

THE JOURNAL OF PEDIATRICS

September 2005 • Volume 147 • Number 3

Copyright © 2005 by Mosby, Inc.

NOTES FROM THE ASSOCIATION OF MEDICAL SCHOOL PEDIATRIC DEPARTMENT CHAIRS, INC.

- PEDIATRIC SUBSPECIALTY TRAINING FELLOWSHIPS AT CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER (CCHMC) **277**
William F. Balistreri, MD, Alan Jobe, MD, and Thomas F. Boat, MD, Cincinnati, Ohio

EDITORIALS

- IMPROVEMENTS IN HEALTHCARE: HOW CAN WE CHANGE THE OUTCOME? **279**
James D. Acton, MD, and Dr. Uma Kotagal, MBBS, MSc, Cincinnati, Ohio

- DAILY ACTIVITY AND DISEASE STATUS IN CYSTIC FIBROSIS: AN IMPORTANT AREA FOR RESEARCH **281**
Rosalind L. Smyth, MD, Liverpool, United Kingdom

- TOWARD BETTER EVIDENCE FOR PARENT TRAINING PROGRAMS FOR AUTISM SPECTRUM DISORDER **283**
John G. Frohna, MD, MPH, Ann Arbor, Michigan

- TRANSITION/ADAPTATION IN THE DELIVERY ROOM AND LESS RDS: "DON'T JUST DO SOMETHING, STAND THERE!" **284**
Alan H. Jobe, MD, PhD, Cincinnati, Ohio

- SAY NO TO DRUGS? **286**
Pasquale J. Accardo, MD, and Jennifer A. Accardo, MD, Richmond, Virginia, and Baltimore, Maryland

MEDICAL PROGRESS

- ASSESSMENT AND TREATMENT OF ACUTE ASTHMA IN CHILDREN **288**
Bradley E. Chipps, MD, and Kevin R. Murphy, MD, Sacramento, California, and Omaha, Nebraska

COMMENTARY

- IMPROVING SUBSPECIALTY HEALTHCARE: LESSONS FROM CYSTIC FIBROSIS **295**
Michael S. Schechter, MD, MPH, and Peter Margolis, MD, PhD, Providence, Rhode Island, and Chapel Hill, North Carolina

ORIGINAL ARTICLES

- COMBINING IMMUNOREACTIVE TRYPSINOGEN AND PANCREATITIS-ASSOCIATED PROTEIN ASSAYS, A METHOD OF NEWBORN SCREENING FOR CYSTIC FIBROSIS THAT AVOIDS DNA ANALYSIS **302**
Jacques Sarles, MD, Patrice Berthézène, MSc, Christian Le Louarn, BSc, Claude Somma, MD, Jean-Marc Perini, MD, Michael Catheline, MD, Sophie Mirallié, MD, Karine Luzet, BSc, Michael Roussey, MD, Jean-Pierre Farriaux, MD, Jacques Berthelot, MD, and Jean-Charles Dagorn, PhD, Marseille, Lille, Nantes, and Angers, France

NEWBORN SCREENING FOR CYSTIC FIBROSIS IS ASSOCIATED WITH REDUCED TREATMENT INTENSITY	306
Erika J. Sims, PhD, Jonathan McCormick, MRCPCH, Gita Mehta, MA MPhil, and Anil Mehta, FRCPC FRCP (Edin), Dundee, United Kingdom	
CYSTIC FIBROSIS BIRTH RATES IN CANADA: A DECREASING TREND SINCE THE ONSET OF GENETIC TESTING	312
Annie Dupuis, PhD, David Hamilton, PhD, David E. C. Cole, MD, PhD, and Mary Corey, PhD, Toronto, Ontario, and Halifax, Nova Scotia, Canada	
GESTATIONAL AND NEONATAL CHARACTERISTICS OF CHILDREN WITH CYSTIC FIBROSIS: A COHORT STUDY	316
Filippo Festini, RN, BA, BSN, Giovanni Taccetti, MD, Teresa Repetto, MD, Maria Francesca Reali, MD, Silvia Campana, DSc, Gianfranco Merçni, BSc, Lore Marianelli, MD, and Maurizio de Martino, MD, Florence, Italy	
SEX DIFFERENCES IN HABITUAL PHYSICAL ACTIVITY AND LUNG FUNCTION DECLINE IN CHILDREN WITH CYSTIC FIBROSIS	321
J. Schneiderman-Walker, MSc, D. L. Wilkes, MSc, L. Strug, PhD, L. C. Lands, MDCM, PhD, S. L. Pollock, MSc, MD, H. C. Selvadurai, MD, PhD, J. Hay, PhD, A. L. Coates, BEng, MDCM, and M. Corey, PhD, Toronto and St. Catharines, Ontario, and Montreal, Quebec, Canada, and New South Wales, Australia	
MILD TO MODERATE CYSTIC FIBROSIS IS NOT ASSOCIATED WITH INCREASED FRACTURE RISK IN CHILDREN AND ADOLESCENTS	327
Alisha J. Rovner, BA, Babette S. Zemel, PhD, Mary B. Leonard, MD, MSCE, Joan I. Schall, PhD, and Virginia A. Stallings, MD, Philadelphia, Pennsylvania, and Baltimore, Maryland	
COMMENTARY	
FIRST BACTERIAL INFECTION AS AN ALTERNATIVE CLINICAL END POINT FOR REGULATORY APPROVAL OF AGENTS TARGETING THE PRIMARY CYSTIC FIBROSIS DEFECT	332
Donald R. VanDevanter, PhD, Seattle, Washington	
ORIGINAL ARTICLES	
A CONTROLLED TRIAL OF A TRAINING COURSE FOR PARENTS OF CHILDREN WITH SUSPECTED AUTISM SPECTRUM DISORDER	335
Helen McConachie, MA, MPhil, PhD, Val Randle, BSc, PhD, Donna Hammal, BSc, MSc, and Ann Le Couteur, BSc, MBBS, FRCPsych, FRCPC, Newcastle, United Kingdom	
VARIABLES ASSOCIATED WITH THE EARLY FAILURE OF NASAL CPAP IN VERY LOW BIRTH WEIGHT INFANTS	341
Amer Ammari, MB, BS, Mandhir Suri, MD, Vladana Milisavljevic, MD, Rakesh Sahni, MD, David Bateman, MD, Ulana Sanoeka, MD, Carrie Ruzal-Shapiro, MD, Jen-Tien Wung, MD, and Richard A. Polin, MD, New York, New York	
SHORT- AND LONG-TERM CARDIOVASCULAR EFFECTS OF MIXED AMPHETAMINE SALTS EXTENDED RELEASE IN CHILDREN	348
Robert L. Findling, MD, Joseph Biederman, MD, Timothy E. Wilens, MD, Thomas J. Spencer, MD, James J. McGough, MD, Frank A. Lopez, MD, and Simon J. Tulloch, MD, on behalf of the SLI381.301 and .302 study groups, Cleveland, Ohio, Boston, Massachusetts, Los Angeles, California, Maitland, Florida, and Rockville, Maryland	
REGIONAL VARIATION IN ICU CARE FOR PEDIATRIC PATIENTS WITH ASTHMA	355
Susan L. Bratton, MD, MPH, Folafoluwa O. Odetola, MD, Jamie McCollegan, BS, Michael D. Cabana, MD, MPH, Fiona H. Levy, MD, MBA, and Heather T. Keenan, MDCM, PhD, Salt Lake City, Utah, and St. Louis, Missouri	

continued on page 6A

PEDIATRICIANS' SCREENING URINALYSIS PRACTICES	362
Colin M. Sox, MD, MS, and Dimitri A. Christakis, MD, MPH, Boston, Massachusetts, and Seattle, Washington	
REDUCED NOCTURNAL BLOOD PRESSURE DIP AND SUSTAINED NIGHTTIME HYPERTENSION ARE SPECIFIC MARKERS OF SECONDARY HYPERTENSION	366
Tomáš Seeman, MD, PhD, Daniela Palyzová, MD, Jiří Dušek, MD, PhD, and Jan Janda, MD PhD Prof, Prague, Czech Republic	
SLEEP DISTURBANCE AND RAGE ATTACKS IN OPSOCLONUS-MYOCLONUS SYNDROME: RESPONSE TO TRAZODONE	372
Michael R. Pranzatelli, MD, Elizabeth D. Tate, C-FNP, MN, William S. Dukart, MD, Mary Jo Flint, MD, Michael T. Hoffman, MD, and Amy E. Oksa, MD, Springfield and Elmhurst, Illinois, Ronceverte, West Virginia, Overland Park, Kansas, and Dickinson, North Dakota	
INLET PATCH: HETEROTOPIC GASTRIC MUCOSA—ANOTHER CONTRIBUTOR TO SUPRAESOPHAGEAL SYMPTOMS?	379
Sahasini Macha, MD, Sushma Reddy, MD, Raja Rabah, MD, Ronald Thomas, PhD, and Vasundhara Tolia, MD, Detroit, Michigan	
HOME NOCTURNAL HEMODIALYSIS IN CHILDREN	383
Denis F. Geary, MB, MRCP(UK), FRCP(C), E. Piva, RN, J. Tyrrell, RN, M. J. Gajaria, BSc, CDP, G. Picone, MSW, L. E. Keating, BA, MSc, and E. A. Harvey, MD, FRCP(C), Toronto, Ontario, Canada	
GRAND ROUNDS	
SLEEP TERRORS IN CHILDHOOD	388
Thornton B. A. Mason II, MD, PhD, and Allan I. Paek, MBChB, PhD, Pennsylvania, Philadelphia	
50 YEARS AGO IN <i>THE JOURNAL OF PEDIATRICS</i> —CONGENITAL SPINAL DERMAL SINUSES	392
Sarah S. Long, MD, Philadelphia, PA	
CLINICAL AND LABORATORY OBSERVATIONS	
CONTROLLED SLEEP RESTRICTION FOR RHYTHMIC MOVEMENT DISORDER	393
Tamar Etzioni, BSc, Neri Katz, MD, Eli Hering, MD, Sarit Ravid, MD, and Giora Pillar, MD, PhD, Haifa, Holon, and Tirat Hacarmel, Israel	
CONTINUOUS GLUCOSE MONITORING IN ADOLESCENTS WITH CYSTIC FIBROSIS	396
Craig Jefferies, FRACP, Melinda Solomon, MD, Kusiel Perlman, MD, Neil Sweezey, MD, and Denis Daneman, MD, Toronto, Ontario, Canada	
FAILURE OF CONVENTIONAL STRATEGIES TO IMPROVE NUTRITIONAL STATUS IN MALNOURISHED ADOLESCENTS AND ADULTS WITH CYSTIC FIBROSIS	399
Daina Kalnins, MSc, RD, Mary Corey, PhD, Lynda Ellis, RN, Paul B. Pencharz, MB, ChB, PhD, FRCPC, Elizabeth Tullis, MD, FRCPC, and Peter R. Durie, MD, FRCPC, Toronto, Ontario, Canada	
OVERWEIGHT AND OBESITY IN Δ F508 HOMOZYGOUS CYSTIC FIBROSIS	402
Dagmar Kastner-Cole, MRCP, Colin N. A. Palmer, PhD, Simon A. O'gston, PhD, Anil Mehta, FRCP, and Somnath Mukhopadhyay, PhD, Dundee, Scotland, United Kingdom	

INSIGHTS

CONGENITAL LEFT BRACHIOCEPHALIC VEIN AND SUPERIOR VENA CAVA ANEURYSMS IN AN INFANT 405

Akihisa Nitta, MD, Hiroshi Suzumura, MD, Kenichi Kano, MD, and Osamu Arisaka, MD, Mibu, Japan

CURRENT BEST EVIDENCE

CLINICAL RESEARCH ABSTRACTS FOR PEDIATRICIANS 406

LETTERS

THE ROLE OF SMALL BOWEL BACTERIAL OVERGROWTH IN INFANTILE COLIC 410

Jay A. Hochman, MD, and Cathy Simms, RN, Atlanta, Georgia

IMPROVING CARE FOR ASTHMA 411

Miles Weinberger, MD, Iowa City, Iowa

Michael D. Cabana, MD, MPH, Ann Arbor, Michigan 411

REPLY 412

Sharon R. Smith, MD, and Robert C. Strunk, MD, Hartford, Connecticut, and St. Louis, Missouri

READER SERVICES

INFORMATION FOR READERS 10A

ANNOUNCEMENTS 11A

CHANGE OF ADDRESS FORM 326

OPPORTUNITIES AVAILABLE 12A

GUIDE FOR AUTHORS

available at www.jpeds.com



PEDIATRIC SUBSPECIALTY TRAINING FELLOWSHIPS AT CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER (CCHMC)

WILLIAM F. BALISTRERI, MD, ALAN JOBE, MD, AND THOMAS F. BOAT, MD

The increasing public demand for highly specialized, disorder-specific care of children is not being met.¹ To close this gap, departments of pediatrics must recruit and promote excellence in academic subspecialty training for the investigators and teachers of tomorrow. Thus the goal of fellowship training is to prepare subspecialists for a successful academic career, recognizing that subspecialty issues are multidimensional; subspecialists must be prepared to provide high-quality child health care, educate future health care researchers, providers, and acquire new knowledge.²

In recognition of these issues, the American Board of Pediatrics (ABP) changed the training requirements leading to subspecialty certification for fellows beginning their training after July 1, 2004 (see www.abp.org). The new requirements emphasize mentored "career development" with evaluation of trainees at a local level and require early decision-making by trainees regarding their career goals and their ultimate role on the academic "team." These changes are an opportunity to break away from the traditional model of "one size fits all" fellowship training.³ Programs can create individualized development plans and reconfigure fellowships to accommodate an array of career goals (master clinician, productive researcher, superb teacher) and provide flexible training that prepares the trainee to meet current and projected needs and aspirations (Figure 1; available online at www.jpeds.com). This, in turn, can lead to development of varied and enriched training opportunities with academic potential that could attract trainees with a wide range of interests.

