of the dissemination of these skills is to continue, then it is incumbent on specialist training programs in neonatology to incorporate appropriate accreditation structures for ultrasound.

The best models of collaboration are in health care systems in which the method of remuneration of the doctors encourages cooperation rather than competition in the provision of services. It is predictable and understandable that where departmental and/or personal income streams are threatened by a process, there will be barriers. Neonatologists involved in ultrasound need to be able to collaborate, and it must not be in their interest to compete for income. The authors of this review would not support neonatologists developing ultrasound skills if the motivation were financial rather than clinical. In Australia, one proposal being considered is that functional echocardiography...
should not be seen as a separately billed item but rather be incorporated into the current daily “provision of intensive care” item as are other physiological monitoring techniques such as invasive blood pressure.

Our experience has shown that clinical point-of-care ultrasound complements rather than replaces the need for consultative ultrasound. The reasons for the neonatologist developing echocardiographic skills are very different to the cardiologist, and recognition of this allows development and appropriate use of functional echocardiography. The neonatologist requires timely, longitudinal monitoring of changes in the hemodynamic physiology of the sick neonate. This is an extension of the clinical care of the infant rather than a consultative diagnostic modality. It is our observation that most pediatric cardiologists do not have the time or clinical motivation to provide this longitudinal information 24/7. Equally, the pediatric cardiologist provides an essential specialized consultative skill to the neonatologist, focused on diagnosis or exclusion of congenital heart disease and the provision of a confirmation of the hemodynamics, usually at a single point in time. The significant distinction between these two different approaches means that the skills of each should be complementary rather than exclusive and can be used together to improve the clinical care of neonates.

CONCLUSION

The area of functional echocardiography is being developed and driven by neonatologists as an extension of their clinical skills and to enable them to assess the cardiovascular status of their patients. There is a wealth of hemodynamic information that can be derived from functional echocardiography in the sick neonate. Often, this new hemodynamic information will provide clinical information that is different from the assumed underlying physiology. For functional echocardiography to fulfill its clinical potential, it needs to be available at any time in the NICU. Because most NICUs do not have external diagnostic services to provide longitudinal hemodynamic follow-up at the bedside, neonatologists should be able to develop echocardiographic skills in close collaboration with their cardiologist colleagues. Finally, the impact of the use of functional echocardiography on neonatal outcome needs to be assessed.

Two of the authors (NE and MK) are indebted to several visionary pediatric cardiologists in the UK and at The Children’s Hospital, Westmead in Sydney, Australia who helped us develop our skills during our training and continue to provide support and advice to our clinical services. The third author (IS) acknowledges and appreciates the enormous support he and his faculty have received from the Division of Pediatric Cardiology at the Children’s Hospital Los Angeles, University of Southern California (USC) in setting up the system of jECHO in the USC Division of Neonatology.

REFERENCES


50 Years Ago in The Journal of Pediatrics

OBSERVATIONS ON THE CLINICAL USE OF v-CILLIN IN PEDIATRIC PRACTICE

In the 1940s, researchers had developed phenoxymethyl penicillin (penicillin V), an acid-stable form of penicillin that could resist inactivation by stomach acids. In view of the obvious advantages of oral administration of penicillin in children, the authors studied the use of penicillin V in a series of 84 patients between the ages of 5 months and 12 years. Subjects were included if they were diagnosed with an infection and were ill enough that they would usually be treated with a course of parenteral procaine penicillin G. None of the bacterial isolates were analyzed for antibiotic sensitivities. The patients were diagnosed with acute tonsillitis or pharyngitis (n = 53), otitis media (n = 20), or laryngotracheobronchitis or bronchopneumonia (n = 11). Depending on clinical features such as fever pattern, patient response was classified into 4 categories: excellent, good, satisfactory, and unsatisfactory. Sixty-five patients showed excellent or good response, 12 satisfactory, and 7 unsatisfactory (therapeutic failure). Both appeared to respond to the course of penicillin V. The results were stated to be favorable when compared with results expected from treatment with courses of twice-daily intramuscular penicillin G. The authors concluded that the oral suspension of penicillin V was proven to be effective in the treatment of respiratory tract infections, as well as being well tolerated by children.

Much has changed in the past 50 years. Current studies with similar objectives would usually require more subjects (including suitable control subjects) and appropriate statistical analyses to convince pediatricians of the virtues of the antibiotic in question. More importantly, although penicillin resistance was reported shortly after it became widely available for clinical use in the 1940s, it has become increasingly apparent only over the past 2 decades that antibiotic resistance poses a major threat to our ability to combat bacterial infections. In contrast to what would currently be expected, none of the subjects from whom *Staphylococcus aureus* was isolated showed unsatisfactory response. The convenience of treating most types of infections with the same antibiotic has long gone. Judicious use of antibiotics, sensitivity testing of suspected pathogens, rationalization of therapeutic regimes, and stringent infection control measures are now important ways to help prevent infection of individuals, as well as reduce the spread of resistant organisms.

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The Chinese University of Hong Kong
Prince of Wales Hospital, New Territories
Hong Kong
10.1016/j.jpeds.2006.09.009
Pediatric Workforce: A Look at Pediatric Infectious Diseases 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 pediatric infectious diseases. 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 1994, pediatric infectious diseases became the 12th ABP subboard to offer a certification examination, with the first examination yielding 501 board-certified pediatric infectious diseases subspecialists. Today, approximately 1000 pediatricians have been certified by the ABP as pediatric infectious diseases physicians. 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. In 2005, the ABP contacted all accredited pediatric infectious diseases training programs in the United States (n = 61) and Canada (n = 8) to obtain tracking information. All programs contacted returned their tracking information, for a 100% response rate.

RESULTS

Pediatric Infectious Diseases Fellow Tracking

Table I provides the total number of fellows in training since the 1997-98 academic year, with a breakdown by sex and medical school. The number of fellows enrolled in pediatric infectious diseases has been steadily increasing since 1997. The percentage of women in pediatric infectious diseases training is currently 58.1%. This percentage has fluctuated from a low of 48.1% in 1998 to a high of 61.0% in 2003. The number of American Medical School Graduates (AMG) fellows has increased since 1997, from 51.6% to 63.7%, with a peak of 63.8% in 2002.

The Figure illustrates the number of fellows in training at each level. Since 1997-98, the average drop rate from training year 1 to training year 3 has been 13%. The decline may be attributed to many factors such as personal leave, visa restrictions, and ABP-approved abbreviated training pathways. In addition, physicians who have completed fellowship training in Canada only need 2 years of training to be certified by the Royal College of Physicians and Surgeons of Canada. These varying factors make it difficult to ascertain whether the drop rate is a true reflection of those actually leaving the subspecialty.

Pediatric Infectious Diseases Career Data

The ABP has 2 primary opportunities to gather information about career interest in pediatric infectious diseases: 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 pediatric infectious diseases certification examination. This section highlights results from both the 2005 general pediatrics and pediatric infectious diseases applications.

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 which the ABP awards or jointly awards certificates. Pediatric infectious diseases was
selected by 6% of these 866 applicants, making it the eighth most selected pediatric subspecialty.

The infectious diseases certifying examination is given every 2 years. In 2005, there were 91 first-time applicants for the pediatric infectious diseases certification examination. Of these applicants, 53.8% were women and 63.7% were AMG fellows. Approximately 41.8% plan to practice exclusively in pediatric infectious diseases in an academic setting. An additional 2.2% plan to practice exclusively in pediatric infectious diseases, but in a private practice or combined private practice and academic setting.

Certified Diplomates

As a pediatric subspecialty, infectious diseases is the seventh largest ABP discipline, with approximately 1000 certified practitioners (as of 12/31/2005). The mean age of certified pediatric infectious diseases physicians is 49.5 years, with approximately 96% ranging from 31 to 65 years of age.

The ratio of current ABP-certified infectious diseases physicians-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 Table II 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 pediatric infectious diseases physicians with known addresses in 1 of the 50 states or the District of Columbia. Pediatric infectious diseases physicians older than the average retirement age of 65 years were excluded. On the basis of these adjustments, the total number of certified pediatric infectious diseases physicians categorized in Table II is 887.

Only 3 states (Alaska, Montana, and South Dakota) do not have a practicing ABP-certified infectious diseases physician. Twenty-eight states have a pediatric infectious diseases physician-to-child ratio of at least 1 per 100,000 children, with the District of Columbia having the largest ratio (6.4 per 100,000), followed by Maryland (4.3 per 100,000). The 61 infectious diseases training programs in the United States are distributed across 27 of the 50 states and the District of Columbia, as noted by the asterisk in Table II. 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.3,4

In 2005, the number of pediatric infectious diseases physicians in training (training years 1-3) remained fairly stable from the previous year (an increase of only 2 fellows), but it has more than doubled since 1997. The growing proportion of women selecting pediatric infectious diseases as a discipline supports the claim of increased involvement of women in pediatric subspecialties.5

Although the data in Table II provide the pediatric infectious diseases physician-to-child ratio, the data do not indicate who is 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 pediatric infectious diseases. 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.6,7

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 3 states do not have an ABP-certified infectious diseases physician. In addition, the FOPE II survey results indicate that only 4% of infectious disease physicians practice in rural areas.3,4

Also contributing to a growing need for infectious diseases physicians, the FOPE II survey results indicate that 25% of infectious diseases physicians believe that the volume of referrals has increased and 39% also believe that the referral complexity has increased. However, approximately 65% of pediatric infectious diseases physicians anticipate 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. Before this study, the last large-scale workforce study specifically for pediatric infectious diseases was in 1995.8 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.

REFERENCES
Table II. Number of American Board of Pediatrics-certified pediatric infectious diseases diplomates by state

<table>
<thead>
<tr>
<th>State</th>
<th>Number of ABP diplomates in pediatrics infectious diseases</th>
<th>Child population</th>
<th>Physician to child ratio (per 100,000 children)</th>
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<tbody>
<tr>
<td>Alabama* (1)</td>
<td>13</td>
<td>1,094,533</td>
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<tr>
<td>Alaska</td>
<td>0</td>
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<td>100</td>
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<td>Colorado* (1)</td>
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<td>4</td>
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<td><strong>Total</strong></td>
<td><strong>887</strong></td>
<td><strong>73,277,998</strong></td>
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*Note: States with an asterisk denote those with a pediatric infectious disease training program. The number in parentheses indicates the number of programs tracked in the 2005–2006 academic year.
Diagnosis and Localization of Focal Congenital Hyperinsulinism by $^{18}$F-Fluorodopa PET Scan

OLGA T. HARDY, MD, PHD, MIGUEL HERNANDEZ-PAMPALONI, MD, PHD, JANET R. SAFFER, PHD, MARKO SUCHI, MD, PHD, EDUARDO RUCHELLI, MD, HONGMING ZHUANG, MD, PHD, ARUPA GANGULY, PHD, RICHARD FREIFELDER, PHD, N. SCOTT ADDICK, MD, ABASS ALAVI, MD, AND CHARLES A. STANLEY, MD

Objectives To assess the accuracy of $^{18}$F-fluoro-L-dihydroxyphenylalanine ($^{18}$F-DOPA) PET scans to diagnose focal versus diffuse disease and to localize focal lesions in infants with congenital hyperinsulinism.

Study design Twenty-four infants with hyperinsulinism unresponsive to medical therapy were studied. Patients were injected intravenously with $^{18}$F-DOPA, and PET scans were obtained for 1 hour. Images were coregistered with abdominal CT scans.

Results The diagnosis of focal or diffuse hyperinsulinism was correct in 23 of the 24 cases (96%) and equivocal in 1 case. $^{18}$F-DOPA PET identified focal areas of high uptake of radiopharmaceutical in 11 patients. Pathology results confirmed that all 11 had focal adenomatosis, and the locations of these lesions matched the areas of increased $^{18}$F-DOPA uptake on the PET scans in all of the cases.

Conclusions $^{18}$F-DOPA PET scans were 96% accurate in diagnosing focal or diffuse disease and 100% accurate in localizing the focal lesion. These results suggest that $^{18}$F-DOPA PET imaging should be considered in all infants with congenital hyperinsulinism who need to have pancreatectomy. (J Pediatr 2007;150:140-5)

Congenital hyperinsulinism, the most common cause of persistent hypoglycemia in infants and children, is most often associated with recessive mutations of the β-cell ATP-sensitive potassium (K$_{ATP}$) channel. The channel is encoded by two adjacent genes on chromosome 11p15.1, SUR1 and Kir6.2. In cases of diffuse disease, patients have mutations of both alleles encoding the K$_{ATP}$ channel resulting in dysregulation of insulin secretion from all β-cells. Recessive K$_{ATP}$ mutations may also cause focal hyperinsulinism in which there is an area of β-cell adenomatosis caused by loss of heterozygosity for the maternal 11p region and expression of a paternally derived K$_{ATP}$ channel mutation. Surgical intervention is often necessary to control hypoglycemia in both forms of K$_{ATP}$ hyperinsulinism but is only curative in the cases of focal disease.

Surgical treatment of infants with congenital hyperinsulinism depends on being able to distinguish between focal and diffuse disease and to locate focal lesions. Functional tests of insulin responses to secretagogues before surgery are unable to reliably distinguish focal versus diffuse disease, in part because some disease-causing mutations of the K$_{ATP}$ channel retain partial function. Focal lesions are rarely identifiable at surgery and cannot be detected by using conventional imaging techniques such as computed tomography, magnetic resonance imaging, transabdominal or intraoperative ultrasound, or by the use of radiolabeled octreotide scans. Interventional radiologic techniques such as selective pancreatic arterial calcium stimulation with hepatic vein insulin sampling (ASVS) and transhepatic portal venous insulin sampling (THPVS) are invasive, technically difficult, and are also not reliable in either diagnosing or localizing focal lesions.

Neuroendocrine cells have an affinity for taking up and decarboxylating amino acid precursors. Consequently, amino acid precursors such as L-dihydroxyphenylalanine (L-DOPA) may be taken up by these cells and become decarboxylated to dopamine through the action of aromatic amino acid decarboxylase (AADC). Neuroendocrine cell...
was identified by haplotype analysis through the use of mic-
available before surgery. Loss of heterozygosity in focal lesions
MA). In all cases, results of mutation analyses were not
exons and flanking intronic regions of genomic DNA from
focal. This preliminary report provides analysis of the first 24
cases and suggests that the accuracy of [18F]-DOPA PET
scans is better than anticipated for both diagnosis and
localization of focal hyperinsulinism.

METHODS

Subjects

All of the patients included in this study were referred
to the Hyperinsulinism Center at the Children’s Hospital of
Philadelphia between December 2004 and November 2005
for surgical treatment of medically uncontrollable hyperinsul-
linism. Patients not requiring surgery and patients who had
previous pancreatectomies were excluded. The diagnosis of
hyperinsulinism was based on previously described criteria:
fasting hypoglycemia accompanied by inadequate suppression
of plasma insulin, inappropriately low plasma free fatty acid
and plasma β-hydroxybutyrate concentrations, and an inap-
propriate glycemic response to glucagon injection. Two of
the infants underwent ASVS testing before surgery. Mutation
analysis of K_\text{ATP} genes was performed by sequencing coding
exons and flanking intronic regions of genomic DNA from
peripheral blood leukocytes (Athena Diagnostics, Worcester,
MA). In all cases, results of mutation analyses were not
available before surgery. Loss of heterozygosity in focal lesions
was identified by haplotype analysis through the use of mic-
rosatellite markers and by absence of p57^KIP2 immunostaining
in paraffin-embedded surgical specimens.

Surgical Technique and Intraoperative Frozen
Section Evaluation

All of the infants underwent pancreatectomy between 2
weeks and 18 months of age. PET scans were performed at
least 12 hours before surgery (6 half-lives). The results of the
interpretation of the PET scan were made available to the
surgeon to help in the identification of potential focal lesions.
During surgery, biopsy specimens from three areas of the
pancreas were obtained and examined for β-cells with en-
larged nuclei suggestive of diffuse disease. The absence of
nuclear enlargement indicated the presence of a focal lesion.
Findings from the PET scan were compared with the findings
at pathology, based on permanent sections, as described by
others. The determination of focal versus diffuse disease
was made on the permanent histologic sections by two path-
ologists who were masked to the results of the PET scan.

Imaging Technique

[18F]-DOPA PET scans were performed at the Uni-
versity of Pennsylvania PET Imaging Facility. The [18F]-
DOPA was administered under an Investigational New Drug
(#48923) reviewed by the Radiation Safety Committee, In-
stitutional Committees, and the Food and Drug Administra-
tion. The Investigational New Drug was modified to allow
inclusion of children, and the Food and Drug Administration
dosimetry studies are part of that application. The isotope was
manufactured by the Cyclotron Facility at the University of
Pennsylvania on the day of the test, using the procedure
previously published. Typical yields were 10 to 15 mCi for
a 500 micro-amp-minute irradiation. Specific activity of the
compound is approximately 500 to 1000 Ci/mol at end of
synthesis. Patient injection occurred about 45 minutes after
completion of the synthesis. Medications that could poten-
tially interfere with pancreatic β-cell function, such as dia-
zoxide, octreotide, and glucagon, were discontinued 5 days, 2
days, and 12 hours, respectively, before the procedure. All
patients received intravenous dextrose infusion for control of
hypoglycemia and to enhance elimination of isotope from the
kidneys. Plasma glucose was monitored before and every 60
minutes during the procedure. Rates of intravenous glucose
infusion were adjusted as needed to maintain plasma glucose
levels greater than 70 mg/dL. In one case, the patient was
catheterized to facilitate bladder emptying. For obtaining
PET images, patients were intubated and sedated with gen-
eral anesthesia. Patients were injected intravenously with 3 to
6 MBq/kg (0.08 to 0.16 mCi/kg) of [18F]-DOPA, which is
approximately one-tenth of the total adult dose. After injec-
tion, five or six consecutive 10-minute-long scans were per-
formed. The images were acquired through the use of a
dedicated brain PET camera based on Anger-logic gadolin-
ium oxyorthosilicate (GSO) detectors, designed and built by
the Physics and Instrumentation Group at the University of
Pennsylvania. This instrument has both axial and transverse
fields of view of 25 cm and is therefore suited for imaging the
whole body in infants. An abdominal CT was obtained sep-
ately to define the anatomy of the pancreas and adjacent
tissue before surgery. The CT image was coregistered with the
PET scan to assist in defining the location of focal lesions
by using standard software that is available for this purpose.

The study protocol was approved by the Food and Drug
Administration and the institutional review boards of the
Children’s Hospital of Philadelphia and the University of
Pennsylvania. Written informed consent was obtained from
the parents of the patients.

Image Interpretation

The image set for each patient was visually interpreted
by one of the investigators at the completion of the exami-
nation. Images were reviewed in all three planes as well as

Diagnosis and Localization of Focal Congenital Hyperinsulinism by 18F-Fluorodopa PET Scan
Table I. Clinical features of infants with hyperinsulinism studied with [18F]-DOPA PET scan before surgery [median (range)]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diffuse disease</th>
<th>Focal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>6/6</td>
<td>8/4</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>83%</td>
<td>83%</td>
</tr>
<tr>
<td>Age at first symptoms (d)</td>
<td>1 (1-4)</td>
<td>1 (1-90)</td>
</tr>
<tr>
<td>Age at PET (wk)</td>
<td>5 (2-72)</td>
<td>7 (2-56)</td>
</tr>
<tr>
<td>ASVS performed</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

maximum intensity projection views, and the presence and the pattern of uptake in the pancreas were taken into consideration in generating final reports for these scans. The image examination was considered positive for focal disease when the uptake of the radiotracer in part of the pancreas was qualitatively higher when compared with the uptake in the remaining pancreatic tissue and other surrounding background organs. In contrast, when the entire pancreas was visualized with nearly uniform [18F]-DOPA uptake, the examination was considered to represent diffuse disease.

Statistical Analysis

Based on previous reports on ASVS and THPVS from Paris and Philadelphia, we assumed that 50% of surgical cases would have focal disease and that at least 70% of focal lesions would be correctly localized by [18F]-DOPA PET test.16,19 Sample size estimates based on these assumptions indicated that 52 total cases (26 focal cases) would provide an estimate of test accuracy between 52% and 88% (95% confidence interval, CI). The efficient-score method was used to calculate 95% CIs for proportions.28

RESULTS

Table I summarizes the clinical features of the 24 infants with medically unresponsive hyperinsulinism who were studied with [18F]-DOPA PET scans before surgery. Most of the infants in both groups were large for gestational age, presented with hypoglycemia at birth, and were referred for pancreatectomy within a few months after birth.

ASVS testing was done in patient 13 and patient 15 before surgery. In both, ASVS showed a step-up in insulin release after calcium infusion in the gastroduodenal artery, suggesting a focal lesion in the head of the pancreas. Although the ASVS test was correct in diagnosing focal disease in both cases, it was correct in localizing the lesion only in patient 13 (Table II).

After intravenous injection of [18F]-DOPA, the uptake of isotope into pancreas and other tissues, such as liver, was rapid and then remained essentially constant from 10 to 60 minutes. There was also uptake early in the kidneys and bladder that decreased with time as radiopharmaceutical was excreted in the urine. Drainage of urine through a Foley catheter helped decrease the intensity of uptake in the bladder region in one patient. No patients became hypoglycemic during the PET scan.

Figures 1 and 2 show illustrative PET scans of cases with diffuse and focal hyperinsulinism. Figure 1A shows the maximum intensity projection image from a diffuse case (patient 4) with uniform [18F]-DOPA uptake throughout the pancreas. The intensity of uptake in the pancreas was greater than in the liver and surrounding tissue but less than in the renal calyces. Figure 1 (B through D) shows the same case with the abdominal CT scan and PET scan separate and coregistered, which confirms that the diffuse uptake of [18F]-DOPA was in the pancreas.

Figure 2 shows a focal case (patient 23) in which there was a discrete area of [18F]-DOPA uptake in the head of the pancreas. There was also uptake in the neighboring normal pancreatic tissue, but it was less intense than in the head of the pancreas (Figure 2A). Coregistration of the PET and CT scans from patient 23 (Figure 2, B through D) demonstrates that the location of the focal uptake was in the head of the pancreas.

Diffuse uptake of [18F]-DOPA was observed throughout the pancreas of patient 17, with areas of intense uptake in the head, body, and tail of the pancreas. This scan was interpreted as being either consistent with diffuse disease or, possibly, an extensive focal lesion. The latter possibility was confirmed at surgery, where an extensive area of islet adenomatosis occupied 80% to 90% of the pancreas and extended throughout the body, tail, and most of the head of the gland.

Table II summarizes the results of the PET scans and the histologic diagnoses in the 24 cases studied. In all of the 12 diffuse cases, the preoperative interpretation of the PET scan was the same as the histologic diagnosis of diffuse disease. In 11 of the 12 cases of focal disease, focal uptake of isotope on PET correctly diagnosed the presence of focal disease. As noted above, the one case with an extensive focal lesion was suggested but not definitively diagnosed as a focal lesion by PET. However, in all of the 12 cases of focal disease, the PET scan correctly indicated the location of the lesions. There were no side effects observed that could be attributed to the radiopharmaceutical.

As shown in Table II, mutation analysis of the two K<sub>ATP</sub> genes identified two mutations consistent with diffuse disease in 7 of the 11 diffuse cases in whom mutation analysis was completed. In two other diffuse cases, only one of the expected two mutations could be identified. In two of the diffuse cases, no mutation could be found in either maternal or paternal allele. Among the 12 focal cases, mutation analysis showed a paternal-only mutation in 11 cases. Immunohistochemical staining for p57<sup>KIP2</sup> and haplotype analysis demonstrated loss of heterozygosity for the maternal 11p region in all of the 12 focal cases.

In addition to the 24 cases who fit the study inclusion criteria, [18F]-DOPA PET scans were done in 3 additional patients. In one of these patients who did not fit inclusion criteria, medical treatment with octreotide was sufficiently
effective so that surgery was not considered mandatory. However, a focal lesion was suspected on the basis of the presence of a single paternal Kir6.2 or SUR1 mutation. The PET scan showed focal uptake in the head of the pancreas suggesting a focal lesion; surgery was elected that revealed a focal lesion, which was excised. In a second patient, two prior pancreatectomies at another institution had removed 98% of the pancreas but failed to improve hypoglycemia. A focal lesion was detected in the head of the pancreas but not completely excised in the second surgery. [18F]-DOPA PET scan showed areas of focal uptake not only in the remaining head of the gland but also in four ectopic extrapancreatic areas. At surgery, the residual focal lesion in the head of the pancreas was resected, as were four ectopic focal adenomatosis lesions in the wall of the jejunum. (Details of this case will be reported separately.) In the third case, the parents declined surgical treatment on the basis of the interpretation of the [18F]-DOPA PET scan as diffuse disease. Although these three patients could not be included in our study of the [18F]-DOPA PET scan accuracy, the test did correctly localize the focal lesions in two of the three patients.

**DISCUSSION**

These preliminary results suggest that [18F]-DOPA PET is accurate in both the diagnosis of focal or diffuse Table II. Results of preoperative [18F]-DOPA PET scans in 24 infants with congenital hyperinsulinism

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>[18F]-DOPA PET diagnosis</th>
<th>Histologic diagnosis</th>
<th>Kir6.2 or SUR1 mutations</th>
<th>LOH by haplotyping and immunostaining</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>g3992-9a</td>
<td>G173R</td>
</tr>
<tr>
<td>3</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>31aa insertion</td>
<td>g1630+1t</td>
</tr>
<tr>
<td>5</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>del20aa</td>
<td>none</td>
</tr>
<tr>
<td>6</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>R837X</td>
<td>15aa insertion</td>
</tr>
<tr>
<td>7</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Q219X</td>
<td>none</td>
</tr>
<tr>
<td>8</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>R620C</td>
<td>E501L</td>
</tr>
<tr>
<td>9</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Q444H</td>
<td>Q444H</td>
</tr>
<tr>
<td>10</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>11</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>g3992-9a</td>
<td>1388delF</td>
</tr>
<tr>
<td>12</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>R999X</td>
<td>R999X</td>
</tr>
<tr>
<td>Focal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Head</td>
<td>Head and neck</td>
<td>E282K</td>
<td>none</td>
</tr>
<tr>
<td>14</td>
<td>Head</td>
<td>Head</td>
<td>D310V</td>
<td>none</td>
</tr>
<tr>
<td>15</td>
<td>Body</td>
<td>Body</td>
<td>g1630+1t</td>
<td>none</td>
</tr>
<tr>
<td>16</td>
<td>Head</td>
<td>Head</td>
<td>g2041−21a</td>
<td>none</td>
</tr>
<tr>
<td>17</td>
<td>Extensive lesion</td>
<td>Extensive lesion</td>
<td>R1461C</td>
<td>none</td>
</tr>
<tr>
<td>18</td>
<td>Tail</td>
<td>Tail</td>
<td>D1472N</td>
<td>none</td>
</tr>
<tr>
<td>19</td>
<td>Tail</td>
<td>Tail</td>
<td>E490X</td>
<td>none</td>
</tr>
<tr>
<td>20</td>
<td>Head</td>
<td>Head</td>
<td>g3992−9a</td>
<td>none</td>
</tr>
<tr>
<td>21</td>
<td>Tail</td>
<td>Tail</td>
<td>G954X</td>
<td>none</td>
</tr>
<tr>
<td>22</td>
<td>Head</td>
<td>Neck</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>23</td>
<td>Head</td>
<td>Head</td>
<td>del6aa</td>
<td>none</td>
</tr>
<tr>
<td>24</td>
<td>Head</td>
<td>Head</td>
<td>t1176+2c</td>
<td>none</td>
</tr>
</tbody>
</table>

ND, not done; LOH, loss of heterozygosity.

Figure 1. [18F]-DOPA PET of patient 4 with diffuse disease. A, Diffuse uptake of [18F]-DOPA is visualized throughout the pancreas on this depth-weighted maximum intensity projection sagittal image. Intensity is greater than that observed in the liver and surrounding tissue. Also note physiologic distribution in the kidneys. Transverse views show B, normal pancreatic tissue on abdominal CT; C, diffuse uptake of [18F]-DOPA in pancreas; and D, confirmation of pancreatic uptake of [18F]-DOPA with coregistration. H indicates head of pancreas; T, tail of pancreas.
pancreatic tissue on abdominal CT; the pancreas, the surgeon can perform a proximal pancreatec-

dification of the focal lesion. Diagnosis was correct in 23 of 24 cases and equivocal in 1 case (96%; CI, 77% to 98%). Of the 12 focal lesions, [18F]-DOPA PET localized the focal lesion in all of the cases, providing a 95% CI between 70% and 100%.

In assessing the accuracy of this new technique, it is important to differentiate diagnosis of the form of hyperinsulinism from localization of the focal lesion. There may be clinical situations in which surgery would not be considered unless the patient has focal disease. In such cases, it is crucial to know the accuracy of the PET scan in diagnosing focal hyperinsulinism so that patients with focal disease can undergo curative surgery. In the current series, the sensitivity of [18F]-DOPA PET in diagnosing focal disease was 92% and the specificity was 100%. The positive predictive value of [18F]-DOPA in diagnosing focal disease was 100% (11/11) and the negative predictive value was 92% (12/13). Localization is a separate issue because successful surgery depends on finding and removing the focal lesion. For example, if [18F]-DOPA PET definitively identifies the lesion in the head of the pancreas, the surgeon can perform a proximal pancreatectomy with Roux-en-Y and preserve the tail of the pancreas.

The accuracy of [18F]-DOPA PET in our series is consistent with data reported in two smaller series of cases. Otonkoski and colleagues reported that [18F]-DOPA PET was able to correctly diagnose focal versus diffuse disease in nine patients and accurately localized the lesion in all of their five focal cases. Ribeiro et al showed that in nine patients who had surgical treatment, [18F]-DOPA PET accurately diagnosed focal versus diffuse disease and correctly localized the lesion in all five focal cases. Both series included cases in which the [18F]-DOPA PET scan suggested diffuse disease, but surgery to confirm the diagnosis was not done. This is in contrast to our study, in which histopathologic diagnosis was available for all of the 24 cases.