The goal of the Department of Pediatrics at Cincinnati Children's Hospital Medical Center (CCHMC) is to produce subspecialists who are recognized as being exceptionally well trained for academic careers. Thus our obligation is to recruit outstanding candidates and offer expanded training opportunities in basic and clinical research with training in education and other skills of value to pediatrics. We describe our plan to incorporate these principles and the ABP guidelines into all Pediatric Subspecialty Training Programs at our institution.

THE PSTC

The revised ABP requirements specify that a fellow must satisfy specific criteria for clinical training, complete core academic requirements, and produce a scholarly written work. Each subspecialty program director (PD), division director, and department is responsible for developing the content and for evaluation of "scholarly

activities." The ABP requirements state that the ability of a program to provide a satisfactory scholarly experience for all trainees must be evaluated periodically; however, no requirements for internal review of subspecialty training and mechanisms for external review are stated. Therefore, to fulfill the oversight and mentoring requirements of the ABP, to promote training excellence at CCHMC, and to monitor progress across the department, a standing committee, the Pediatric Subspecialty Training Committee (PSTC), was formed. (The organizational structure of the PSTC is shown in Figure 2; available at www.jpeds.com). Primary activities of the PSTC are to (1) monitor institutional components of training, such as the introduction to research course and teaching skills training, (2) ensure that divisions are adhering to ABP and institutional policies regarding fellowship curricula, (3) provide guidance to PDs, and (4) make recommendations to the chair concerning necessary adjustments for fellowship programs. The PSTC delineates overall department-wide responsibilities for fellowship training (Table; available at www.jpeds.com). The PSTC was also charged with documenting effective mentoring, assessing outcomes, and preparing for external peer review. The PSTC requests that each fellowship program use an online tracking form to provide a brief yearly report detailing each fellow's accomplishments to each fellow, the Scholarship Oversight Committees (SOC), and the PSTC.

SCHOLARSHIP OVERSIGHT COMMITTEES

The major change is the mandate that review of scholarly activity occur at the local level. Thus, each ABP-approved subspecialty trainee must have an SOC, which should function in a manner analogous to a thesis committee for a postdoctoral candidate and advocate for their career development. The PSTC asked divisions to develop a plan for forming an effective SOC for each trainee that would suit divisional needs and resources and serve as a model for scholarship in the subspecialty.

The ABP requirement states that the SOC should consist of 3 or more individuals, at least one of whom is based outside the subspecialty discipline. In general, the SOC should include the primary mentor supervising the scholarly activity, a mentor for the fellows' clinical training and career development, and a mentor capable of providing insight and perspective in the area of scholarship being pursued by the trainee. For training programs with small numbers of fellows, the PSTC encourages exploration of innovative solutions, such as using members of divisions with common interests to form the SOC, with a different person for each trainee serving as the mentor on the scholarly activity. Although a fellowship PD may serve as a trainee's mentor and participate in the activities of the oversight committee, the ABP recommends that the PD should not

From the Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Cincinnati Children's Hospital Medical Center. The opinions expressed herein by the author(s) do not necessarily reflect the official endorsement of The Association of Medical School Pediatric Department Chairs, Inc. (*J Pediatr* 2005;147:277-8)

be a standing member. Even if a PD may not be an unbiased judge of the scholarly performance of a fellow-in-training, the PD is ultimately responsible for certifying the fellow as board eligible. The PSTC encourages each division to adapt to these constraints in ways that best fit the needs of their fellows. One option is to have the PD serve as an ad hoc nonvoting member of the SOC. Another suggestion is for the division to have an "education committee" that includes the PD. One or more members of the education committee could serve on the SOC for each fellow.

To initiate the process, the PSTC requested that each entering fellow be closely mentored to help that fellow identify an area of scholarship and possible research mentors. Once an area of scholarship is identified, an SOC needs to be formed and must be active for at least 2 years of the subspecialty training. The time frame for forming an SOC depends on how each division structures the scholarly experience of the fellows. The SOC then judges whether a specific activity is appropriate to meet the ABP guidelines for scholarly activity, approves the plan, determines the course of action, and ensures successful completion of the project.

The SOC meets regularly to review the general path the fellow has chosen, develop the program, detail the specific steps that are important for the fellow's success, and counsel the fellow. The fellow proposes the project for his/her scholarly activity to the SOC. A written report by the chair of each trainee's SOC is given to the PD and the fellow at least twice a year to set specific goals for further progress and allows both the SOC and PD to constructively counsel the fellow. The PD and the Chair of the fellow's SOC are expected to determine whether additional meetings are necessary for fellows who need more guidance or who are changing the focus of their scholarship activity. It is the responsibility of the PD to document the SOC meetings and the progress of each fellow; a concise form was developed to allow us to track subspecialty training (www.groups/web-services/research-comm/bissler/fellow-progress.html).

WORK PRODUCT

As part of the certification process, the fellow must prepare a work product of scholarly activity. The new ABP statement allows for a broader definition of scholarly activity: "an experience that provides the basis for a career of scholarly contributions" (www.abp.org). Involvement in scholarly activities must be hypothesis-driven, participatory, and result in the generation of a specific written "work product." The ABP requires submission of the work and a comprehensive document that delineates the roles of the fellow in each aspect of the activity and the relationship of the scholarly activity to the trainee's career development plan.

The PSTC supports the concept that development of a plan for the scholarly work is the responsibility of the fellow with the assistance of his/her SOC and the subspecialty PD. The PSTC requests a copy of the work to monitor the overall quality of fellowship training, but the PSTC does not judge the adequacy of the individual work product to be submitted to the ABP for subspecialty certification.

CORE CURRICULUM

All programs must include a core curriculum in scholarly activities that offers all the elements required by ABP for subspecialty certification. The PSTC further defines the "elements" (eg, a Research Core Curriculum, a Bioethics Course, and a Teaching Development course) and prepares a guide for CCHMC subspecialty fellowship and elective programs. The core elements will be offered as a series of lectures and be made available online.

EXPERIENCE TO DATE

One division has had an "SOC-type" process for fellowship oversight in place since 1995. Of the 25 fellows who have entered the T32-sponsored Fellowship Training Program in the Division of Pediatric Gastroenterology, Hepatology, and Nutrition at CCHMC in the past 10 years, 10 are still in the program. Preliminary assessment of the outcome of the 15 graduates is instructive and emphasizes the diversity of academic phenotypes chosen; for example, 4 obtained master's degrees in epidemiology and biostatistics, and one a master's degree in public health. Thirteen currently have faculty positions or are continuing with advanced research training; 9 hold extramural funding awards or are currently continuing with advanced research training, one entered private practice, and one is an industry-based research scientist.

CONCLUSION

The revised ABP criteria and responsibilities for training requirements leading to subspecialty certification for fellows encourage a focus on "career development" of the individual trainee. To maximally benefit from this type of program, the trainees and their mentors must initiate a plan that includes early decision-making and emphasizes evaluation of the trainee at a local level through a committed mentoring structure. The committee must review, coordinate, and certify the trainee. This effort requires a department-wide commitment. We believe that the end result will be subspecialists who are better prepared for success in academic medical centers.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.08.020

REFERENCES

1. Jones MD Jr, Boat TF, Stockman JA 3rd, Clark EB, Minaga-Miya K, Gilchrist GS, et al. Federation of Pediatric Organizations subspecialty forum. *J Pediatr* 2001;139:487-93.
2. Goldman L. Covering all the bases in academic medicine. *J Clin Invest* 2003;111:S1-7.
3. American Academy of Pediatrics. Federation of Pediatric Organizations: statement on pediatric fellowship training. *Pediatrics* 1991;87:265.

IMPROVEMENTS IN HEALTHCARE: HOW CAN WE CHANGE THE OUTCOME?

As consumers, each of us expects to receive consistent, high-quality healthcare, but at times we are disappointed. Healthcare has lagged behind other service industries in incorporating quality principles into the design of the delivery system and the expectations of healthcare professionals. Numerous reports, including *To Err is Human: Building a Safer Health System*¹ and *Crossing the Quality Chasm: A New Health System for the 21st Century*,² highlight these deficiencies. National experts, citing many examples of unsafe and ineffective care, conclude that our healthcare system is “broken” and requires fundamental change to deliver the quality services expected.

After World War II, Japan’s leaders recognized the need to redesign their industry standards to rebuild their economy. They enlisted the assistance of William Deming, who demonstrated that focusing on quality resulted in better products/services, as well as increased customer and employee satisfaction. The Toyota Corporation’s rise to dominance in the auto industry is a widely used example of this revolution. The application of “improvement science” methods to healthcare has increased over the last decade, and successful results have been documented by disease-specific groups³ and national organizations, such as the Institute for Healthcare Improvement,⁴ as they promote learning and accelerate change across the healthcare community. However, there remain few reports in the literature of well-designed studies that rigorously apply improvement methods to healthcare delivery systems.⁵

In this issue of *The Journal*, Schechter and Margolis provide a well-organized discussion of some of the concepts and methods used in healthcare quality improvement, sharing practical experiences associated with cystic fibrosis (CF) as a representative model of chronic illness.⁶ The authors describe the wide variation in care processes and associated variation in outcomes among CF centers, and emphasize the need to focus on decreasing unwarranted variation. They explain Dr. Edward Wagner’s model of chronic illness care and the importance of adopting a successful care model that meets the needs of patients, families, and providers. They also point out the benefits of specific improvement strategies, including using data to guide and monitor the impact of system changes and implementing rapid changes by using repeated plan/do/study/

act (PDSA) cycles. They highlight the importance of maintaining transparency, sharing information, and learning freely from each other to accelerate the rate of improvement. These strategies can be applied to microsystems within an institution, as demonstrated by the CF and other improvement teams within Cincinnati Children’s Hospital,⁷ as well as across systems within a broader healthcare community, as demonstrated by the collaboration of CF centers in the “breakthrough learning collaborative” described by the authors.

Care of children with CF begins at diagnosis and spans the transitions of childhood, adolescence, and adulthood. It must anticipate a variety of complications over an individual’s lifetime and must be designed to manage stable periods of chronic illness interspersed with episodes of acute deterioration. The current healthcare system is better designed to react to acute problems than to anticipate needs and maintain health, and is thus ill-prepared to effectively manage chronic illnesses. The increasing prevalence of chronic conditions like CF has changed the demands placed on the healthcare system, and in most circumstances the multidisciplinary infrastructure required to coordinate chronic illness care does not exist, contributing to variation in care practices and clinical outcomes.² Correcting this misalignment of needs and services requires changing some deeply rooted elements of the current healthcare system.

The wide variation in CF processes, as described by Schechter and Margolis, provides evidence of the opportunity for improvement. This situation has developed despite concerted efforts by the CF Foundation to address potential sources of variation, such as supporting clinical trials to strengthen the evidence for care practices, summarizing existing evidence in consensus practice guidelines, and providing all CF centers access to the “green book” that contains examples of how to use PDSA cycles, run charts, and other improvement tools. To decrease variation in care processes and improve clinical outcomes, the basis of the underlying variation itself must first be understood.

See related article, p 295.

Reprint requests: Dr. James D. Acton, Division of Pulmonary Medicine, Cincinnati Children’s Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229. E-mail: james.acton@cchmc.org.

J Pediatr 2005;147:279-81.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.06.027

CF Cystic fibrosis
PDSA Plan/do/study/act

Unwanted variation in care includes changes that are not explained by the illness itself, the recommendations of evidence-based medicine, or patient preference.

John Wennberg describes 3 different sources of variation in medical care.⁸ “Effective” care refers to the appropriate application of proven tests or treatments based on evidence-based recommendations, such as routine preventative care including scheduled clinic visits, pulmonary function tests (PFTs), and chest physiotherapy. “Preference-sensitive” care exists when a patient has multiple treatment options that have different anticipated outcomes, such as whether or not to pursue lung transplantation. “Supply-sensitive” care is any intervention whose frequency of use depends largely on the availability of the resource to the patient. A common example of this type of care is when the hospitalization rate is significantly higher than expected in an institution largely because they have a higher-than-average bed capacity. Wennberg suggests that 3 key changes are necessary to reduce system-wide unintentional variation in healthcare practices and outcomes:

- The academic medical community must continuously and systematically evaluate the evidence supporting routine practice of medicine to improve effective care.
- Strategies must be implemented to better support patients and families as active partners in decision making to improve preference-sensitive care.
- The healthcare management and reimbursement structure must better reflect the complex demands of chronic illness care to improve supply-sensitive care.⁹

Regardless of whether unwanted variation occurs in association with effective, preference-sensitive, or supply-sensitive care, it can be minimized by identifying the source of the variation and making system-based changes to support evidence-based and patient-centered care.

Even with an understanding of variation, a good care model, and the ability to apply improvement tools, change is hard, and initiating real improvement is often harder, especially in academic centers. One way to begin is by using available clinical data, such as that maintained in patient registries. These population-based data can help guide improvement by identifying variations in key outcomes and underlying key processes. In addition, using such data will document that changes are effective and lead to improved process performance and ultimately to better outcomes. For example, the National CF Patient Registry maintained by the CF Foundation is being used to aid centers in benchmarking their outcomes, support multicenter improvement collaboratives, and segment patient populations to more effectively customize care. However, the absence of an organized patient registry should not become a barrier to improvement, and simple spreadsheets or databases can be instituted quickly to collect and manage data for focused improvement projects. The Cincinnati CF team faced this challenge when initiating efforts to improve the influenza vaccination rates within their center without an existing database. Although a database was ultimately created, improvement during the first season was supported by handwritten checklists and a simple spreadsheet used to graphically monitor progress.