The current data suggest that [18F]-DOPA PET has the potential to be more accurate than ASVS or THPVS in diagnosing focal versus diffuse disease and localizing the focal lesion. ASVS correctly diagnosed diffuse disease in only 4 of 13 cases and localized the focal lesion in only 73% of 33 cases.7 Of 45 cases of focal disease, THPVS localized the focal lesion correctly in only 75%.6 In addition, even though PET scans require general anesthesia and a minimal dose of radioactivity, the method is much less invasive than ASVS or THPVS and does not require exposure to hypoglycemia or large volumes of blood.

The results of mutation analysis and testing of focal lesions for loss of heterozygosity in Table II are consistent with the concept that diffuse disease is caused by recessive mutations of the K<sub>ATP</sub> channel and that focal disease is caused by expression of a paternally derived channel mutation. Evidence for loss of heterozygosity for 11p was demonstrated in all of the focal cases. Mutations in Kir<sub>6.2</sub> or SUR1 genes were found in both focal and diffuse cases. However, as has been noted in previous series, sequencing of coding regions of peripheral blood genomic DNA failed to uncover all of the expected mutations.4,5 Mutations could have been present but escaped detection if, for example, they were in regions of DNA not sequenced. Because of the possibility of undetected mutations, DNA sequencing can be informative for diagnosing diffuse disease (mutant maternal allele) but not focal disease.

On the basis of the preliminary results of our study, the [18F]-DOPA PET scan was 96% accurate (CI, 70% to 100%) in diagnosis of focal hyperinsulinism and 100% accurate in localizing the focal lesion. When combined with data from the two other recent reports, the overall accuracy of PET scans has been 100% in localizing focal lesions (21/21; CI, 81% to 100%). These encouraging results suggest that [18F]-DOPA PET imaging should be strongly considered in all infants with congenital hyperinsulinism who fail medical therapy and need to have pancreatectomy.

We are grateful for the help of the Children's Hospital of Philadelphia Department of Anesthesiology, the staff at the University of Pennsylvania PET Imaging, and Cyclotron Facilities and the Department of Radiology Nuclear Medicine Section (Nancy Win-tering). We are also indebted to the expert nursing team of the Hyperinsulinism Center (Laura Wanner, Lori Halaby, Susan O'Rourke, Marie Smolenski) and to Nkecha Hughes, Andrea Matter, and Courtney MacMullen for their expert assistance with these studies.

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Longitudinal Lipid Screening and Use of Lipid-Lowering Medications in Pediatric Type 1 Diabetes

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Objective Because cardiovascular disease (CVD) is the leading cause of death in patients with type 1 diabetes (T1D) and dyslipidemia is an important CVD risk factor, we investigated dyslipidemia and its treatment in children with T1D.

Study design Subjects had T1D (n = 360), repeated lipid measurements (n = 1095; mean, 3.04 ± 0.94; range, 2 to 11), and were seen between 1994 and 2004. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL), and non-HDL cholesterol (non-HDL) were categorized on the basis of published guidelines. Age, diabetes duration, sex, body mass index, HbA1c, and lipid-lowering medication use were recorded. Predictors of TC, HDL, and non-HDL were determined.

Results Sustained abnormalities existed for TC ≥200 mg/dL (16.9%); HDL < 35 mg/dL (3.3%); and non-HDL ≥130 mg/dL (27.8%), ≥160 mg/dL (10.6%), and ≥190 mg/dL (3.3%). Lipid-lowering medications were started on 23 patients. In mixed model longitudinal data analyses, HbA1c was significantly related to TC and non-HDL. Body mass index z-score was inversely related to HDL.

Conclusions In this retrospective, longitudinal study of pediatric patients with T1D with repeated lipid measurements, sustained abnormal levels for TC, HDL, and non-HDL were present. Prospective longitudinal data for dyslipidemia in youth with T1D are needed. (J Pediatr 2007;150:146-50)

Despite guidelines for the management of dyslipidemia in children and longitudinal studies of serum lipids in the general pediatric population, there are fewer data on lipids in pediatric subjects with type 1 diabetes (T1D). The antecedents of adult cardiovascular disease (CVD), the primary cause of death in T1D, are present in children. Studies including the Bogalusa Heart Study, the Pathological Determinants of Atherosclerosis in Youth study, and the Young Finns Study demonstrate tracking of CVD risk factors into adulthood. Furthermore, the relation of CVD risk factors in childhood relate to abnormalities in surrogate markers of atherosclerosis and/or atherosclerotic lesions in pathology evaluations. Dyslipidemia is a significant CVD risk factor, and CVD is the leading cause of death in patients with T1D. We have previously reported that 18.6% of children with T1D had abnormal total cholesterol (TC) or high-density lipoprotein (HDL) levels in a retrospective cross-sectional analysis, but published longitudinal data on lipids in the T1D pediatric population are limited. In this study, we used electronic medical records to retrospectively examine TC, HDL, and non-HDL levels in 360 pediatric patients with T1D with repeated lipid measurements and determine the use and effectiveness of lipid-lowering medications during a 10-year period (1994 to 2004). We hypothesized that (1) untreated sustained abnormal TC, HDL, and non-HDL levels would not normalize despite standard diet and lifestyle counseling and attempts to control HbA1c; (2) TC, HDL, and non-HDL would be significantly related to HbA1c and body mass index (BMI) over time; (3) in the time period studied (1994 to 2004), lipid-lowering medication would be rarely used in children with T1D with dyslipidemia; and (4) children taking lipid-lowering medication would have no significant adverse events and would have significant improvements in their repeat TC, HDL, and non-HDL after pharmacologic treatment.
Study subjects were diagnosed with T1D (as defined by American Diabetes Association [ADA] criteria)\textsuperscript{22} <21 years at their initial visit at the Barbara Davis Center for Childhood Diabetes between January 1, 1994, and June 30, 2004, and had screening lipids measured. Screening lipid levels were obtained as part of routine diabetes care. Since fasting status was not routinely recorded, only TC, HDL, and calculated non-HDL levels (TC minus HDL) were analyzed.

To ensure that only patients with T1D were studied, only subjects either with autoantibody determinations positive for diabetes-associated autoimmunity or specifically physician-diagnosed as T1D were included. Furthermore, to exclude the lipid abnormalities of untreated diabetes, those subjects with serum lipids measured within the first month of T1D diagnosis were excluded. During the study period, 2173 subjects with serum lipids measured within the first month of 1095 observations (mean observations per patient, 3.04 ± 0.94; range, 2 to 11). TC and HDL were measured in commercial laboratories as part of standard clinical practice. The Colorado Multiple Institutional Review Board approved this study.

The electronic database was queried for lipid-lowering medication usage. In addition, each patient’s electronic medical record was reviewed to determine lipid-lowering medication usage, dosage, start and stop dates, and whether any adverse effects were documented. Records were reviewed beginning one visit before the first lipid screen through the end of the study period for each patient. Finally, individual diabetologists were queried, and stored paper charts were reviewed for selective confirmation of lipid-lowering medication status. No discrepancies between electronic and paper charts were found.

Data were obtained on 360 patients (Table I), for a total of 1095 observations (mean observations per patient, 3.04 ± 0.94; range, 2 to 11). TC, HDL, and non-HDL were considered to be changed if they increased or decreased by one or more category from baseline at the patient’s last visit. Longitudinal data analysis was performed with the use of SAS Proc Mixed with SP (POW) structure for unequally spaced data, with diabetes duration, HbA1c (log transformed due to non-normal distribution), and BMI z-score as independent variables and TC, HDL, and non-HDL as dependent variables (Table II). This longitudinal analysis method fully utilizes all available data points and accounts for different time intervals between measurements. Since age and diabetes duration are so closely correlated in children with T1D, separate models were constructed, using age and diabetes duration. The use of lipid-lowering medications (yes/no) was included as a covariate. Therefore, the direction and magnitude of the $\beta$-coefficient for the lipid-lowering medication variable signifies the difference in lipid level for medication status. The Wilcoxon signed-rank or Kruskal–Wallis test was used to evaluate dif-

<table>
<thead>
<tr>
<th>Variable</th>
<th>n = 360 subjects</th>
<th>Males (n = 190)</th>
<th>Female (n = 170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>13.6 ± 4.1</td>
<td>13.5 ± 4.0</td>
<td>13.6 ± 4.1</td>
</tr>
<tr>
<td>Male/female, % male</td>
<td>190/170</td>
<td>52.8%</td>
<td>47.2%</td>
</tr>
<tr>
<td>Diabetes duration, years</td>
<td>4.5 ± 0.3</td>
<td>4.4 ± 3.4</td>
<td>4.7 ± 3.5</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.8 ± 1.6</td>
<td>8.8 ± 1.5</td>
<td>8.8 ± 1.6</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>0.62 ± 1.00</td>
<td>0.61 ± 1.11</td>
<td>0.62 ± 0.90</td>
</tr>
<tr>
<td>TC, mg/dL</td>
<td>176.8 ± 39.5</td>
<td>174.3 ± 38.5</td>
<td>179.2 ± 40.4</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>54.8 ± 15.9</td>
<td>53.8 ± 17.4</td>
<td>55.7 ± 14.4</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mg/dL</td>
<td>122.0 ± 38.1</td>
<td>120.5 ± 35.7</td>
<td>123.4 ± 40.2</td>
</tr>
<tr>
<td>Mean follow-up time, years</td>
<td>2.9 ± 2.1</td>
<td>2.7 ± 2.0</td>
<td>3.1 ± 2.1</td>
</tr>
<tr>
<td>TC ≥200 mg/dL, %</td>
<td>18.9%</td>
<td>19.4%</td>
<td>18.4%</td>
</tr>
<tr>
<td>HDL cholesterol &lt;35 mg/dL, %</td>
<td>4.2%</td>
<td>4.1%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Non-HDL ≥130 mg/dL, %</td>
<td>34.2%</td>
<td>34.1%</td>
<td>34.2%</td>
</tr>
<tr>
<td>Non-HDL ≥160 mg/dL, %</td>
<td>11.4%</td>
<td>11.2%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Non-HDL ≥190 mg/dL, %</td>
<td>5.8%</td>
<td>6.5%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Lipid-lowering medications use, %</td>
<td>6.4%</td>
<td>5.3%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

No significant differences between sexes.

### METHODS

The proportion of subjects with non-HDL ≥160 mg/dL and ≥190 mg/dL is also reported. TC and HDL were measured in commercial laboratories as part of standard clinical practice. The Colorado Multiple Institutional Review Board approved this study.
Table II. Longitudinal predictors of total cholesterol, high-density lipoprotein, and non–high-density lipoprotein

<table>
<thead>
<tr>
<th>Variable</th>
<th>β-coefficient (SE)</th>
<th>P value</th>
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<tbody>
<tr>
<td>TC (n = 358)</td>
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<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>95.61 (17.39)</td>
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</tr>
<tr>
<td>Diabetes duration</td>
<td>0.0454 (0.3239)</td>
<td>.89</td>
</tr>
<tr>
<td>Lipid medication: No</td>
<td>−39.53 (4.35)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Lipid medication: Yes</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Log₁₀A₁c</td>
<td>123.94 (17.18)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>0.25 (1.08)</td>
<td>.82</td>
</tr>
<tr>
<td>HDL (n = 358)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>43.53 (7.03)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td>0.0255 (0.1291)</td>
<td>.84</td>
</tr>
<tr>
<td>Lipid medication: No</td>
<td>3.57 (1.73)</td>
<td>.04</td>
</tr>
<tr>
<td>Lipid medication: Yes</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Log₁₀A₁c</td>
<td>9.35 (6.97)</td>
<td>.18</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>−0.99 (0.43)</td>
<td>.02</td>
</tr>
<tr>
<td>Non-HDL (n = 358)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>49.27 (16.64)</td>
<td>.0033</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td>−0.0265 (0.3024)</td>
<td>.93</td>
</tr>
<tr>
<td>Lipid medication: No</td>
<td>−43.89 (4.02)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Lipid medication: Yes</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Log₁₀A₁c</td>
<td>118.27 (16.53)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>1.19 (1.01)</td>
<td>.24</td>
</tr>
</tbody>
</table>

Note: Parameter estimates obtained using SAS Proc Mixed.
Two patients lacked complete data for analysis.

ferences in continuous variables, and the χ² test of independence was used to evaluate differences in discrete characteristics. Results were considered significant at α < 0.05. Finally, for patients on lipid-lowering medications (n = 23, Table III; available at www.jpeds.com), the following are reported for each patient: lipid measurements immediately before initiation of medication, the most-improved lipid measurements, the time interval between premedication and final lipid measurements, the final lipid measurements, and the percent change in lipid.

RESULTS

Baseline characteristics of study patients are shown in Table I. There were no statistically significant differences between male and female subjects at baseline. At the first visit, 68 of 360 (18.9%) patients had TC ≥200 mg/dL, 15 (4.2%) had HDL <35 mg/dL, 123 (34.2%) had non-HDL ≥130 mg/dL, 41 (11.4%) had non-HDL ≥160 mg/dL, and 21 (5.8%) had non-HDL ≥190 mg/dL. Those patients with TC ≥200 mg/dL had worse glycemic control (Hba1c = 9.7% ± 2.1%, P < .0001) and were older (age: 14.5 ± 3.9 years, P = .0013) than those with normal cholesterol (Hba1c = 8.5% ± 1.2%; age: 13.8 ± 4.2 years) or cholesterol between 170 and 200 mg/dL (Hba1c = 8.8% ± 1.4%; age: 12.6 ± 3.9 years) but were similar in BMI z-score and duration of diabetes.

On at least one visit during the study period, 123 (34.2%) had TC ≥200 mg/dL, 54 (9.4%) had HDL <35 mg/dL, 172 (47.8%) had non-HDL ≥130 mg/dL, 68 (18.9%) had non-HDL ≥160 mg/dL, and 35 (9.7%) had non-HDL ≥190 mg/dL. An abnormality of any of these (TC, HDL, or non-HDL) on at least one visit during the study period was found in 191 (53.1%), whereas 148 (41.1%) had either abnormal TC ≥200 mg/dL or HDL <35 mg/dL. Sustained abnormalities existed for 61 (16.9%) patients with TC ≥200 mg/dL, 12 (3.3%) with HDL <35 mg/dL, 100 (27.8%) with non-HDL ≥130 mg/dL, 38 (10.6%) with non-HDL ≥160 mg/dL, and 12 (3.3%) with non-HDL ≥190 mg/dL. Lipid measurements were not related to time of follow-up (data not shown). Among patients with baseline lipid abnormalities, 30 of 68 (44%) with TC ≥200 mg/dL, 6 of 15 (40%) with HDL <35 mg/dL, 77 of 123 (63%) with non-HDL ≥130 mg/dL, 17 of 41 (41%) with non-HDL ≥160 mg/dL, and 6 of 21 (29%) with non-HDL ≥190 mg/dL were also abnormal at their final visit.

After adjustment for the use of lipid-lowering medications, mixed-model longitudinal data analyses demonstrated significant relations between Hba1c and TC (P < .0001) and Hba1c and non-HDL (P < .0001) but not Hba1c and HDL (P = .18). BMI z-score had a negative relation to HDL (P = .02), but there was no relation between BMI z-score and TC (P = .82) or non-HDL (P = .24) (Table II). Diabetes duration was not related to TC, HDL, or non-HDL. In a separate model, age was not related to HDL (P = .77), TC (P = .63), or non-HDL (P = .96). As expected, patients not taking lipid-lowering medications had significantly lower TC and non-HDL and higher HDL compared with patients taking lipid-lowering medications, as indicated by the β-coefficients in Table II.

Lipid-lowering medications were started in 23 of the 360 (6.4%) patients, including 19 exclusively taking statins (Table III). Of the 23, 12 had non-HDL ≥190 mg/dL, 7 had non-HDL between 160 and 189 mg/dL (including one who was <12 years of age), and 4 had non-HDL <160 mg/dL. Of the 7 patients with non-HDL between 160 and 189 mg/dL, all had LDL >130 mg/dL and/or hypertension. Of the 4 patients who had non-HDL <160 mg/dL, 2 had LDL >130 mg/dL, 1 had hypertension, and 1 had a BMI of 36 kg/m². One patient was prescribed ezetimibe (No. 21), one was started on a statin and then continued in combination with ezetimibe (No. 14), another was started on a fibrate but switched to a statin and then ezetimibe (No. 4), and another was prescribed a statin and later a fibrate (No. 17). Of the 23 taking medications, 10 had TC <200 mg/dL on the final measurement, whereas 13 did not. There were no recorded major adverse effects from lipid-lowering medications. There were no significant differences between those who improved and those who did not improve on lipid-lowering medications with respect to age, duration of diabetes, BMI, or Hba1c. As expected, those placed on lipid-lowering medications had higher TC (248 ± 64 mg/dL vs 172 ± 32 mg/dL; P < .0001), non-HDL (195 ± 67 mg/dL vs 117 ± 30 mg/dL; P < .0001), and Hba1c (10.1% ± 2.1% vs 8.7% ± 1.5%, P = .0005) than the rest of the study population. Table III shows lipid levels at the visit before beginning lipid-lowering
medications. Although more than half of the patients taking lipid-lowering medication did not have TC <200 mg/dL at the final measurement as desired for pharmacologic treatment, their most-improved lipid measurement showed a mean decrease in TC (–25% ± 17%) and non-HDL (–30% ± 20%) and an increase in HDL (+8% ± 17%) while taking lipid-lowering medication (Table III). This suggests that more rigorous therapy as well as patient education on the importance of continued therapy may be needed.

**DISCUSSION**

Since the use of lipid-lowering medication in children with T1D is a relatively new recommendation from the ADA,1,3 lipid-lowering medications were started in few patients; however, these patients had a higher mean TC, non-HDL, and HbA1c than the rest of the study population. Patients started on lipid-lowering medications had improvement in lipid levels, although these improvements were not uniformly sustained. Compliance with medications could not be assessed with this study. Similarly, although diet and lifestyle counseling as well as attention to glycemic control have long been part of our center’s multidisciplinary approach, individual patient response to this counseling cannot be provided. A limitation of this report is that patients’ TC and HDL were not performed in a standard research laboratory. Only a subset of patients had their lipids measured more than once introducing a selection bias. There are also no data on pubertal stage. Although we report no serious adverse events with lipid-lowering medications similar to studies in adults,24 data on the safety of these agents in T1D youth require further study, including the long-term use and potential teratogenic issues for female adolescents who may become pregnant.25,26 Monitoring of liver function tests (on which we do not report data) and musculoskeletal symptoms are recommended.1 Our data also suggest that life-long attention to lifestyle modification in addition to pharmacologic treatment may be required to meet and sustain recommended lipid goals.

Although numerous longitudinal reports in childhood exist, data on lipids in children with T1D are limited and consist of cross-sectional7–9,19,27 and short-duration (2 weeks and 6 months) longitudinal reports that support the importance of glycemic control20,21 for lipid health. The study reported by Schwab et al.28 is noteworthy for reporting dyslipidemia (TC, LDL, or HDL) in 28.6% in a large, cross-sectional study of young (<26 years) German and Austrian patients. In this report, only 0.4% reported receiving pharmacologic treatment. We report that 40% to 63% of children with abnormal lipids remain abnormal, but others follow a variable course from their first to last visit. Although repeat lipid determination before pharmacologic treatment is recommended,3 the intrasubject variability of lipids over time in children with T1D cannot be fully addressed with these retrospective data.

Current clinical guidelines in pediatrics are based on expert opinion and extrapolation from the adult literature.1–3 The ADA recommendations for children with T1D are to screen for dyslipidemia in children ≥2 years of age in the presence of a positive or unknown family history; otherwise, screening should occur at ≥12 years of age (once glycemic control has been obtained in the newly diagnosed patient) and then repeated every 5 years if normal. Treatment with medication is recommended for LDL ≥160 mg/dL. In addition, blood glucose control and dietary and exercise counseling are emphasized. In children with LDL levels between 130 and 159 mg/dL, glucose control and dietary and exercise counseling are recommended for 6 months, with medication to be considered if the LDL remains >130 mg/dL. The treatment goals are LDL <100 mg/dL, HDL >35 mg/dL, and TG <150 mg/dL.1,3 Ideally, screening blood samples should be obtained in the fasting state. However, given the difficulties of obtaining fasting samples (which include safety issues in patients with T1D), the Adult Treatment Panel III (ATP-III) suggests screening with nonfasting TC and HDL, followed by a complete fasting lipoprotein panel if screening results are abnormal.23 Non-HDL is used as a secondary target in adults, particularly among patients with elevated triglycerides.23

Our findings support the importance of regular screening for dyslipidemia in children with T1D. The variability reported indicates the importance of repeated lipid measurements. Future research needs include prospective longitudinal data on the natural history of dyslipidemia, safety and efficacy data from clinical trials of lipid-lowering medications, and ultimately the long-term relation of dyslipidemia and its treatment to future health outcomes in youth with T1D.

We thank Alex Brown and the Information Technology staff at the Barbara Davis Center for Childhood Diabetes in Denver, Colorado.

**REFERENCES**


Table III. Change in total cholesterol, high-density lipoprotein, and non–high-density lipoprotein in patients (n = 23) taking lipid-lowering medications

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age, y</th>
<th>Sex (M/F)</th>
<th>Premedication*</th>
<th>Most improved‡</th>
<th>Final</th>
</tr>
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<tbody>
<tr>
<td>TC</td>
<td>HDL</td>
<td>Non-HDL</td>
<td>TC %Δ</td>
<td>HDL %Δ</td>
<td>Non-HDL %Δ</td>
</tr>
<tr>
<td>1</td>
<td>13.7</td>
<td>F</td>
<td>313</td>
<td>45</td>
<td>268</td>
</tr>
<tr>
<td>2</td>
<td>21.5</td>
<td>M</td>
<td>298</td>
<td>55</td>
<td>243</td>
</tr>
<tr>
<td>3</td>
<td>24.5</td>
<td>M</td>
<td>251</td>
<td>46</td>
<td>205</td>
</tr>
<tr>
<td>4</td>
<td>18.0</td>
<td>F</td>
<td>441</td>
<td>45</td>
<td>396</td>
</tr>
<tr>
<td>5</td>
<td>23.5</td>
<td>F</td>
<td>259</td>
<td>50</td>
<td>209</td>
</tr>
<tr>
<td>6</td>
<td>14.8</td>
<td>M</td>
<td>242</td>
<td>41</td>
<td>201</td>
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<tr>
<td>7</td>
<td>19.0</td>
<td>F</td>
<td>188</td>
<td>66</td>
<td>122</td>
</tr>
<tr>
<td>8</td>
<td>14.7</td>
<td>F</td>
<td>211</td>
<td>38</td>
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<tr>
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<td>216</td>
<td>60</td>
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<td>225</td>
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<td>16</td>
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<td>16.5</td>
<td>M</td>
<td>208</td>
<td>45</td>
<td>163</td>
</tr>
<tr>
<td>19</td>
<td>16.7</td>
<td>F</td>
<td>322</td>
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<td>177</td>
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<tr>
<td>20</td>
<td>13.4</td>
<td>F</td>
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<td>62</td>
<td>205</td>
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Table III. Continued

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<th>Patient no.</th>
<th>Age, y</th>
<th>Sex (M/F)</th>
<th>TC</th>
<th>HDL</th>
<th>Non-HDL</th>
<th>Most improved‡</th>
<th>Final</th>
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<tr>
<td></td>
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<td>TC %Δ</td>
<td>HDL %Δ</td>
<td>%Δ</td>
<td>Time interval, y</td>
<td>TC %Δ</td>
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<td>14.8</td>
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<td>54</td>
<td>151</td>
<td>0.3</td>
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<tr>
<td>23</td>
<td>15.6</td>
<td>M</td>
<td>226</td>
<td>46</td>
<td>180</td>
<td>0.5</td>
<td>226</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td></td>
<td>163 ± 3.7</td>
<td>256 ± 57</td>
<td>52 ± 11</td>
<td>203 ± 59</td>
<td>25% ± 17</td>
</tr>
</tbody>
</table>

*Before medication start, patient may have had additional previous lipid measurements. TC, HDL, and non-HDL in mg/dL.
†Medications used are statins (HMG CoA reductase inhibitors), except for patient No. 4 (fibrate, then statin, then ezetimibe), No. 14 (statin, then ezetimibe), No. 17 (statin then fibrate), and No. 21 (ezetimibe).
‡“Most improved” lipid levels are for each individual measurement (TC, HDL, and non-HDL); therefore TC minus HDL does not always equal non-HDL in the “Most improved” columns.
Objective  To report the accuracy of ultrasound scanning (US) in predicting neurodevelopmental and sensorineural outcome in patients with congenital cytomegalovirus (CMV) infection.

Study design  Fifty-seven neonates with congenital CMV infection underwent brain US and were observed prospectively for motor skills, developmental quotient, and hearing function.

Results  Abnormal results on US were found in 12 of 57 neonates. US lesions were more frequent in newborns with clinical and laboratory signs of congenital CMV infection at birth (10/18) than in newborns who had no symptoms at birth (2/39; P < .001). At least 1 sequela developed in all neonates with symptoms who had abnormal US results, whereas none of the neonates with symptoms who had normal US results had long-term sequelae (P < .001). In the population without symptoms, sensorineural hearing loss developed in 3 of 37 (8.1%) neonates with normal US results, whereas severe sequelae developed in 1 of 2 neonates with abnormal US results.

Conclusions  A good correlation was found between cerebral US abnormalities and the prediction of outcome in newborns who were congenitally infected with CMV and had symptoms at birth. US could be performed as the first neuroimaging study in these newborns. Data are insufficient to permit any suggestions for the population without symptoms. (J Pediatr 2007;150:157-61)

Congenital cytomegalovirus (CMV) infection can cause a wide spectrum of brain damage related to inflammatory and teratogenic effects, including meningoencephalitis, calcifications, microcephaly, disturbance of neuronal migration, germinal matrix cysts, ventriculomegaly, and cerebellar hypoplasia.1 Computed tomography (CT), magnetic resonance imaging (MRI), and cerebral ultrasound scanning (US) are well-documented means for detecting brain lesions and other anomalies of the central nervous system (CNS).2-5 CT has been used to detect CNS lesions, predicting neurodevelopmental outcome,3,6 and to identify infants at risk of impaired hearing and those who could benefit from ganciclovir treatment.7,8 US is the safest means to image the neonatal brain and, unlike CT, is readily available at the bedside. The use of US to predict the neurodevelopmental and sensorineural outcome of congenital CMV infection has not been reported.

We undertook a systematic prospective US study of all neonates in whom congenital CMV infection was diagnosed, correlating cerebral US features with neurodevelopmental and sensorineural sequelae.

METHODS

Between January 1997 and September 2003, 57 newborns in whom congenital CMV infection was diagnosed were referred to our tertiary care hospital, where we have set up a multidisciplinary team specializing in the treatment of patients with congenital CMV infection.

Congenital CMV infection was diagnosed on the basis of isolation of the virus from urine within the first 2 weeks of life in neonates born from mothers with a suspected or...
ascertained CMV infection during pregnancy.\(^9\) Virus isolation was performed in cell cultures with the "shell vial" procedure.\(^{10}\) Newborns congenitally infected with CMV were defined as symptomatic when they had clinical signs, laboratory signs, or both at birth, including intrauterine growth retardation, microcephaly, seizures, chorioretinitis, hepatosplenomegaly, petechiae, elevated serum transaminase levels, neutropenia, and thrombocytopenia. US was obtained by using an Esaote AU5 with a 7.5-MHz sector probe transducer. Cranial US was performed in all cases within the first week of life and repeated at 1 and 3 months of age when results were negative. Neonates with abnormal US findings were re-examined weekly with US during the first month of life and then monthly until they were 6 months old. Two independent investigators (G.A. and F.S.), who were blinded to clinical findings, reviewed all scans and obtained the same results for the presence of lesions related to CMV congenital infection. US results were classified as normal or abnormal. Pathologic scans were defined as having periventricular/parenchymal calcifications, ventriculomegaly, cysts, cerebellar lesions (hyper-echogenicity, hypoplasia), or "candlestick" lenticulostriate vasculopathy (LSV).\(^{1,4}\) Ventricular size was measured at the midbody of the lateral ventricles on a sagittal view. Ventriculomegaly was classified as mild, moderate, or severe, according to Allan.\(^{11}\) Scans showing only mild ventriculomegaly (ie, ventricular size between 3 and 5 mm) were not considered pathologic. In addition, isolated LSV (ie, increased echogenicity at the level of vessels in the basal ganglia and thalamus) was not considered pathologic. LSV is not a specific marker of intrauterine infection and has also been reported in neonates with chromosomal trisomies, alcohol and drug exposure, asphyxia, heart disease, or respiratory distress, and in disease-free newborns.\(^{12,13}\) Moreover, longitudinal studies have shown that this US finding is not in itself associated with a poor prognosis.\(^{14,15}\)

Ophthalmologic examination was performed in the neonatal period. Hearing function was assessed by brainstem auditory evoked responses (BAER) in the neonatal period, at 6 and 12 months of age, and yearly audiometric tests until school age. The BAER threshold was defined as the lowest intensity level at which wave V could be detected and replicated. Sensoirneuronal hearing loss (SNHL) was defined as a BAER threshold >25 dB detected in at least 2 different evaluations or by an air conduction threshold at 1 or more frequencies >20 dB. Tympanometry was routinely performed to exclude middle ear disorders, and children with conductive hearing loss in the absence of SNHL were not considered to have hearing loss.