Improvement in clinical care and outcomes results when data support an active process of planned change in the delivery of care. One of the first steps in creating active change is engaging the right people in the process. Improvement efforts have conventionally involved the multidisciplinary team that provides clinical care. Experience has shown the value of including other contributors, such as colleagues from other specialties, experts in healthcare quality improvement and systems change, and administrative leaders within the healthcare institution. One group—perhaps the most important group—that is frequently omitted is the patient and his or her family. Evidence shows that the best clinical outcomes result when a patient participates in his or her care as an active member of the care team, and growing experience suggests that this involvement also supports more effective and efficient system change. Some CF centers have begun to include patients and families in their quality improvement activities. In Cincinnati, patients and families have been included as full members of all improvement teams, and although this process presents some challenges, we have identified some important steps in making this partnership successful. These include maintaining open communication in both directions, ensuring a common vision or goal, expecting mutual respect for all opinions, and making a commitment to transparency of data, outcomes, and the progress of improvement. The CF Foundation has also recognized the importance of maintaining transparency with regard to data on outcomes and the results of quality improvement efforts. They have recently begun the process of sharing center-specific outcome data among CF centers, and eventually with patients and families, to accelerate improvement by learning from each other. This partnership and the work associated with substantially improving the quality of CF care can be very intense. Thoughtful attention to these and other details will help ensure a productive experience.

Identifying a purpose, assembling a team, and even conceiving a plan are not sufficient to guarantee improvement. Many well-intentioned and well-planned projects never realize their intended results because of inertia or lack of focus. Change is facilitated by first setting clear and focused goals, then connecting these goals with a timeline to set expectations for action. More effective change can also be achieved by setting “stretch goals,” ones that far exceed the outcomes and performance produced by the current system. Experience from the improvement teams at Cincinnati Children’s Hospital suggests that direct patient and family involvement can produce more aggressive goals for change. The Cincinnati CF team has accepted accountability for improvement by stating their improvement goals as promises to the patients and families; for example:

- We will protect you from harm related to your care.
- We will respect and value your time.
- No place will preserve your lung function better.
- We will optimize your nutritional status.
- You may be involved in your care as much as you desire.
- We will support our staff so they can focus on your needs.

- You will get the care you need regardless of race, age, gender, education, or ability to pay.

These promises are then linked to performance through outcome measures, such as lung function, nutritional status, access to care, and patient and family satisfaction.

As difficult as initiating improvement can be, sustaining improvement is equally challenging. Reliability is a concept that describes a system's likelihood of achieving the desired results with each application; for example, education interventions alone deliver the expected results only 60% of the time. There is often a tendency to create improvement by educating more, planning better, and working harder; however, this will not help maintain the benefits of the performance.¹⁰ Practices achieving 97% to 99% reliability make quality improvement a central factor in every aspect of the care system and clarify how quality improvement relates to every person's role on a daily basis. These systems are designed to support reliability by using strategies like defaulting decisions to the desired action, reminding patients and caregivers about visits and interventions, and using evidence-based care guidelines.¹¹

To sustain the process of improvement indefinitely, every element discussed here and in the article of Schechter and Margolis must be intrinsic characteristics of the care system, and their application cannot be dependent on any individual.

The call to action has been sounded. It comes from the Institute of Medicine and other high-level organizations, from disease-specific organizations like the CF Foundation, and from individual healthcare professionals. Most importantly, however, it comes from patients and families who have the most invested in both the care and the improvement process. We must improve our understanding of how to effect improvements in healthcare systems and how to access tools and experts in system improvement. The question at hand is whether we will accept the challenge and make the commitment to change the outcomes.

James D. Acton, MD
Division of Pulmonary Medicine
Cincinnati Children's Hospital Medical Center
Cincinnati, OH 45229

Dr. Uma Kotagal, MBBS, MSc
Director, Health Policy and Clinical Effectiveness
Cincinnati Children's Hospital Medical Center
Cincinnati, OH 45229

REFERENCES

1. Institute of Medicine CoQoHCiA. To err is human: building a safer health system. Washington, DC: National Academy Press; 2000.
2. Institute of Medicine CoQoHCiA. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academy Press; 2001.
3. O'Connor GT, Quinton HB, Traven ND, Ramunno LD, Dodds TA, Marciniak TA, et al. Geographic variation in the treatment of acute myocardial infarction: the Cooperative Cardiovascular Project. *JAMA* 1999; 281:627-33.
4. Berwick D, Kabcenell A, Nolan T. No Toyota yet, but a start: a cadre of providers seeks to transform an inefficient industry before it's too late. *Mod Healthcare* 2005;35:18-9.
5. Homer CJ, Forbes P, Horvitz L, Peterson LE, Wypij D, Heinrich P. Impact of a quality improvement program on care and outcomes for children with asthma. *Arch Pediatr Adolesc Med* 2005;159:464-9.
6. Schechter M, Margolis P. Improving subspecialty healthcare: lessons from cystic fibrosis. *J Pediatr* 2005;147:295-301.
7. Muething S, Schoettker PJ, Gerhardt WE, Atherton HD, Britto MT, Kotagal UR. Decreasing overuse of therapies in the treatment of bronchiolitis by incorporating evidence at the point of care. *J Pediatr* 2004;144: 703-10.
8. Wennberg JE. Practice variation: implications for our health care system. *Managed Care* 2004;13(9 Suppl):3-7.
9. Wennberg JE. Practice variations and health care reform: connecting the dots. *Health Aff (Millwood)* 2004;suppl web exclusive:VAR140-4.
10. Weick KE, Sutcliffe KM. Managing the unexpected: assuring high performance in an age of complexity. San Francisco: Jossey-Bass; 2001.
11. Muething SE, Kotagal U. Reliability of the health care delivery system. *J Pediatr* 2005;146:581-2.

DAILY ACTIVITY AND DISEASE STATUS IN CYSTIC FIBROSIS: AN IMPORTANT AREA FOR RESEARCH

See related article, p 321.

Since the 1960s, survival in people with cystic fibrosis (CF) has consistently improved with each successive birth cohort, and these trends are very similar in the United States and Europe.¹⁻³ The other finding, replicated between different populations, is the difference in survival between males and females with CF. Contrary to the trends in most diseases of childhood, survival in females with CF is consistently worse than males. There is, as yet, no clear explanation for this finding. Although nutritional status,

pulmonary function, and airway microbiology at a given age are strong predictors of mortality at later ages, neither these factors, nor others, such as pancreatic insufficiency, age at diagnosis, mode of presentation, and race, account for the poorer survival among females.³ It therefore seems likely that an environmental or lifestyle difference between boys and girls, which

The author is grateful to Dr John Reilly, University of Glasgow, UK, for helpful comments and discussion.

Reprint requests: Professor Rosalind L. Smyth, School of Reproductive and Developmental Medicine, University of Liverpool Institute of Child Health, Alder Hey Children's Hospital, Liverpool L12 2AP, United Kingdom. E-mail: r.l.smyth@liv.ac.uk.

J Pediatr 2005;147:281-3.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.04.067

CF Cystic fibrosis
FEV₁ Forced expiratory volume in 1 second

operates from childhood, may account for this consistent and important difference in survival.

In urban, industrialized populations, childhood is the most physically active time of life and is followed by an invariable decline in levels of physical activity in adolescence and young adult life. The 2001 Youth Risk Behavior Survey,⁴ conducted by the Centers for Disease Control and Prevention in the United States defined sufficient physical activity in high-school students as that which made them sweat and breath hard for ≥ 20 minutes on ≥ 3 of the 7 days preceding the survey. Only two thirds (64.6%) of students reported this level of activity, which was significantly more likely to be reported in male students (72.6%) than female students (57%). This significant sex difference was identified for all the ethnic and age groups. Overall, students in grades 9, 10, and 11 (71.9%, 67%, and 61.3%, respectively) were significantly more likely than students in grade 12 (55.5%) to report sufficient vigorous physical activity.

A number of studies have examined the decline in physical activity in young people during and after puberty. A study by Kimm et al⁵ prospectively followed white and black girls from 9 or 10 years of age to 18 or 19 years of age and found substantial declines in physical activity during these years, so that by 16 or 17 years of age, 56% of black girls and 31% of white girls reported that they did not engage in any leisure-time physical activity. A study in the United Kingdom by Reilly et al,⁶ where activity was measured by an accelerometer, found that in children as young as 5 years of age time spent in sedentary behavior was high in girls (81%) and boys (76%), but, even at this early age, girls showed significantly less mean physical activity levels than boys.

Decline in physical activity with age in children is of concern, but this also must be set in the context that it is generally accepted that children in the 21st century take much less regular exercise than previous generations. The activities of today's children have not been compared with those of previous generations, using objective measures. However, there is much indirect evidence to suggest that changes to lifestyles, such as increased television viewing, use of computers and computer games, and being driven rather than walking to school, have caused our children to lead a much more sedentary lifestyle than their parents. In population-based cohort studies, the main concerns about declining levels of physical activity have focussed on the growing epidemic of obesity among children and adults. However, associations between reduced physical activity and cardiovascular disease, development of bones and muscles, and quality-of-life, are well recognized.

There is as yet very little evidence from observational studies that level of activity affects disease status in CF. In spite of this, in the last decade, the potential impact of exercise programs in improving respiratory status in CF has received a lot of attention. A number of randomized controlled trials have investigated whether prescribed regimens of physical training improve or prevent deterioration in clinical outcomes such as spirometric lung function in patients with CF. These have been the subject of a Cochrane systematic review,⁷ which concluded that any decision about the efficacy of these interventions was

limited by the small size, short duration, and incomplete reporting of most of the trials.

Of all measures of disease status, the one that is of most relevance to patients and clinicians is rate of change in forced expiratory volume in 1 second (FEV₁), which, in turn, is closely associated with survival. Corey et al,⁸ in a longitudinal analysis of patients with CF from a large center in Canada, found a small, but highly significant difference in rate of decline in FEV₁ with gender, with males having a slower rate of decline. This study also confirmed that decline in FEV₁ is a strong predictor of mortality in CF.

So we know that levels of physical activity in normal populations are less in girls than boys and show a steep decline in later childhood and adolescence. It is tempting to impute that some of the differences between males and females in mortality and decline in lung function in CF may be because of differences between the sexes in amounts of physical activity, but, until recently, clear evidence of this has been lacking. The article by Schneiderman-Walker et al⁹ in this issue of the *Journal* has shown that, in children with CF between 7 and 17 years of age, not only are activity levels greater for boys than girls, but when the children are followed prospectively over 2 years, those girls with the lowest activity levels had more rapid decline in FEV₁, whereas this relationship between activity level and decline in FEV₁ was not seen in boys. In this study, the average total activity (which includes low-intensity exercise such as walking) was 5.4 hours per day for girls and 6.5 hours per day for boys. These activity levels seem quite high, and it would have been interesting if the study had included a comparison between these self-reported levels of activity and an independent, objective measure, such as an accelerometer.

In a study from Australia,¹⁰ investigators compared activity levels in children with CF with those of matched controls. In prepubescent children, there were no differences between boys and girls in either group, but children with CF with mild disease were significantly more active than controls. In pubescent children, activity levels in girls were significantly less than in boys in both the control and CF groups. As with the younger age group, pubescent boys and girls with mild CF disease were more active than controls. Unlike the study by Schneiderman-Walker, these groups were not followed prospectively and there was no comparison between activity levels and rate of decline in FEV₁.

There is still much to be learned about the relationships between activity, age, gender, lung function decline, and mortality in people with CF. One can speculate that, if children with CF are much less active than previous generations, this factor may have counteracted the very positive influences, which have improved survival from this disease in the last four decades. The study by Schneiderman-Walker et al is relatively small, and the length of follow-up relatively short. If reduction in activity levels of children with CF contributes to decline in lung function and earlier death, this should be a high priority for intervention studies. In designing such clinical trials, it will be particularly important to elucidate in a prospective, longitudinal study what changes in activity occur with age, the impact of influences such as transfer to secondary

school, and the amounts and intensities of physical activity that are likely to make a difference.

Rosalind L. Smyth, MD
Head of Division of Child Health
School of Reproductive and Developmental Medicine
University of Liverpool
Liverpool, UK

REFERENCES

1. FitzSimmons SC. The changing epidemiology of cystic fibrosis. *J Pediatr* 1993;122:1-9.
2. Dodge JA, Morison S, Lewis PA, Coles EC, Geddes D, Russell G, et al. Incidence, population, and survival of cystic fibrosis in the UK, 1968-95. UK Cystic Fibrosis Survey Management Committee. *Arch Dis Child* 1997;77:493-6.
3. Rosenfeld M, Davis R, FitzSimmons S, Pepe M, Ramsey B. Gender gap in cystic fibrosis mortality. *Am J Epidemiol* 1997;145:794-803.
4. Grunbaum JA, Kann L, Kinchen SA, Williams B, Ross JG, Lowry R, et al. Youth risk behavior surveillance: United States, 2001. *MMWR Surveill Summ* 2002;51:1-62.
5. Kimm SY, Glynn NW, Kriska AM, Barton BA, Kronsberg SS, Daniels SR, et al. Decline in physical activity in black girls and white girls during adolescence. *N Engl J Med* 2002;347:709-15.
6. Reilly JJ, Jackson DM, Montgomery C, Kelly LA, Slater C, Grant S, et al. Total energy expenditure and physical activity in young Scottish children: mixed longitudinal study. *Lancet* 2004;363:211-2.
7. Bradley J, Moran F. Physical training for cystic fibrosis. *Cochrane Database Syst Rev* 2002;CD002768.
8. Corey M, Edwards L, Levison H, Knowles M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. *J Pediatr* 1997;131:809-14.
9. Schneiderman-Walker J, Wilkes DL, Strug L, Lands LC, Pollock SL, Selvadurai HS, et al. Sex differences in habitual physical activity and lung function in children with cystic fibrosis. *J Pediatr* 2005;147:321-6.
10. Selvadurai HC, Blimkie CJ, Cooper PJ, Mellis CM, Van Asperen PP. Gender differences in habitual activity in children with cystic fibrosis. *Arch Dis Child* 2004;89:928-33.

TOWARD BETTER EVIDENCE FOR PARENT TRAINING PROGRAMS FOR AUTISM SPECTRUM DISORDER

Autism is a condition, generally considered to be part of a spectrum, in which children experience variable degrees of difficulty with communication, social interaction, and a propensity toward repetitive behaviors and lack of imagination. These difficulties manifest in a variety of ways that interfere with social interaction and often result in considerable behavioral challenges to parents and other caregivers.

Autism spectrum disorder (ASD) has been increasingly recognized and is currently believed to affect 30 to 60 per 10,000 children.¹ One thing seems clear: for ASD, early intervention is key.² Over the years, a variety of treatments have been proposed for children with ASD: dietary, pharmacologic, sensory, and behavioral modification. Knivsberg et al³ have looked at the effect of a gluten and casein-free diet and found improved development in treated children. No randomized study has shown benefit from secretin treatment.⁴ Sinha et al, has reviewed studies using auditory integration therapy as a modality for improving sound sensitivity and found no reliable, significant changes.⁵ One of the most frequent interventions involves training parents⁶ and other caregivers in methods to help their children. The study by McConachie et al,⁷ in this issue of *The Journal*, adds to the literature on parent training. This controlled trial compares the outcomes for parents of 51 preschool children with suspected ASD who either started on a 3-month course called "More Than Words" shortly after recruitment (immediate intervention) or who had to wait for a course, since one was not available at the time of diagnosis (delayed control). This program is designed to assist parents in social interaction with their child and enhance communication skills.

Through the program, parents may increase their confidence during interactions with their child and benefit from connections with other parents and professional therapists. The authors evaluated the ability of the training to enhance parents' interaction with their child; decrease parental stress; increase the child's communication and language skills; and decrease behavioral problems. Appropriate, valid instruments were used to measure the outcomes. Seven months after recruitment, compared with those in the delayed control group, parents in the intervention group were noted to use more facilitative interaction strategies, and their children had larger vocabularies. However, they were not able to document changes in parental stress. This could be due to the short timeframe or to a lack of adequate power to detect a difference between the groups.

This study is subject to many of the limitations found in other intervention studies for ASD. First, the included population is heterogeneous. This could make it more difficult to detect a difference between groups or it could mean that any differences found may have been due to changes within a subpopulation of children with ASD. On the other hand, the broad inclusion criteria reflect the reality of practice where we are not able to define precisely where a child is along the autism spectrum.

See related article, p 335.

Reprint requests: John G. Frohna, MD, MPH, Departments of Pediatrics, Internal Medicine, and Medical Education, University of Michigan, 3116 Taubman, Box 0368, Ann Arbor, MI 48109-0368.

J Pediatr 2005;147:283-4.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.05.036

Second, the timing of the intervention can affect the outcome, with earlier treatment more likely to be beneficial. This was less of an issue in this study, since the children in the two groups were about the same age, and the time from diagnosis to intervention was comparable. Third, because ASD is a developmental disorder, changes in child and parent behaviors occur naturally over time. Using a delayed control group could be problematic, as the children may differentially improve with time. For this study, this is less of an issue owing to the short duration of follow-up; any differences between the groups probably would be small.

One of the strengths of this study is that it is controlled, unlike many of the studies addressing parental training for children with ASD.⁶ The gold standard for intervention studies is the randomized, controlled trial. Although the two groups in this study appear similar, random assignment would help minimize potential sources of bias. However, randomized trials in ASD are exceedingly rare. This has been attributed in part to the difficulty in randomly assigning children into trials when parents have a strong belief that intervention will make a difference or when there is a strong desire to get treatment for their child.⁶ The sample size in this study, although not large, is larger than that in many of the prior studies in ASD. Nonetheless, expanding this study to include more children and multiple institutions would strengthen the results.

The evidence of effectiveness for various interventions for ASD is far from robust. However, the benefits found in "More Than Words" continue the positive trends seen in other

controlled trials of parent training courses. If larger, randomized trials confirm this evidence, these programs could be expanded to benefit the children and parents who struggle with ASD on a daily basis.

John G. Frohna, MD, MPH
 Departments of Pediatrics, Internal Medicine, and
 Medical Education
 University of Michigan
 Ann Arbor, MI 48109-0368

REFERENCES

1. Fombonne E. Epidemiological surveys of autism and other pervasive developmental disorders: an update. *J Autism Dev Disord* 2003; 33:365-82.
2. Bryson S, Rogers S, Fombonne E. Autism spectrum disorders: early detection, intervention, education, and psychopharmacological management. *Can J Psychiatry* 2003;48:506-16.
3. Knivsberg AM, Reichelt KL, Høien T, Nodland M. A randomised, controlled study of dietary intervention in autistic syndromes. *Nutr Neurosci* 2002;5:251-61.
4. Sturmey P. Secretin is an ineffective treatment for pervasive developmental disabilities: a review of 15 double-blind randomized controlled trials. *Res Dev Disabil* 2005;26:87-97.
5. Sinha Y, Silove N, Wheeler D, Williams K. Auditory integration training and other sound therapies for autism spectrum disorders. *Cochrane Database System Rev*. 2004;(1):CD003681.
6. Diggle T, McConachie HR, Randle VR. Parent-mediated early intervention for young children with autism spectrum disorder. *Cochrane Database System Rev* 2003;1:CD003496.
7. McConachie H, Randle V, Hammal D, Le Couteur A. A controlled trial of a training course for parents of children with suspected autism spectrum disorder. *J Pediatr* 2005;147:335-40.

TRANSITION/ADAPTATION IN THE DELIVERY ROOM AND LESS RDS: "DON'T JUST DO SOMETHING, STAND THERE!"

It is old news that neonatology has changed strikingly with the increased survival of smaller and smaller infants. However, to appreciate the results obtained using continuous positive airway pressure (CPAP) reported by Ammari et al in this issue of *The Journal*,¹ let's step back to the 1980s—prior to the frequent use of antenatal corticosteroids or surfactant therapy and to multiple changes in obstetric management of the delivery of low birth weight infants. Most infants <28 weeks gestation were ventilated, had multiple complications, and had a high mortality rate. Avery et al² reported in 1987 that the use of CPAP in New York at Columbia University seemed to be associated with less bronchopulmonary dysplasia than did the ventilator management practiced by other neonatal units, an observation that was reinforced by similar comparisons by Van Marter et al³ in

1992. The weakness of the current report by Ammari et al¹ is that it is simply their clinical experience with the use of CPAP to stabilize infants after delivery at Columbia from 1999 to 2002. We remain without randomized controlled trials designed to test the perceived benefits of CPAP, a gap that hopefully will be filled by ongoing trials. However, what I find remarkable about the report is the high percentage of infants with birth weights <1000 g who can breathe in the delivery room and who do not have severe respiratory

See related article, p 341.

Supported in part by Grants HD-12714 and HL-65397 from the National Institutes of Health and Human Development.

Reprint requests: Alan H. Jobe, MD, PhD, Cincinnati Children's Hospital Medical Center and The University of Cincinnati College of Medicine, Division of Pulmonary Biology, 3333 Burnet Ave, Cincinnati, OH 45229-3039. E-mail: alan.jobe@cchmc.org.

J Pediatr 2005;147:284-6.
 0022-3476/\$ - see front matter
 Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.05.003

CPAP	Continuous positive airway pressure
RDS	Respiratory distress syndrome
VLBW	Very low birth weight

Table. Percent of infants initially stabilized with intubation or CPAP and outcome at 72 hours of age¹

	N	Initial stabilization		Outcome at 72 hours*	
		Intubation	CPAP	CPAP Fail	CPAP Success
Birth weight					
<699 g	79	27%	73%	40%	33%
700-999 g	90	11%	89%	18%	71%
1000-1250 g	92	1%	99%	8%	92%
Gestational age					
23-25 wk	87	31%	69%	38%	31%
26-28 wk	106	5%	95%	17%	78%
29-31 wk	54	0%	100%	7%	93%

CPAP Fail, Intubation; CPAP success, no therapy other than CPAP for 72 hours.

*Percents calculated for overall population (Intubation + CPAP fail + CPAP success = 100%).

distress syndrome (RDS). These 2 outcomes are contrary to the clinical experiences of many neonatologists and may be important to understanding the incidence of bronchopulmonary dysplasia.

We all use the Neonatal Resuscitation Textbook, published by the American Academy of Pediatrics and American Heart Association for certification in delivery room care.⁴ The program emphasizes a staged sequence of interventions for neonatal resuscitation. I emphasize the word *resuscitation* because when the beeper goes off with a call to the delivery room, the charge is to resuscitate an infant. In fact, few infants need resuscitation. The vast majority of infants need only a bit of assistance (drying, stimulation, clearance of secretions) to allow transition or adaptation after birth. The remarkable recent experience of many clinicians who have allowed very low birth weight infants (VLBW) to transition without bagging or intubation is that they actually can do it! The report by Ammari et al¹ demonstrates this clearly (Table). They found that about 70% of infants with birth weights <699 g or gestations of 23 to 25 weeks could be transitioned using primarily CPAP. Very few older gestation or larger infants required intubation. Conceptually, this translates to the majority of VLBW infants not needing resuscitation with its invasive implications. My bias is that the delivery room beeper should initiate a focus on transition-adaptation, and, with patience and after a bit of time, resuscitation if necessary. As in many areas of medicine, it may be better to just stand there rather than do something—such as to manipulate the VLBW infant to induce a vagal response.

What is the downside of a focus on emphasizing transition-adaptation rather than resuscitation? The standard of care being promoted, on the basis of the surfactant trial data, is that better outcomes result from intubation and surfactant treatment very soon after delivery.^{5,6} If an infant can even briefly transition before the decision to give surfactant is made, an elective intubation seems preferable to an emergency intubation. There is perhaps nothing more dangerous for the preterm lung than an anxious physician with an endotracheal tube and a bag. Although early surfactant is good for infants with RDS, there is no information to judge the

benefits of surfactant for infants without RDS. A brief transition may help identify the infant in whom significant RDS will develop.

What was the incidence of RDS in the population from Columbia? If we assume that only infants that were treated with surfactant had significant RDS, then about 50% of the intubated infants and 50% of the infants in whom CPAP failed (intubated by 72 hours of life) or about 16% of the total population of infants with birth weights <1250 g had RDS. Another way to estimate the maximal occurrence of RDS would be to assume that all ventilated and CPAP failure infants had significant RDS, which is an RDS rate of 34% for the overall population and 47% for infants with birth weights <1000 g (Table). These numbers are very low relative to reports of surfactant treatment for infants of this weight category. For example, in 2000 about 80% of infants with birth weights of 401 to 1500 g in the Vermont Oxford Network Database received surfactant.⁵ Certainly surfactant treatment overestimates the incidence of RDS by the treatment of infants without surfactant deficiency, and the Columbia group may not treat some infants with mild RDS that others would choose to treat. However, few clinicians would anticipate good survival rates for infants <1000 g with severe RDS using CPAP alone. The conclusion, whatever the precise numbers, is that many very low birth weight (VLBW) infants have no or mild RDS.

How is it possible that many VLBW infants do not have RDS? The human fetal lung normally matures functionally after about 35 week's gestation. Human lungs begin to have identifiable type II cells after about 22 weeks gestation, but surfactant in the airspaces does not increase (based on the lecithin to sphingomyelin ratio) until after 30 weeks.⁷ Multiple factors are contributing to the low incidence of RDS. First, there are no normal preterm infants—they are all abnormal or they would not have been born preterm. The human lung has a remarkable capacity to mature early—as much as 12 weeks early! Clinically, maturation means the ability to exchange oxygen and carbon dioxide, but pulmonary function and structure may be far from normal. For example, the clinician is content with a PO₂ of 35 mm Hg (saturation of

about 90%) in room air, whereas the arterial PO₂ with a normal lung in room air would be about 100 mm Hg. Maternal corticosteroids contribute to the early functional maturation of the fetal lung.⁸ Antenatal exposure of the VLBW infant to chorioamnionitis is frequent, and this antenatal inflammation is a potent promoter of functional lung maturation and increased surfactant.^{9,10} These modulators of lung maturation together with obstetric practices to delay the delivery of preterm infants after the onset of preterm labor must be contributing to less RDS. Another contributing factor may be how infants are treated in the delivery room. A preterm lamb will breathe with CPAP with a surfactant pool of only about 3 mg/kg.¹¹ The surfactant pool size at term is about 100 mg/kg, and the treatment dose of surfactant also is 100 mg/kg. However, if the lung is injured by overstretch or ventilation without positive end-expiratory pressure, then surfactant function degrades, and the infant may have “iatrogenic” RDS.¹² Perhaps the very low incidence of RDS at Columbia results from avoidance of lung injury in the delivery room with the use of CPAP. Unnecessary intubation and ventilation soon after birth may cause RDS. Most initial ventilation does not control positive end-expiratory pressure, peak pressure, or tidal volume, and often 100% unhumidified and cold oxygen is used. The optimal decision pathways for delivery room respiratory management and surfactant remain to be validated by clinical trials, but the epidemiology of RDS certainly has changed.

Alan H. Jobe, MD, PhD
Cincinnati Children's Hospital Medical Center
The University of Cincinnati College of Medicine
Division of Pulmonary Biology
Cincinnati, OH 45229-3039

REFERENCES

1. Ammari A, Suri MS, Milisavljevic V, Sahni R, Bateman DA, Sanocka U, et al. Variables associated with the early failure of nasal CPAP in very low birth weight infants. *J Pediatr* 2005;147:341-7.
2. Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. *Pediatrics* 1987;79:26-30.
3. van Marter LJ, Pagano M, Allred EN, Levitorn A, Kuban KC. Rate of bronchopulmonary dysplasia as a function of neonatal intensive care practices. *J Pediatr* 1992;120:938-46.
4. Kattwinkel J, ed. *Textbook of Neonatal Resuscitation*. 4th ed. American Academy of Pediatrics and American Heart Association; 2000.
5. Horbar JD, Carpenter JH, Buzas J, Soll RF, Suresh G, Bracken MB, et al. Timing of initial surfactant treatment for infants 23 to 29 weeks' gestation: is routine practice evidence based? *Pediatrics* 2004;113:1593-602.
6. Horbar JD, Carpenter JH, Buzas J, Soll RF, Suresh G, Bracken MB, et al. Collaborative quality improvement to promote evidence based surfactant for preterm infants: a cluster randomised trial. *BMJ* 2004;329:1004.
7. Gluck L, Kulovich MV, Borer Jr RC, Keidel WN. The interpretation and significance of the lecithin-sphingomyelin ratio in amniotic fluid. *Am J Obstet Gynecol* 1974;120:142-55.
8. Crowley P. Prophylactic corticosteroids for preterm birth. *The Cochrane Library*, Issue 2. Oxford: Update Software 2001 (3).
9. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *N Engl J Med* 2000;342:1500-7.
10. Jobe AH, Newnham JP, Willet KE, Moss TJ, Ervin MG, Padbury JF, et al. Endotoxin induced lung maturation in preterm lambs is not mediated by cortisol. *Am J Respir Crit Care Med* 2000;162:1656-61.
11. Mulrooney N, Champion Z, Moss TJ, Nitsos I, Ikegami M, Jobe AH. Surfactant and physiological responses of preterm lambs to continuous positive airway pressure. *Am J Respir Crit Care Med* 2005;171:1-6.
12. Wada K, Jobe AH, Ikegami M. Tidal volume effects on surfactant treatment responses with the initiation of ventilation in preterm lambs. *J Appl Physiol* 1997;83:1054-61.