Psychomotor development was assessed at 6, 12, and 24 months of age by using the Brunet-Lezine test rating posture, coordination, speech and socialization.\(^{16}\) The global score was calculated as a ratio between observed developmental age and anagaphic age (developmental quotient [DQ]). Scores of DQ ≤0.85 were considered to be abnormal in accordance with Grossman.\(^{17}\) At 3 months of age and at every follow-up examination, an expert physiatrist assessed the psychomotor development of the infants with a 3-axis grid including neurovegetative, motor, and relational/behavioral items combining the Milani-Comparetti neuroevolutive assessment.\(^{18}\) Brazelton behavioral assessment,\(^{19}\) and Prechtl general movement assessment.\(^{20}\) This comprehensive assessment method allowed detection of suspicion for abnormal psychomotor development, to permit early referral (before 4-6 months of age) for rehabilitation. Motor delay was defined as functional deficits in motor skills and unachieved developmental milestones requiring rehabilitation.

Cranial CT, MRI, or both was performed in all surviving infants with abnormal US results. MRI was performed in 2 cases during the neonatal period and in 6 cases between 4 and 12 months of age. CT was done in the first trimester of fetal life.

Informed consent was obtained from the parents or legal guardians of the infants studied.

Data were recorded in an Excel database and analyzed with the SPSS 5.0 software (SPSS, Chicago, IL). The chi-square statistic was used to test the relationship between US findings and outcome.

RESULTS

Twelve of 57 (21.0%) neonates referred to our institution with a diagnosis of congenital CMV infection showed cerebral US abnormalities typical of congenital CMV infection. Eighteen of 57 (31.6%) showed clinical or laboratory signs of congenital infection at birth. US lesions were more frequent in newborns with clinical and laboratory signs of congenital CMV infection at birth (10/18) than in newborns who had no symptoms at birth (2/39; \(P = .000\)). Clinical data for patients with normal and abnormal US results are reported in Table I. In most cases, US showed a varying combination of calcifications, ventriculomegaly, cysts, cerebellar anomalies, and LSV. Lesions were detected at the first US examination and remained stable in all cases, with the exception of a periventricular cyst that enlarged during the first week of life. No infant with normal US results at birth developed lesion(s) at subsequent evaluations. Further investigations were performed in the 11 surviving infants with pathologic US findings: 3 underwent CT, 4 underwent MRI, and 4 underwent both CT and MRI. CT results confirmed US findings in all cases, and no additional abnormalities were detected. Although the MRI missed calcifications in 2 cases, it disclosed additional findings in 6 cases compared with US, including migrational disorders, leukodystrophy, and delayed myelinization. In 1 case, US missed a temporal horn cyst, 5 mm in diameter, that was evident on MRI.

Follow-up data until patients were a minimum of 12 months old (mean age ± 5D at last follow-up visit, 42.3 ± 11.3 months) were available for 56 of 57 patients; 1 infant died in the neonatal period of aortic thrombosis.\(^{21}\)

Of the 11 surviving neonates with abnormal US results, only 1, who had moderate ventriculomegaly and a hyper-echoic lesion at the level of the germinal matrix that evolved into a cyst, had a normal outcome at follow-up. Strabismus
Cranial Ultrasound Scanning and Prediction of Outcome in Newborns with Congenital Cytomegalovirus Infection

Table I. Clinical data of neonates with congenital cytomegalovirus infection according to neural ultrasound scanning findings

<table>
<thead>
<tr>
<th></th>
<th>Children with normal US results (n = 45)</th>
<th>Children with pathological US results (n = 12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>18/27</td>
<td>5/7</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD) gestational age in weeks</td>
<td>38.3 (2.5)</td>
<td>38.0 (2.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD) birth weight in grams</td>
<td>3054 (676)</td>
<td>2875 (767)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of neonates with symptoms at birth (%)</td>
<td>8 (18)</td>
<td>10 (83)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Clinical and laboratory signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrauterine growth retardation, n (%)</td>
<td>1 (2)</td>
<td>2 (17)</td>
<td>NS</td>
</tr>
<tr>
<td>Petechiae, n (%)</td>
<td>2 (4)</td>
<td>8 (67)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hepatosplenomegaly, n (%)</td>
<td>0</td>
<td>4 (33)</td>
<td>.001</td>
</tr>
<tr>
<td>Microcephaly, n (%)</td>
<td>0</td>
<td>6 (50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chorioretinitis</td>
<td>1 (2)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>5 (11)</td>
<td>8 (67)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>0</td>
<td>1 (8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: Not statistically significant.
*Elevated serum transaminase level, neutropenia, thrombocytopenia.

DISCUSSION

CMV infection is the most common intrauterine infection in developed countries, with a prevalence of 0.2% to 2.2% in live neonates. Cerebral lesions, including meningoencephalitis, calcifications, microcephaly, disturbance of neuronal migration, germinal matrix cysts, ventriculomegaly and cerebellar hypoplasia, may develop in patients who are congenitally infected. The severity of the neuropathologic findings at birth correlates with poor outcome, including hearing loss, mental retardation, cerebral palsy, seizures, and chorioretinitis.1

Early identification of neonates at risk is important to help healthcare providers counsel parents and give adequate treatment and follow-up care. Neonatal clinical signs correlate with neurologic outcome in congenital CMV infection: sequelae can develop in as many as 80% of infants with symptoms, whereas available data suggest that either audiologic or developmental problems develop in 5% to 15% of newborns without symptoms in the first year of life.22-26 These findings indicate that the presence of symptoms at birth does not necessarily differentiate children in whom sequelae will or will not develop. The addition of CT scans improves the prognostic accuracy in patients with clinical signs: as many as 90% of infected infants with symptoms who have cerebral lesions on CT examination have neurodevelopmental or sensorineural sequelae.3 CT may also reveal rarer anomalies in infected newborns without symptoms who have poor developmental performance.24

Although CT is the most widely used and accepted imaging technique for investigating the brain in neonates who are congenitally CMV infected, we aimed to find the least invasive prognostic indicator in this population.27 Most of the lesions related to fetal infection are readily disclosed by US, including calcifications, ventriculomegaly, cysts in the germinal matrix, and cerebellar atrophy.1,4,5 In addition, US is the safest imaging technique for the evaluation of the newborn brain. It is also useful as a screening tool, available at the bedside, and feasible even in the most critical situations, whereas CT is not usually available in neonatal intensive care units, and newborns must be transported. Further, US is the same imaging tool used in the perinatal period, making US-
based prognostic data useful to physicians involved in prenatal care.

Postnatal cerebral US was performed in both patients with symptoms and patients without symptoms in our cohort because cerebral lesions have been detected even in patients without symptoms. All newborns with symptoms who had abnormal US results showed at least 1 sequela or died, whereas none of the newborns with symptoms who had normal US results had any long-term sequelae (*P* < .001).

These findings are in agreement with those reported by Boppana et al, who used cerebral CT scanning to establish prognosis in a population of neonates with symptoms.3 Our data indicate a good correlation between cerebral US abnormalities and the prediction of outcome in newborns with congenital CMV infection who have symptoms at birth, suggesting that US may be performed as the first diagnostic study to detect brain lesions in these patients.

Only 2 of 39 neonates who were infected but had no symptoms had cerebral US abnormalities in our study. The first was a term newborn with ventriculomegaly associated with a globular hyperechogenicity at the germinal matrix level. At the time of diagnosis, we were not able to differentiate between a germinal matrix hemorrhage and a microinfarction of the germinal matrix suggestive of CMV infection. The finding was classified as abnormal; the patient's outcome was normal. Severe psychomotor and auditory deficits developed in the second newborn, who had ventriculomegaly, calcifications, and cysts. Adverse psychomotor outcome associated with SNHL occurred in 1 of 39 infants without symptoms (2.6%). US permitted identification of cerebral lesions, associated with poor outcome, early in this patient's life. In the asymptomatic population, US failed to predict isolated SNHL in 3 patients. Our data are too limited to reach any conclusions on the usefulness of cerebral US in congenitally infected newborns without symptoms at birth.

Although we did not find changes in the course of time in calcifications, ventriculomegaly, cerebellar hypoplasia, and subependymal cysts, follow-up US can serve as a means to track porencephalic cysts or hemorrhages. None of the cases in which the first US results were negative showed further lesions at subsequent examinations, indicating that repeat US may not be warranted in these children.

MRI may be a particularly useful imaging modality for detecting white matter lesions or gyral abnormalities, which are relatively common in congenital CMV infection after the neonatal period.2,28,29 MRI also is considered to be the best neuroimaging technique for studying abnormalities of migration.30 US has a low sensitivity in detecting gyral abnormalities or myelinization deficits because the conic shape of US hinders exploration of the cortical surface and the grey and white matter are difficult to distinguish.31 MRI detected gyral and white matter disorders not disclosed by US in 6 of our cases. As a complementary examination, MRI may be best performed after the first 6 months of life to study the myelination of the cerebral cortex.
linization pattern. It has yet to be defined whether and when MRI should be performed in infants with congenital CMV infection who have no symptoms.

REFERENCES


Comparative Efficacy and Cost of Asthma Care in Children with Asthma Treated with Fluticasone Propionate and Montelukast

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Objective To assess the comparative efficacy of fluticasone propionate (FP) and montelukast (MON), using administrative claims for pediatric asthma in a clinical setting.

Study design This retrospective observational study used the PharMetrics Integrated-Outcomes Database. Children age 4 to 17 years with an ICD-9-CM 493.xx for asthma, therapy with an inhaled corticosteroid in the 12 months before the index medications, and an index claim for FP or MON between January 2001 and December 2003 were studied. FP- and MON-treated children were propensity-matched based on health care utilization. Asthma-related parameters studied included treatment failure, hospitalizations, and total cost of care.

Results The children treated with MON were more likely to experience treatment failure (odds ratio [OR] = 2.55; 95% confidence interval [CI] = 2.19 to 2.96) and to be admitted to the hospital for asthma-related care (OR = 1.99; 95% CI = 1.15 to 3.44) compared with those treated with FP. Furthermore, the children treated with MON incurred significantly higher asthma-related treatment costs compared with those treated with FP (parameter estimate = 0.418; P < .0001).

Conclusions In children with asthma, treatment with FP is associated with better outcomes and lower cost than treatment with MON. (J Pediatr 2007;150:162-7)

The National Asthma Education and Prevention Program (NAEPP)\(^1\) recommends inhaled corticosteroids (ICSs) as the preferred treatment for children with mild persistent asthma. Specifically, the NAEPP reports that for the long-term management of asthma in children, “studies comparing inhaled corticosteroids to cromolyn, nedocromil, theophylline, or leukotriene receptor antagonists are limited, but available evidence shows that none of these long-term control medications appear to be as effective as inhaled corticosteroids in improving asthma outcomes.”\(^1\) This recommendation is further supported by the 2005 Global Initiative for Asthma (GINA).\(^2\) In addition, observational studies in children and adults have demonstrated a decreased risk of major exacerbations associated with the use of ICS.\(^3\) The Cochrane Review on initial pediatric controller therapy concluded that ICS therapy is the treatment of choice for mild persistent asthma compared with leukotriene receptor antagonists (LTRAs).\(^6\) Since the publication of that report, 3 additional clinical trials have compared ICS and LTRA.\(^7\) The Childhood Asthma Research and Education Network\(^7\)\(^8\) conducted a study comparing fluticasone propionate (FP) and montelukast (MON) in children with mean baseline forced expiratory volume in 1 second (FEV\(_1\)) of 94% to 96% predicted. MON was associated with more treatment failures requiring oral corticosteroids (P = .019), and FP produced a significantly greater improvement in multiple measures of lung function, including FEV\(_1\) (6.8% and 1.9%; P < .001), and a greater reduction in exhaled nitric oxide (eNO) (P = .0028).\(^7\)\(^8\) A second direct comparison of FP and MON in children with asthma and baseline FEV\(_1\) of 75% to 76% predicted demonstrated the superiority of FP for lung function, decreased rescue albuterol use, and reduced nighttime symptom scores.\(^9\) A third study comparing FP and MON in children with mild persistent asthma and a baseline FEV\(_1\) of 87% to 88% affirmed the primary endpoint of noninferiority for MON but demonstrated an increased relative risk of 1.56 (95% CI = 1.17 to 2.06) for rescue medication use (excluding short-acting β-agonist use), greater use of β-receptor agonists

CI Confidence interval  LTRA Leukotriene receptor antagonist
ED Emergency department MON Montelukast
FEV\(_1\) Forced expiratory volume in 1 second NAEPP National Asthma Education and Prevention Program
FP Fluticasone propionate OCS Oral corticosteroid
GINA Global Initiative for Asthma OR Odds ratio
ICS Inhaled corticosteroid SABA Short-acting beta agonist
LABA Long-acting beta agonist

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Supported by GlaxoSmithKline. Dr Stempel is a consultant to GlaxoSmithKline. Dr Kruzikas is an employee of NDCHealth, and Ms Manjunath is an employee of GlaxoSmithKline. All 3 authors were involved in study design, analysis, writing, and the decision to submit this manuscript.

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(P = .003), 68% greater use of oral corticosteroids, and increased relative risk of an asthma attack (1.26 [95% CI = 1.04 to 1.52]) for MON compared with FP. These studies demonstrate the consistent superiority of FP over MON for a broad range of both objective and subjective clinical endpoints in children with a range of baseline lung function.

Along with clinical studies, several observational studies in a general population of asthmatics have demonstrated lower cost and better outcomes with ICSs compared with LTRAs. Only 1 study was not able to demonstrate these differences between FP and MON. We designed a database study comparing health outcomes and costs to gain insight into the treatment differences between FP and MON in children age 4 to 17 years with a diagnosis of asthma receiving maintenance treatment with controller medications.

**METHODS**

**Database**

The study was based on medical and pharmaceutical claims in the PharMetrics Patient-Centric Database, which covers roughly 36 million unique patients from approximately 75 health plans across the United States. The database includes both inpatient and outpatient diagnoses and procedures, as well as both standard and mail order prescription records; available data on prescription records include the National Drug Code (NDC), as well as days supplied and quantity dispensed. All medical and pharmaceutical claims include dates of service. Additional data elements include demographic variables (eg, age, sex, geographic region), health plan type (eg, health maintenance organization, preferred provider organization), payer type (eg, commercial, self-pay), provider specialty, and start and stop dates for plan enrollment.

The database is in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and contains encrypted unique patient identifiers to integrate pharmacy and medical claims. All analyses were based on secondary databases in which patient information was encrypted and patient privacy protected.

**Sample Selection**

Patients were selected for inclusion based on the following criteria: (1) an index prescription claim for FP or MON between January 1, 2001 and December 31, 2003; (2) age 4 to 17 years at the time of the index claim; (3) at least 1 prescription claim for ICS within 12 months before the index FP or MON claim; (4) a documented asthma diagnosis based on codes of the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM; code 493.xx) 6 months before and/or 12 months after the index FP or MON claim; and (5) continuous plan enrollment for 12 months before and 12 months after the index prescription claim.

Exclusion criteria were applied to ensure a more homogeneous population and allow the evaluation of patient outcomes based on asthma treatment regimen. Patients were excluded if they had a switch or augmentation of FP or MON therapy within 60 days of the index claim or if they had prescription claims for a non-ICS asthma-controller medication within 12 months before the index FP or MON claim. Medications considered non-ICS controllers included LTRAs, long-acting beta agonists (LABAs), methylxanthines, and cromones. Patients were excluded from analyses if they had prescription claims for omalizumab, high-dose FP/salmeterol (500 µg/50 µg), or high-dose FP (220 µg) during the 12 month pre- or post-period, or diagnoses for the following conditions during the 2-year study: cystic fibrosis (ICD-9-CM codes 277.xx), chronic obstructive pulmonary disease (ICD-9-CM codes 491.xx, 494.xx, 496.xx), bronchopulmonary dysplasia (ICD-9-CM codes 770.7x), or respiratory distress syndrome (ICD-9-CM codes 769.xx).

**Study Groups**

Two treatment cohorts of interest were studied: FP monotherapy and MON monotherapy. Propensity matching was used to match the FP and MON cohorts. Propensity matching is a methodology used to match study cohorts based on specific characteristics before conducting multivariate analyses, to reduce the potential for selection bias and patient-level differences between comparison groups. FP and MON patients were propensity-matched based on pre-index patient age, previous health care utilization (hospitalizations and emergency department [ED] visits), use of oral corticosteroids (OCSs) and short-acting beta agonists (SABAs), season of the index prescription date, US Census region, physician specialty, and diagnosis of allergic rhinitis. Physician specialty was defined as either primary care (ie, pediatrician, general practitioner, family practitioner or internal medicine,) or specialist (ie, allergist, pulmonologist, ear/nose/throat).

**Metrics**

Patient cohorts were compared with respect to patient characteristics to confirm the comparability of treatment groups. The patient characteristics included age, sex, US Census region, and payer. Comparability was further evaluated by analyzing health care utilization during the 12 months before the index prescription claim, focusing on asthma-related hospitalizations, ED visits, noncontroller asthma medication use, and asthma-related total treatment costs.

Three outcomes were defined for evaluation: (1) treatment failure (defined as asthma-related hospitalizations, ED visits, OCS use, or switch/augmentation of index therapy); (2) asthma-related hospitalization alone; and (3) asthma-related costs. Patients were followed for up to 12 months after the index prescription date or until switch/augmentation of therapy, whichever occurred first. Costs were calculated as per member per month and annualized to provide estimates of 12-month costs if patients were discontinued due to switch/augmentation.
Statistical Analysis

Bivariate analyses compared FP and MON treatment cohorts with respect to patient demographics (age, sex, or region), plan type, and previous health care utilization. Continuous variables were analyzed using Student t-tests, and categorical variables were evaluated using χ² analyses.

Multivariate regression techniques controlled for confounding factors while evaluating the impact of treatment regimens on patient outcomes. Logistic models were used to examine separately the likelihood of treatment failure as well as asthma-related hospitalizations, and generalized linear model regression analyses were used to model asthma-related total treatment costs. Nonlinear transformations of treatment costs were done to account for heteroscedasticity in the variances. Because direct interpretation of log-transformed results was not possible, smearing methods were used to estimate the magnitude of the effects of independent variables. For all multivariate analyses, treatment cohort was the main independent variable of interest. All models further controlled for patient age, sex, US Census region, payer type, season of index prescription date, comorbidities, previous health care utilization, and previous asthma-related total treatment costs.

RESULTS

A total of 4974 children were available for analyses, including 2961 (60%) patients treated with FP and 2013 (40%) patients treated with MON. From this group, 3647 children were propensity-matched with 50% in each of the FP and MON treatment cohorts. The mean age of the sample was approximately 10 years, and approximately 40% of the population was female. Table I shows the similarities in baseline demographics between the 2 cohorts. Significant differences by payer are seen. Compared with the FP cohort, MON patients were more likely to be covered by commercial plans (68% vs 58%; P = .0001) or to pay for expenses out of pocket (8% to 5%; P = .0002), and were less likely to have Medicaid or other/unknown payer coverage (13% vs 21%; P = .0001 and 12% vs 16%; P = .0003, respectively).

Analyses of previous health care utilization confirmed similarities between treatment cohorts with regard to previous hospitalizations and ED visits, physician specialty, and previous treatment with OCSs, SABAs, and claims for allergic rhinitis and antihistamine products. During the baseline period, the patients indexed to FP had significantly higher use of ICSs during the 12-month pre-period (3.36 claims vs 2.92 claims; P = .0001), whereas the patients indexed to MON incurred significantly higher pre-period asthma-related total treatment costs ($833 vs $671; P = .0005). The mean number of dispensings of the index medication (standard deviation [SD]) in the post-index year was significantly higher (P < .0001) for MON, 4.03 (3.58), compared with 2.46 (2.77) for FP.

Differences in Asthma-Related Outcomes Based on Treatment Regimen

Significant differences in outcomes between the 2 treatment groups were found before adjusting for any potential patient-level differences, as shown in Table II. There were more treatment failures in the MON cohort than in the FP cohort (49% vs 26%; P = .0001). In the pre-period (while receiving ICS therapy), the 2 indexed treatment groups experienced a similar number of hospitalizations for asthma; however, in the post-period, significantly more children were hospitalized in the MON group (2.4%) compared with the FP group (1.5%; P = .0445). The percentages of children with ED visits and claims for OCS in the post-index period were 7% and 12%, respectively, for both the FP and MON cohorts (P = not significant). Furthermore, annualized asthma-related mean costs were significantly higher for the MON patients ($1316) compared with the FP patients ($861; P = .0001).

These observed differences between the cohorts persisted after adjusting for confounding variables, such as age, payer, previous utilization, and previous asthma-related costs. Children in the MON group were more than 2.5 times more likely to experience treatment failure than those in the FP group (odds ratio [OR] = 2.55; 95% confidence interval [CI] = 2.19 to 2.96). In addition, the risk of a switch in or an augmentation of therapy was 3 times more likely with MON
compared with FP (OR = 3.20; 95% CI = 2.75 to 3.76). An increased risk of treatment failure was also associated with Medicaid coverage, self-pay, previous ED care, previous OCS therapy, and higher pre-period asthma treatment costs (Table III).

When hospitalizations were examined as a separate measure, adjusted multivariate analyses confirmed that the MON-treated children were nearly twice as likely to be admitted to the hospital for asthma-related care after the index event (OR = 1.99; 95% CI = 1.15 to 3.44) An increased risk of hospitalization was also associated with other independent factors, including Medicaid coverage (OR = 2.38; 95% CI = 1.27 to 4.46), self-pay (OR = 2.66; 95% CI = 1.06 to 6.68), and previous hospitalizations (OR = 4.32; 95% CI = 2.18 to 8.58). The likelihood of hospitalization decreased with increasing age (OR = 0.92; 95% CI = 0.86 to 0.99).

In addition to the increased risk for treatment failure and hospitalization seen in the MON cohort, these children also incurred significantly higher asthma-related costs after adjusting for independent factors (parameter estimate = 0.418; P < .0001) (Table IV). Smearing techniques revealed an adjusted mean cost of $910 (SD = $364) for the FP-treated children compared with an adjusted mean cost of $1382 (SD = $552) for the MON-treated children. After controlling for confounding factors, asthma-related costs were on average 52% higher in MON-treated patients than in FP-treated patients.

**DISCUSSION**

This observational study in children with a diagnosis of asthma who were treated with FP or MON has assessed both outcome measures and costs and demonstrates that FP when compared to MON is associated with a lower risk of treatment failure (ED/hospitalization and switch in augmentation of therapy), a decreased risk of asthma-related hospitalizations, and significantly lower cost of asthma care in children. These findings are consistent with those of several previous double-blind controlled clinical trials demonstrating better outcomes associated with FP compared with MON,7-10 2 meta-analyses demonstrating better outcomes with ICSs compared with LTRAs,6,15 and recommendations of the evidence-based NAEPP and GINA guidelines.1,2

The strength of our study is that patients in each treatment cohort were well matched on various demographic and utilization-related factors. This is particularly important given the complexities of care in pediatric asthma, because younger age of the child,16 previous hospitalization and ED events, and previous use of OCSs and SABAs are all identified as important variables that may increase the risk of treatment failure or subsequent health care utilization.17 Medicaid and self-pay are also important variables that increase the risk of treatment failure compared with commercial insurance. The higher rate of Medicaid insurance in the FP-treated children may have biased the results against FP.

Asthma control may be highly variable,18 and there is evidence indicating that appropriate therapy with consistent use of ICS-containing controller drugs is important in improving outcomes.19-21 Our study suggests that continuing ICS treatment in the year after the claim was associated with a decreased risk of treatment failure and hospitalization compared with changing from ICS to MON. The summer months are commonly reported as a period of improved control with lower rates of hospitalization.22 Children who used ICSs during the summer months may be at decreased risk for asthma exacerbations in the fall.23

An additional strength of our study was the use of a large commercial claims database that provides an opportunity to analyze cost data and determine the costs of asthma care. The improved outcomes associated with FP in our study were also associated with lower costs, making FP the preferred medication in this comparison. Some concern has been raised about using pharmacy costs, due to varying contractual arrangements.24 However, the data contained in this analysis are from more than 75 plans across the country and report the actual costs paid by the plans inclusive of co-payments.

We also reported that adherence with both controllers was suboptimal, although it was significantly greater with MON than with FP. The greater adherence to MON therapy did not protect against the greater risk for hospitalization or the need to switch or augment controller therapy for asthma. The finding of superior outcome associated with FP compared with MON is
supported by additional pediatric reports and recommendations published after the guidelines,8-10,25 and previous observational studies in the general population.12,13,26,27

Our results differ from those reported by Allen-Ramey et al.14 Although both that study and our study used propensity matching, the 2 studies had several differences in study design. The Allen-Ramey et al study did not require a diagnosis of asthma, but allowed patients to be included on the basis of 2 or more prescriptions of either MON or FP; 19% of patients were included based on pharmacy claims only, and this may have included some patients in the MON group who were being treated for other diseases, such as allergic rhinitis. There is some uncertainty as to whether the results can be attributed to asthma or to asthma therapy. In a second study by these same authors, they again did not require a medical claim for asthma.28 Both studies do not report the cost of asthma care. In addition, patients in both of the Allen-Ramey et al studies were excluded from the analysis if they switched or augmented therapy. However, changes in medication patterns can be termed a treatment failure. In our study, it was demonstrated that nearly twice as many children treated with MON required an additional or alternative controller medication compared with those treated with FP.

Furthermore, our study required active ICS therapy in the year before the index medication, along with a diagnostic code for asthma, which strongly increased the likelihood that the therapies were being compared for the treatment of asthma. Alternative controllers were not selected, because there is minimal use of cromones and theophylline, and LTRAs may be prescribed for both asthma and allergic rhinitis. The modest use of SABAs in both cohorts suggests that this population of children had a milder form of persistent asthma. The higher use of ICSs by the FP cohort in the baseline year may suggest that this cohort had greater disease intensity, but yet the results demonstrate less treatment failure and better outcomes at lower cost with FP.

One of the limitations of observational claims data is the lack of information on disease severity. However, propensity matching based on resource utilization ensures that pre-period ED, inpatient, and OCS use were similar between groups and serves as a surrogate for establishing comparable severity or asthma control in the study population. The 5% rate of hospitalization and 11% rate of ED visits in the baseline period are representative of the general pediatric population.16 Another limitation associated with observational claims data is the inability to demonstrate cause and effect of an intervention. However, resource utilization and the pattern of medication dispensing in pediatric practice are more generalizable than those observed in controlled clinical trials, in which the study subjects are often highly selected and may be atypical of practice settings. For example, the differences in acute exacerbations may be minimized in a clinical trial design that allows for patients to use additional or alternative controllers, but are captured in an observational design. In general, the results from controlled clinical trials and observational studies are comparable.29,30

In conclusion, this study found that in children age 4 to 17 years with a diagnosis of asthma and previous treatment with ICS, treatment with FP resulted in significantly lower risk of asthma-related hospitalization, decreased risk of treatment failure, and a lower cost of asthma-related care compared with treatment with MON. The results of this observational study are consistent with the findings of randomized clinical trials.

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Clinical Spectrum and Histopathologic Features of Chronic Hepatitis C Infection in Children

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Objective To define the natural history and outcomes of children infected with hepatitis C virus (HCV) at birth or in early childhood.

Study design This retrospective, prospective study identified 60 HCV-infected children through a transfusion look-back program (group 1) and by referrals (group 2). Perinatal/transfusion history, clinical course, and laboratory studies were correlated with findings from 42 liver biopsy specimens.

Results Mean age at infection was 7.1 months, and duration of infection 13.4 years. The sources of infection were blood transfusion (68%), perinatal transmission (13%), and both (7%). Most patients were asymptomatic; three referral patients had advanced liver disease at presentation. Mean alanine aminotransferase level was normal in 25%, 1 to 3 times normal in 62%, and greater than 3 times normal in 13%. Liver biopsy specimens showed minimal to mild inflammation in 71%, absent or minimal fibrosis in 88%, and bridging fibrosis in 12%. Age at infection and serum gamma-glutamyltransferase correlated with fibrosis; serum alanine aminotransferase correlated with inflammation unless complicated by comorbidity. Repeat biopsies within 1 to 4 years in four patients showed no significant progression in three and cirrhosis in one. Two patients died after liver transplantation.

Conclusions Children with chronic HCV infection are generally asymptomatic. By 13 years after infection, 12% of patients had significant fibrosis. Patients enrolled by referral had more severe liver disease than those identified through the look-back program, demonstrating the importance of selection bias in assessing the long-term outcome of HCV infection. (J Pediatr 2007;150:168-74)

Hepatitis C virus (HCV) progresses insidiously and incrementally and results in potentially serious complications such as cirrhosis and hepatocellular carcinoma in approximately 20% and 4% of adult patients, respectively. However, data on the natural history and histopathology of HCV-related liver disease in children are conflicting. Studies from Japan and Europe point to relatively benign clinical and histopathologic liver disease, whereas studies from the United States suggest a more aggressive course, with development of early fibrosis. Geographic variation in genotypes and diversity of the infected population studied may account for some of these differences, in addition to as-yet-unknown viral/host factors. The lack of uniformity in the descriptions of the natural history, clinical presentation, and histologic features of HCV infection in children prompted us to evaluate a cohort of 60 HCV-infected children followed in our institute over a 5-year period.

The broad objectives of this study were to identify children with HCV who were infected perinatally or during early childhood, follow their natural history through adolescence, correlate clinical and laboratory data with liver histology, identify children who would benefit from medical therapy, and follow treatment or natural outcomes.

ALT Alanine aminotransferase
HCV PCR Hepatitis C polymerase chain reaction
EIA Enzyme immune assay
GGTP Gamma-glutamyltranspeptidase
HAI Histologic Activity Index
LKM Liver kidney microsomal antibodies
RIBA Recombinant immunoblot assay
ULN Upper limit of normal

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Study Subjects

Children (n = 2100) who received blood/blood product transfusions between 1982 and 1992 were tested for HCV through a look-back program established at Children’s National Medical Center, Washington, DC. The primary objective was to study the natural history of HCV infection in children who had no other risk factors for liver disease than HCV acquired through transfusions in the newborn period or early in life. Patients with sickle cell disease, hemophilia, renal disease, and malignancy within 5 years of treatment were excluded from the study. Study subjects included 30 HCV-positive children who were transfused before the availability of anti-HCV testing, identified, and recalled by the look-back program (group 1). In addition, we studied 30 children (group 2), identified through referrals for evaluation of elevated liver enzymes and/or a known history of hepatitis C or jaundice. Included in the referral group were 6 adoptees identified as HCV-positive during evaluation by their primary care physician. Potential sources of HCV infection were investigated through a questionnaire administered to parents and to children above the age of 14 years. Parental blood samples were obtained for anti-HCV testing for all patients from group 1 and those patients from group 2, when there were no obvious risk factors for HCV infection. The onset of infection was considered to be the date of a transfusion or the date of any surgery before 1992 or the date of birth when the mother was anti-HCV positive; in the case of adopted children, the age at infection was presumed to be the date of birth. Patients were recruited and followed from 1996 through 2001; the study was approved by the institutional review board of our institute.

Laboratory Data

HCV status was evaluated through the use of an HCV enzyme immune assay (EIA, second and third generation, Abbott Laboratories, Chicago, IL) and confirmed with a second-generation recombinant immunoblot assay (RIBA 2, Chiron Strip Immunoblot assay, Chiron, Emeryville, CA). Anti-HCV positive or indeterminate patients were further tested for qualitative and quantitative HCV RNA by polymerase chain reaction (RT-PCR and Cobas Amplicor HCV Monitor v2.0 assay, Roche Diagnostics, Branchburg, NJ). Viral genotype was identified by line-probe assay (InnoLiPa, Innogenetics, Belgium). Alanine aminotransferase (ALT), gamma-glutamyltranspeptidase (GGTP), creatinine phosphokinase, albumin, and serum iron were measured in serum by Ektachem 500 (Ortho Diagnostics, Raritan, NJ). Alpha-fetoprotein was measured by EIA (Immuno I, Bayer, Tarrytown, NY). At the initial visit, other causes of liver diseases including alpha-1-antitrypsin deficiency, Wilson disease, autoimmune hepatitis, and coinfections with HIV and hepatitis A and B were investigated. An abdominal sonogram with Doppler study of portal venous flow was performed to identify mass lesions in the liver, splenomegaly, and portal hypertension.

Patients had follow-up visits at 4- to 6-month intervals. Anti-HCV EIA/RIBA, HCV PCR, and quantitative HCV-RNA were done once or twice a year unless signs and symptoms prompted more frequent analyses. A negative test for HCV RNA on at least two samples tested within 1 year was considered as evidence for viral clearance.

Liver Biopsy

After informed consent was obtained, liver biopsy was performed if the ALT was 2 times the age-related normal value on two or more visits or if autoimmune markers were present. If the ALT was less than 1 1/2 times normal, a biopsy was deferred during the initial 6 to 12 months but was recommended subsequently, within the 5-year study period. Most of the liver biopsy specimens were obtained by a closed, ultrasound-guided procedure, using 16- to 18-gauge Bard Monopty needles. Transjugular biopsies were performed if the patients had thrombocytopenia. All specimens were stained by hematoxylin and eosin, Masson trichrome, periodic acid-Schiff, Perl stain for iron, and Rhodamine stain for copper. Two independent pathologists, blinded to the clinical information, evaluated the biopsy specimens, using the scoring systems of Batts and Ludwig and the Knodell Histologic Activity Index (HAI). The ALT levels at the time of biopsy were recorded.

Statistical Analysis

The continuous data were summarized as mean ± standard deviation (SD), range, and minimum and maximum observations. The nominal, categorical, or ordinal data were summarized by count and/or proportion (%). With the use of the Wilcoxon and Kruskall-Wallis statistics, the two groups were compared with respect to the averages of variables such as age an infection, age at biopsy, duration of infection, laboratory values, and biopsy grade and stage. To assess the effects of these covariates on the dependent variables, namely the histologic grade and stage, cumulative logistic regression models with proportional odds ratios were fitted to each group and to the two groups of patients pooled together. The HAI grade was compressed into three ordinal values to reduce the number of proportional odds ratio assumptions needed in the model, that is, HAI grade 0 for the original grades 0 to 4, 1 for 5 to 8, and 2 for 9 and above. A value of P < .05 was considered significant.

RESULTS

Demography and Clinical Features

Demographics, source of infection, and follow-up data for the 60 patients are given in Table I. The majority of subjects were infected in infancy at a mean age of 7.1 months. The mean age at diagnosis was 11.9 years, and duration of infection to the end of the study was 13.4 years. Transfusion was the primary source of infection, occurring in 68%. The reasons for HCV testing included a history of transfusion in
48%, elevated aminotransferase levels in 28%, HCV-positive parent in 8%, screening of adoptees in 8%, and blood donor screening and acute jaundice in 2% each. Patients were mostly asymptomatic. Symptoms, when reported, were mild and transient and were similar in both groups. They included fatigue in 17 patients (28%), diffuse abdominal pain in 10 (17%), nosebleeds in 7 (12%), poor weight gain in 7 (12%), muscle aches in 5 (8%), and headaches in 2 (3%). Two patients from group 2 presented with acute, self-limited jaundice and two others with edema of the legs, shortness of breath, and laboratory evidence of chronic liver failure.

Biochemical and Virologic Indexes

The ALT varied widely among the patients and in the same patient at different times during the study period (mean ± SD = 98.0 ± 115.7 U/L). The mean values from each patient were expressed as normal, 1 to 1½ times age-adjusted upper limit of normal (UNL), 1½ to 3 times UNL, and above 3 times the UNL (Table II; available at www.jpeds.com). Twenty-eight of 60 (47%) patients had mean ALT levels within the normal range or below 1½ times the UNL, 24 (40%) had mean ALT levels 1½ to 3 times the UNL, and 8 (13%) had mean values above 3 times the UNL. A few patients skewed the data with inordinately high ALT at presentation, although ALT levels generally normalized during the follow-up period. They included an infant with vertically acquired HCV (1786 U/L), a patient with myopathy27 presumed to be secondary to HCV infection (1005 U/L), and a transfused infant coinfected with HIV and cytomegalovirus (801 U/L). Serum bilirubin, albumin, and iron levels were normal in all patients except in two, who presented initially with acute obstructive jaundice and early liver failure. The mean ALT during the follow-up period (group 1 = 86.3 ± 113.6 U/L vs group 2 = 109.6 ± 95.4 U/L) and at the time of liver biopsy (Table IV) was significantly higher in group 2 versus group 1 patients.

The majority of patients (n = 50, 83%) tested positive for antibodies to HCV and HCV RNA throughout the 5-year study period. One patient was HCV RNA–positive but EIA-negative on two consecutive tests 6 months apart but subsequently converted to seropositivity after 24 months.28 Seven anti–HCV and HCV RNA–positive patients were lost to follow-up after the initial testing. One patient each from the two groups was HCV RNA–positive at enrollment but thereafter remained negative for the duration of the study. Viral genotype was performed on 45 patients (group 1 = 26, group 2 = 19); 80% of group 1 and 78% of group 2 were of genotype 1 and the rest were of genotype 2 and 3. The mean viral load at the time of liver biopsy did not differ significantly between groups 1 and 2, and only 15% had viral loads >2 million copies/mL.

Radiologic Findings

Abdominal sonogram with Doppler study of the portal venous system was performed in 43 of 60 (72%) patients. The study was normal in 27 children (63%). Abnormal findings included mild splenomegaly in 5 patients (12%), gallstones/gall bladder sludge in 3 (7%), and abnormal echogenicity in 2 (5%). Splenomegaly was found only in the referral group (group 2). Abdominal CT scans in 2 of 5 patients with splenomegaly showed nodularity of the liver and esophageal varices.
Forty-two initial liver biopsy specimens were scored by HAI25; the results are summarized in Table III. These 42 biopsy specimens and 2 additional biopsy specimens were also scored by using the classification of Batts and Ludwig.24 Correlation between the two systems of classification was excellent, both for the grade and stage of histology (Spearman correlation for grade: $r = 0.75$, $P = 0.0001$; for stage: $r = 0.62$, $P = 0.0001$; Pearson correlation linear regression analysis for grade: $r = 0.78$; and stage $r = 0.79$). Overall, the inflammatory changes (the sum of portal, perportal, and lobular inflammation) were mild (grade 0 to 8) in 71%, moderate (grade 9 to 12) in 24%, and severe (grade 13 to 18) in 5%. Fibrosis was absent or mild, with only perportal expansion in 88%, and bridging fibrosis was seen in 12%. All of the patients with severe inflammation (5%) and bridging fibrosis (12%) belonged to the referral group. None of the initial biopsy specimens showed cirrhosis. Lymphoid aggregates were present in 18 of 41 (44%). Mild steatosis was identified in four biopsy specimens (10%) and bile duct involvement (Pousson lesions) in three (7%). Stainable iron was detected in the biopsy specimens from two patients who had received multiple transfusions for acute leukemia and thalassemia major. Four patients had repeat liver biopsy procedures over a span of 1 to 4 years. Three biopsy specimens showed no histologic progression; one showed progression to early cirrhosis over the course of 4 years. Bridging fibrosis was seen in five of group 2 patients. Combining the initial and follow-up biopsy specimens, bridging fibrosis or early cirrhosis was found in 6 (14%) of 42 patients undergoing percutaneous biopsy procedure. In addition, two patients were found to have cirrhosis at the time of liver transplantation.

### Table III. Histopathologic findings on liver biopsy by HAI scoring system (group 1: n = 19; group 2: n = 23)

<table>
<thead>
<tr>
<th>Score</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perportal inflammation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Marked</td>
<td>4-6</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Lobular inflammation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Marked</td>
<td>4</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Portal inflammation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Marked</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total grade (0-18)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>0-4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Mild</td>
<td>5-8</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>9-12</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Marked</td>
<td>13-18</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Stage fibrosis (0-4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Perportal/expansion</td>
<td>1</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Bridging fibrosis</td>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Sum of portal, perportal, and lobular inflammation.

### Histology

The clinical outcome of the 60 patients is summarized in the Figure. Of the 50 patients who had continuous follow-up, 47 (94%) had clinical and laboratory evidence of mild liver disease. Two patients underwent liver transplantation for portal hypertension and chronic liver failure; both of them died of complications from the transplantation. The native liver of one of them showed evidence of hepatocellular carcinoma. A third patient whose repeat biopsy specimen showed evidence of cirrhosis continued to exhibit deterioration in liver function. The only patients with cirrhosis were from the referral group and had acquired HCV infection through perinatal transmission.

### DISCUSSION

We describe the demographic, virologic, and histopathologic data on 60 children and adolescents with chronic HCV infection, evaluated during a 5-year period. The onset of infection was reasonably established in 88%, based on transfusion history and/or perinatal transmission from HCV-infected mothers. The mean duration of infection, based on the history of exposure, was 13 years. Histologic data were available for 60% of the children, and only 13% had treatment that would alter the natural history of the infection. We evaluated patients in two clinical settings. The primary focus of our study was HCV-infected children (group 1) who were transfused at our institution in the years before the availability of testing for HCV. Group 2 included patients referred to us for evaluation of established liver disease. Although inclusion of these patients introduced a referral bias, a prospective study...
of sufficient length to analyze the full spectrum of HCV outcomes in children is not feasible and hence we chose to combine a retrospective, prospective cohort analysis with that of an equal number of referral cases in whom more severe outcomes were expected and indeed found. This dual approach aimed to achieve a balanced approximation of the full and varied spectrum of HCV outcomes, as demonstrated in studies of HCV infection in adults.1-4 We were surprised to find that only 1.5% of the 2100 transfusion recipients investigated in the look-back study were HCV-infected despite the absence of donor screening at the time of their transfusions. Other look-back studies in children29-31 have reported HCV infection in 0.3% to 6% of blood transfusion recipients. The lower-than-expected prevalence of HCV positivity in our look-back study may have been due in part to our entry criteria that excluded children with concurrent diseases. Only 2 of the 30 patients in group 1 appeared to have cleared HCV infection spontaneously.

Clinical and laboratory evaluation of the identified cases in our study showed an excellent correlation between ALT and the histologic grade on liver biopsy in group 1. Patients in group 2 had concurrent pathology such as hepatitis B and decompensated cirrhosis that may have affected the ALT. Twenty-six of 28 children (93%) with normal ALTs or levels persistently less than $1 \frac{1}{2}$ times the ULN had only mild liver disease by biopsy. Patients with ALT greater than 3 times the ULN generally had more severe pathology; however, two patients with persistently normal ALTs also had advanced liver disease. Although ALT was an excellent correlate of liver histology, discrepancy between ALT and histology in 7% of our patients attests to the continued value of liver biopsy, as has been supported by other pediatric and adult studies.14,16,32-34

The characteristic features of chronic HCV-associated hepatitis found in adults, namely, lymphoid aggregates and follicles, macrovesicular steatosis, and bile duct damage, were relatively rare in our series.35 Early cirrhosis was documented in only one patient on a repeat biopsy procedure, and frank cirrhosis was found in two other patients at the time of liver

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**Table IV. Comparison of cohort and referral groups at the time of liver biopsy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (cohort)</th>
<th>Group 2 (referral)</th>
<th>Kruskal-Wallis test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at infection (mo)</td>
<td>4.6 ± 1.8</td>
<td>7.3 ± 1.65</td>
<td>0.157</td>
</tr>
<tr>
<td>Age at biopsy (y)</td>
<td>15 ± 1.8*</td>
<td>8.8 ± 5.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Duration of infection (y)</td>
<td>14.1 ± 2.8*</td>
<td>8.3 ± 4.5</td>
<td>0.0002</td>
</tr>
<tr>
<td>ALT at biopsy</td>
<td>61 ± 59.5</td>
<td>154.7 ± 255.5*</td>
<td>0.001</td>
</tr>
<tr>
<td>GGTP</td>
<td>34.1 ± 21.4</td>
<td>114.1 ± 197.7</td>
<td>0.49</td>
</tr>
<tr>
<td>AFP</td>
<td>3.7 ± 3.7</td>
<td>26.2 ± 78.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Viral load (million)</td>
<td>1.7 ± 2.8</td>
<td>2.0 ± 3.5</td>
<td>0.09</td>
</tr>
<tr>
<td>HAI grade</td>
<td>5.1 ± 2.1</td>
<td>7.4 ± 3.4*</td>
<td>0.012</td>
</tr>
<tr>
<td>HAI stage</td>
<td>0.42 ± 0.5</td>
<td>1.2 ± 1.1*</td>
<td>0.012</td>
</tr>
</tbody>
</table>

*P < .05.

---

**Figure.** Clinical outcomes of 60 patients over the 5-year study period.
transplantation. Among four patients with repeat biopsy procedure, only one showed fibrosis progression; this patient already had bridging fibrosis in the initial biopsy specimen and then advanced to early cirrhosis over the course of 4 years. When the biopsy specimens from the two groups were examined separately, we found that the ALT level at the time of the liver biopsy procedure, and the grade and the stage of histology were significantly higher in group 2 than in group 1, even though the duration of infection was longer in the latter (Table IV). Sixty percent of those with no (stage 0) fibrosis belonged to group 1, and all of the patients with stage 3-4 were from group 2. The increased severity of liver disease in group 2 reflects, at least in part, a referral bias wherein these cases represented patients with established liver disease referred for further evaluation. In these patients, the degree of fibrosis correlated with the age at which they were infected: the older the age at infection, the worse the fibrosis. This age relation was not seen in group 1 patients, possibly because the vast majority was infected before age 2. In contrast, Guido et al36 studied the progression of fibrosis in untreated patients who had acquired HCV infection in infancy and found that age at biopsy procedure and duration of infection positively correlated with stage of fibrosis. In their study, 13 of 112 patients had a repeat biopsy procedure at a mean interval of 7.9 years; 54% showed a 1-2 stage increase in fibrosis. The progression was slower than reported in adult patients.37

Long-term cohort studies in children have been limited. One of the earliest longitudinal studies involved 77 children from Europe who were HCV-positive after transfusion-related and community-acquired infection.13 When followed over a 6-year period, 27% had active but mild histologic liver disease, 10% achieved biochemical remission, and only 3% had cirrhosis.13 The same group recently reported that 7% to 10% of these children had subsequent development of anti–LKM antibodies that were associated with a more severe outcome of their liver disease.38 Vogt et al38 emphasized the relatively benign course of liver disease in persons who acquire HCV infection early in life. They evaluated 458 children who had been transfused for cardiac surgery approximately 20 years earlier at a mean age of 2.8 years.18 Fifteen percent were found to be anti–HCV–positive, but only 55% were HCV RNA–positive, suggesting a spontaneous viral clearance in 45%. Liver biopsy specimens in 17 chronically infected patients showed mild histologic disease in (82%); only 1 patient had cirrhosis attributable to HCV infection.18 Casiraghi et al39 reported mild liver disease with slow progression in persons who acquired HCV infection through mini-transfusions in the newborn period; 35 years after exposure, 9 of 11 (82%) had minimal or no inflammatory activity or fibrosis and 2 had stage 3-4 fibrosis. Repeat biopsy procedures in five patients after 5 years showed progression in only one patient.39 Studies in young adults also demonstrate a high spontaneous recovery rate and predominantly mild histologic changes. Two studies involving young women inadvertently exposed to HCV-contaminated Rh immune globulin revealed cirrhosis in less than 4% and bridging fibrosis in only 10% to 15% approximately 25 years after the onset of HCV infection.4,39 Minola et al40 studied 392 patients with post-transfusion HCV infection and calculated that the median time to develop end-stage liver disease was 33 years for those infected between ages 21 and 30 years and 16 years for those infected after age 40. In 77 patients infected below the age of 20 years, only 4% had cirrhosis.6 These and other studies demonstrate that the younger the individual at the time of infection, the less the severity of HCV-related liver disease.6,5,6,18,37 The reasons for this observation are not known but may relate to more vigorous immune responses to an infection acquired early in life, reduced fibrogenic mechanisms in children and/or the confounding effects of alcohol, and obesity and infections in adult patients.6,40 Although children tend to have more indolent HCV infection than adults, the development of severe liver disease can be accelerated in the presence of comorbid conditions such as thalassemia,9 iron overload,9,21 childhood cancer,7,8,22,23 and HIV coinfection.40

Retrospective studies involving patients referred to tertiary care centers for identified liver diseases demonstrate yet another population of patients with more severe outcomes.21,22 Illustrative of these retrospective studies, Badizadeg et al21 examined 50 liver biopsy specimens from 40 HCV-infected children ages 2 to 18 years and found significant fibrosis in 78%, including bridging fibrosis and architectural distortion in 58% and cirrhosis in 8%. The degree of fibrosis correlated positively with age and duration of infection. These study subjects are comparable to our group 2 (referral) patients.

We conclude that children who acquire HCV infection early in life generally manifest only mild liver disease over the first two decades of their infection. However, it is apparent that severe liver disease may develop in select groups of children infected with HCV. Despite the inherent bias of patient selection, referral studies prove that cirrhosis and rarely hepatocellular carcinoma are potential sequelae of childhood HCV infection and emphasize the need for identification and careful follow-up of those with potential risk factors. However, only a very long-term, prospective study on unselected cohort groups can provide an accurate accounting of the relative proportion of children who manifest severe outcomes. It is uncertain at present whether the slow progression of hepatitis C in immunocompetent children will accelerate as they grow older or will remain stable. This question has considerable implications for therapy. A slowly progressive course of HCV infection in children would favor deferred treatment, given that the multiple side effects of the currently available therapy observed in adults might be compounded by growth retardation in children. On the other hand, if pediatric trials show that children tolerate antiviral therapy well with high sustained response rates, early treatment would be preferred over the potential for serious liver disease decades later. Our natural history study and other pediatric studies10-20 suggest that treatment can be deferred to adolescence or later as long as patients are followed closely. However, it is important that this premise be tested by
longer-term natural history studies and by carefully conducted pediatric drug treatment trials to assess toxicity and sustained response rates.

We thank Dr Albert Hoang and Dr Robert McCarter for their help with the statistical analyses of our data during the revision of this paper, following the demise of Dr Kantilal Patel.

REFERENCES

Table II. Comparison of ALT values among study cohorts

<table>
<thead>
<tr>
<th>ALT (U/L) (mean ± SD)</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT during study period (n = 60)</td>
<td>98.0 ± 115.7</td>
<td>86.3 ± 133.6</td>
<td>109.6 ± 95.4*</td>
</tr>
<tr>
<td>ALT at biopsy (n = 42)</td>
<td>131.5 ± 22</td>
<td>61.0 ± 59.5</td>
<td>154.7 ± 255.5*</td>
</tr>
<tr>
<td>Patients with normal ALT (%)</td>
<td>15 (25%)</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>ALT &gt;1 to 1½ times normal</td>
<td>13 (22%)</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>ALT &gt;1½ to 3 times normal</td>
<td>24 (40%)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>ALT &gt;3 times normal</td>
<td>8 (13%)</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

*P = < .05.
Objective To test the hypothesis that fetal alcohol syndrome (FAS), with the full phenotype, and fetal alcohol effect (FAE), with some but not all of the features, can be combined under the umbrella term fetal alcohol spectrum disorders (FASD).

Study design We investigated the long-term sequelae of intrauterine alcohol exposure using physical examination, psychological interviews, and a behavioral checklist in a 20-year follow-up study of 37 patients with FASD originally diagnosed as having FAS or FAE in infancy and childhood.

Results Although the characteristic craniofacial malformations of FAS/FAE diminish over time, microcephaly, a poorly developed philtrum and a thin upper lip, and, to a lesser degree, short stature and underweight (in boys) persist. In females, adult body weight increases. Persistent mental handicaps, including intellectual disability, limited occupational options, and dependent living, are the major sequelae, and the scores for various behavioral problems are significantly increased.

Conclusions The devastating effects of intrauterine exposure to alcohol persist into early adulthood and severely limit careers and independent living. (J Pediatr 2007;150:175-9)

Jones and Smith were the first to describe a distinct pattern of craniofacial abnormalities and central nervous system dysfunction in 11 children whose mothers were chronic alcoholics.1 These authors coined the term fetal alcohol syndrome (FAS) to describe an entity characterized by craniofacial abnormalities, growth retardation, delayed psychomotor maturation, and impaired intellectual development. This syndrome also was independently identified by French authors,2 and FAS became recognized as a major cause of intellectual disability and was studied intensively with regard to such issues as pathogenesis, development, and intervention. The findings have been documented in numerous publications.3-6

The teratogenic effects of alcohol on the developing fetus represent a continuum known as fetal alcohol spectrum disorders (FASD). Updated methodologies for diagnosing FASD have been published recently,7 but traditionally, various diagnostic schemes have been used to categorize these adverse outcomes. Originally, FAS identified those children who displayed the full phenotype, with fetal alcohol effects (FAE) applied to individuals demonstrating some, but not all of the features of FAS.8 The terms FAS and FAE do not exactly correlate with some more recently updated diagnoses for the FASD. In this report, the diagnostic categories FAS and FAE are used, because these represent the diagnostic classifications available 20 years ago, when this study cohort was developed.

The estimated incidence of FAS is at approximately 1 per 1000 live births; that of FAE, in 3 to 5 per 1000 live births.9,10 FASD is a leading cause of marked developmental delay, including intellectual disability and other psychopathologies, such as attention deficit hyperactivity disorder (ADHD).3-6 Few studies have addressed the long-term sequelae of FAS/FAE.5,12-15 More extensive studies include the secondary disability study by Streissguth et al5,16 from the United States, the 21-year longitudinal analysis of the effects of prenatal alcohol exposure on young adult drinking by Baer et al,18 and our own findings from more than 10 years of follow-up.19 Here we report on more than 20 years of follow-up of our original cohort.

METHODS

In our previous report on the 10-year follow-up, we presented findings on 60 children and adolescents living in Berlin and various other locales throughout Germany.19 We were planning for a long-term follow-up at approximately 20 years so as to study adaptation in young adulthood in patients who had been in care of the first author over many years. Of these 60 subjects, 52 qualified for a 20-year follow-up between the years...
with regard to age (mean age, 26.3 years; SD, 2.1; t 
follow-up study. The 12 dropouts did not differ significantly
not available at follow-up with the 37 participants in this
compared the 12 subjects who refused to cooperate or were
ing using the Wechsler Intelligence Test.
retardation (IQ 70 to 85), and 15 with mental
borderline intelligence (IQ 70 to 85), and 15 with mental
delay, or intellectual impairment); and (c) characteristic
dysfunction (ie, any neurologic abnormality, developmental
delay, and hyperactivity. In contrast, the very marked cranio-
facial features present early in life had mostly disappeared,
although an elongated philtrum and a thin upper lip were still

To test any potential bias resulting from attrition, we
compared the 12 subjects who refused to cooperate or were
not available at follow-up with the 37 participants in this
follow-up study. The 12 dropouts did not differ significantly
with regard to age (mean age, 26.3 years; SD, 2.1; t = 1.91;
P = not significant [NS]), sex distribution (7 males, 5 fe-
male; \( \chi^2 = .07; P = NS \)), FAS versus FAE distribution
(7 FAS vs 5 FAE; \( \chi^2 = .01; P = NS \)), and intelligence
distribution (3 normal intelligence, 4 borderline intelligence, 5
mentally retarded; \( \chi^2 = .29; P = NS \)). Therefore, there was
no evidence of any major bias resulting from attrition to
the sample.
The initial FAS diagnosis was made in accordance with
criteria in use at the time of examination, as defined by the
Research Society on Alcoholism: (a) prenatal or postnatal
growth retardation (height and weight below the 10th per-
centile for age or gestational age; (b) central nervous system
dysfunction (ie, any neurologic abnormality, developmental
delay, or intellectual impairment); and (c) characteristic craniofacial abnormalities, including at least 2 of the follow-
ing: microcephaly (ie, head circumference below the 3rd per-
centile), microphthalmia, short palpebral fissures, poorly de-
veloped philtrum, thin upper lip, and flattening of the
maxillary area. According to the Research Society on Alco-
holism diagnostic criteria, the designation FAE is applied
when a child shows 2 of criteria (a), (b), and (c). Maternal
alcohol abuse during pregnancy was ascertained by obtaining
a careful history from the biological mother and/or family
members, including the analysis of all available medical
records.

At follow-up, the assessment procedure included the
following:
1. Physical examination (performed by H.L.S.), with special
emphasis on the characteristic craniofacial malformations
and measurement of growth variables according to Prader
et al, leading to the calculation of the body mass index
(BMI), including transformation into percentiles based on
German norms according to Kromeyer-Hauschild et al.
2. A coded item list based on an interview (performed by
J.W.) dealing with academic and occupational career, do-

cumentary arrangements, and independent living.
3. The Young Adult Behavior Checklist (YABCL), a ques-
tnaire for assessing emotional and behavioral problems
in young adults.
The interview was conducted with the subject's caregiver
or closest relative: a parent (in 8% of cases), a foster parent (in
35% of cases), or a caring person in the institution where the
subject lived at the time of the examination (41%). In 16% of
cases, the subject’s partner was interviewed. The same informant
who gave the interview filled out the YABCL.
Informed consent was obtained from all patients who
were competent, or from caregivers otherwise. Statistical tests
included t tests, \( \chi^2 \) tests, McNemar tests, and multivariate
analysis.

RESULTS

Signs and symptoms at initial examination and follow-
up are listed in Table II. Despite a substantial reduction
of symptoms across time, a sizeable number of subjects still
exhibited growth retardation, microcephaly, developmental
delay, and hyperactivity. In contrast, the very marked cranio-
facial features present early in life had mostly disappeared,
prominent. Various other physical and organ defects had been surgically corrected before follow-up; operations included cleft palate repair (in 2 subjects), ventricular septal defect repair (in 3 subjects), complex heart defect repair (in 1 subject), and minor operations for phimosis, cryptorchidism, and hernias.

Many subjects, even some formerly severely affected ones, exhibited some degree of catch-up growth in height and weight and normalization of BMI (Table III; available at www.jpeds.com). As expected, much less catch-up growth was recorded for head circumference (Fig 1). Of the 31 subjects (83.8%) with microcephaly (ie, head circumference below the 3rd percentile) on first assessment, 17 (45.9%) remained microcephalic at follow-up. Comparing the proportions of subjects scoring below and above the 3rd percentile in the total sample revealed significant changes in height (McNemar exact $P = .01$), weight (McNemar exact $P < .001$), head circumference (McNemar exact $P = .001$), and BMI (McNemar exact $P = < .001$). In males, these changes were significant only by trend for height (McNemar exact $P = .07$), significant for weight (McNemar exact $P = .004$), significant only by trend for head circumference (McNemar exact $P = .06$), and significant for BMI (McNemar exact $P = .001$). In females, the changes in the proportion of subjects scoring below the 3rd percentile were not significant for height, but were significant for weight (McNemar exact $P = .03$), head circumference (McNemar exact $P = .02$), and BMI (McNemar exact $P = 0$).

Additional comparisons of the continuous BMI at first assessment and follow-up are given in Table IV. A strong trend is seen for normalization in the total sample and the 2 sex groups; however, this trend is less strong in males.

Furthermore, there is a clear correlation between intellectual disability at first assessment and reduced head circumference at follow-up, as shown in Table V (available at www.jpeds.com). The prevalence of microcephaly at follow-up was significantly greater in those subjects who were intellectually disabled at first assessment ($\chi^2 = 10.3$; degrees of freedom $df = 2; P = .006$).