SAY NO TO DRUGS?

It is one of the stranger ironies of modern history that what is possibly the single greatest achievement of twentieth century medicine is also one of its most contentious advances. Almost half a century ago, the first use of psychotropic drugs to improve the quality of life of persons with significant psychopathology (recall the film *Awakenings*¹ based on Oliver Sacks' book²) opened the door to a radically new era of psychopharmacology. Such advances had been unimagined in the past. As might have been expected with such an effective and popular treatment, there were examples of abuse, misuse, overuse, and perhaps even the development of a sometimes too-easy dependence on drugs for a “quick fix.” But the positive achievement remains important, and the rebound in the public mind, is, if anything, an inverted recognition of the very degree of that success.

What does it say to the use of such psychopharmacology that, in many communities, upwards of half of pediatricians (typically even more family practitioners) may not prescribe medications for attention deficit-hyperactivity disorder (ADHD). The reasons proffered relate to the excessive (and unreimbursed) time needed to perform an adequate evaluation, the complexities of medication management, and concerns about follow-up frequency and side effects. Families who do not pursue pharmacologic approaches to ADHD will not always rely on behavioral and counseling interventions but rather may divert their time, energy, and resources to unproven

See related article, p 348.

Reprint requests: Pasquale J. Accardo, MD, Virginia Commonwealth University, Developmental Research in Pediatrics, 307 College Street, Richmond, VA 23298. E-mail: paccardo@chva.org.
J Pediatr 2005;147:286-7.
0022-3476/\$ - see front matter
Copyright © 2005 Elsevier Inc. All rights reserved.
10.1016/j.jpeds.2005.04.060

alternative therapies such as restrictive diets, additives, herbal preparations, vitamin supplements, magnet therapy, sensory diets, and electroencephalographic biofeedback. Parental fears of addiction risk (unfounded) and other side effects that are typically dose-related (and therefore manageable) combine with a mystical preference for a more “natural” approach.

While it is difficult to make broad unqualified comparisons, the drugs used to treat children with ADHD are among the most effective and safest psychoactive drugs currently used in pediatrics. Indeed, they are probably among the safest drugs in use in pediatrics. The article by Findling et al³ in this issue of *The Journal* further supports this wide safety margin. But is safety the real issue behind increasing public concern?

Challenging behaviors can always be improved with intensive behavioral programming. The application of positive behavioral supports derived from an appropriate functional behavioral analysis as mandated by Individuals with Disabilities Education Act amendments⁴ should be available to all special needs students.

The use of drugs to improve behavior can be difficult for lay persons to discriminate from “mind control.” To positively impact the disruptive classroom behavior of some children with ADHD can suggest the specter of drugs to create a docile citizenry, passive in response to governmental oppression. The fact remains that while psychopharmacology is an *accepted* mode of intervention, it is not a *required* mode of treatment. Drugs can never be a required therapeutic component of ADHD for the simple reason that they do not always work.

The fact that ADHD is more often mild and that it rather inconsistently impacts on behavior contribute to the misperception of ADHD as a motivation problem: “If only he tried harder. . .”⁵ Understanding the role of medication in ADHD management requires a more accurate understanding of the roots of the misbehavior that characterizes the syndrome. Accardo’s Laws of Misbehavior⁶ apply to children with ADHD. While at first glance they may appear to be counsels of despair, they represent the first step needed to understand that the behavior of a child with ADHD is mostly due to brain dysfunction. They underline the fact that the major goal for the use of stimulant medication is to allow the child with ADHD to more effectively assume control of his own behavior rather than having drugs “control” his behavior.

IRRELEVANCE PRINCIPLE

In general, parents are irrelevant to the misbehavior of their children with ADHD. ADHD is a brain-based condition and not a failure of parenting techniques.

IRRESPONSIBILITY PRINCIPLE OR INNOCENT CHILD HYPOTHESIS

In general, children with ADHD are not responsible for their misbehavior. ADHD is a brain-based condition and not a failure of children to learn appropriate behavior.

UNMOTIVATION PRINCIPLE OR BEHAVIORAL INDETERMINACY PRINCIPLE

The misbehavior of children with ADHD has no consistent correlation to the effort they invest in controlling it. Increasing the motivation of children with ADHD to improve their behavior does not produce consistent behavioral improvement.

Even when medication radically improves a child’s behavioral performance, there typically persists some residuum of challenging behaviors that will still require adult understanding of the above rules. The strongest moral imperative for the use of psychopharmacologic approaches to ADHD is the ability of such medication to foster the development of ethical behavior in children with ADHD. Decreasing hyperactivity and impulsivity allows the child with ADHD to proactively weigh the consequences of an action rather than being left in a perpetual limbo of regret for past missteps. Parents and physicians can “say no to drugs” but still say yes to helping children by the appropriate use of medication.

Pasquale J. Accardo, MD
Developmental Research in Pediatrics
Virginia Commonwealth University
Richmond, VA 23220

Jennifer A. Accardo, MD
Neurodevelopmental Disabilities
Kennedy Krieger Institute/Johns Hopkins University School of Medicine
Baltimore, MD 21205

REFERENCES

1. Marshall P (dir.) *Awakenings*. Columbia Tristar, 1990.
2. Sacks O. *Awakenings*. New York: Harper Collins; 1974.
3. Findling R, Biederman J, Wilens T, Spencer TJ, McGough JJ, Lopez FA, Tulloch SJ. The short- and long-term cardiovascular effects of mixed amphetamine salts extended release in children. *J Pediatr* 2005;147: 348-54.
4. Crimmins D, Farrell AF, Smith PW, Bailey A. *Positive strategies: developing individualized supports in schools*. Valhalla, NY: Westchester Institute for Human Development; 2004.
5. Ounsted C. Could do better if he tried. In: Apley J, Ounsted C, eds. *One child*. Philadelphia: JB Lippincott; 1982. p. 48-53.
6. Accardo PJ, Mink J. *Contemporary Issues in ADD/ADHD*. Exceptional Parent and Child Neurology Foundation Web Seminar, November 4, 2005.

ASSESSMENT AND TREATMENT OF ACUTE ASTHMA IN CHILDREN

BRADLEY E. CHIPPS, MD, AND KEVIN R. MURPHY, MD

Over the last decade, significant advances in asthma therapy have been made. Yet asthma remains the leading cause of emergency care in children, and hospitalization rates continue to increase. The direct costs of asthma are estimated to exceed 6 billion dollars per annum in the United States alone¹; 35% to 50% of this expense occurs in the emergency department (ED) and hospital.

In 2002, asthma affected approximately 6.1 million children younger than 18 years of age, with an inner-city prevalence of 8.6%.^{2,3} Thus, asthma is a disease that pediatricians can expect to encounter. The ability to effectively treat asthma is therefore essential. This article will discuss the assessment of acute pediatric asthma and we will review recent studies pertaining to its treatment.

DETERMINING SEVERITY

A reliable estimate of the severity of airway obstruction is difficult to ascertain on clinical grounds. Many signs can characterize a severe episode: accessory muscle activity, a paradoxical pulse >25 mm Hg, a heart rate >130 beats/min, a respiratory rate >25 to 30 breaths/min, a limited ability to speak, a peak expiratory flow (PEF) or forced expiratory volume (FEV₁) <50% predicted, and an oxygen saturation (SpO₂) <91% to 92%.⁴⁻⁶ These symptoms and signs may or may not develop simultaneously, may or may not impair the patient at the same level, and can be present in any combination.

The PEF is measured in the first 150 to 200 milliseconds of the expiratory maneuver and primarily reflects flow from the large airways. This measurement is highly dependent on patient effort and muscle strength. Thus, an inaccurate measurement is possible when PEF is measured during a severe episode. As the severity of airway obstruction increases during an acute asthma attack, residual volume may dramatically increase, reaching values up to 60% to 70% of total lung capacity. This physiologic event can result in initial flow transients that lead to higher PEF than would be expected.⁷ The most recent National Heart, Lung, and Blood Institute guidelines suggest that PEF be obtained in the assessment and treatment of acute asthma in children.⁴ PEF can be used especially in older children to follow trends and assess response to β -agonists.

PREDICTIVE SCORING INDEXES

The measurement of the severity of an acute asthma exacerbation is an important guide to treatment and response to therapy. Several asthma scoring systems estimate the degree of airway obstruction in children when standard measurements cannot be performed. These systems combine a number of physical signs such as respiratory rate, inspiratory/expiratory ratio, and accessory muscle use, to form a score that estimates the severity of an acute asthma exacerbation. Smith and Strunk developed a Pulmonary score (PS) for younger children (<6 years), who had little experience with peak flow meters, or children in significant respiratory distress, in whom it is difficult to obtain an accurate peak flow measurement (Table I).⁸⁻¹⁰ This measure, based on respiratory rate, wheezing, and accessory muscle use, uses a scoring scale from 0 to 9. When tested in children who present to the ED with mild to severe asthma, the PS correlated well with PEF.

Arterial oxygen saturation may also be used to predict the need for hospital admission. Geelhoed et al⁹ found that children presenting with SpO₂ <91% needed hospitalization with a sensitivity of 1.00 and a specificity of 0.84; however, an SpO₂ >96% was needed to predict successful discharge from the ED. It has been suggested that admission to the hospital should be considered in children with a PS >2, PEFR <80%, and room air O₂ saturation <95%, 30 to 45 minutes after the last treatment.¹⁰

Other authors have attempted to develop scoring systems in older children and adults based on response to therapy. Rodrigo and Rodrigo¹¹ studied 184 patients (age, 18 to

From Capital Allergy and Respiratory Disease Center, Sacramento, California, and Midwest Childrens Chest Physicians, Omaha, Nebraska.

Submitted for publication Aug 31, 2004; last revision received Dec 29, 2004; accepted Apr 21, 2005.

Reprint requests: Bradley E. Chipps, MD. E-mail: bchipps@capitalallergy.com.

J Pediatr 2005;147:288-94.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.04.052

CS	Corticosteroids	PEF	Peak expiratory flow
ED	Emergency department	PS	Pulmonary score
IB	Ipratropium bromide	SVN	Small-volume nebulizer
ICS	Inhaled corticosteroids	VHC	Valved holding chamber
MDI	Metered-dose inhaler		

Table I. Pulmonary index

Score	Respiratory rate		Wheezing*	Accessory muscle use (sternocleidomastoid activity)
	<6 Y	≥6 Y		
0	<30	<20	None	No apparent activity
1	31-45	21-35	Terminal expiration with stethoscope	Questionable increase in activity
2	46-60	36-50	Entire expiration with stethoscope	Increased activity
3	>60	>50	Inspiration and expiration without stethoscope	Maximal activity

From Smith SR, Strunk RC. Acute asthma in the emergency department. Reprinted with permission.¹⁰

*If no wheezing due to minimal air exchange, score 3.

Table II. Predictive index scoring system

Variable	Score		
	Score 0	Score 1	Score 2
PEF variation at 30 minutes (L/min)	>50	50-20	<20
PEF at 30 minutes (% predicted)	>45	45-35	<35
Accessory muscle use at 30 minutes	0-1	2	3

PEF: Peak expiratory flow.

Table 2 from Rodrigo G, Rodrigo C. A New Index for Early Prediction of Hospitalization in Patients with Acute Asthma. Reprinted with permission.¹¹

50 years) who presented to the ED for an acute asthma episode with FEV₁ or PEF <50% predicted. A predictive scoring index was developed (Table II).¹¹ Each patient received a score between 0 and 2 for each of the three variables; the three scores were added together to obtain a final score (0 to 6). In the analysis sample, 163 patients (89%) were discharged (relapse rate within 7 days was 10%) and 21 patients (11%) were hospitalized. An index score > 4 30 minutes after starting therapy demonstrated a sensitivity of 0.86, a specificity of 0.96, a positive predictive value of 0.75, and a negative predictive value of 0.98 for hospital admission. These data suggest that severity may best be determined by early response (within 30 minutes) to treatment rather than by the patient's initial presentation, a conclusion that has been supported by others.¹²

Characteristics identifying patients at a particular risk for life-threatening deterioration are summarized in Table III. Although there is no single variable that can describe the severity of an acute asthma episode, it appears, however, that a combination of PEF <50% predicted, SpO₂ <91%, and lack of response to initial bronchodilator treatment are the most reliable factors in predicting need for hospitalization and relapse after discharge from the ED.

TREATMENT

β₂-adrenergic agonists (β-agonists) are the most effective known bronchodilators and have been the first-line treatment of acute childhood asthma for several decades. In

Table III. Characteristics identifying patients at particular risk for life threatening deterioration

- Infants < 1 year old
- Prior history of life-threatening exacerbation
- Less than 10% improvement in PEF in the emergency department
- PEF or FEV₁ <25% of predicted value
- PCO₂ ≥40mm Hg
- Wide daily fluctuations in PEF
- Patient cannot recognize airflow obstruction

children, there are a number of important considerations concerning types of β-agonist, doses, delivery systems, and factors important to positive clinical outcomes.