The psychosocial and career development interview revealed that 18 subjects (49%) had received special education only, 14 (38%) had passed primary school, and only 5 (13%) had a secondary school education. By occupational status, only 5 subjects (13%) had ever held an “ordinary” job. These findings were disappointing, because 25 subjects (69%) had received at least some preparatory job training and 21 (58%)
had either started or progressed to formal occupational training. However, 7 (19%) terminated job training prematurely due to a mismatch between mental and personal capacities and vocational skill requirements.

Assessment of domestic arrangements in young adulthood showed that 27% lived in institutions, 35% were in a dependent-living situation with assistance from others, 14% were able to live independently alone, 8% lived with a partner, 8% had their own family, and 8% lived with his or her father plus a mother surrogate.

The YABCL profiles of the 8 subscales are shown in Fig 2. Because of the lack of local norms, the raw scores were transformed into \( z \) scores (mean = 0; SD = 1). For the total group, significant deviations from the mean are seen on the following subscales: thought disorder (\( t = 2.79; P < .01 \)), attention problems (\( t = 5.57; P < .001 \)), intrusive behavior (\( t = 3.52; P < .01 \)), and aggressive behavior (\( t = 3.48; P < .01 \)). The profiles for the 2 sex subgroups did not differ significantly on multivariate analysis (Wilks’ \( \lambda = .63; F = 1.68; df = 8/23; P = NS \)).

**DISCUSSION**

In contrast to previous cross-sectional studies, this prospective longitudinal and long-term outcome study reports the consequences of prenatal alcohol exposure in an age-homogenous sample of young adults diagnosed with FAS or FAE in childhood. The 20-year follow-up allows a definite estimation of remaining handicaps, because all subjects in the present study are past childhood and adolescence.

Despite the physical changes, including disappearance of some of the features of FAS/FAE, many young adults still can be identified based on their residual signs and symptoms. Although some catch-up growth occurred, a large proportion of the subjects had growth deficiency. The apparent normalization of BMI is due predominantly to the fact that a large proportion of the sample is getting fatter. As in our previous 10-year follow-up, and in accordance with the follow-up observations of Streissguth et al, males seemed to be more impaired than females in all aspects of growth deficiency. At the same time, the development of growth variables in males was less consistent, whereas females showed a strong postpubertal increase in body weight.

There was a significant association between early intellectual disability and persistent microcephaly, although a minority of subjects with microcephaly had borderline or even normal intelligence. The association between intelligence in childhood and head circumference at follow-up also matches the generally relatively high stability of intelligence over time and the clinically and developmentally useful classifications of the 3 major groups of normal intelligence, borderline intelligence, and mental retardation.

The vocational development of our cohort was marked by a large group of subjects who had received special education at school and later experienced unemployment or worked in sheltered workshops only. Despite the preparatory job training and occupational programs in which the subjects had been enrolled, a high rate of vocational disability was noted. Similarly, the handicapping effects of FAS/FAE were reflected in the high proportion of young adults in assisted-living conditions and the small number of subjects who were able to live independently. In contrast to Streissguth et al, we did not find major crime and incarceration in our sample.

Finally, an assessment of emotional and behavioral problems showed that FAS/FAE subjects were characterized by features predominately of an externalizing or disruptive character and independent of sex effects. Most notably, the predominance of attention problems matches the findings of ADHD symptoms in FAS/FAE children found in our earlier studies and also reported by others. These problems and higher scores for aggressive and delinquent problems point to a high persistence from childhood to young adult-

### Table IV. Comparison of BMI at first assessment and follow-up

<table>
<thead>
<tr>
<th></th>
<th>First assessment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Total sample (n = 37)</td>
<td>10.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Males (n = 20)</td>
<td>10.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Females (n = 17)</td>
<td>11.7</td>
<td>5.0</td>
</tr>
</tbody>
</table>

NS, not significant.
hood, as shown in the study by Streissguth et al., whereas the higher scores for thought problems and intrusive behavior indicate some newly emerging additional mental problems in young adulthood. Additional analyses not presented here have shown that the specific features of the emotional and behavioral problem profiles in these subjects were independent of intellectual impairment and whether or not the subjects had been diagnosed with FAS or FAE. Thus, the subjects with the minor variant FAE experienced similar handicaps and problems as those with FAS.

These findings are similar to those identified in the cross-sectional study of Streissguth et al., who identified 8 protective factors that contributed to a less impaired life in a subsample of their subjects. Our longitudinal sample exhibited 7 of these 8 protective factors: (1) being diagnosed before age 6 years (in 32 of 37 subjects); (2) living in a stable home for over 70% of one’s lifetime; (3) staying in each living situation for more than 2.8 years; (4) experiencing a good-quality home environment between age 8 and 12 years; (5) having applied for therapeutic help and assistance; (6) having a diagnosis of FAS rather than FAE, making early diagnosis feasible (in 22 of 37 subjects); and (7) having basic needs met for at least 13% of one’s lifetime. There was only a slightly higher rate of subjects who had experienced violence against themselves in early childhood (3 of 37 subjects) (the eighth factor), whereas in the study by Streissguth et al., no subject who experienced violence was included in the subsample with less impaired life. Although almost all of the 8 protective factors were also present in our study, the outcome in the entire sample was significantly impaired. Thus, our data do not corroborate the protective function of these factors.

These differences may be due in part to transnational differences in patient selection, health care systems for diagnosing and treating FASD, and social systems, including special education and rehabilitation. A limitation of our study is the relatively small sample of referred patients. Furthermore, we know very little about any potential postnatal effect of the social environment on ultimate functioning other than the limited effects of rehabilitation.

This long-term follow-up study documents the devastating effects of intrauterine exposure to alcohol. Despite substantial efforts at rehabilitation, only a very small group of patients was able to live a normal adult life.

REFERENCES

### Table I. Sample characteristics

<table>
<thead>
<tr>
<th></th>
<th>FAS (n = 22)</th>
<th>FAE (n = 15)</th>
<th>Total (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At first assessment</td>
<td>3.2 ± 2.8</td>
<td>2.3 ± 1.4</td>
<td>2.8 ± 2.3</td>
</tr>
<tr>
<td>At follow-up</td>
<td>24.7 ± 3.5</td>
<td>21.6 ± 3.3</td>
<td>23.4 ± 3.7</td>
</tr>
<tr>
<td>Duration of follow-up, years (mean ± SD)*</td>
<td>21.5 ± 2.0</td>
<td>19.3 ± 3.3</td>
<td>20.6 ± 2.8</td>
</tr>
</tbody>
</table>

*Sex, n
- Males: 12 (FAS), 8 (FAE), 20 (Total)
- Females: 10 (FAS), 7 (FAE), 17 (Total)

*F = 7.39; df = 1; P = 0.1.

### Table III. Follow-up of morphometric variables

<table>
<thead>
<tr>
<th></th>
<th>Follow-up</th>
<th>First assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;3rd</td>
<td>&lt;10th</td>
</tr>
<tr>
<td>Height</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3rd percentile</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>&lt;25th percentile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25th percentile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3rd percentile</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>&lt;25th percentile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25th percentile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head circumference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3rd percentile</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>&lt;25th percentile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25th percentile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3rd percentile</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25th percentile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25th percentile</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table V. Association of intelligence at first assessment with head circumference at follow-up

<table>
<thead>
<tr>
<th>Head circumference</th>
<th>&lt;3rd percentile</th>
<th>&gt;3rd percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Normal intelligence, IQ &gt; 85 (n = 12)</td>
<td>4</td>
<td>33</td>
</tr>
<tr>
<td>Borderline intelligence, IQ 71 to 85 (n = 10)</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Mental retardation, IQ &lt; 70 (n = 15)</td>
<td>12</td>
<td>80</td>
</tr>
</tbody>
</table>
Clinical and Laboratory Features, Hospital Course, and Outcome of Rocky Mountain Spotted Fever in Children

STEVEN C. BUCKINGHAM, MD, GARY S. MARSHALL, MD, GORDON E. SCHUTZE, MD, CHARLES R. WOODS, MD, MS, MARY ANNE JACKSON, MD, LORI E. R. PATTERSON, MD, AND RICHARD F. JACOBS, MD, AS THE TICK-BORNE INFECTIONS IN CHILDREN STUDY GROUP

Objectives To describe the clinical characteristics and course of children with laboratory-diagnosed Rocky Mountain spotted fever (RMSF) and to identify clinical findings independently associated with adverse outcomes of death or discharge with neurologic deficits.

Study design Retrospective chart review of 92 patients at six institutions in the southeastern and southcentral United States from 1990 to 2002. Statistical analyses used descriptive statistics and multiple logistic regression.

Results Children with RMSF presented to study institutions after a median of 6 days of symptoms, which most commonly included fever (98%), rash (97%), nausea and/or vomiting (73%), and headache (61%); no other symptom or sign was present in >50% of children. Only 49% reported antecedent tick bites. Platelet counts were <150,000/mm³ in 59% of children, and serum sodium concentrations were <135 mEq/dL in 52%. Although 86% sought medical care before admission, only 4 patients received anti-rickettsial therapy during this time. Three patients died, and 13 survivors had neurologic deficits at discharge. Coma and need for inotropic support and intravenous fluid boluses were independently associated with adverse outcomes.

Conclusions Children with RMSF generally present with fever and rash. Delays in diagnosis and initiation of appropriate therapy are unacceptably common. Prognosis is guarded in those with hemodynamic instability or neurologic compromise at initiation of therapy. (J Pediatr 2007;150:180-4)
Table I. Demographic and historical features of 92 children with Rocky Mountain spotted fever

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease classification</td>
<td></td>
</tr>
<tr>
<td>Confirmed†</td>
<td>34 (37)</td>
</tr>
<tr>
<td>Probable‡</td>
<td>58 (63)</td>
</tr>
<tr>
<td>Male sex</td>
<td>43 (47)</td>
</tr>
<tr>
<td>Age, years</td>
<td>5.8 (3.7-9.1)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>85 (92)</td>
</tr>
<tr>
<td>Reported tick bite</td>
<td>45 (49)</td>
</tr>
<tr>
<td>Days from bite to symptom onset</td>
<td>4 (2-9)</td>
</tr>
<tr>
<td>Reported exposure to wooded area</td>
<td>31 (34)</td>
</tr>
<tr>
<td>Days of symptoms at admission</td>
<td>6 (4-8)</td>
</tr>
<tr>
<td>Healthcare visit before admission</td>
<td>80 (86)</td>
</tr>
<tr>
<td>No. of visits before admission</td>
<td>1 (1-2)</td>
</tr>
</tbody>
</table>

*Median (interquartile range) or no. of patients (%).
†Confirmed by fourfold rise in \( R \text{rickettsii} \) antibody titer (29 patients), demonstration of \( R \text{rickettsii} \) antigen by immunostaining of tissue specimens (5 patients), or both (1 patient).
‡Single reactive \( R \text{rickettsii} \) antibody titer and clinically compatible symptom complex.

Clinical and Laboratory Features, Hospital Course, and Outcome of Rocky Mountain Spotted Fever in Children

Table II. Symptoms and signs before or during admission in 92 children with Rocky Mountain spotted fever

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>89 (98)</td>
</tr>
<tr>
<td>Any rash</td>
<td>89 (97)</td>
</tr>
<tr>
<td>Maculopapular only</td>
<td>32 (35)</td>
</tr>
<tr>
<td>Any petechial component</td>
<td>57 (62)</td>
</tr>
<tr>
<td>Involving palms and soles</td>
<td>60 (65)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>67 (73)</td>
</tr>
<tr>
<td>Headache*</td>
<td>52 (61)</td>
</tr>
<tr>
<td>Myalgia*</td>
<td>38 (45)</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>31 (36)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32 (34)</td>
</tr>
<tr>
<td>Conjunctival injection</td>
<td>30 (33)</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>30 (33)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>27 (29)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>23 (25)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>21 (23)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>17 (18)</td>
</tr>
<tr>
<td>Seizure</td>
<td>16 (17)</td>
</tr>
<tr>
<td>Meningismus</td>
<td>15 (16)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>15 (16)</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Coma</td>
<td>9 (10)</td>
</tr>
</tbody>
</table>

*Excludes children <2 years of age; denominator is 85 for these characteristics.

The southcentral United States. Each site’s institutional review board approved the study design and waived requirements for informed consent. Possible RMSF cases were identified by reviewing hospital databases for patients with discharge ICD-9 codes for rickettsioses (i.e., 082.0-083.9) and by reviewing records of each site’s laboratory, pediatric infectious disease consultation service, and infection control service. These medical records were reviewed, and only patients who met previously established criteria for confirmed or probable RMSF were included in the final study population.

Demographic, clinical, and laboratory data were abstracted from medical records using a standard case report form. Clinical features were considered present only if their presence was documented in the medical record. The term “admission” refers to a patient’s first presentation to one of the study institutions, regardless of whether the patient was hospitalized at that time. Altered mental status was defined as any disturbance in the subject’s level of consciousness. Coma was considered present if a patient was described as “comatose” or “unresponsive,” and if this state could not be attributed to pharmacologic interventions. Seizures were defined by any notation of a “seizure,” “convulsion,” or “seizure-like activity.” An intravenous fluid bolus was defined as an infusion of \( \geq 10 \) mL/kg of colloid or crystalloid. The results of the first complete blood count with differential obtained after admission were recorded, as were the results of the first serum chemistry and coagulation tests obtained within 72 hours of admission. Some clinical and laboratory data from 15 patients included in this report have been presented elsewhere.

Case report forms were forwarded to one site (Memphis), where data were analyzed using Statview (SAS Institute, Cary, NC). Bivariate statistical comparisons were performed using Fisher’s exact or Wilcoxon’s rank sum tests. Multiple logistic regression was used to identify clinical variables independently associated with adverse outcome, which was defined as death or discharge from the hospital with a functionally significant neurologic deficit. Independent variables present in at least 10% of the study population and for which bivariate \( P \) values were <.10 were included in the initial multiple logistic regression model. Independent variables were then removed via backward elimination; only those for which multivariate \( P \) was <.05 were retained. After a tentative final model was created, previously eliminated independent variables were individually forced back into the model and retained if \( P \) was then <.05.

RESULTS

Clinical and Laboratory Characteristics

Demographic and historical characteristics of the 92 patients with RMSF are listed in Table I. Ninety percent of cases were diagnosed between April 1 and August 31, and 61% in May, June, and July (Figure 1; available at www.jpeds.com). Most patients were taken to healthcare providers before admission; one child had five separate healthcare visits. Nonetheless, only 4 patients were prescribed an anti-rickettsial antibiotic (in all cases, doxycycline) before admission.

Data regarding symptoms and physical findings at the time of admission are listed in Table II. Traditionally recognized symptom constellations had poor sensitivity: 58% of patients had fever, rash, and headache noted, and 45% had fever, rash, and a history of tick attachment noted.
The results of initial laboratory studies are shown in Table III. Most patients had thrombocytopenia; 6 had platelet counts of <30,000/mm³. No patient had documented cerebrospinal fluid hypoglycorrachia. Fifty-one patients had a chest radiograph obtained within 48 hours of admission; 17 of these (33%) were interpreted as showing an infiltrate or pneumonia.

Course and Outcome

As illustrated in Figure 2, children were first brought to medical care providers after a median of 2 days of symptoms; however, they did not receive effective anti-rickettsial therapy until after a median of 7 days of symptoms. Eighty-nine patients were hospitalized, and 3 were managed as outpatients. Thirty-three patients (36%) spent time in an intensive care unit, 15 (16%) were mechanically ventilated, 38 (41%) received at least one intravenous fluid bolus, and 16 (17%) received inotropic medications. After admission, all but 3 patients received anti-rickettsial therapy, consisting of: doxycycline only (66 patients), chloramphenicol only (10), tetracycline only (7), doxycycline plus chloramphenicol (5), and tetracycline plus chloramphenicol (1). Since 1994, only doxycycline has been used for anti-rickettsial therapy.

The time from symptom onset to initiation of anti-rickettsial therapy ranged from 0 to 15 days. Children who visited a healthcare provider within the first 2 days of symptoms started anti-rickettsial therapy significantly later than did those who first sought care later in their course of disease (median time from visit to starting therapy, 4.5 days vs 1 days; \( P = .007 \)). No other clinical variable was significantly associated with time to initiation of anti-rickettsial therapy (data not shown).

Three children died: a 4-year-old girl, a 6-year-old boy, and a 15-year-old boy. All were Caucasian. One had an underlying seizure disorder and was admitted with a rapidly progressive illness on the day of symptom onset. The others were previously healthy and were admitted after 3 and 6 days of symptoms, respectively. These last two visited healthcare providers 2 and 3 days before admission, respectively, and received therapy for presumed streptococcal pharyngitis (with benzathine penicillin and cephalexin, respectively); neither received prescriptions for anti-rickettsial antibiotics. All three patients had fever, respiratory failure, renal insufficiency, and altered mental status on admission and required mechanical ventilation, inotropic cardiac support, and transfusions of blood products. The cause of death was multiorgan failure in two patients, and diffuse cerebral edema in the third patient.

Thirteen of 89 surviving patients (15%) were discharged from the hospital with documented neurologic deficits, which included: speech and/or swallowing dysfunction (6 patients), global encephalopathy (4 patients), ataxia or other gait disturbances (4 patients), and cortical blindness (1 patient). Two of these children were discharged to inpatient rehabilitation centers, and 4 others continued with physical or occupational therapy after discharge. Follow-up data were available for 5 patients who were discharged with neurologic deficits. One had weakness that had resolved by 10 days after discharge; the other 4 had persistent abnormalities documented from 2 months to 4 years after discharge.

Two patients had digital necrosis. One suffered amputation of one finger and mummification of three others; the other had dry necrosis of tips of multiple toes.

Predictors of Adverse Outcomes

All 16 patients who died or were discharged with focal neurologic deficits had altered mental status and required care in an intensive care unit; thus, these variables had undefined

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood leukocytes/μL</td>
<td>9500 (5500-14,700)</td>
</tr>
<tr>
<td>No. with &gt;15,000/mm³</td>
<td>22/92 (24)</td>
</tr>
<tr>
<td>No. with &lt;4000/mm³</td>
<td>8/92 (9)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.2 (10.4-12.6)</td>
</tr>
<tr>
<td>Platelets/mm³</td>
<td>128,000 (72,200-228,000)</td>
</tr>
<tr>
<td>No. with &lt;150,000/mm³</td>
<td>54/92 (59)</td>
</tr>
<tr>
<td>No. with &lt;100,000/mm³</td>
<td>38/92 (41)</td>
</tr>
<tr>
<td>Sodium, mEq/dL</td>
<td>148/91 (52)</td>
</tr>
<tr>
<td>No. with &lt;135 mEq/dL</td>
<td>10 (7-15)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.6 (0.4-0.7)</td>
</tr>
<tr>
<td>Alanine transaminase, U/L</td>
<td>55 (36-78)</td>
</tr>
<tr>
<td>Aspartate transaminase, U/L</td>
<td>83 (44-125)</td>
</tr>
<tr>
<td>Bilirubin, mg/dL</td>
<td>0.6 (0.4-1.0)</td>
</tr>
<tr>
<td>Albumin, mg/dL</td>
<td>3.0 (2.4-3.4)</td>
</tr>
<tr>
<td>Prothrombin time, sec</td>
<td>12.7 (11.9-14.1)</td>
</tr>
<tr>
<td>Partial thromboplastin time, sec</td>
<td>30.9 (28-37.9)</td>
</tr>
<tr>
<td>Cerebrospinal fluid‡</td>
<td>68 (35-126)</td>
</tr>
</tbody>
</table>

*Obtained within 72 hours of admission.
†Median (interquartile range) or no. of subjects (%).
‡Cerebrospinal fluid was examined in 38 patients.
involved the palms and/or soles. However, the onset of rash occurred after a shorter interval in the present study (median, 1 day of illness) than was noted by Helnick et al for patients >14 years of age (3 days) or children (2 days). In the present study, every child had at least one of the findings of fever, rash, or headache; however, as noted previously, the combination of all three was present in less than two-thirds of patients. Although children in the present study experienced numerous other signs and symptoms, none was present in more than half of patients. Furthermore, as reported elsewhere, laboratory findings generally were nonspecific and difficult to differentiate from those that would be expected, for example, in viral syndromes. These data suggest that no constellation of clinical and laboratory abnormalities has adequate sensitivity for their absence to exclude the diagnosis of RMSF in a child.

This study has several limitations. First, only data that were recorded in medical records was analyzed. Because historical and physical examination findings were only considered present if they were documented, the results might underestimate the true rates of some clinical findings. A second possible limitation reflects the imperfect specificity of serologic testing for RMSF. The authors’ previous seroprevalence study found *Rickettsia* antibodies titers of ≥1:64 in 12% of children in the southeastern and southwestern United States. Thus, it is possible that some patients in the present study had elevated RMSF antibody titers but were acutely ill from a different cause and were mistakenly classified as having probable RMSF. Patients who met criteria for probable disease, however, had clinical findings, hospital courses, and outcomes similar to those of patients with confirmed disease, as was previously reported by Dalton et al. Thus, it is unlikely that the present study’s results have been substantially skewed by inappropriately including patients with diseases other than RMSF. On the contrary, by using more stringent enrollment criteria than were used in the pediatric studies from the 1970s, many patients who truly did have RMSF must have been excluded. Another limitation, then, is that this study’s results can only be considered representative of patients in endemic areas who are ill enough to have serologic tests performed, and they cannot necessarily be generalized to all patients with RMSF. Finally, owing to serologic cross-reactivity among spotted fever group rickettsiae, it is conceivable that some patients in this series were infected with spotted fever rickettsiae other than *Rickettsia*; of note, this limitation must also apply to all previous serologically based studies of RMSF.

The diagnosis of RMSF and initiation of appropriate therapy were delayed substantially in most patients in this study. Delays occurred not because patients with RMSF failed to seek medical attention, but because their treating clinicians failed to consider RMSF. Such diagnostic misadventures are understandable, given the nonspecificity of the usual presenting clinical and laboratory features of RMSF. In previous studies, factors associated with delayed diagnosis of RMSF included: absence of history of tick attachment, absence of rash or delay in appearance of rash; absence of

### DISCUSSION

The results of this study reaffirm some established beliefs regarding the epidemiology and clinical manifestations of RMSF in children and call others into question. As in previous studies, more than 90% of patients were admitted between April and September—although cases were also diagnosed in colder months. Although RMSF has been considered to affect young males predominantly, more than half of the patients in this study were female. Fewer than half of the present study’s patients reported an antecedent tick bite, a rate even lower than the 56% to 66% reported in previous studies. Similarly, exposure to a wooded area proved to be a poorly sensitive predictor of RMSF.

As in previous studies, nearly all patients in this study had a rash, which frequently became petechial and involved the palms and/or soles. However, the onset of rash

### Comparisons of Patients with Confirmed versus Probable Disease

Compared with patients with probable disease, those with confirmed disease were older (median age, 6.5 years vs 4.8 years, *P* = .02; more frequently reported exposure to a wooded area (17 of 34 vs 14 of 58, *P* = .02); had lower median platelet counts (87,000/μL vs 158,000/μL, *P* < .001); and had lower median serum concentrations of sodium (132 mEq/dL vs 135 mEq/dL, *P* = .02) and albumin (2.5 mg/dL vs 3.1 mg/dL, *P* = .006). These groups did not differ significantly in any of the other clinical and laboratory characteristics listed in Tables I, II, and III; in the timing of the disease course (Figure 2); or in adverse outcome rates. Two of 3 patients who died had confirmed disease; the third died without convalescent sera collected.

The diagnosis of RMSF and initiation of appropriate therapy were delayed substantially in most patients in this study. Delays occurred not because patients with RMSF failed to seek medical attention, but because their treating clinicians failed to consider RMSF. Such diagnostic misadventures are understandable, given the nonspecificity of the usual presenting clinical and laboratory features of RMSF. In previous studies, factors associated with delayed diagnosis of RMSF included: absence of history of tick attachment, absence of rash or delay in appearance of rash; absence of...
headache; illness outside peak months of tick activity; illness with complaints other than fever, rash, or headache; and presentation to a healthcare provider early in the disease course. In the present study, however, only the last of these factors was significantly associated with delayed initiation of anti-rickettsial therapy. These results suggest that clinicians fail to recognize and prescribe appropriate therapy for children with RMSF in general, and not just in those with incomplete constellation of symptoms.

Numerous clinical factors were associated with adverse outcomes in bivariate analyses; however, multiple logistic regression revealed only coma, inotropic support, and fluid boluses as independently associated with adverse outcomes. These results, and the findings that all patients with adverse outcomes required care in an intensive care unit and had altered mental status, suggest that neurologic outcomes in RMSF are closely tied to patients’ disease severity, particularly with regard to level of consciousness and to hemodynamic stability. Similarly, Conlon et al reported that neurologic involvement was independently associated with mortality from RMSF; in that study, elevated serum creatinine at presentation was the only other factor independently predictive of mortality. Because only 4 patients received sulfonamides (and none was exposed before admission), this study could not evaluate the reputed association between exposure to this class of antibiotics and adverse outcome in RMSF.

Experts recommend that patients with suspected RMSF promptly receive anti-rickettsial therapy, preferably with doxycycline, because delays in the initiation of appropriate therapy have been associated with increased mortality in adults. Although this study did not demonstrate a clear association between timing of anti-rickettsial therapy and outcome, such therapy should still be prescribed for children once the diagnosis of a tick-borne rickettsial illness is strongly considered. It would be inappropriate to conclude, based on this study’s results, that timing of therapy is irrelevant because only 25% of patients received therapy during the first 4 days of illness—a time frame clearly associated with decreased mortality in previous studies. Moreover, 2 of 3 children who died sought medical care early in their illness courses but were not prescribed anti-rickettsial therapy at these visits.

Clinicians frequently are presented with opportunities to start therapy early in the disease course in children with RMSF. This diagnosis should be considered in children in the first few days of their illness who have any single compatible finding, especially during the spring and summer. Children generally improve markedly after starting anti-rickettsial therapy—as demonstrated by, on average, defervescence within 2 days and hospital discharge within 5 days. These outcomes certainly are worth achieving.

The authors wish to acknowledge the assistance of Nancy C. Tucker, RN, and Amy Hayden, MD, in reviewing medical records for this study.

REFERENCES

Figure 1. Monthly distribution of confirmed (solid bars) and probable (hatched bars) cases of Rocky Mountain spotted fever in children.

Table IV. Clinical variables significantly associated with adverse outcome in children with Rocky Mountain spotted fever: results of bivariate analyses

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Crude Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered mental status</td>
<td>Undefined</td>
<td></td>
</tr>
<tr>
<td>Intensive care unit admission</td>
<td>Undefined</td>
<td></td>
</tr>
<tr>
<td>Inotropic support</td>
<td>105</td>
<td>19.1-581</td>
</tr>
<tr>
<td>Coma</td>
<td>75.0</td>
<td>8.3-679</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>39.1</td>
<td>9.1-168</td>
</tr>
<tr>
<td>Intravenous fluid bolus*</td>
<td>34.6</td>
<td>4.3-277</td>
</tr>
<tr>
<td>Seizure</td>
<td>31.2</td>
<td>7.8-126</td>
</tr>
<tr>
<td>Blood product transfusion</td>
<td>31.2</td>
<td>7.8-126</td>
</tr>
<tr>
<td>Albumin &lt;3.0 mg/dL</td>
<td>17.6</td>
<td>2.1-147</td>
</tr>
<tr>
<td>Bilirubin &gt;1.5 mg/dL</td>
<td>14.0</td>
<td>2.8-69.1</td>
</tr>
<tr>
<td>Blood urea nitrogen &gt;15 mg/dL</td>
<td>8.5</td>
<td>2.5-28.5</td>
</tr>
<tr>
<td>Creatinine &gt;1.1 mg/dL</td>
<td>8.5</td>
<td>1.7-43.2</td>
</tr>
<tr>
<td>Meningismus</td>
<td>6.6</td>
<td>1.9-22.6</td>
</tr>
<tr>
<td>Triad of fever, rash, and headache</td>
<td>6.6</td>
<td>1.4-31.2</td>
</tr>
<tr>
<td>Partial thromboplastin time &gt;45 sec</td>
<td>6.4</td>
<td>1.2-33.7</td>
</tr>
<tr>
<td>Platelet count &lt;150,000/μL</td>
<td>6.3</td>
<td>1.3-29.6</td>
</tr>
<tr>
<td>Headache</td>
<td>6.3</td>
<td>1.3-29.6</td>
</tr>
<tr>
<td>Petechial rash</td>
<td>5.4</td>
<td>1.1-25.3</td>
</tr>
<tr>
<td>Alanine aminotransferase &gt;55 U/L</td>
<td>4.9</td>
<td>1.2-20.0</td>
</tr>
<tr>
<td>Aspartate aminotransferase &gt;100 U/L</td>
<td>3.5</td>
<td>1.1-11.7</td>
</tr>
</tbody>
</table>

*Any infusion of ≥10 mL/kg or ≥1L of colloid or crystalloid.
Parental Depression Following the Early Diagnosis of Cystic Fibrosis: A Matched, Prospective Study

CLAIRE GLASSCOE, PHD, GILLIAN A. LANCaster, PHD, ROSALIND L. SMYTH, MD, AND JONATHAN HILL, FRCPsych

Objective To assess risks for parental depression following the diagnosis of cystic fibrosis (CF) in a child.

Study design Matched cohort study in NW England: 45 parental couples with a child diagnosed with CF were compared with 45 control couples matched for age, sex, and position in the family of the index child. The Beck Depression Inventory (BDI-II) with a clinical cut-off ≥13 for dysphoria (mild depression) was the main outcome. A stratified analysis was conducted using the Mantel-Haenszel risk-ratio estimator (RRMHT) with eight strata for each of the matching variable combinations.

Results Heterogeneity was found within the dataset. Parents with a child with CF ≤9 months of age at baseline had an elevated prospective risk of depression (mothers RRMHT [95% confidence interval(CI)] = 2.6 [1.05, 6.42]; fathers RRMHT [95%CI] = 2.26 [0.97, 5.28]). The absence of a group effect for depression at follow-up after adjusting for the matching (mothers RRMHT [95%CI] = 1.1 [0.59, 2.05], fathers RRMHT [95%CI] = 1.42 [0.66, 3.08]) masked this heterogeneity.

Conclusion This hypothesis-generating finding suggests that parents may be more vulnerable to depression when their child is diagnosed with a life-shortening condition during the first few months of life. Mood in parents of infants diagnosed early needs to be monitored longitudinally and preventative strategies devised. (J Pediatr 2007;150:185-91)

Cystic fibrosis (CF) affects 1 in 2,500 live births in those of European descent. Early diagnosis is important for survival, and national neonatal screening programs for CF have been established in many parts of the Western world. Previous studies have indicated that the majority of parents adapt well to having a child with cystic fibrosis, although elevated levels of depression and reduced partner satisfaction have been reported. Cross-sectional studies of parental depression may not, however, adequately reflect the multiple ways that the illness impacts on the family. Parents, the affected child, and siblings have to come to terms with a diagnosis that implies a premature death, to respond over many years to a physical condition that generally fluctuates markedly, and to cope day to day with the practical demands of administering treatment in the home. Parental mental health therefore is likely to fluctuate over time, and it may be influenced by multiple interacting risk factors. Prospective, longitudinal studies with representative samples, defined in terms of time since diagnosis, are needed.

Studies of depression in the general population find that subclinical levels increase risk for further dysfunction and episodes of depression predict further episodes in an escalating cycle of vulnerabilities. Maternal depression is known to influence emerging parent-child attachment status. It not only influences maternal reports of childhood behavioral difficulties but is also associated with cognitive, emotional, and behavioral difficulties in developing children. Studies of fathers’ role or the relationship between fathers’ mood and child development are scarce. Although an early diagnosis of CF avoids delay the start of treatment, which may reduce anxiety in parents, potential adverse effects of the news of a life-shortening condition in a newborn infant on the formation of the parent-child relationship are now cause for concern. Preliminary findings from a longitudinal study suggest elevated risk for depression associated with a diagnosis given in infancy. This study aimed to identify the persistent risk to mothers’ and fathers’ mood associated with a clinical diagnosis for CF that might have implications for an early diagnosis through screening. The parameters and demands of doing this methodologically were explored with a design that had two principal features; it was prospective and matched with possible sources of heterogeneity anticipated from the matching variables. The ultimate aim was to identify a population-based approach for the prevention of mood disorder in parents dealing with the new challenge of a chronic life-shortening condition in a child diagnosed in infancy.
METHODS

Design

The aim of the design was to ensure as far as possible two groups for comparison that differed only with respect to whether a couple had had a child recently diagnosed with CF. The groups were matched for the index child’s age (±3 months), sex, and position in the family (first/not first) and were compared on a further six parameters including parental age, length of couple relationship, family composition, family size, income, and family stress over the preceding 12 months. Baseline interviews in the CF group of parents were scheduled to take place within 3 months of the diagnosis and follow-up interviews 9 months later; thus the study period aimed to capture the first year following the diagnosis. The control group participants were seen twice, 9 months apart.

Recruitment

This study was a consecutive sample of incident CF cases from two main centers in the North West of England, UK. Ethical approval was obtained from Liverpool Children’s Ethics Committee, Salford and Trafford Ethics Committee, and Wirral Ethics Committee, and full written consent was obtained from each participant. All parents of children diagnosed with CF between September 1998 and January 2002 attending the centers and their peripheral clinics were selected for this study. Families in which two primary caretakers (biological, step, foster, or adoptive) were living with the first child to receive a diagnosis of CF were approached for their participation by the consultant pediatrician responsible for the child’s care or their specialist CF nurse. Participating mothers and fathers in the CF group were recruited from Royal Liverpool (n = 16) and Booth Hall (n = 9) Children’s Hospitals and 11 peripheral clinics (n = 20). Control families with no diagnosis of CF in a child were recruited from three general practice (GP) clinics: one large clinic covering two areas in the city of Liverpool (n = 30) and two smaller clinics on the Wirral peninsular (n = 7 and n = 8). These general practices served a broad socioeconomic range with Jarman indexes (Jarman score: a zero value represents the national average deprivation score with a national range of −50 to 75) of between 20-39 and −13-42 (Liverpool) and 4-66 and zero (Wirral). A systematic matching procedure was used to select control families. Each selected family received a letter of invitation from their child’s family doctor.

Couples were excluded from both groups where (a) only one parent was living with the index child; (b) either parent had a psychotic illness where the interview and questionnaires would have unsettled them; (c) either parent had a physical illness that rendered him or her incapable of providing child care; (d) there had been a recent child death; (e) there were complex social problems with statutory services involved and participation in the study would disrupt child protection plans; (f) they had moved and were untraceable by reasonable means; or, (g) English was not the first or second language. Where two children were being assessed for CF simultaneously in the same family then the first child to receive a diagnosis was regarded as the index child. Where the child was diagnosed in utero then the date of the birth was regarded as the date of diagnosis because that point marked the beginning of treatment.

Matching Variables

The matching variables reflected three anticipated sources of heterogeneity: (1) age of the child at baseline (±3 months) because the demands of a newborn baby may be associated with postnatal depression in mothers; (2) sex of the child because male and female children are known to have different physical vulnerabilities and prognostic outcome; and (3) position in the family of the child (first/not first) because birth order and the number of siblings in the family are known to be associated with different psychosocial outcomes. A query was entered into the GP databases for each identified child with CF, to produce a list of matches based on the child’s age (±3 months) and sex. This list was then refined to include children matched for position in the family (first/not first). One child was randomly selected from ten suitable matches until each identified child had one matched control for comparison.

Outcome Measure

The primary outcome was depression reported by parents with the second edition of the Beck Depression Inventory (BDI-II). This is a 21-item self-report instrument for measuring severity of depression in adults and adolescents 13 years of age and older. The BDI-II is a widely used measure that has been extensively validated. It is reported to have good internal consistency and discriminant validity. Clinical cutoffs for the BDI-II of 0 to 12 for nondepressed, 13 to 19 for dysphoria, and 20 to 63 for dysphoric or depressed were calculated by Dozois et al using the procedure described by Kendall et al. These empirically derived cutoffs had overall correspondence rate of 91% with the original (sensitivity = 81%; specificity = 92% and k coefficient of 0.7). A low clinical cutoff of 13 was selected to indicate dysphoria (mild depression), and the term dysphoria is preferred as this was a questionnaire-based assessment. Versions of this inventory have been utilized as a screening measure for depressive illness in the general population.

Data Analyses

Emphasis was placed on estimation of parameter effect sizes and 95% confidence intervals (95% CI). To compare the risk-ratio of depression in the two matched groups a stratified analysis using the Mantel Haenszel risk–ratio estimator (RMH) was used and is presented with 95% CI. For the purpose of these analyses, the continuous age matching variable was transformed into a dichotomous variable (≤9 months/≥10 months). This cutoff was chosen because it...
represented the median age of children in the CF group at baseline.

The method for dealing with a stratified dataset described by Greenland\textsuperscript{31} (pp. 283-5) was followed. This involved examination of the dataset for stratum-specific effects before pooling across strata. Analyses were conducted using formulae 15.20 and 15.22, p. 271.\textsuperscript{31} Where the data were sparse and zero dysphoric participants in one or other group created one empty cell, then 0:5 was added to all four cells in the $2 \times 2$ table for that stratum.\textsuperscript{32} Where there were no dysphoric participants in both groups, the stratum $RR_{MH}$ was not computed.

RESULTS

The Sample

The Figure shows the recruitment rate was (50/56) 89% for the CF group and (58/81) 72% for the control group. Of the four families excluded in the CF group there was one lone parent, in two families child protection investigations were underway, and in one other the parents did not speak English. Forty-five matched couple pairs were identified and entered into the analyses and of these 39 pairs of fathers and 41 pairs of mothers completed the study at both time points. Sixty-two percent of couples in the CF group were seen within 3 months, 82% within 4 months, and all were seen within 9 months of the diagnosis. A sensitivity analysis was conducted for the main analysis, with and without the eight late recruits revealing no change in the main trends reported.

Characteristics at Baseline

The sample, described in Table I, comprised 45 matched pairs of parents with the identified child ranging in age from 3 months to 11 years, 4 months. The median age at diagnosis in months (interquartile range) was 6 (2.5,31.5). Matching variables were examined within the two groups to assess the success of the matching process. Children in the CF group had a median age of 1.5 months younger than children in the control group (median difference [95%CI] $[-1.5 [-2, -1])$. The medians for the lower age stratum were 5 months for the CF group and 6 months for the control group yielding a median group difference with 95%CI of $[-1[-3,0])$. The groups did not differ significantly with respect to the other two matching variables, or as a function of six potential confounders summarized in Table I as parental age, length of the couple relationship, family composition, size, income, and stress.

Prevalence of Dysphoria

The prevalence of dysphoria (Table II) reported by mothers in the whole group was similar in both groups at baseline and follow-up. Thirty-three percent of CF group fathers reported dysphoria at baseline compared with 18% of control fathers, and 18% of CF group fathers reported dysphoria at follow-up compared with 10% of control fathers. The paired percentage difference [95%CI] for group comparisons of fathers showed no clear differences (baseline 15.5%[2,44] and follow-up 7.7%[2,24]).

The proportion of couples where both partners were dysphoric in the CF couples was 22% compared with 11% of control couples at baseline, and 15% of CF couples compared with 5% of control couples at follow-up. The percentage paired group differences [95%CI] were in the predicted direction, although confidence intervals were wide (baseline 20% [2,39], follow-up 13% [2,34]).

Effect Measure Modification and Risk for Depression

A stratified analysis assumes homogeneity of effect and thus the stratum-specific effects were examined before pooling as detailed in the Greenland protocol.\textsuperscript{31} This procedure revealed a heterogeneous pattern of elevated risk estimates in the strata for those with children $\leq 9$ months of age in contrast to those $>9$ months of age at baseline (not shown) and at follow-up (Table III). Despite matching for age, fathers in the CF group were more likely to experience dysphoria at baseline with a child $\leq 9$ months than in the control group ($RR_{MH}$ 95%CI = 3.51 [1.17,10.52]) and the effect for mothers showed a similar trend ($RR_{MH}$ 95%CI = 2.1 [0.81,5.44]). This pattern persisted at follow-up (Table III), when mothers in the CF group relative to controls were more likely to report dysphoria with a child $\leq 9$ months ($RR_{MH}$ 95%CI = 2.6 [1.05,6.42] and fathers with a child $\leq 9$ months showed an almost identical trend in the same direction ($RR_{MH}$ 95%CI = 2.26}
These estimates varied very little in a sensitivity analysis excluding the eight late recruits, and they suggest an important finding of heterogeneity for age that needs to be reported rather than treated as bias to be eliminated.

By contrast to the stratum-specific analysis there was no prospective pooled main effect for mothers ($RR_{MITH}^{95\%CI} = 1\cdot1\, [0\cdot59,2\cdot05]$) or fathers ($RR_{MITH}^{95\%CI} = 1\cdot42\, [0\cdot66,3\cdot08]$). Thus, no pooled main effect was established.

### Table I. Sample characteristics at baseline

<table>
<thead>
<tr>
<th>Matching variables</th>
<th>CF group (n = 45)</th>
<th>Control group (n = 45)</th>
<th>Difference [95%CI]</th>
</tr>
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<tbody>
<tr>
<td><strong>Age of child</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of months (median, interquartile range)</td>
<td>10 (5.5, 34)</td>
<td>12 (7.35.5)</td>
<td>-1.5 [-2, -1]‡</td>
</tr>
<tr>
<td>≤9 months (n, %)</td>
<td>20 (44.4%)</td>
<td>16 (35.6%)</td>
<td>9% [-0.4%, 18%]§</td>
</tr>
<tr>
<td>≥10 months (n, %)</td>
<td>25 (55.6%)</td>
<td>29 (64.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex of child</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>21 (46.7%)</td>
<td>21 (46.7%)</td>
<td></td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>24 (53.3%)</td>
<td>24 (53.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Position in the family</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First (n, %)</td>
<td>27 (60%)</td>
<td>27 (60%)</td>
<td></td>
</tr>
<tr>
<td>Not first (n, %)</td>
<td>18 (40%)</td>
<td>18 (40%)</td>
<td></td>
</tr>
<tr>
<td><strong>Potential confounding variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age of parents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother (mean, SD)</td>
<td>31.13 (5.45)</td>
<td>31.2 (6.17)</td>
<td>-0.07 [-2.3, 2.2]†</td>
</tr>
<tr>
<td>Father (mean, SD)</td>
<td>33.64 (6.08)</td>
<td>33.87 (5.39)</td>
<td>-0.22 [-2.17, 1.73]†</td>
</tr>
<tr>
<td><strong>Length of couple relationship</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 years (n, %)</td>
<td>13 (28.8%)</td>
<td>13 (28.8%)</td>
<td></td>
</tr>
<tr>
<td>6-10 years (n, %)</td>
<td>14 (31.1%)</td>
<td>9 (20%)</td>
<td>11% [-8%, 29%]§</td>
</tr>
<tr>
<td>≥11 years (n, %)</td>
<td>18 (40%)</td>
<td>23 (51.1%)</td>
<td>-11% [-29%, 8%]§</td>
</tr>
<tr>
<td><strong>Family composition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact nuclear (n, %)</td>
<td>37 (82.2%)</td>
<td>38 (84.4%)</td>
<td>2% [-12%, 16%]§</td>
</tr>
<tr>
<td>Reconstituted (n, %)</td>
<td>8 (17.8%)</td>
<td>7 (15.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Family size</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of children (median, interquartile range)</td>
<td>2 (1, 2)</td>
<td>2 (1, 2)</td>
<td></td>
</tr>
<tr>
<td><strong>Family income</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10,000 (n, %)</td>
<td>4 (8.9%)</td>
<td>5 (11.1%)</td>
<td></td>
</tr>
<tr>
<td>10,000-24,999 (n, %)</td>
<td>23 (51%)</td>
<td>17 (37.8%)</td>
<td>9% [-11%, 28%]§</td>
</tr>
<tr>
<td>25,000-35,999 (n, %)</td>
<td>12 (26.7%)</td>
<td>14 (31.1%)</td>
<td>-4% [-23%, 15%]§</td>
</tr>
<tr>
<td>≥35,000 (n, %)</td>
<td>6 (13.3%)</td>
<td>9 (20%)</td>
<td>-4% [-19%, 10%]§</td>
</tr>
<tr>
<td><strong>Family Stress</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother (median, interquartile range)</td>
<td>12 (7.5, 17.5)</td>
<td>10 (5.16)</td>
<td>2 [-1, 5]‡</td>
</tr>
<tr>
<td>Father (median, interquartile range)</td>
<td>10 (4, 6)</td>
<td>10 (5, 15)</td>
<td>1 [-1.5, 4]‡</td>
</tr>
</tbody>
</table>

*Parenting Stress Index (Abidin, 1995) - subscale family stress with possible range 0-79.
†Paired mean difference.
‡Paired median difference.
§Paired percentage difference.

### Table II. Prevalence of dysphoria (mild depression) in the CF and control groups at baseline and follow-up

<table>
<thead>
<tr>
<th>Dysphoria (BDI-II)</th>
<th>Clinical cutoff</th>
<th>CF Group</th>
<th>Control Group</th>
<th>CF/Control Paired Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n Count</td>
<td>%</td>
<td>n Count</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>(≥13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mothers</td>
<td></td>
<td>45</td>
<td>20</td>
<td>45</td>
</tr>
<tr>
<td>Fathers</td>
<td></td>
<td>45</td>
<td>15</td>
<td>45</td>
</tr>
<tr>
<td>Both partners in a couple</td>
<td></td>
<td>45</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>(≥13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mothers</td>
<td></td>
<td>41</td>
<td>15</td>
<td>41</td>
</tr>
<tr>
<td>Fathers</td>
<td></td>
<td>39</td>
<td>7</td>
<td>39</td>
</tr>
<tr>
<td>Both partners in a couple</td>
<td></td>
<td>39</td>
<td>6</td>
<td>39</td>
</tr>
</tbody>
</table>

Dysphoria (BDI-II) - Beck Depression Inventory - Beck, 1996.
for dysphoria in the CF compared with the control group as a whole.

**DISCUSSION**

The overall finding was that there was no elevated rate of depression in the CF group of parents. However, examination of effects within predetermined strata for age revealed differences in those parents with a child of ≤9 months of age at baseline in contrast to parents with a child ≥10 months of age. This hypothesis-generating finding suggests that parents may be more vulnerable to depression when their child is diagnosed with a life-shortening condition during the first few months of life. Preliminary results from a study of mother-infant relationships in the context of newborn screening for CF support this contention.20

This study was designed to recruit a consecutive sample of incident CF case patients and their families within a defined time since diagnosis and to follow them prospectively. We aimed to assess families within 3 months of diagnosis, and we achieved this in 62%, with 82% assessed within 4 months. In practice, some of these children had complicated medical procedures that involved travel to specialist units in other parts of the country, which effectively precluded the families’ involvement in this study until the child’s condition had stabilized. Although 3 months was set for the time of the first interview, there was no reason to think that 3 months was clearly preferable to 4 months. A sensitivity analysis showed no difference in the effects observed when the late recruits were excluded from the analyses.

The design enabled effect-measure modification by the matching variables to be examined. This has not been done before, and only summary effects for the whole group are available elsewhere.7-9 The stratum-specific findings presented are not based on a priori considerations, but neither are they post hoc. Stratified analyses carry an assumption of uniform effects. To consider this assumption the first step is to examine stratum specific effects—if heterogeneity is found, then it should be reported as a finding and consideration should be given to whether the strata should be pooled or regarded separately. Small group sizes meant the data could be quite sparse in the eight strata created by the three matching variables. The advantage of using the Mantel Haenszel

### Table III. Prospective effect of CF/control group membership on dysphoria† in mothers and fathers after adjusting for matching variables and sparse data. Overall estimates and subgroups for upper and lower age strata at follow-up are displayed

<table>
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<tr>
<th>Pooled Effects BDI Time B</th>
<th>Number of participants with dysphoria</th>
<th>Number participants in each stratum</th>
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<th>Group Effects $RR_{MH}^*$</th>
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$RR_{MH}$ - Mantel Haenszel risk-ratio; Rothman and Greenland, 1998.
LL & UL - lower and upper limits for 95% confidence intervals.
$RR_{MH}^*$ - pooled Mantel Haenszel risk-ratio.
†Dysphoria - Beck Depression Inventory cut-off ≥13; Beck, 1996.
statistic here is that it remains robust in sparse data. The overall effect for the pooled strata was not significant; however, we have shown the importance of assessing the heterogeneity in the strata because this may be masked through pooling.

Matching on age was important, not only because the risks may be different in infancy, but also because it ensured comparability over a large age distribution up to 11 years. We used a caliper-matching strategy for age based on $\pm 3$ month criterion within a 6-month age span. Where the CF infant was <3 months of age at diagnosis, the available age span was necessarily reduced. This and the length of time taken to recruit a control child once he or she had been identified as a potential match resulted in a marginally older control group. Although the differences between the groups were small, we cannot rule out the possibility that this age difference influenced the effect in the parents of the younger children. We took care to establish as far as possible comparability across the groups by selecting controls with a systematic matching procedure from three general practice lists. Moreover, comparision across six key parameters showed no significant difference between the groups. It remains possible, however, that the groups did differ on other parameters not measured such as a history of depression in the parents.

A low clinical cutoff for mild depression allowed for examination of the spread of effect and risk for further dysfunction. The inclusion of fathers was a strong point of this study and has rarely been done. We did not specify biological parents, and step, foster, and adoptive parents were included as were those parents who separated before follow-up. In practice, only one family was excluded in the CF group because of being a single parent. If lone parents had been included in the sample at baseline, then we would have needed to control for one versus two parents as lone parenthood represents very different risks for depression. This would have placed a heavier burden on the analyses.

The results from this study indicate a need for further investigation to understand the mechanisms at play and the long-term implications for adaptation in the families of children with cystic fibrosis. It is well established that depression in mothers is disadvantageous to the parent-child bonding and subsequent development in children. This adverse combination is even more important to identify when the child is sick and the illness is progressive, as there are potential long-term implications for the psychological health of parents and their children. With the advent of newborn screening for CF in place in several parts of the Western world, and due to commence shortly in the UK, the vast majority of children with CF will be diagnosed in infancy and this may mean that more parents are vulnerable to depression. Any risks to parental mental health associated with newborn screening for CF need to be documented longitudinally and preventive strategies need to be developed to manage them.

The authors are grateful to all the families in this study who generously gave their time to participate in a collective endeavour. We would like to thank staff within the hospital CF centers and GP clinics located in the North West of England for their support and help in recruiting the families that took part. We would also like to thank our three anonymous reviewers for their helpful comments on the draft manuscript.

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50 Years Ago in The Journal of Pediatrics

INTRATHecal HYDROCORTISONE IN THE TREATMENT OF TUBERCULOUS MENINGITIS

Tuberculosis remains a global health hazard, with an annual incidence of 8.8 million cases worldwide and 1.8 million deaths.

Meningitis is a particularly severe form of tuberculosis, with death and severe neurological deficit being reported in a significant proportion of patients despite treatment. Rupture of a subependymal or parameningeal tubercle into the subarachnoid space initiates a cascade of inflammatory response that leads to complications such as intracranial vasculitis and communicating hydrocephalus. Adjunctive therapies to improve the clinical outcome of tuberculous meningitis have been studied for decades. The anti-inflammatory effect of corticosteroids remains the most biologically plausible way to abort the pathologic sequelae. Choremis et al reported in this journal 50 years ago their experience with the use of intrathecal corticosteroid in treating 82 children with tuberculous meningitis. They compared three different treatment regimens. In the first group of 24 patients, “standard” therapy of intramuscular and intrathecal streptomycin and isoniazid was given. The second group of 29 patients was given, in addition to the standard therapy, cortisone intramuscularly. In the third group of 29 patients, intrathecal streptomycin was replaced by intramuscular and/or intrathecal cortisone, which was given in addition to intrathecal corticosteroid in treating 82 children with tuberculous meningitis. They compared three different treatment regimens. In the first group of 24 patients, “standard” therapy of intramuscular and intrathecal streptomycin and isoniazid was given. The second group of 29 patients was given, in addition to the standard therapy, cortisone intramuscularly. In the third group of 29 patients, intrathecal streptomycin was replaced by intramuscular and/or intrathecal cortisone, which was given in addition to intrathecal corticosteroid in treating 82 children with tuberculous meningitis. The three groups, though not formally controlled, were comparable to each other. Using the patient’s general condition, resolution of electroencephalographic abnormalities, and changes in sugar and protein levels in the cerebral spinal fluid as outcome measures, the authors concluded that patients who received the third treatment regimen had the best clinical improvement, even though no statistical analysis was presented. The authors also pointed out that two cases allocated to the third treatment regimen, early blockage in the cerebral spinal fluid circulation was relieved by the cisternal infusion of hydrocortisone.

The treatment for tuberculous meningitis has changed since the study was published. The use of anti-tuberculous drugs in the intrathecal route is rarely indicated nowadays, and adjunctive dexamethasone given systemically rather than intrathecally has been reported as effective. A recently published prospective, randomized, placebo-controlled trial involving 545 patients over 14 years of age with tuberculous meningitis in two hospitals in Vietnam showed that adjunctive treatment with dexamethasone significantly reduced mortality rates. The burden of tuberculosis remains a global challenge, and research work similar to that by Choremis et al and Thwaites et al are essential in guiding us in the right direction.

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10.1016/j.jpeds.2006.09.007

REFERENCES
Prolonged QTc Intervals and Decreased Left Ventricular Contractility in Patients with Propionic Acidemia

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Objective  To investigate electrophysiological and functional signs of myocardial damage in patients with propionic acidemia (PA), an inborn error of metabolism caused by deficiency of propionyl CoA carboxylase (PCC).

Study design  In an observational longitudinal study 10 patients with PA (6 boys and 4 girls) ranging between 2.5 and 20.2 (median 9.0) years of age at last follow-up were investigated over a period of up to 20 (mean 7.4) years using 12-lead electrocardiograms (ECGs), 24-hour continuous ECG recordings, bicycle exercise testings, and echocardiography with special focus on repolarization abnormalities such as corrected QT interval (QTc) prolongation, ventricular dysrhythmias, and left ventricular systolic function.

Results  QTc interval was prolonged (>440 ms) in 70% of patients beyond infancy. Continuous ECG recordings revealed rhythm disturbances in 20% of patients. M-mode echocardiographic left ventricular function was reduced (fractional shortening [FS] <30%) in 40%. One patient showed signs of dilated cardiomyopathy.

Conclusions  The majority of patients with PA (even in clinically stable situations) have disturbances in cardiac electrophysiology that can contribute to cardiac complications. Possible mechanisms include effects of toxic metabolites or deprivation of essential substrates. To avoid life-threatening complications, we recommend regular cardiological evaluations in this group of patients. (J Pediatr 2007;150:192-7)

Propionic acidemia (PA) is a recessive disorder caused by a deficiency of propionyl CoA carboxylase (PCC), an enzyme involved in the catabolism of valine, isoleucine, methionine, threonine, cholesterol and odd-carbon numbered fatty acids, thymine, and uracil.¹ Mutations of both the PCCA gene mapped to chromosome 13q32 and the PCCB gene mapped to chromosome 3q13.3-q22 have been described.²,³ Accumulating propionyl-CoA or its metabolites may result in hypoglycemia, hyperammonemia, and hyperglycinemia.⁴-⁶ Different long-term complications occur and involve mainly the central nervous system, feeding difficulties, and metabolic crises in catabolic situations.⁷,⁸ Because of the great genetic heterogeneity² the clinical picture varies between severe early-onset forms manifesting during the first days of life, and mild late-onset variations, which show first signs during adulthood.

Cardiomyopathy and sudden cardiac death have been described as complications of several metabolic disorders.⁹,¹⁰ In patients with PA, these life-threatening complications are frequent.¹¹⁻¹⁵ Deficiencies in carnitine or selenium and acidosis are possible causes. Furthermore, electrophysiological changes such as prolongation of the QT interval, which has been observed in patients with PA,¹¹,¹⁶ can occur in patients with cardiomyopathy and can predispose them to life-threatening ventricular arrhythmias.¹¹,¹² However, electrophysiological changes have not been reported in this patient group.

The aim of this study was to characterize electrocardiographic and echocardiographic changes in patients with PA before to life-threatening arrhythmia or loss of ventricular function.

METHODS

Ten patients with PA followed by our institutions between July 2000 and December 2005 (Department of Pediatrics, Innsbruck Medical University, Austria, 9 patients; Children’s Hospital, Private Medical University, Salzburg, Austria, 1 patient) were included in this study. Age ranged between 1 day and 12 months at diagnosis, and

<table>
<thead>
<tr>
<th>ASD</th>
<th>Atrial septal defect</th>
<th>PCC</th>
<th>Propionyl CoA carboxylase</th>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
<td>QTc</td>
<td>Corrected QT interval</td>
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<td>Fractional shortening</td>
<td>VEB</td>
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<td>PA</td>
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between 2.5 and 20.2 (median 9.0) years at the latest follow-up investigation (Table I; available at www.jpeds.com). Time of follow-up ranged between 1.0 and 20.0 (mean 7.4) years. Diagnosis was established on the basis of urinary excretion of the characteristic organic acids in all patients, and it was confirmed by reduced enzymatic activity of PCC in fibroblasts (Dr Regula Baumgartner, Department of Pediatrics, University of Basel, Switzerland) and/or mutational analysis of the PCCA and PCCB genes in all but one patient (Table I).2,3,17 Three different homozygous mutations were present. Patients 2 and 3, 4 and 5, 6 and 7, and 8 and 9 are siblings, whereas patients 8 and 9 are cousins of patients 2 and 3. The mutation of patients 1 through 3 and 8 and 9 (reference 3) and of patients 7 and 8 (reference 2) have been published elsewhere.2,3 In all cases therapy consisted of restricted natural protein intake (1.1 to 1.5 g/kg daily), special amino acid supplementation (free of valine, leucine, methionine, and threonine, to achieve adequate protein intake for age), L-carnitine (50-100 mg/kg body weight/day), and vitamin supplementation. All patients grew well (between 10th and 97th weight percentile). Seizures in patients 4 and 5 were present. Diagnosis was established on the basis of urinary excretion of the characteristic organic acids in all patients, and repeated clinical investigations during routine follow-up examinations. Twenty-four-hour continuous ECG recordings were done in all patients at least once (maximum seven recordings per patient) using a Lifecard CF Holter recorder system (Del Mar Reynolds Medical, Hertford, UK). Follow-up recordings were performed in yearly intervals if rhythm disturbances were present. After an initial automatic processing of the data, an experienced observer reviewed the classification of abnormal beats (total number of ventricular ectopic beats [VEB], and total number of VEB occurring in couplets). Besides analysis of rhythm disorders, QTc at maximum heart rate was determined.

In patients >6 years of age, we performed upright, graded exercise testing on an ERG-900 bicycle ergometer (Ergoline, Bitz, Germany). The test protocol scheduled an initial 2-minute period with approximately 0.5 W/kg body weight (15, 20 or 25 W, respectively), followed by increments of 0.5 W/kg body weight every 2 minutes, until exhaustion. Each patient was verbally encouraged to continue exercising until his or her maximum voluntary exercise capacity was attained. After exercise, patients were immediately placed in the supine position to monitor ECG, heart rate, and blood pressure for 10 minutes. QTc was determined before, during exercise at the end of each workload level, and after exercise every 2 minutes for at least 10 minutes until heart rate returned to the resting value. The maximum QTc was selected from these measurements.