Delivery Systems

Inhaled β-agonists may be delivered via metered-dose inhalers (MDI), which are increasingly used in combination with a valved holding chamber (VHC). The development of VHCs has greatly improved the efficacy of MDIs for young children by creating a reservoir of aerosol that can be inhaled for 3 to 5 seconds after actuation, eliminating the need for hand-breath coordination and for slow, deep inhalation.¹³

An alternative to the MDI is the small-volume nebulizer (SVN). Advantages to SVNs include use at any age, administration while asleep, use of oxygen or helium plus oxygen as driving gas, and variable drug combination (β-agonist, anticholinergic, epinephrine, inhaled corticosteroid).

Extensive literature comparing MDI + VHC with SVN (Table IV) supports the equivalence of the two delivery systems in treating acute asthma.¹⁴⁻¹⁷ However, there is an increasing body of evidence, including a recent meta-analysis, which finds the efficacy of MDI with spacing device superior to that of SVNs, particularly in regard to onset of action, cost-effectiveness, convenience, and reduction of hospitalization.¹⁸⁻²⁰ In one such study, Rubilar et al¹⁹ studied 123 patients with moderate to severe wheezing seen in the ED. Patients were randomly chosen for treatment by either MDI-VHC or SVN. In the first hour, the MDI-VHC group was given 2 puffs of albuterol every 10 minutes for 5 doses; the SVN group

Table IV. Summary of study design and results in studies comparing treatments for acute childhood asthma*

Source, y	Setting	Mean age (Range), y	No. subjects, MDI/SVN	Dose ratio, MDI:SVN	Variables measured			Results of MDI vs SVN
					Clinical outcomes	SaO ₂	PFT	
Freelander and Van Asperen	ED	7.6 (3-13)	14/14	1:2	Yes	No	Yes	=
Fuglsand and Pedersen	ED	10.0 (7-14)	21/21	1:1	Yes	No	Yes	Better
Pendergast et al,	ED	4.5 (3-7)	18/9	1:2, 1:4	Yes	No	No	=
Ba et al,	Hospital	11.9 (7-18)	14/13	1:4	Yes	No	Yes	=
Lee et al,	Office	3.2 (0.5-6)	16/17	1:3	Yes	Yes	No	=
Kerem et al,	ED	10.3 (6-14)	17/16	1:5	Yes	Yes	Yes	=
Lin et al,	ED/Clinic	10.3 (6-14)	56/55	1:6	Yes	Yes	Yes	Better
Parkin et al,	Hospital	3.0 (1-5)	30/30	1:4	Yes	No	No	=
Chou et al,	ED	7.7 (NA)	71/81	NA	Yes	Yes	Yes	= or Better
Williams et al,	ED	10.4 (6-18)	42/18	1:6.9	Yes	Yes	Yes	=
Schuh et al,	ED	9.1 (5-17)	30/30/30 ¹	1:5:10	Yes	Yes	Yes	All =
Mandelberg et al,	ED	1.4 (0.8-4)	23/19	1:6.9	Yes	Yes	No	=
Plain et al,	ED	2.1 (1-5.2)	32/32	1:3	Yes	Yes	No	=

*MDI indicates metered-dose inhaler, SVN, small-volume nebulizer; SaO₂, oxyhemoglobin saturation; PFT, pulmonary function tests; NA, not available; and ED, emergency department.

¹MDI low dose 2 puff MDI high dose 6-10 puff MDI (100 mcg albuterol) neb = 0.15 mg/kg albuterol.

received 0.25 mg/kg albuterol every 20 minutes for 3 doses. Patients who did not respond in the first hour received another hour of the same treatment in addition to a dose of intramuscular betamethasone. Success (determined by a clinical score ≤ 5 ; range, 0 to 12) after the first hour was 90% in the MDI-VHC group and 71% in the SVN group; after the second hour, success was 100% in the MDI-VHC group and 94% in the SVN group. However, in children younger than 2 years of age, optimal delivery of drug may not be achieved easily when crying.²¹

Medications and Doses

Medications available for aerosol therapy include racemic albuterol (a 50:50 mixture of [R]- and [S]-albuterol) and levalbuterol (the pure [R]-enantiomer). Levalbuterol is 100-fold more potent in β_2 -receptor binding than (S)-albuterol and is primarily responsible for the bronchodilating effects of the racemic compound. Levalbuterol is available in unit dose vials of 0.31 mg, 0.63 mg, and 1.25 mg. The racemic mixture is available in a solution of 5 mg/mL or unit dose vials. It has been suggested that the total dose of racemic albuterol required to maximally bronchodilate adult patients with an asthma exacerbation is between 5 and 10 mg.²² There does not appear to be any advantage in giving quantities larger than 10 mg once pulmonary function approaches discharge criteria as judged by PEF measurement.²³ A similar prospective, randomized study is needed to define optimal dosing in children.

Recently, Carl et al²⁴ studied 547 patients (age, 1 to 18 years) with acute asthma presenting to the ED. Every 20 minutes, patients received either 2.5 mg racemic albuterol

or 1.25 mg levalbuterol via nebulizer, until they either met discharge criteria or reached a maximum of six treatments within 2 hours, at which point they were admitted. Patients who did not meet the discharge criteria after the first treatment were given 2 mg/kg per day of oral prednisone (maximum, 60 mg). In the racemic albuterol group, 122 patients (45%) required hospitalization, whereas a significantly lower number of patients in the levalbuterol group (101 patients or 36%) were admitted. The relative risk of admission in the racemic albuterol group compared with the levalbuterol group was 1.25 (95% CI, 1.01 to 1.51, $P = .04$). However, children who reported frequent use of racemic albuterol before coming to the ED were almost twice as likely to be hospitalized as patients with little or no previous albuterol use. Similarly, in another study, adult patients who presented to the ED with high serum levels of the (S)-enantiomer had the poorest response to ED treatment.²⁵ These studies suggest that repeated doses of racemic albuterol may be associated with more severe bronchospasm, increased airway hyperreactivity, and blunted bronchodilator responses caused by tachyphylaxis. Before recommending that all patients be treated only with levalbuterol, more data are required, especially because of its significant cost.

Parenteral β -agonist (epinephrine or terbutaline sulfate), administered by subcutaneous injection, is primarily indicated for bronchodilation associated with a systemic anaphylactic reaction (for example, to food, insect sting, and allergy immunotherapy).²⁶ The recommended dose of aqueous epinephrine is 0.01 mg/kg to a maximum of 0.3 mg in children; terbutaline is recommended at 10 to 12 μ g/kg.²⁷ The long-acting β -agonist formoterol, however, has an onset of

action similar to albuterol, and 4.5 μg was found to be as effective as 180 μg of albuterol for acute asthma when delivered via MDI.²⁸ This drug is being investigated in the treatment of acute asthma.

ANTICHOLINERGICS

Recent data have shown that the addition of ipratropium bromide (IB) to β -agonists improves outcomes in acute pediatric asthma. IB is available as an MDI (18 μg per puff) and as a solution (200 $\mu\text{g}/\text{mL}$) in unit dose vials of 500 μg .

Schuh et al²⁹ reported the outcome of 120 children (age, 5 to 17) with severe asthma ($\text{FEV}_1 < 50\%$) in a three-arm, randomized study. Three groups all received 0.15 mg/kg (0.03 mL/kg) of nebulized albuterol every 20 minutes for 3 doses. In addition, group A received 250 μg of IB every 20 minutes, whereas group B received 250 μg of IP in the initial dose only. Group C did not receive IB (Figure 1). None of the patients received corticosteroid or other additional form of bronchodilator therapy. Group A showed the greatest improvement in FEV_1 , with an increase of 27% after three doses, whereas FEV_1 in group B increased by 22% and in group C by 15% (Figure 1). There was no statistical difference in side effects or hospitalization rate among the three groups, except in patients with severe asthma (initial $\text{FEV}_1 < 30\%$), where the hospitalization rate was 27% for group A, 56% for group B, and 83% for group C. This study was not powered for admission rate but rather dose and efficacy.

Qureshi et al³⁰ reported similar results in a randomized, double-blinded, placebo-controlled study of 434 children (age, 2 to 18 years) presenting with an acute asthma exacerbation. In the group receiving albuterol (2.5 mg) plus IB (250 μg), 27.4% were admitted to the hospital compared with 36.5% in the group receiving albuterol only. As in the Schuh study, effects were more evident in children with severe asthma (PEF $< 50\%$, asthma score 12 to 15, with maximum score of 15), where 37.5% of patients receiving albuterol + IB were admitted compared with 52.6% of the control group. There was no significant decrease in admission rates in patients with mild to moderate/acute asthma.

Some studies have found that there is no significant difference between albuterol + IB and albuterol alone. In a report by Ducharme and Davis,³¹ a group of 298 children (age, 3 to 17 years) with mild to moderate acute asthma were given 250 μg of IB every 30 minutes in addition to low-dose or high-dose albuterol. There was no significant difference in either group for respiratory resistance, symptoms, hospital admission, or ED relapse. No additional benefit is derived in hospitalized patients who are treated with 250 μg IB added to frequency dosed albuterol.^{32,33} However, when patients are stratified according to disease severity, IB, though less effective in patients with mild to moderate asthma, significantly improves symptoms and reduces hospitalization rates in some patients with severe disease, especially when a multiple dose protocol is used.

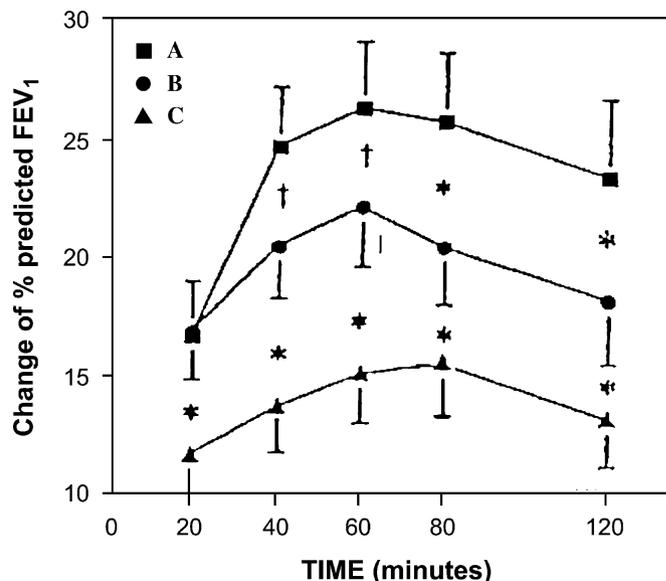


Figure 1. Mean difference (\pm SEM) from baseline of percentage of predicted FEV_1 with time in group A (three ipratropium doses), group B (one ipratropium dose), and group C (no ipratropium). Repeated-measures analysis of variance: $P = .0001$ * $P < .01$. † $P < .05$. Reprinted with permission.²⁹

CORTICOSTEROIDS

Extensive data demonstrate that the use of systemic corticosteroids (CS) in the treatment of acute asthma has a beneficial effect. The most commonly used agents are oral prednisone and methylprednisolone (intravenous or intramuscular). Oral prednisone is recommended at 2 mg/kg per day (60 mg maximum) for 5 to 10 days. Oral dexamethasone (DEX 0.6 mg/kg per day max 16 mg for 2 days) has been compared with prednisone (Pred. 2 mg/kg per day 60 mg max for 5 days) in children 2 to 18 years of age with acute asthma in the ED. The primary outcome was need to return for acute care: There was no difference in relapse rates at 10 days DEX (7.4%) and Pred. (6.9%). The prednisone group had higher incidence of vomiting in the ED (3% vs 0.3%), nonadherence to protocol (4% vs 0.4%), and more missed school days (19.5% vs 13.5%).³⁴ Methylprednisolone is recommended at 2 to 4 mg/kg divided into 3 or 4 doses per day, with a maximum single dose of 125 mg. Higher doses are not thought to offer additional benefit and may be associated with increased side effects. Studies have shown that intravenous, intramuscular, and oral administrations produce equal effects.^{35,36} The clinical effects of corticosteroids occur at 1 to 3 hours and maximal effects at 4 to 8 hours. Intervention with CS incorporated into the early stages of emergency department treatment, in most studies,³⁷⁻⁴⁰ though not all,^{41,42} led to reduced hospital admissions.

There is little evidence that inhaled corticosteroids (ICS) are effective in the treatment of pediatric acute asthma, regardless of severity. Although most data indicate that systemic CS are superior to ICS in treating asthma exacerbations,⁴³⁻⁴⁵ some studies did not reach this conclusion.^{46,47} When therapy combining ICS and systemic CS is used,

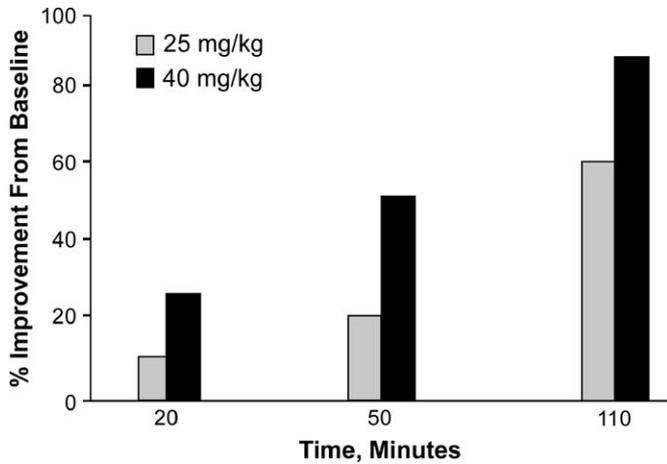


Figure 2. Comparison of percent improvement of PEF from baseline with low- and high-dose intravenous magnesium sulphate. Reprinted with permission.⁵³ ©2000, American Medical Association. All rights reserved.

studies yield mixed results.⁴⁸⁻⁵⁰ Overall, without further data, ICSs appear to play a marginal role in treating severe acute asthma. Though ICS may be effective in treating mild asthma symptoms in children at home, systemic CS should be used in moderate to severe exacerbations.