All patients underwent a complete transthoracic echocardiographic examination using a System Five echo machine (General Electric Vingmed Ultrasound, Horten, Norway). We performed two-dimensional guided M-mode measurements of the left ventricle to measure cardiac performance according to recommendations of the American Society of Echocardiography20; therefore we determined left ventricular end-diastolic, end-systolic, luminal, and wall diameters, and we calculated fractional shortening (FS). Anatomy and function of the mitral and aortic valve were assessed by two-dimensional echocardiography, color flow mapping, and pulsed-wave and continuous-wave Doppler recordings. Cardiomyopathy was classified as dilated on the basis of mor-
and function of the ventricles, when dilatation of both ventricles and poor pump function were present. All images were digitally stored as raw data with the EchoPac System, version 6.4.1 (General Electric Vingmed).

RESULTS

Maximum QTc was abnormal (>440 ms) in 70% of patients beyond infancy (patients 1-6, 10; Table II, Figure 1, and Figure 2; available at www.jpeds.com), and clearly prolonged (>460 ms) in 60% of patients (patients 1-6) in their standard 12-lead ECGs. In 2 of the 6 patients (patients 3 and 5), prolonged QTc at the initial examination at 3 and 7 years of age remained increased during follow-up, whereas in the other four patients an initially normal QTc (<440 ms) increased to prolonged values at 3, 13, 14, and 16 years of age, respectively (Figure 3). The four younger patients (patients 7-10) showed QTc values <460 ms at all investigations beyond infancy. At the last follow-up investigation, QTc was normal (410-440 ms) in 40% of patients, mildly increased (440-460 ms) in another 40%, and significantly prolonged (>460 ms) in 20%.

Interobserver reproducibility, which was calculated in seven patients, was 1.14% for QT measurements, and 1.11% for QTc determinations. No correlation between prolonged QTc values and routinely investigated biochemical variables (electrolytes including calcium and magnesium, blood gas analysis, ammonia concentrations, plasma aminoacids, and
patients did not exceed resting QTc measurements. Physical activity. However, QTc values of the five young patients during episodes of maximum heart rate as a result of merging of T and P waves disappeared. Individual maximum QTc values during exercise and during recovery were similar in all five patients. In the five younger patients, bicycle ergometry could not be performed because of technical reasons.

Alternatively, QTc was determined manually in all patients—since then. An 8-year-old girl, after a 2-week history of feeling “poorly” became acutely ill and succumbed to heart failure and ventricular fibrillation in 12 hours. Another 4 1/2–year-old girl became comatose during a simple infection because of a metabolic decompensation and died 2 days after admission as a result of arrhythmia. A 23-year-old woman presented with a 1-week history of shortness of breath caused by an adult-onset cardiomyopathy. Three further cases of dilated cardiomyopathy were reported, one of the case patients underwent liver transplantation, which also improved the diagnostic criteria of both PA and asymptomatic long-QT syndrome.

We followed a cohort of 10 pediatric patients with three different genotypes of PA longitudinally. The electrophysiological investigations confirmed the finding of prolonged QTc interval (>440 ms) in 70% of them, which is an independent risk factor for sudden cardiac death. Throughout childhood, QTc prolongation seems to fluctuate, but it tends to increase (Figure 3), and affected all patients >4 years of age, although in 3 of the 4 younger patients QTc intervals ranged below the upper normal limit.

In view of the two reported cases with fatal arrhythmia, the overall incidence of ventricular dysrhythmia in

**Figure 3.** QTc values from standard electrocardiograms of patients 4 (left) and 2 (right) were plotted against age. The trend lines show the increase of QTc length with age. The arrows indicate the upper normal limit of QTc.
our young patient group was low (20%) and no patient showed sustained ventricular tachycardia during the 24-hour Holter ECG. Sinus arrest and sinus bradycardia occurred in two siblings (patients 4 and 5) treated with valproic acid for seizures. The relationship between sinus arrest, which has not required treatment, and valproic acid remains unclear. In the same two patients, we observed isolated VEB, which were regarded as normal, and a couplet of VEB was detected once.

The most frequent ECG abnormality apart from QTc prolongation was preterminal T wave inversion in leads V6 to V6a, a sign of repolarization abnormality, which was associated with QTc prolongation and older patient age. Because of genetic heterogeneity and phenotypic variability in PA, the frequency of ECG alterations may be different in other study populations.

Our observations are not obviously connected to the metabolic state of the patients, as most of the investigations in our cohort were performed in stable out patient under control conditions. We observed no obvious correlation between routinely investigated biochemical variables (blood gas analysis, ammonia concentrations, plasma amino acids, and acylcarnitine profile) and the electrophysiological results. However, QTc prolongation in patients with PA may be related in some direct way to the underlying metabolic defect. Some authors claim that deficiency of carnitine may induce electromyocardial changes. It seems possible that this is an underlying mechanism, although all of our patients were supplemented with L-carnitine and regular determinations of free carnitine in blood were normal (data not shown). Notably, total and free carnitine concentrations were reported to be low in heart muscle of a patient with PA and cardiac hypertrophy at postmortem despite carnitine supplementation and repeatedly normal plasma carnitine levels.

Three further mechanisms seem possible. First, there might be a direct toxic effect from one or a combination of metabolites present in the metabolism of these patients, causing prolonged repolarization of the myocardium over time. Similar mechanisms are described for several drugs. Second, an intracardiac depletion of an essential—that is, an anaplerotic—substrate in the intermediary metabolism, with trapping of another, might cause energy deficiency in the myocardium and lead to pathology. A third possibility for the prolongation of QTc intervals could be the inhibition of the oxidative phosphorylation in mitochondria by propionyl CoA in similar to the way methylmalonic acid affects respiratory chain complex II and causes nephropathy. The myocardium is similar to the way methylmalonic acid affects respiratory oxidazation phosphorylation in mitochondria by propionyl CoA. QTc prolongation might be a direct toxic effect from one or a combination of metabolites present in the metabolism of these patients, causing repolarization abnormalities in myocardium over time.

The possibility that some patients with PA have a genetic abnormality, that is, a variant of the congenital long-QT syndrome, as proposed by Schwartz et al and Kakavand et al seems unlikely, as the QT prolongation is not permanently present in the patients with PA, and the younger patients seem less affected than the older ones, suggesting that this is an ongoing progressive process. On the other hand, it is possible, that the presence of ion-channel polymorphisms causing minor alterations in ion-channel function, like the D85N polymorphism in the KCNE1 gene, which has been associated with drug-induced QTc prolongation, plays a modifying role. Further specific studies to elucidate the mechanism involved would be of interest.

We recommend regular electrocardiographic and echocardiographic investigations in all these patients including at least yearly ECGs with determination of QTc and regular 24-hour Holter monitoring to detect life-threatening, but treatable ventricular arrhythmias.

We wish to thank all colleagues involved in the medical care of our patients.

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50 Years Ago in The Journal of Pediatrics

SPONTANEOUS PNEUMOTHORAX IN THE FIRST TEN DAYS OF LIFE

Howie VM, Weed AS. J Pediatr 1957;50:6-15

By the 1950s, the transition of early newborn care from home to hospital in the United States was well established. Hospital care afforded ready access to newer technologies such as radiographic imaging, which in turn was a means of revealing pathologic findings to clinicians in a new context. Extra-pleural air accumulation, once considered an autopsy diagnosis, was now being identified in viable neonates, raising new questions about treatment and prognosis.

Howie and Weed's retrospective case series provided clinicians with an initial perspective of pneumothorax in the early neonatal period. The authors subdivided their patients into 4 categories—mantle, alternating, bilateral or tension pneumothorax—on the basis of radiographic and clinical criteria. They noted a wide range of reported incidence, likely related to selection bias and lack of standardized techniques for newborn infant chest radiography. Howie and Weed's series focused on symptomatic term and late pre-term infants and preceded the era of positive pressure assisted ventilation for the management of newborn respiratory distress. However, their case series demonstrated the importance of identifying and treating tension pneumothorax through “prompt aspiration and continuous drainage by underwater trap.” They also reported on several infants successfully treated by using direct needle aspiration of the extra-pleural air collection. Although they also cite oxygen therapy as a component of management, they did not specifically refer to the notion of nitrogen washout.

Howie and Weed did note an association between pneumothorax and other pulmonary pathologies, including atelectasis and interstitial emphysema. Later case series reflected this as well, proposing needle aspiration, chest tube placement, nitrogen washout, or careful observation, depending on the severity and the presence of tension phenomena. By the 1970s, the epidemiology of extra-pleural air leak shifted from term to pre-term infants, as treatments for hyaline membrane disease and mechanical ventilation techniques became more widespread.

In the 21st century, we still understand pneumothorax in the early neonatal period as a protean phenomenon that may require anything from careful observation to chest tube placement. Because of the lack of prospective trials to date, Howie and Weed’s approach remains a relevant component of our management.

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10.1016/j.jpeds.2006.07.039

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Figure 2. The standard ECG of patient 1 at 20 years of age shows borderline prolongation of QTc interval (447 ms) and preterminal T wave inversion in leads II, aVF, and V₄ to V₆.
A term baby girl was born via cesarean section because of a nonprogressive labor, with Apgar score of 10 at 1 and 5 minutes. Her birth weight was 3310 g. Meconium-stained amniotic fluid was noted, but the baby was vigorous and had normal physical examination at birth. She is the first-born child to parents who are first-degree cousins of Arab ethnicity. The mother is known to have factor V-Leiden deficiency, and she had a history of four unexplained early-stage miscarriages. She was treated with low-molecular-weight heparin during pregnancy. There was no report on polyhydramnion during the pregnancy. The father had a history of cow’s milk allergy. There are no known metabolic or genetic disorders in their families.

INITIAL PRESENTATION

The baby was doing well for the first 3 days. She received cow’s milk–based formula and gradually switched to exclusive breast feeding on the third day. On her fourth day of life, she presented with multiple yellowish-watery stools. She had clinical signs of mild dehydration without fever or vomiting, and her vital signs were normal. The abdomen appeared neither tender nor distended, and the rest of her physical examination was normal. The laboratory findings revealed hypernatremia of 151 mEq/L, and severe metabolic acidosis: blood pH, 7.11; HCO₃⁻, 8.2 mEq/L; and base excess of −21.5. There was no leukocytosis, and the serum level of C-reactive protein was normal.

HOSPITAL COURSE

Working Diagnosis: Infectious Diarrhea and Dehydration-Induced Metabolic Acidosis?

The infant was treated with intravenous fluids as well as antibiotics after obtaining blood and stool cultures, assuming an infectious etiology. After 24 hours of rehydration therapy, the diarrhea, dehydration, and hypernatremia resolved; however, the severe metabolic acidosis persisted: blood pH, 7.27; HCO₃⁻, 9.5 mEq/L, and base excess, −17.5. This discrepancy between the rapid response to rehydration and the intractable metabolic acidosis raised the possibility of alternative diagnoses.

Metabolic Acidosis

The differential diagnosis of metabolic acidosis is wide, and the first diagnostic step should be the calculation of serum anion gap (sAG; calculated as: [Na⁺ – (HCO₃⁻ + Cl⁻)]). Increased sAG indicates overload of an acid with an additional anion, suggesting clinical conditions such as lactic acidosis, ketoacidosis, and amino or organic acidemia. A normal sAG metabolic acidosis implies a decreased H⁺ excretion or excessive HCO₃⁻ losses, as a result of either renal or gastrointestinal causes. In children and adults the upper limit of normal sAG is 12 mEq/L, whereas a higher threshold is used in infants (16 ± 4 mEq/L).¹

In our case, the sAG level was borderline (sAG = 16 mEq/L); therefore, both normal and increased anion gap metabolic acidosis etiologies were approached. For an increased sAG etiology, there were no clinical or laboratory findings of sepsis, the metabolic acidosis persisted long after the initial dehydration had resolved, and serum lactate was normal, thus excluding lactic acidosis. Although there was a known consanguinity, there was no family history of inborn errors of metabolism and physical examination showed no dysmorphic features. Laboratory evaluation to exclude amino or organic acidemias was negative. The absence of ketonuria, and normal blood glucose levels, excluded ketoacidosis. Because increased sAG etiologies were excluded, normal AG metabolic acidosis etiologies were approached. As the diarrhea seemed to resolve, renal tubular acidosis (RTA) was the major working diagnosis at this stage.

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Renal Tubular Acidosis

RTA is characterized by normal sAG hyperchloremic metabolic acidosis resulting from either impaired HCO₃⁻ reabsorption or impaired H⁺ excretion. In proximal RTA (type 2) the threshold for bicarbonate reabsorption in the proximal tubule is lower than normal (15-16 mEq/L rather than 22-23 mEq/L). Because 85% of the filtered bicarbonate is normally reabsorbed in the proximal tubule, high doses of oral bicarbonate are needed to normalize the HCO₃⁻ serum level in patients with proximal RTA. In these patients, serum bicarbonate levels will not reach the normal range, despite provision of very large amounts of bicarbonate. On the other hand, even without administration of bicarbonate, the serum level will not drop below 15 to 16 mEq/L (the proximal tubule threshold for HCO₃⁻ reabsorption). In the present case, the serum HCO₃⁻ level was substantially below that level (<10 mEq/L). After intensive bicarbonate supplementation, the serum level was within the normal range (23 mEq/L). These findings made the diagnosis of proximal RTA unlikely. In addition, proximal RTA is rarely isolated; it is usually a part of Fanconi’s syndrome, which causes other proximal tubule reabsorption abnormalities (e.g. glycosuria, phosphaturia, and aminoaciduria). These abnormalities were absent in this case.

In distal RTA (type 1), the distal tubule cells are unable to secrete H⁺ to the tubule lumen because of abnormal H⁺/Na⁺ exchanger. Normally, the distal tubule cells secrete H⁺ ions coupled with NH₃ to form NH₄⁺, which is excreted in the urine as NH₄⁺/Cl⁻. This distal tubule urine acidification mechanism allows alleviation of metabolic acidosis, a function that can be assessed by the calculation of the urine anion gap (uAG), calculated as: (Na⁺ + K⁺) – Cl⁻. In normal subjects, in conditions of metabolic acidosis, the increased excretion of NH₄⁺/Cl⁻ results in negative uAG (excess of Cl⁻) and a low urine pH. In contrast, patients with distal RTA present with alkaline urine pH, and zero or positive uAG. In our case, during metabolic acidosis, the increase of urine pH was alkaline (5.0), whereas the uAG was negative (~21.8 mEq/L), which contradicts the diagnosis of distal RTA. In addition, serum potassium levels are frequently abnormal in RTA. Therefore, the laboratory findings in our case did not match the characteristic presentations the RTA types. This, along with the persistent diarrhea, made a gastrointestinal tract etiology highly probable.

Diarrhea

Infectious diarrhea, the most common identified cause of diarrhea in the first week of life, was ruled out based on negative stool samples for bacteria, parasites, and viruses. The volume of diarrhea reached 150 to 200 mL/kg/day, apparently ceased with fasting (60 mL/kg/day), and recommended on breast-feeding; thus, an osmotic diarrhea was presumed. Stool sample analysis can provide supportive findings for identifying the mechanism of diarrhea; osmotic versus secretory. Osmotic diarrhea is characterized by lower pH (<5.0), lower sodium concentration (<70 mEq/L), and positive reducing substances. In the present case, stool sample examination revealed a sodium content of 61 mEq/L, potassium of 50 mEq/L, chloride of 57 mEq/L, pH of 6, and mildly positive reducing substances.

Two congenital carbohydrate malabsorption disorders can present with severe osmotic diarrhea within the first few days of life: congenital lactase deficiency and glucose-galactose malabsorption. Both are rare autosomal recessive disorders. Because the diarrhea did not resolve on hydrolyzed formula (Neocate®) containing glucose polymer, an etiology of disaccharidase deficiency was unlikely. Subsequently, the infant was fed a carbohydrate-free formula (RCF, Ross Carbohydrate Free®) with no resolution of the diarrhea or metabolic acidosis. This ruled out glucose-galactose malabsorption, and any other carbohydrate malabsorption.

At this stage, the baby was nil per os, receiving total parenteral nutrition. In contrast to the previous fasting trials, the diarrhea persisted. This raised the suspicion that some of the watery diarrheal stools were previously mistaken for urine because of their clear nature without any content. Rectal nasogastric (NG) tube insertion revealed a large amount of clear watery diarrhea. Therefore, the working diagnosis was protracted diarrhea of infancy (PDI). The causes of PDI can be classified into two categories based on the findings of intestinal biopsy: PDI with normal villi (without villus atrophy), and PDI with villus atrophy. In the category of normal villous PDI, congenital ion transport defects cause secretory diarrhea presenting at birth. The most common congenital ion transport defect is the chloride-bicarbonate exchanger, in which HCO₃⁻ is not secreted into the gastrointestinal tract lumen, leading to alkalosis. Obviously, the severe metabolic acidosis in our case did not support this diagnosis. In addition, the fecal chloride concentration, which did not exceed the fecal sodium level, did not support the diagnosis of congenital chloride diarrhea. Congenital sodium diarrhea, a disorder of the intestinal H⁺/Na⁺-exchanger, is characterized by hyponatremia, alkaline diarrhea, and high concentration of stool sodium. In the other congenital ion transport defects (sodium co-transporters), abnormal reabsorption of sodium is involved, which usually results in hyponatremia, unlike our case. Therefore, an ion transporter defect was unlikely. Other reported causes of protracted diarrhea with normal villi include heparan sulphate deficiency, glycosylation defect, and a mutation in the neurogenin-3, a protein that is required for endocrine-cell development in the pancreas and intestine.

Protracted diarrhea of infancy with villous atrophy can be a result of infectious or post-infectious enteropathy, and autoimmune or allergic enteropathy, the IPEX syndrome (i.e., Immune dysregulation, Polyendocrinopathy, Enteropathy, X-Linkage). In these disorders, an immune process is involved, and histologically the villus atrophy is characterized by T-cell infiltration. Based on the report by Cuenod et al, the etiology of villous atrophy may be classified as immune-mediated or developmental. PDI with villous atrophy but without an inflammatory infiltrate is caused by two primary
structural enteropathies: microvillus inclusion disease (MID) and tufting enteropathy. MID is a severe enteropathy, the second most common cause (following infectious) of protracted diarrhea starting at the first few days of life, although, few may present later up to 2 months of age, whereas, tufting enteropathy usually presents later, in the first few months of life. MID is characterized by an abnormal accumulation of periodic acid-Schiff (PAS) positive material in the apical cytoplasm of epithelial cells, an increase in “secretory granules” by electron microscopy, and the presence of microvillous-lined vacuoles, or inclusions, within the apical cytoplasm of surface epithelial cells. It is hypothesized that the PAS stain abnormality and the electron microscopy secretory granules represent the same phenomenon. The characteristic feature of tufting enteropathy is the presence of focal epithelial “tufts” composed of closely packed enterocytes on light microscopy.3

The next diagnostic step therefore was to perform intestinal biopsies, which were retrieved from the duodenum by upper endoscopy. Mucosal samples examined by light and electron microscopy were compatible with MID. Figure 1 shows CD10 (1A), PAS (1B), and alkaline phosphatase (1C) stains compatible with MID. Figure 2 shows the duodenal electron micrograph from this patient showing the typical findings of MID.

Because all patients with MID have poor prognosis and remain dependent on parenteral nutrition, the only treatment option for them is small bowel transplantation. Ruemmele et al have recently reported a survival rate of 86% after intestinal transplantation in seven patients with MID.15

**AMBULATORY COURSE**

The baby, who is now 18 months old, is thriving on total parenteral nutrition and is dependent on 50 mEq/L of bicarbonate day. An attempt of oral feedings with hydrolyzed formula failed.

The mother has recently delivered a preterm (36 weeks) girl, who developed watery diarrhea and metabolic acidosis on the 3rd day of life. Subsequent duodenal and rectal biopsies demonstrated the characteristic findings of MID.

It has been proposed that the primary molecular defect in MID involves membrane trafficking of immature/differen-
Similar to other reports of occurrence among siblings, our cases strongly suggest an autosomal recessive inherited pattern. In addition to siblings’ data, a cluster of unrelated cases of MID has been reported in the Navajo population (Arizona, US). This clustering of cases suggests a “founder effect,” in which rare genes in the general population are more frequent in a genetically isolated population that has shared ancestor genes. No specific genes have been identified or have been proposed as participants in the pathogenesis of MID.

References


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Gaucher Disease: Progressive Mesenteric and Mediastinal Lymphadenopathy Despite Enzyme Therapy

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A 5-year-old male with Gaucher’s disease type 3 developed progressive mesenteric and mediastinal lymphadenopathy over 12 months, despite enzyme replacement therapy, contributing to the development of a protein-losing enteropathy. These complications are unique, indicating poorly accessible, differentially responsive compartments in patients with Gaucher’s disease who are receiving enzyme therapy. (J Pediatr 2007;150:202-6)

Gaucher’s disease is an autosomal recessively inherited disorder resulting from mutations in the gene encoding the lysosomal enzyme, acid β-glucosidase (GCase, glucocerebrosidase). The consequent defective activity of GCase results in accumulation of glucosylceramide (glucocerebroside) in cells of monocyte/macrophage lineage. These lipid-laden macrophages, Gaucher cells, reside within the liver, spleen, bone marrow, and lymph nodes, leading to hepatosplenomegaly, anemia, thrombocytopenia, destructive bone disease, and lymphadenopathy, respectively.

Three phenotypes of Gaucher’s disease have been described, based on the absence, or presence and severity, of neurological signs. Gaucher’s disease type 1, the non-neuronopathic variant that accounts for ~90% of all cases of the disease in the Western world, is restricted to the visceral organs. Gaucher’s disease types 2 and 3 are considered neuronopathic variants of the disease and are distinguished by the age at onset and rate of progression of neuronopathic signs. Gaucher’s disease type 2 has early onset (~3–6 months), severe, rapidly progressing neurological deterioration and visceral disease, followed by death at 1 to 2 years. Gaucher’s disease type 3 has later onset of neurological disease, including characteristic eye movement abnormalities (saccadic initiation defects) and varying degrees of visceral disease. The neuronopathic diseases are thought to result from CNS storage of the deacetylated analogue of glucosylceramide, glucosylsphingosine,1 and subsequent neuronal death.

Regular, periodic intravenous infusions of imiglucerase (Cerezyme) have proven safe and effective in ameliorating the visceral manifestations of Gaucher’s disease.2 Excellent hematologic responses and reductions in hepatosplenomegaly occur within 0.5 to 2 years of such enzyme therapy. However, the diminished or lack of response of lung or CNS involvement, respectively, to enzyme therapy has highlighted the presence of restricted or inaccessible compartments to the intravenously administered drug.

A 5-year-old Caucasian male with Gaucher’s disease type 3 is reported with progressive mesenteric lymphadenopathy as a result of massive sequestration of Gaucher cells within lymph nodes despite enzyme replacement therapy. The progressive mediastinal and mesenteric lymphadenopathy and the related severe protein-losing enteropathy with its associated complications are unique and indicate another restricted compartment.

CASE REPORT

This previously reported Caucasian male3 was the 7-lb, 11-oz product of a term pregnancy to a 34-year-old gravida III, para II mother and a 35-year-old father. The pregnancy was complicated by preeclampsia, and a cesarean section was performed for failure to progress. At birth the infant was 19.75 inches in length (25th percentile).

Hepatosplenomegaly was noted at 9 months. Evaluation showed elevated serum aminotransferase levels, anemia, and thrombocytopenia. Magnetic resonance imaging (MRI) of the abdomen confirmed hepatomegaly (581 mL; ~2.5× normal) and splenomegaly (294 mL; ~16× normal). Significantly, no lymphadenopathy was apparent. A
liver biopsy showed typical Gaucher cells, but these were not observed on the bone marrow biopsy. Brain MRI and skeletal radiographs were normal.

Gaucher’s disease was documented by severely decreased acid β-glucosidase activity in peripheral leukocytes. DNA sequencing of GBA showed two alleles; one encoding three mutations (D409H, L444P, and A456P) in exons 9 and 10, and the other allele encoded a K79N mutation in exon 4.3 At that time, the patient was developmentally delayed in gross and fine motor skills and speech, but without neurological signs. However, at 2 years of age, he was noted to have saccadic initiation failure and hyperreflexia, predominately in the lower extremities.

Enzyme therapy (60 U/kg/2 weeks) with mannose-terminated recombinant glucocerebrosidase (imiglucerase [Cerezyme], Genzyme Corporation, Cambridge, Mass) was initiated shortly after the diagnosis. Marked improvement was evident at 4.5 years of age by decreased hepatosplenomegaly (2.5/1100 to 1.4/1100 normal, and 16/1100 normal to 5.7/1100 normal, respectively), and the biomarkers, chitotriosidase (from 39,845 to 11,031 nmol/hour/mL; normal 4–76 nmol/hour/mL), acid phosphatase (from 39.4 to 19.1 U/L; normal 3.1–7 U/L), and angiotensin converting enzyme (from 250 to 160 U/L; normal 13–100 U/L) levels. The hematocrit (from 31% to 39.5%; normal 35%–45%) and platelet counts (from 78 to 271 K/μL; normal 135–466 K/μL) also improved. Imiglucerase-specific antibodies were not detected.

At 1.5 years of age, the patient was evaluated for intermittent wheezing and dyspnea that clinically improved after bronchodilator and inhaled corticosteroid therapy but that never required oral corticosteroid therapy. Chest computerized tomography (CT) evaluation showed significant mediastinal lymphadenopathy, focal “ground glass” opacities, and alveolar infiltrative disease. No calcifications or bronchiectasis were observed. Diagnostic testing for pulmonary infection was unrevealing. Bronchoscopic examination revealed a normal airway anatomy without compression of the large or medium airways. Bronchoalveolar lavage revealed 5% to 10% lipid-laden macrophages, consistent with Gaucher cells.

Repeat chest CT at 5 years of age (Figure 1) revealed progression of lung disease, demonstrated by miliary nodularity and diffuse alveolar infiltrates, in addition to mediastinal and hilar lymphadenopathy. Polysomnography demonstrated mild hypoventilation without signs of obstructive or central apnea, without desaturation. Spirometry and plethysmography were not obtained because the patient was too young to cooperate. The etiology of his pulmonary disease was presumed to be a result of Gaucher’s disease and asthma.

At 3 years of age, intermittent bouts of diarrhea and abdominal bloating led to abdominal MRI that showed large, nodular, soft tissue masses posterior and anterior to the left renal vein. By 4 years of age, these masses encased the aorta, superior mesenteric artery, inferior vena cava, renal vein, and mesentery, resulting in a mass effect on the vasculature but no obstruction to circulation. The mesenteric masses were palpable on physical examination, but only minor lymphadenopathy was present elsewhere.

The mesenteric masses further progressed in size by 5 years of age (Figure 2). Alpha-fetoprotein, β-human chorionic gonadotropin, homovanillic acid, and vanillic mandelic acid were within normal ranges. Laparotomy revealed extensive adenopathy throughout the root of the mesentery (Figure 3). The diffuse nature of the adenopathy and its location throughout the mesentery made a surgical solution untenable. Multiple biopsies of the mesenteric masses demonstrated nodular histiocytic lesions surrounded by a dense fibrous capsule and rims of lymphoid tissue, consistent with lymph node replacement (Figure 4A,B). The lesions had
dense aggregates of CD-68 (a macrophage marker) positive, single and multinucleated cells with prominent reactive changes and occasional mitotic activity. The centers of the lesions contained proteinaceous eosinophilic material and large histiocytes, some resembling Gaucher cells (Figure 4C). Intracellular and extracellular lipid, cholesterol clefts, and dystrophic calcification were visible throughout the biopsied materials. Ultrastructural examination revealed cells with membrane-bound tubular-appearing structures characteristic of Gaucher cells (Figure 4D). There were no signs of malignancy. No microorganisms were visualized. Gram and acid-fast bacillus stains were negative. The liver biopsy was essentially normal.

Cytomegalovirus and Epstein-Barr virus infections were excluded by polymerase chain reaction or serological studies. *Actinomyces israelii* was cultured from only one of several biopsied mesenteric lymph nodes. Stool viral and bacterial cultures were negative, but antigen studies on two occasions were positive for *Clostridium difficile*. Long-term (8 weeks) intravenous penicillin was followed by oral penicillin (1 year) and metronidazole therapy to treat *A. israelii* and *C. difficile* infections, respectively. However, the lymphadenopathy and abdominal distention were unchanged.

Hypoalbuminemia was noted at 5 years of age and since that time, serum albumin levels have ranged from 1.7 to 2.6 g/dL (normal 3.4–5.2 g/dL). Normal hepatic synthetic function, renal evaluation demonstrating absent proteinuria, and normal serum immunoglobulin levels with the exception of a mildly diminished IgG level, combined with large amounts of
stool α-1-antitrypsin, indicated a protein-losing enteropathy. Numerous serious complications have resulted, including ascites and peripheral edema. More recently, a severe, progressive, and difficult-to-control thrombophilia, with significant thrombus formation in the right internal jugular, brachiocephalic, and subclavian veins developed, likely a complication of the protein-losing enteropathy.4

At 5.5 years of age, the frequency of recombinant enzyme infusions was increased to 60 U/kg/week. Despite this change and symptomatic management, the patient continues to exhibit marked abdominal distention without a reduction of the intra-abdominal lymphadenopathy. In addition, he continues to exhibit progression of mediastinal lymphadenopathy and pulmonary disease. An enteral, medium chain triglyceride–containing diet has been instituted, which has stabilized the hypoalbuminemia, but the other sequelae of the protein-losing enteropathy continue to progress.

**DISCUSSION**

Since the inception of enzyme therapy for Gaucher's disease, selected tissues including lung, CNS, and lymph nodes have had diminished/absent responses compared with other tissues.5,6 This indicates that certain organs are poorly accessible to intravenously administered enzyme therapy products; however, the mechanistic bases are not well understood.

The present case is the second report of a child with Gaucher's disease exhibiting massive mesenteric lymphadenopathy. In comparison, Lim and colleagues reported a 13-month-old female with Gaucher's disease type 3 who, despite enzyme replacement therapy, developed significant mesenteric lymphadenopathy that had been stable in size for 3 years when reported.7 The present case is much more severe, demonstrating progression of the mesenteric masses over 2 years,

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**Figure 4.** Histology of biopsied mesenteric masses/lymph nodes. A, A dense fibrous capsule and rim of lymphoid tissue (arrowheads). The peripheral (P) and central portions (CN) are magnified in (B) and (C), respectively. B, Replacement of major parts of the lymph node with engorged large storage cells, many of which resembled Gaucher cells (C). C, These Gaucher cells contained fine to coarsely fibrillar Periodic Acid Schiff positive material (arrows). D, Ultrastructural examination revealed degenerating cells containing lipid droplets (arrowheads) and abundant fibrillar inclusions typical for Gaucher's disease. Original magnification ×40 (A); ×200 (B); ×400 (C); ×12,000 (D).
coincident with similar progression of mediastinal lymphadenopathy, protein-losing enteropathy, thrombophilia, and parenchymal and interstitial lung disease, despite relatively mild neurological manifestations. No other cause, other than Gaucher’s disease, has been discovered to explain these events.

The clinical course in this patient further illustrates that lymph nodes, including mesenteric and mediastinal nodes, and the lungs are relatively sequestered or poorly accessible to intravenous enzyme therapy. The protein-losing enteropathy and related consequences appear to be a result of lymphatic obstruction, resulting in inadequate drainage of the intestinal lymphatic tissue and increased hydrostatic pressure in the lacteals, particularly in the face of normal liver biopsy and liver synthetic function studies. The \textit{C difficile} or \textit{A israelii} might have contributed to the development of the lymphadenopathy, but it preceded these infections and did not decrease or resolve with adequate therapy for either potential infection.

Increased intensity of enzyme therapy (60 U/kg/week) appears ineffective for the current patient. Alternatives of substrate reduction therapy and bone marrow transplantation are being considered, but each has significant potential complications for this patient. The diarrhea induced by miglustat in most Gaucher’s patients (~90%) would be unwelcome in this patient. Stem-cell transplant would be complicated by the existing lung involvement. Moreover, the apparent poor vascularization of the enlarged nodes may inhibit access by donor macrophages following transplant.

With the advent of enzyme therapy, the Gaucher’s disease phenotypes have been transformed into an evolving spectrum of continuing disease involvement. Consequently, unanticipated and unexpected results of partial treatment of specific, poorly accessible organs complicate disease management. Such unusual cases highlight the need for comprehensive therapies in affected patients, as well as the presence of poorly accessible/differentially responsive compartments in patients with Gaucher’s disease and other lysosomal diseases receiving enzyme therapy or other therapeutic modalities.

REFERENCES

Recipient Twin Limb Ischemia with Postnatal Onset

ROLAND SPENCER BROADBENT, MB, CHB

After the occurrence of 3 local cases of limb ischemia in newborn twins, we reviewed the literature to investigate this combination systematically. This review reveals a distinct condition: postnatal onset limb ischemia affecting recipient twins in twin-twin transfusion syndrome. *(J Pediatr 2007;150:207-9)*

Twin-twin transfusion syndrome (TTTS) occurs during fetal life when vascular communications between monochorionic twins feed more blood to one twin, the recipient, than to the other, the donor. Perinatal limb ischemia in twins has not been recognized as a distinct entity, apart from a small series of antenatal-onset cases.1 The 3 cases reported here, all postnatal cases in recipient twins, prompted a review of the literature where postnatal-onset limb ischemia occurred in a twin. The hypothesis was that like the index cases, limb ischemia in the published cases would occur in TTTS recipients.

**PATIENTS AND METHODS**

**Case 1**

This female recipient twin was born at 25 weeks gestation, after severe polyhydramnios in this twin and oligohydramnios in the other fetus. She weighed 700 g, and her monochorionic co-twin weighed 510 g. A low umbilical artery catheter (UAC) was inserted and infused with heparinized saline 1 U/mL. Intravenous indomethacin 0.2 mg/kg was given at 7 hours. At 24 hours, the right leg became discolored. The catheter was removed, after which the leg reperfused normally. Another catheter was then inserted into the same umbilical artery, and again the leg became ischemic. Leg pulses were absent to palpation and Doppler examination. The catheter was withdrawn until the tip was in the umbilical artery within the anterior abdominal wall. An arteriogram (Figure) demonstrated complete occlusion of the right external iliac artery. Removing the catheter produced no improvement. Arterial flow reappeared on day 3, and the limb recovered fully.

**Case 2**

Signs of TTTS developed at 19 weeks in this monochorionic pregnancy. Severe polyhydramnios in the larger twin and oligohydramnios (stuck twin) in the other twin persisted until the membranes ruptured after amnioreduction at 24 weeks. The recipient twin weighed 610 g, 200 g more than her cotwin. A low UAC was inserted and infused with heparinized saline 1 U/mL. Mild hypotension was treated with low-dose intravenous dopamine. Three doses of intravenous indomethacin, (0.1 mg/kg, 0.2 mg/kg, and 0.2 mg/kg) were given in the first 30 hours. At 36 hours of age, the left leg became ischemic, and the arterial catheter was removed. Doppler ultrasound imaging revealed absent arterial flow in the left external iliac artery and distally. Despite intravenous thrombolytic therapy with tissue plasminogen activator (t-PA), extensive gangrene developed, and an above-knee amputation was required.

**Case 3**

This infant was the larger of monochorionic twins. Antenatal scans at 24 weeks showed severe polyhydramnios in this and stuck twin in the other. Labor began after amnioreduction at 25 weeks, and delivery was by caesarian section. The recipient twin weighed 680 g. A low UAC was inserted and infused with heparinized saline 1 U/mL. No indomethacin was given. On the second day, the right leg became white from the mid-thigh to the toes, resolving after 5 minutes. Several hours later, the right leg became dusky; the UAC was withdrawn, whereupon the leg returned to its normal color.

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<td>t-PA</td>
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<td>UAC</td>
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Methods

We searched the literature for twins with neonatal-onset limb ischemia to ascertain the characteristics of this combination. Peer-reviewed articles were found by searching Pubmed and Google Scholar, using “twin” along with “fetus,” “newborn,” “limb,” “arm,” “leg,” “necrosis,” “ischemia,” and “gangrene” in various combinations. The most recent search was done in July 2006. Authors were contacted to obtain further information. Cases were accepted if there was evidence of limb ischemia with onset in the newborn period in a twin. TTTS was accepted where this was stated in the article, or where there was polyhydramnios around the larger (recipient) and oligohydramnios around the smaller (donor) twin, with nothing to indicate dichorionicity. The recipient has the higher hemoglobin level of the 2. Severe polycythemia was considered to be present if so reported or if hematocrit was >70 or hemoglobin was >220 g/L.

RESULTS

The literature search revealed 13 cases of neonatal onset limb ischemia in 1 of twins. The sex of both twins was known in 8 cases, all like-sexed except for the twin with meningitis reported by Letts et al.2 Sepsis appears to be the cause of that case of ischemia; in the interest of clarity, that case is excluded here. The Table reports 15 cases, the remaining 12 from the literature and the 3 reported here. TTTS was accepted where this was stated in the article, or where there was polyhydramnios around the larger (recipient) and oligohydramnios around the smaller (donor) twin, with nothing to indicate dichorionicity. The recipient has the higher hemoglobin level of the 2. Severe polycythemia was considered to be present if so reported or if hematocrit was >70 or hemoglobin was >220 g/L.

DISCUSSION

Carr et al1 reported 6 prenatal cases of limb ischemia in TTTS and noted that some, but not all, had polycythemia. All were recipient twins, although the authors did not draw attention to this fact. The present report demonstrates that postnatal-onset limb ischemia in twins also occurs in TTTS.
Both in utero and ex utero, it is the recipient that is affected; hence the term recipient twin limb ischemia (RTLI).

Cases 8, 11, 13, and 15 show that postnatal-onset RTLI does occur without an arterial catheter in place, although an arterial catheter was present in 10 cases. Where the location of the catheter was known (in cases 1, 2, 3, and 6), it was same side as the ischemia. In case 1, the ischemia resolved when the initial catheter was removed but recurred when it was replaced. In case 3, the ischemia resolved as soon as the catheter was withdrawn. These findings support the hypothesis that UACs played a part in these ischemic episodes. Judging from case 6, the period of risk extends into the second week.

Intra-arterial thrombus was reported in cases 8, 9, 12, 13, and 15. The filling defects in the arteriogram (Figure) also suggest intra-arterial thrombus in case 1. Thrombolytic treatment with t-PA was unsuccessful in case 2 but successful in cases 9 and 15.

Severe polycythemia is a risk factor for neonatal limb ischemia, but it is not the primary etiology in RTLI; it occurred at onset in only 2 of 10 cases. Indomethacin administration preceded onset of the ischemia in 4 cases, but this is insufficient information to indicate whether indomethacin increases the risk of limb ischemia.

**REFERENCES**

We describe an association between congenital patent ductus venosus and hyper immunoglobulin E syndrome in a pair of siblings. The possibility that this is a separate entity or a genetically linked association is discussed. (J Pediatr 2007;150:210-2)

Congenital portosystemic shunts (PSS) are rare malformations involving the vasculature leading into and out of the liver. The clinical consequences of a shunt from the portal vein to the systemic veins are portal hypertension and hepatic encephalopathy. Congenital shunts have been occasionally associated with other malformations that include heterotaxia, Goldenhar’s syndrome, biliary atresia, mental retardation, and genitourinary malformations.1

Congenital patent ductus venosus (PDV) is a rare disorder involving a shunt from the fetal umbilical vein to the inferior vena cava. Spontaneous closure of the ductus venosus is the rule in normal infancy, usually immediately or within the first few weeks after birth.2 There is no evidence linking hypercoagulable states and the development of PDV at present. Familial congenital PDV has been reported only 3 times to date, in 2 case reports involving 2 sets of 3 siblings each and in 1 set of twins without underlying diseases or syndromes.3-5

Hyper immunoglobulin E (IgE) syndrome (HIES) is a rare primary immunodeficiency syndrome characterized by recurrent staphylococcal infections, pneumonia, eczema, prominent jaw with coarse facies, and markedly elevated serum IgE levels, usually >2000 IU/L. Most cases are sporadic; however, families with autosomal dominant (AD) and autosomal recessive modes of inheritance have been described.6

An association between HIES and vascular liver anomalies has not been described. We present 2 siblings with identical portosystemic hepatic shunt–PDV and HIES and discuss whether these 2 entities are separate or share a common genetic pathway.

CASE REPORT

Patient 1

A 5-year-old male previously diagnosed with HIES was admitted to our hospital because of a staphylococcal hepatic abscess and peritonitis. The diagnosis of HIES was established on the basis of clinical features, including recurrent skin abscesses, eczemas, recurrent oral thrush, prominent teeth, and upper jaw with coarse facies. Immunologic workup revealed IgE levels usually above 4000 units/mL (normal < 230). Other immunoglobulin levels were within the normal range.

Absolute eosinophil counts were in excess of 2000/mL (normal < 800). Neutrophil function testing did not detect chemotactic or bacteriocidic abnormalities; superoxide formation was normal. There was no response to a Candida sp. skin test, and the response to the diphteria tetanus (DT) skin test was normal. Lymphocytic subpopulation and response to mitogen was normal.

Past history revealed 4 normal siblings and a younger sister described below as patient 2. The patient’s parents are of non-consanguineous Arab origin. His father has a

<table>
<thead>
<tr>
<th>AD</th>
<th>Autosomal dominant</th>
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<tr>
<td>HIES</td>
<td>Hyper immunog lobulin E syndrome</td>
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<tr>
<td>IgE</td>
<td>Immunoglobulin E</td>
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<tr>
<td>PDV</td>
<td>Patent ductus venosus</td>
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<tr>
<td>PSS</td>
<td>Portasystemic shunt</td>
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</table>

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hypereosinophilic syndrome with recurrent episodes of cellulitis and cutaneous fungal infection. The father’s abdominal ultrasound scan demonstrated a normal liver with normal liver vasculature.

Physical examination revealed microcephaly, prominent teeth and upper jaw as mentioned, and prominent ears. The liver was not palpable; the spleen was palpated 2 cm below the costal margin. A neurologic and developmental assessment revealed that the boy had mild mental retardation with attention deficit disorder with hyperactivity. No neurologic focal findings or asterixis were demonstrated.

Relevant laboratory test results include alanine amino transferase of 39 units/L (norm < 41), aspartate aminotransferase of 52 units/L (norm < 38), mildly increased alkaline phosphatase of 744 units/L (norm 145-320), and albumin of 4.1 g/dL (norm 3.8-5.4). The ammonia was constantly elevated above 200 units/L (normal range 9-33 U/L). The result of echocardiography was interpreted as normal. A liver biopsy specimen from an area of nodularity disclosed congestion without evidence of inflammation and without fibrosis. The electroencephalography result was normal. During the post-laparotomy assessment, contrast-enhanced abdominal computed tomography and ultrasound Doppler examination demonstrated a shunt from the left portal vein through a PDV to the infradiaphragmatic inferior vena cava. The right portal vein was hypoplastic (Figure).

**Patient 2**

Briefly, patient 2 is the 9-year-old sister of patient 1. Her history was unremarkable except for a periodontal abscess and Thalassemia minor. Because of an enlarged liver palpated 2 cm below costal margins and palpable spleen (edge) on physical examination and a brother known to have congenital PDV and HIES, she was evaluated for the latter 2. Her facial characteristics show prominent teeth and upper jaw very similar to her brother’s. Neurologic and developmental assessment was normal. She, like her sibling, had never had cyanosis.

Her blood test revealed elevated ammonia of 130 units/L, normal alanine amino transferase, aspartate aminotransferase, and alkaline phosphatase. Her total IgE is 1896 units/L (normal 9-33 U/L), mildly increased alkaline phosphatase, and absolute eosinophil count was 390/mL. Liver ultrasonography with Doppler scanning demonstrated similar findings to those of her brother—a large shunt through a PDV to a hypoplastic right portal vein. Neither patient had evidence of a hypercoagulable state by laboratory evaluation. Cytogenic analysis was performed on peripheral blood lymphocytes of patient 1 and patient 2 by use of G-bands by trypsin using Giemsa (GTG) banding techniques. No major deletion or translocation of the 4q region did was detected.

**DISCUSSION**

The rarity of coexisting PDV and HIES in 2 siblings and the fact that their father also has elevated IgE with eosinophilia suggests that this is not a coincidence. This association raises several possibilities: a single genetic defect leading to both syndromes, 2 different syndromes occurring in the same individuals, or that the presence of 1 syndrome might lead to the other.

PDV is considered a rare sporadic phenomenon. The only prior evidence for a genetic cause as a possible cause comes from 2 previous reports, each containing 3 siblings (described in the introduction). A second clue is that congenital PSS is not rare in dogs, suggesting that a genetic mutation may cause PSS. The fact that 2 siblings share the same shunt without evidence of a hypercoagulable state lends credence to a genetic hypothesis for PDV.

HIES on the other hand, has been clearly linked to an underlying genetically inherited abnormality in some patients. Grimbacher et al described 19 kindreds with 57 individuals affected with HIES in an AD mode of inheritance. In some of the patients they found linkage to 4q21-4q21.1 locus. A candidate gene is not known. The 2 siblings and their father could fit a hyper IgE-associated AD trait.

One possible explanation of the association we have described is that this is a previously unpublished genetic syndrome. Another possible connection between these 2 rare entities could be 2 rare genetic traits in the same family. In highly consanguineous populations, such as exist in the Middle East, it is not uncommon to find 2 genetic traits in the same family.

Another possible genetic cause may involve a mutation or deletion to a common locus involving more than genes. Regulation of fetal vasculature and closure of intrauterine shunts is often mediated by prostaglandins. The prostaglandin D2 synthase (the hematopoietic type among the 3 isoenzymes) is located downstream from the hyper IgE locus on the 4q21-4q22 locus (omim 602598). Prostaglandin D2 is a cofactor in the development regulation of the fetal circulation in animal models.9-12
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Erythromycin for treatment of feeding intolerance in preterm infants

To the Editor:

Nuntnarumit et al1 reported that intermediate doses of oral erythromycin (EM) were effective and safe for the treatment of feeding intolerance in preterm infants. Their protocol used an intermediate oral dose instead of intravenous low-dose EM. Inclusion criteria were relatively loose. Infants were enrolled for treatment at 6 to 8 postnatal days, and even infants in the control group reached full feeding at a median age of 13 days (range 9-15). Therefore the infants had only mild feeding intolerance. In such a population of premature infants, a degree of feeding intolerance occurs within the first week of life and can possibly improve on stimulation with a small volume of breast milk, a so-called gut stimulation protocol.2 We doubt if these infants required EM treatment or if their protocol would be as effective in premature infants with severe feeding intolerance.

We have accumulated experience with EM treatment for feeding intolerance in premature infants since we began to use it in 1998.3 We now use an intravenous loading dose of EM (30 mg/kg/d) for 2 days, followed by an oral maintenance dose (6 to 10 mg/kg/d) when enteral feeding can be started. EM is continued until full feeding (120 ml/kg/d) is well established. The mean time to full feeding is 11 days. We use EM only in premature infants with feeding intolerance lasting beyond 2 weeks of age.

One complication of EM treatment is hypertrophic pyloric stenosis (HPS). The authors described that, unlike using the antimicrobial dose of EM, no infant had HPS. Several points merit discussion. First, the study that reported infants with HPS induced by the antimicrobial dose of EM were near- or full-term infants.4 Not understanding how the pyloric muscle of the premature infant responds to EM, one can not deduce that an intermediate-dose EM will not induce HPS in premature infants. Second, there is a strong link between systemic EM use in infants and subsequent HPS, with the highest risk in the first 2 weeks of age. We should be very cautious in using EM treatment during this time frame. Third, premature infants with HPS do not exhibit typical symptoms, and it is well known that onset of vomiting presents after the corrected age for a “term baby” instead of the third postnatal week, as do full-term infants.5-7 Fourth, pyloric length and muscle thickness evaluated by ultrasonography in premature infants with HPS are less than the established pyloric muscle index for diagnosis of hypertrophy.5,7-9 The article failed to define diagnostic criteria of HPS for premature infants. Fifth, some infants with HPS may not be identified. Based on rates of 2.65% in infants treated with EM up to 2 weeks of age and 0.25% if untreated, 42 infants would need EM treatment to cause a HPS case.4

We suggest a further randomized controlled trial to clarify efficacy and safety of oral EM in severe feeding intolerance.

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To the Editor:

We read with interest the article by Nuntnarumit et al1 showing that oral erythromycin is effective and safe for treatment of feeding intolerance in preterm infants. We would like to highlight three issues:

1) We are intrigued that even though erythromycin halved the duration of time to enteral feeds in the intervention group, it did not make any difference to the duration of hospital stay.
2) It is inappropriate to reassure readers by commenting that there was no significant difference in adverse effects, namely sepsis, especially when the study was not adequately powered to address this outcome.
3) Our population of babies who suffer from feeding intolerance is more immature (<28 weeks), unlike the more mature babies in the study, and hence we question the applicability of these results to a wider population.

We believe a large, randomized controlled trial is required to find the long-needed answer of what role erythromycin has to play in resolving this problem.

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10.1016/j.jpeds.2006.09.026
To the Editor:

We appreciate the comments regarding our article and would like to thank Drs. Su and Lin for their relevant observations and concerns. All comments are well taken and should be kept in mind in the interpretation of results of erythromycin (EM) trials in preterm infants. We agree that the infants in our study probably had mild feeding intolerance, but the response to EM was dramatic in treated infants as demonstrated by significantly reduced gastric residual and number of feeds withheld within 24 to 48 hours after initiation of the treatment. In cases with more severe feeding intolerance, a higher dose and increased duration of EM may be required.

To our knowledge, no serious complications were reported in more than 184 newborn infants who received EM for prophylaxis or treatment of feeding intolerance either in observational or randomized control trials. Certainly, further studies of dose-response relationship and correlation with blood levels of EM are needed to determine the therapeutic dosage, as well as serious side effects such as hypertrophic pyloric stenosis in this particular group.

We also appreciate the questions and concerns of Drs. Mascarenhas and Lal. The following are responses:

1. The length of hospital stay was not significantly different between the two groups (median 46 days in the group receiving EM vs 60 days in the group receiving placebo, \( P = .07 \)). The small sample size was not sufficient to detect a difference. In this study, infants in the group receiving EM reached full enteral feeding approximately 1 week earlier than in the control group. However, there are many factors that affect the hospital course of premature infants, which could explain the lack of difference in length of stay.

2. We do not recommend routine use of EM. Definitely, larger clinical trials are needed to confirm its safety and efficacy. We have mentioned in the discussion that the calculated sample size in this study has sufficient power to evaluate the efficacy of EM, but not the incidence of side effects.

3. Approximately one fourth of infants in the group receiving EM in our study were below 28 weeks’ gestation. We believe the very preterm infants might have different responses than more mature infants.

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Carotid artery imaging in adult patients: a systematic review

To the Editor:

I read with interest the recent editorial commenting on the findings of a pilot study by Paradisis et al. on the use of milrinone for low systemic flow in the very low birth weight (VLBW) neonate during the immediate postnatal period. Barrington and Dempsey discuss the management options practiced by most neonatologists to treat cardiovascular compromise in this patient population and point out the lack of available evidence supporting the efficacy of these treatment strategies. The authors conclude that there is no published evidence that the use of dopamine (or that of epinephrine or dobutamine) to treat cardiovascular compromise in the VLBW neonate during the immediate postnatal period decreases mortality and improves outcomes, and that it is essential that we now design and perform the right trials to determine whether the use of present treatment modalities is helping these patients rather than harming them. These conclusions correctly sum up the major issues that have plagued the field of neonatal hemodynamics for many years. However, although the description of these major concerns is thought-ful, certain aspects of the discussion on developmental cardiovascular physiology and the effects of vasopressors and inotropes in this patient population warrant a more comprehensive analysis of the frequently conflicting findings.

First, the major debate regarding neonatal cardiovascular compromise and its management centers around the question of whether systemic blood pressure adequately represents the status of systemic, and thus cerebral, blood flow (CBF) in the VLBW neonate with its unique hemodynamic profile in the immediate postnatal period. However, because the lower limits of the normal gestational- and postnatal-age dependent blood pressure range in this patient population are not known and because there are no data available on the effectiveness of the current management, no definite answer can be given to
this question. Instead, Barrington and Dempsey propose that because “there is a very poor relationship between blood pressure and systemic blood flow” and because treatments of hypotension may elevate blood pressure but decrease perfusion,” measurements of flow rather than those of blood pressure should guide management of neonatal circulatory compromise in the VLBW neonate. Although assessment of systemic blood flow is very important in VLBW neonates, especially during the early transitional period, the notion that blood pressure changes in response to treatment are useless in the assessment of systemic and CBF has to be challenged.

As stated by the authors, findings of studies using superior vena cava (SVC) blood flow measurements as a surrogate to CBF suggest that cardiac output (systemic blood flow) rather than blood pressure is the most important factor determining CBF and demonstrate that decreases in systemic blood flow in the VLBW neonate during the first postnatal days are indeed associated with central nervous system injury and poor neurodevelopmental outcome. Furthermore, an earlier study using near infrared spectroscopy (NIRS) also could not find a significant relationship between blood pressure and CBF. However, other investigators using NIRS have found that hypotensive preterm infants on the first postnatal day have low CBF, and that increases in blood pressure in response to dopamine, or epinephrine administration are associated with increases in CBF. In addition, available data indicate that a number of VLBW neonates present with a pressure passive cerebral circulation. Finally, more recent findings using NIRS and functional echocardiography indicate that CBF is clearly affected by both blood pressure and cardiac output in the VLBW neonate during the immediate transitional period. Thus, although long-term outcome data are not available, following the blood pressure response to vasopressor/inotrope administration is practical, as it can provide indirect information on organ blood flow changes (see below). Obviously, the best approach would be to continuously monitor both blood pressure and systemic blood flow in these patients. Unfortunately, the tools available to assess systemic blood flow in the VLBW neonate at the bedside (functional echocardiography and NIRS) have significant limitations. In addition, they have primarily been employed for research purposes, and it is unknown whether their routine clinical use would affect outcome.

Second, the statement that “dopamine appears to elevate blood pressure predominantly by vasoconstriction at the expense of systemic blood flow” is based on a study that used fixed doses of dopamine at 10 and 20 mcg/kg/minute instead of titration of the medication to achieve the desired hemodynamic response. As mentioned earlier, a recent randomized controlled trial comparing the effects of dopamine with epinephrine on blood pressure and CBF in VLBW neonates during the first postnatal day found that, when titrated to achieve an “optimal” blood pressure response, both medications successfully increased blood pressure and CBF at low- to moderate doses. If, at the applied dose range, either dopamine or epinephrine had increased blood pressure by primarily causing a generalized vasoconstriction, CBF would likely have not increased. The authors of this study concluded that their findings provide additional support for the use of mean blood pressure changes as a consistent outcome measure of systemic organ blood flow” in the VLBW neonate during the first postnatal day. Findings of another observational study lend further support to this notion.

Third, as for the inotropic effects of dopamine, several studies have demonstrated that, if carefully titrated, moderate to moderately high doses of the drug increase blood pressure while cardiac output is either increased or unchanged. However, as stated in the editorial, some patients may indeed respond to dopamine with an increase in blood pressure and a decrease in cardiac output. It is of note though that the study cited in the editorial to support the notion that “dopamine may increase blood pressure but decrease perfusion” suffers from significant shortcomings including its small patient population and its use of left cardiac output to assess systemic blood flow in patients with a large patent ductus arteriosus (PDA). As for its findings, out of the 14 preterm neonates enrolled in this study, all responded to medium doses of dopamine with increases in blood pressure, whereas left cardiac output increased in 10 patients by 50 mL/kg/minute and decreased in the remaining 4 patients by only around 20 mL/kg/minute. Again, as all of the patients had a PDA, their left cardiac output cannot be used to assess the changes in systemic blood flow. Taking all the available information into consideration, I do support the notion that dopamine, particularly at high doses, may increase blood pressure at the expense of systemic perfusion in certain patients. However, this type of hemodynamic response is not the rule, especially if the drug is carefully titrated.

In summary, the main conclusions of the editorial about the lack of evidence of the effectiveness of the management of neonatal hypotension with vasopressor/inotropes and the need for well-designed randomized controlled trials evaluating medium- and long-term outcomes of VLBW neonates treated for hypotension and/or low systemic blood flow are of great importance. However, the notions that blood pressure is more or less a useless hemodynamic parameter for the assessment of the cardiovascular status of the VLBW neonate in the immediate postnatal period and that dopamine is a pure vasopressor without positive inotropic effects are not supported by the available findings in the literature.

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10.1016/j.jpeds.2006.09.023

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It has been clear for many years that the unique structural and functional limitations of the neonatal myocardium make it extremely susceptible to increases in afterload, which commonly lead to a decrease in cardiac output.3 Unfortunately, the uncontrolled studies quoted by Dr Seri all have the same limitations that he notes for Zhang et al that left ventricular output (LVO) has been the primary flow measured and that sample sizes have tended to be small (eg, LVO reported in 4 infants).4 The largest of those studies in fact demonstrated exactly what we were stressing—that there is no direct relation between blood pressure and cardiac output.5 That study did not have any measurements taken before the institution of therapy for “hypotension” (defined as a mean arterial pressure less than 30 mm Hg, regardless of gestational or postnatal age) and certainly did not demonstrate that “careful titration” of dopamine doses will produce an increase in systemic perfusion. Similarly, the study by Lundstrom et al,6 the only controlled study of dopamine in the newborn infant that has shown an increase in LVO, did not show any increase in CBF despite the elevation in blood pressure, therefore confirming that cerebral vasoconstriction may occur with dopamine infusion. Three other controlled trials of dopamine in the newborn infant that have included measurements of “cardiac output” have all shown that dopamine, when carefully titrated to achieve the desired increase in blood pressure, caused a decrease in LVO7-9; only one measured right ventricular output9 and showed a decrease in right ventricular output when dopamine was “carefully titrated” to achieve the desired blood pressure response.

It is clear from this discussion that there are many unanswered questions. We maintain that many low birth weight infants with low numerical values for blood pressure do not require treatment. The challenge is to determine how to select those infants who may benefit from intervention and then to determine which interventions may improve their outcomes.

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Reply

To the Editor:

We thank Dr Seri for his thoughtful consideration of our editorial, and we certainly recognize his expertise and major contributions in this area. However, we wish to further clarify some of the issues raised. Blood flow through any vascular bed is determined by the perfusion pressure and the vascular resistance. Thus, cerebral blood flow (CBF), for example, is determined by cerebral vascular resistance and the cerebral perfusion pressure (generally mean arterial pressure minus either central venous or intracranial pressure, whichever is the greater). Published data do not demonstrate that CBF is partly determined by cardiac output but do show a correlation between the two because CBF is a major component of systemic perfusion1 and therefore of venous return to the heart: thus, cardiac output is partly determined by CBF.

Any drug that causes cerebral vasoconstriction has a risk of reducing CBF, even if the perfusion pressure is increased, and such a response to dopamine (an extremely potent α-adrenergic agonist) has been demonstrated in some experimental animal preparations.2