LEUKOTRIENE RECEPTOR ANTAGONISTS

There are two available leukotriene receptor antagonists: zafirlukast and montelukast. To date, no published studies have examined the efficacy of leukotriene receptor antagonists in acute childhood asthma. However, in a placebo-controlled study of adults with acute asthma, Camargo et al⁵¹ found that the addition of montelukast to standard therapy causes rapid benefit. In this study, patients were randomly assigned to receive either 7 mg IV montelukast, 14 mg IV montelukast, or intravenous placebo in addition to aerosol β -agonist and ICS. Over the first 20 minutes, there was no difference in the response between the 7 mg and 14 mg groups. The montelukast-treated groups had a significant improvement in FEV₁ with an increase of 14.8% predicted FEV₁ versus 3.6% predicted in the placebo group over a period of 2 hours.

MAGNESIUM SULFATE

Magnesium sulfate (MgSO₄) has been shown to inhibit smooth muscle contraction, decrease histamine release from mast cells, and inhibit acetylcholine release from cholinergic nerve endings. Normal serum levels range from 1.5 to 2.2 mg/dL whereas at 4 to 6 mg/dL it stimulates bronchodilation. Levels of 12 to 15 mg/dL are associated with respiratory failure, cardiac arrhythmia, and death.

Ciarallo et al⁵² studied the effects of both low- and high-dose MgSO₄ treatments. 31 patients (age, 6 to 18 years), with PEF <60% predicted after receiving three β -agonist treatments, were given 2 mg/kg methylprednisolone followed by either 25 mg/kg MgSO₄ or placebo. Patients were followed

over 120 minutes. All patients in the control group were admitted compared with 73% of the treatment group.

In their second study,⁵³ a higher dose of 40 mg/kg MgSO₄ was given as adjunctive therapy to patients presenting to the ED with PEF <70% predicted. All patients had been treated with β -agonists, anticholinergic drugs, and corticosteroids. Initial improvement occurred within 20 minutes and continued up to 110 minutes. The difference between the low- and high-dose studies are summarized in Figure 2. However, not all studies in children have shown beneficial effects with MgSO₄. For example, a dose of 75 mg/kg (maximum, 2.5 g) MgSO₄ in addition to β -agonist and intravenous methylprednisolone did not change the pulmonary index in children compared with control subjects.⁵⁴ There appears to be no consistent positive response to MgSO₄ when doses from 25 to 75 mg/kg are given. This does not rule out individual patients deriving benefit, so MgSO₄ may be tried when respiratory failure is impending.

METHYLYXANTHINE

Intravenous methylxanthine, a bronchodilator, was first used in the treatment of acute asthma in 1937 and has continued to be used for asthma. Theophylline was commonly used to treat patients hospitalized with asthma exacerbations until numerous studies in the 1990s revealed that theophylline added no benefit to treatment with β -agonists and corticosteroids.⁵⁵⁻⁵⁷ Routine use of theophylline is no longer advocated although it has been shown to have adjunctive benefit in select patients with impending respiratory failure.⁵⁸⁻⁶⁰

OXYGEN AND HELIUM-OXYGEN MIXTURES

Hypoxemia during an acute asthma exacerbation is secondary to ventilation/perfusion mismatch, which may be accentuated by β -agonist treatment. Hypoxemia may be corrected with administration of low-flow oxygen (28%). This level of supplemental oxygen has been shown to be safer than 100% oxygen, especially in adults with more severe airway obstruction who are at risk for CO₂ retention.⁶¹

Helium-oxygen mixtures (Heliox) are available in concentrations of 80% helium/20% oxygen and 70% helium/30% oxygen. Heliox mixtures have a low density compared with air (the 80/20 mixture is approximately one-third the density of air). Heliox, however, is a temporary measure to reduce respiratory resistive work and forestall muscle fatigue until airways obstruction improves with conventional therapy. Some studies have found heliox minimally effective,⁶² whereas others have not.⁶³

Heliox may also be effective as the driving gas for nebulized bronchodilators. The low density of helium improves the deposition of aerosolized particles in the airways, which can lead to a more rapid response to treatment and more significant improvement in airway function.⁶⁴ However, this intervention is expensive and may not benefit the majority of patients.

NONINVASIVE MECHANICAL VENTILATION

Noninvasive ventilation is becoming more widespread. This type of ventilation allows for correction of gas exchange abnormalities with lower inspiratory pressures (<25 cm H₂O) than invasive ventilation. Continuous positive airway pressure has been reported to have a bronchodilatory effect in asthma, to relieve fatigued inspiratory muscles, and to improve gas exchange.⁶⁵ In the ED, the addition of bilevel positive airway pressure to conventional treatment (albuterol, ipratropium, and corticosteroids) can improve lung function and asthma symptoms and significantly reduce the need for hospitalization.⁶⁶

SUMMARY

The National Asthma Education and Prevention Program expert panel has prescribed guidelines for the acute treatment of childhood asthma (Figure 3; available online at www.jpeds.com).⁶⁷ The guidelines emphasize the need for a historic, physical, and physiologic assessment (PEF, FEV₁ and SpO₂) to guide initial therapy. The early use of supplemental oxygen with SpO₂ <90% and inhaled β₂-agonists are the cornerstone of therapy. It is extremely important to select the appropriate delivery system for each patient to improve short-term outcomes. The response to IB is variable, but there is very little risk from the addition of 250 μg IB to β-agonist treatment. The use of CS early in the course of treatment maximizes the chance for successful treatment. When severe asthma is refractory to therapy then MgSO₄, methylxanthine and HeO₂ may be tried in an effort to avoid noninvasive or mechanical ventilation. After successful treatment, it is imperative that the patient receive a written asthma management plan and a follow-up appointment in 3 to 7 days.

We thank Julia McElvain, BA, and Rachel Kiblitau, BA, for editorial assistance.

REFERENCES

1. Smith DH, Malone DC, Lawson KA, Okamoto LJ, Battista C, Saunders WB. A national estimate of the economic costs of asthma. *Am J Respir Crit Care Med* 1987;158:707-93.
2. Crain EF, Weiss KB, Bijur PE, Hersh M, Westbrook L, Stein RE. An estimate of the prevalence of asthma and wheezing among inner-city children. *Pediatrics* 1994;94:356-62.
3. Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for Asthma: United States, 1980-1999. *MMWR Surveillance Summaries*. Atlanta (GA); Vol 51/SS-1, 1-13, 2002.
4. National Asthma Education and Prevention Program Expert Panel. National Asthma Education and Prevention Program Expert Panel Report II: guidelines for the diagnosis and management of asthma. NIH Publication 97-4051. Bethesda, MD: National Institutes of Health; 1997.
5. British Thoracic Society. Guidelines on the management of asthma. *Thorax* 1993;48:S1-24.
6. Boulet LP, Becker A, Bérubé D, Beveridge R, Ernst P, on behalf of Canadian Asthma Consensus Group. Summary of recommendations from the Canadian Asthma Consensus Report. *CMAJ* 1999;161(Suppl 11):S1-2.
7. Eid N, Yandell B, Howell L, Eddy M, Sheikh S. Can expiratory flow predict airflow obstruction in children with asthma? *Pediatrics* 2000;105:354-8.
8. Smith SR, Baty JD, Hodge D. Validation of the pulmonary score: an asthma severity score for children. *Acad Emerg Med* 2002;9:99-104.
9. Geelhead GC, Landau LI, LeSouef PN. Oximetry and peak expiratory flow in assessment of acute childhood asthma. *J Pediatr* 1990;117:907-9.
10. Smith SR, Strunk RC. Acute asthma in the emergency department. *Pediatr Clin North Am* 1999;46:1145-65.
11. Rodrigo G, Rodrigo C. A new index for early prediction of hospitalization in patients with acute asthma. *Am J Emerg Med* 1997;15:8-13.
12. McFadden ER Jr. Acute severe asthma. *Am J Respir Crit Care Med* 2003;168:740-59.
13. Amirav I, Newhouse MT. Metered-dose inhaler accessory devices in acute asthma. *Arch Pediatr Adolesc Med* 1997;151:876-82.
14. Schuh S, Johnson DW, Stephens D, Callahan S, Winders P, Canny GJ. Comparison of albuterol delivered by a metered dose inhaler with spacer versus a nebulizer in children with mild acute asthma. *J Pediatr* 1999;135:22-7.
15. Kerem E, Levison H, Schuh S, O'Brodovich H, Reisman J, Bentur L, et al. Efficacy of albuterol administered by nebulizer versus spacer in children with acute asthma. *J Pediatr* 1993;123:313-7.
16. Mandelberg A, Tsehor S, Houry S, Gilad E, Morag B, Priel IE. Is nebulized aerosol treatment necessary in the pediatric emergency department? *Chest* 2000;117:1309-13.
17. Ploin D, Chapuis FR, Stamm D, Robert J, David L, Chatelain PG, et al. High-dose albuterol by metered-dose inhaler plus a spacer device versus nebulization in preschool children with recurrent wheezing: a double-blind, randomized equivalence trial. *Pediatrics* 2000;106:311-7.
18. Amirav I, Newhouse MT. Aerosol therapy with valved holding chambers in young children: importance of the facemask seal. *Pediatrics* 2001;108:389-94.
19. Rubilar L, Castro-Rodriguez J, Girardi G. Randomized trial of salbutamol via metered-dose inhaler with spacer versus nebulizer for acute wheezing in children less than 2 years of age. *Pediatr Pulmonol* 2000;29:264-9.
20. Castro-Rodriguez J, Rodrigo GJ. β-Agonist through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age: a systematic review with meta-analysis. *J Pediatr* 2004;145:172-7.
21. Wildhaber JH, Dore ND, Wilson JM, Devadason SG, LeSouef PN. Inhalation therapy in asthma: nebulizer or pressurized metered-dose inhaler with holding chamber? In vivo comparison of lung deposition in children. *J Pediatr* 1999;135:28-35.
22. McFadden ER Jr, Strauss L, Hejal R, Galan G, Dison L. Comparison of two dosage regimens of albuterol in acute asthma. *Am J Med* 1998;105:12-7.
23. Emerman CL, Cydulka RK, McFadden ER Jr. Comparison of 2.5 vs 7.5 mg of inhaled albuterol in the treatment of acute asthma. *Chest* 1999;115:92-6.
24. Carl JC, Myers TR, Kirchner HL, Kerckmar CM. Comparison of racemic albuterol and levalbuterol for treatment of acute asthma. *J Pediatr* 2003;143:731-6.
25. Nowak RM, Emerman CL, Schaefer K, Disantostefano RL, Vaickus L, Roach JM. Levalbuterol compared with racemic albuterol in the treatment of acute asthma: results of a pilot study. *Am J Emerg Med* 2004;22:29-36.
26. Nicklas RA, Bernstein IL, Li JT, Lee RE, Spector SL, Dykewicz MS, et al. The diagnosis and management of anaphylaxis. *J Allergy Clin Immunol* 1998;101:S465-527.
27. Simons FER, Gillies JD. Dose response of subcutaneous terbutaline and epinephrine in children with acute asthma. *Am J Dis Child* 1981;135:214-7.
28. Paulwels RA, Sears MR, Campbell M, Villasante C, Huang S, Lindh A, et al. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. *Eur Respir J* 2003;22:787-94.
29. Schuh S, Johnson DW, Callahan S, Canny G, Levison H. Efficacy of frequent nebulized ipratropium bromide added to frequent high-dose albuterol therapy in severe childhood asthma. *J Pediatr* 1995;126:639-45.
30. Qureshi F, Pestian J, Davis P, Zaritsky A. Effect of nebulized ipratropium on the hospitalization rates of children with asthma. *N Engl J Med* 1998;133:479-85.
31. Ducharme FM, Davis GM. Randomized controlled trial of ipratropium bromide and frequent low doses of salbutamol in the management of mild and moderate acute pediatric asthma. *J Pediatr* 1998;133:479-85.

32. Goggin N, Macarthur C, Parkin PC. Randomized trial of the addition of ipratropium bromide to albuterol and corticosteroid therapy in children hospitalized because of an acute asthma exacerbation. *Arch Pediatr Adolesc Med* 2001;155:1329-34.
33. Crave D, Kerckmar CM, Myers TR, O'Riordan MA, Golonka G, Moore S. Ipratropium bromide plus nebulized albuterol for the treatment of hospitalized children with acute asthma. *J Pediatr* 2001;138:51-8.
34. Qureshi F, Zaritsky A, Poirier MP. Comparative efficacy of oral dexamethasone versus oral prednisone in acute pediatric asthma. *J Pediatr* 2001;139:20-6.
35. Ratto D, Alfaro C, Sipsy J, Glovsky MM, Sharma OP. Are intravenous corticosteroids required in status asthmaticus? *JAMA* 1988;260:527-9.
36. Gries DM, Moffitt DR, Pulos E, Carter ER. A single dose of intramuscularly administered dexamethasone acetate is as effective as oral prednisone to treat asthma exacerbations in young children. *J Pediatr* 2000;136:298-303.
37. Scarfone RJ, Fuchs SM, Nager AL, Shane SA. Controlled trial of oral prednisone in the emergency department treatment of children with acute asthma. *Pediatrics* 1993;92:513-8.
38. Storr J, Barrell E, Barry W, Lenney W, Hatcher G. Effect of a single oral dose of prednisone in acute childhood asthma. *Lancet* 1987;1:879-82.
39. Tal A, Levy N, Bearman JE. Methylprednisolone therapy for acute asthma in infants and toddlers: a controlled clinical trial. *Pediatrics* 1990;86:350-6.
40. Connett GJ, Warde C, Wooler E, Lenney W. Prednisolone and salbutamol in the hospital treatment of acute asthma. *Arch Dis Child* 1994;70:170-3.
41. Stein LM, Cole RP. Early administration of corticosteroids in emergency room treatment of acute asthma. *Ann Intern Med* 1990;112:822-7.
42. Wolfson DH, Nypaver MM, Blaser M, Hogan A, Evans R III, Davis AT. A controlled trial of methylprednisolone in the early emergency department treatment of acute asthma in children. *Pediatr Emerg Care* 1994;10:335-8.
43. Schuh S, Reisman J, Alshehri M, Dupuis A, Corey M, Arseneault R, et al. A comparison of inhaled fluticasone and oral prednisone for children with severe acute asthma. *N Engl J Med* 2000;343:689-94.
44. Edmonds ML, Camargo CA, Pollack CV, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma [Cochrane Review]. *Cochrane Database Syst Rev* 2000;4:CD002308.
45. Nakanishi AK, Klasner AK, Rubin BK. A randomized controlled trial of inhaled flunisolide in the management of acute asthma in children. *Chest* 2003;124:790-4.
46. Volovitz B, Bentur L, Finkelstein Y, Mansour Y, Shalitin S, Nussinovitch M, et al. Effectiveness and safety of inhaled corticosteroids in controlling acute asthma attacks in children who were treated in the emergency department: a controlled comparative study with oral prednisolone. *J Allergy Clin Immunol* 1998;102:605-9.
47. Devidayal, Singhi S, Kumar L, Jayshree M. Efficacy of nebulized budesonide compared to oral prednisolone in the treatment of acute bronchial asthma. *Acta Paediatr* 1999;88:835-40.
48. Rodrigo G, Rodrigo C. Inhaled flunisolide for acute severe asthma. *Am J Respir Crit Care Med* 1998;157:698-703.
49. Sung L, Osmond MH, Klassen TP. Randomized, controlled trial of inhaled budesonide as an adjunct to oral prednisone in acute asthma. *Acad Emerg Med* 1998;5:209-13.
50. Nuhoglu Y, Bahceci NN, Barlan IB, Basaran MM. The effectiveness of high-dose inhaled budesonide therapy in the treatment of acute asthma exacerbations in children. *Ann Allergy Asthma Immunol* 2001;86:318-22.
51. Camargo CA, Smithline HA, Malice M, Green SA, Reiss TF. A randomized controlled trial of intravenous montelukast in acute asthma. *Am J Respir Crit Care Med* 2003;167:528-33.
52. Ciarallo L, Sauer AH, Shannon MW. Intravenous magnesium therapy for moderate to severe pediatric asthma: results of a randomized placebo-controlled trial. *J Pediatr* 1996;129:809-14.
53. Ciarallo L, Brousseau RS. Higher dose intravenous magnesium therapy for children with moderate to severe acute asthma. *Arch Pediatr Adolesc Med* 2000;154:979-83.
54. Scarfone RJ, Loisselle JM, Joffe MD, Mull CC, Stiller S, Thompson K, et al. A randomized trial of magnesium in the emergency department treatment of children with asthma. *Ann Emerg Med* 2000;36:572-8.
55. Needleman JP, Kaifer MC, Nold JT, Shuster PE, Redding MM, Gladstein J. Theophylline does not shorten hospital stay for children admitted for asthma. *Arch Pediatr Adolesc Med* 1995;149:206-9.
56. Bien JP, Bloom MD, Evans RL, Specker B, O'Brien KP. Intravenous theophylline in pediatric status asthmaticus. *Clin Pediatr* 1995;34:475-81.
57. Nuhoglu Y, Dai A, Barlan IB, Basaran MM. Efficacy of aminophylline in the treatment of acute asthma exacerbation in children. *Ann Allergy Asthma Immunol* 1998;80:395-8.
58. Yung M, South M. Randomised controlled trial of aminophylline for severe acute asthma. *Arch Dis Child* 1998;79:405-10.
59. Ream RS, Loftis LL, Albers GM, Becker BA, Lynch RE, Mink RB. Efficacy of IV theophylline in children with severe status asthmaticus. *Chest* 2001;119:1480-8.
60. Self TH, Redmond AM, Nguyen WT. Reassessment of theophylline use for severe asthma exacerbation: is it justified in critically ill hospitalized patients? *J Asthma* 2002;39:677-86.
61. Rodrigo GJ, Verde MR, Peregalli V, Rodrigo C. Effects of Short-term 28% oxygen on PaCO₂ and peak expiratory flow rate in acute asthma. *Chest* 2003;124:1312-7.
62. Ho AM, Lee A, Karmakar MK, Dion PW, Chung DC, Contardi LH. Heliox vs air-oxygen mixtures for the treatment of patients with acute asthma. *Chest* 2003;123:882-90.
63. Rodrigo GJ, Rodrigo C, Pollack CV, Rowe B. Use of helium-oxygen mixtures in the treatment of acute asthma. *Chest* 2003;123:891-6.
64. Kress JP, Noth I, Gehlbach BK, Barman N, Pohlman AS, Miller A, et al. The utility of albuterol nebulized with heliox during acute asthma exacerbations. *Am J Respir Crit Care Med* 2002;165:1317-21.
65. Shivaram U, Donath J, Khan FA, Juliano J. Effects of continuous positive airway pressure in acute asthma. *Respiration* 1987;52:157-62.
66. Soroksky A, Stav D, Shpirer I. A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. *Chest* 2003;123:1018-25.
67. Management of Asthma Exacerbations: Emergency Department and Hospital-Based Care <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf>. Accessed on July 20, 2005.

IMPROVING SUBSPECIALTY HEALTHCARE: LESSONS FROM CYSTIC FIBROSIS

MICHAEL S. SCHECHTER, MD, MPH, AND PETER MARGOLIS, MD, PHD

Citing numerous studies that showed deficiencies in the utilization of evidence-based treatments and large variations in the outcomes of care, the Institute of Medicine concluded in 2001 that “Between the health care we have and the care we could have lies not just a gap, but a chasm.”¹ A recent report from the Commonwealth Fund makes it clear that comparable quality problems exist in healthcare delivery for children and adolescents, including those with chronic disease.²

There are an estimated 15 million children in the United States with complex or serious medical problems requiring pediatric subspecialty attention. Although pediatric subspecialists care for a number of conditions whose treatment is uncertain, for many diseases there are specific aspects for which an optimal therapeutic approach has been identified (either by evidence or expert consensus). In these cases, patients are best served by attempts to ensure that their medical care is provided in a systematic and uniform way. Recent analyses of data from the Children’s Oncology Group and the Vermont-Oxford Neonatal Network suggest that the value of these research consortia, which were established primarily to expedite enrollment of subjects into clinical trials, extends beyond research alone. In fact, the standardization of care that results from the use of research protocol-based regimens facilitates the application of optimal treatment approaches and reduces practice-to-practice variability, thereby improving outcomes in control as well as intervention groups.^{3,4}

The system that has been evolving for the care of children with cystic fibrosis (CF) offers an example of how subspecialists can organize and share knowledge that leads to significant improvements in outcomes. In this report, we provide an overview of the components of the CF system, discuss the central role played by the CF registry in showing variation of practice patterns and outcomes, and discuss how the use of collaborative methods can be applied within such a system to support the consistent application of optimal approaches to care. We believe that the CF system provides an example that may be applicable to other pediatric subspecialties that wish to take better advantage of existing knowledge to improve health outcomes for the children for whom they care.

CYSTIC FIBROSIS

Treatment advances have dramatically improved patient survival since CF was first described in 1938 (Figure 1), changing the face of the disease in a relatively short period of time.⁵⁻⁷ The median predicted survival age was 33.5 years in 2003, and about 40% of patients with CF are currently over the age of 18. Nonetheless, there is considerable variability in age at death among the CF population (Figure 2). Much of this variation can be explained by individual patient differences in genetic constitution and environmental or sociodemographic exposures,⁸ but there is a growing appreciation of the degree to which average patient outcomes differ among accredited CF care centers⁹ (Figure 3). There are, in fact, some centers that achieve uniformly superior results across all performance measures. These centers are not necessarily the largest or best known, they differ in size and geographic location, and they do not share a specific unique treatment method. What they have in common is a highly developed system of care that is well adapted to local conditions and allows the consistent and methodical application of therapies based on the best evidence available.¹⁰

System of Care for Children with CF in the United States

Much of the care for children with CF in the United States takes place within centers accredited by the CF Foundation (CFF).¹¹ The CFF was created in 1955 by a consortium

See editorial, p 279 and related articles, p 302, p 306, p 312, p 316, p 321, p 327, p 332, p 396, and p 402.

From the Department of Pediatrics, Brown Medical School, Rhode Island Hospital/Hasbro Children’s Hospital, Providence, Rhode Island; and the Department of Pediatrics and Epidemiology, NC Center for Children’s Healthcare Improvement, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Supported by Cystic Fibrosis Foundation grant CFF SCHECH01C0QI.

Submitted for publication Nov 9, 2004; revision received Jan 25, 2005; accepted Mar 16, 2005.

Reprint requests: Dr Schechter, Brown Medical School, Rhode Island Hospital/Hasbro Children’s Hospital, 593 Eddy St, Suite POB 440, Providence, RI 02903.

J Pediatr 2005;147:295-301.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.03.044

CF	Cystic fibrosis	CFF	Cystic Fibrosis Foundation
----	-----------------	-----	----------------------------

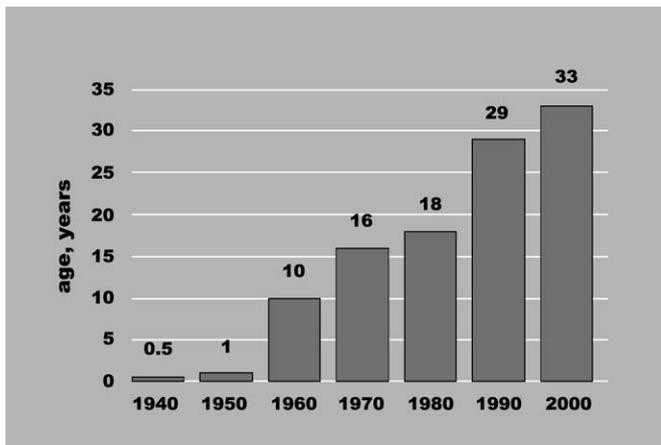


Figure 1. Median age at death of patients with cystic fibrosis, by year.

of parents and physicians with the initial primary goal of encouraging CF-related research, but it quickly broadened its mission to support clinical care and foster teaching about the disease.¹² The CFF has grown tremendously over the years in resources, and its influence is pervasive. It guides the research agenda by interacting with the National Institutes of Health, and, more recently, industry, to solicit and fund a significant portion of all CF research, and it works to ensure the general availability of high-quality medical care for patients with CF through its accreditation system.

There are currently nearly 120 CFF-accredited CF care centers in the United States. Accreditation requires an on-site evaluation to ensure the presence of a multidisciplinary provider team, which includes subspecialty physicians, nutritionists, social workers, respiratory therapists, and physical therapists, as well as adequacy of microbiologic techniques, sweat chloride testing, and other care practices. As survival into adulthood has become commonplace, the CFF has been a strong advocate for the establishment of adult CF care centers to complement existing pediatric clinics, and there are now more than 90 approved adult care programs. Furthermore, the CFF supports the spread of knowledge regarding state of the art care by sponsoring the development of clinical practice guidelines and organizing the annual North American CF conference, which brings together healthcare providers and researchers from all disciplines to an annual assembly with strong international participation. The multidisciplinary “networking” facilitated by the NACF meeting leads to the rapid spread of innovative ideas for care; past examples include the adoption of high fat diets in the 1970s and of more aggressive treatment of *Pseudomonas* airway infection in the 1990s. These novel approaches, initially advocated by a small minority, were then rapidly adopted by the mainstream of CF care centers as word of successes was shared among colleagues.

National CF Patient Registry

A national patient registry containing demographic and clinical data on patients attending accredited care centers in the United States was begun in the mid 1960s; its content

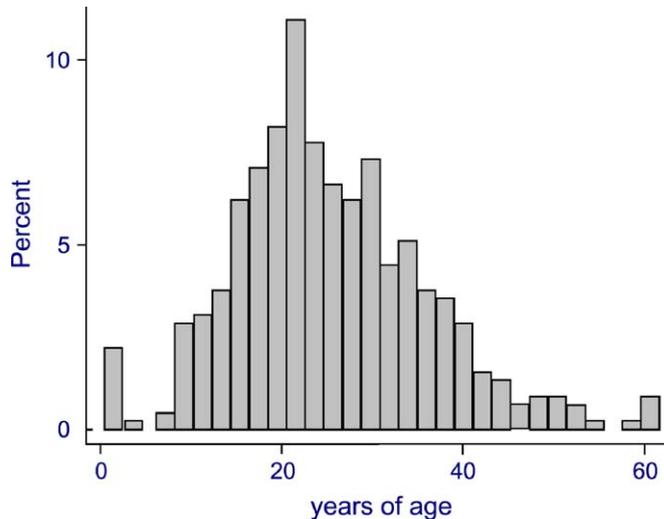


Figure 2. Distribution of age at death for patients with CF dying in 2001 as listed in the National CF Registry.

and use have evolved over the years. It was initially used to generate basic descriptive data regarding the CF population, for example, average age of diagnosis, survival, and microbiologic information, but in the last decade it has been increasingly used for analyses by epidemiologists seeking to identify risk factors and generate hypotheses regarding disease pathogenesis. In its earliest form, the registry was used to show improvements in mortality rate among centers that had evolved a comprehensive treatment program for CF care, which facilitated the spread of this approach.¹³ However, comparisons of outcomes between care centers were deemphasized until 1998, when Gerald O'Connor, a health services researcher with experience in quality improvement, was engaged to perform analyses of the Registry data. Current registry reports now display patient data in ways designed to raise awareness of center-based differences in practice patterns and outcomes (Figure 3 and Figure 4 are examples) and have thus transformed the registry into an important tool to promote quality improvement activities. The registry is now evolving further into a visit-based, web-enabled clinical information system that can provide care centers with data for monitoring individual patients as well as feedback on aggregate center performance of procedures and outcomes.

VARIATION IN CARE IS ASSOCIATED WITH VARIATION IN OUTCOMES

Reports from both the CF Registry and the Epidemiologic Study of CF (ESCF), an industry-sponsored patient registry that operates independently of the CFF, demonstrate that patients with CF do not consistently receive optimal care. For example, although the CF Foundation has formulated relatively conservative guidelines for the regular monitoring of clinical status (timing of clinic visits, pulmonary function testing, airway cultures, and so forth), these routines are followed in only 58% to 79% of patients.¹⁴ Furthermore, surveillance and treatment intensity varies dramatically among

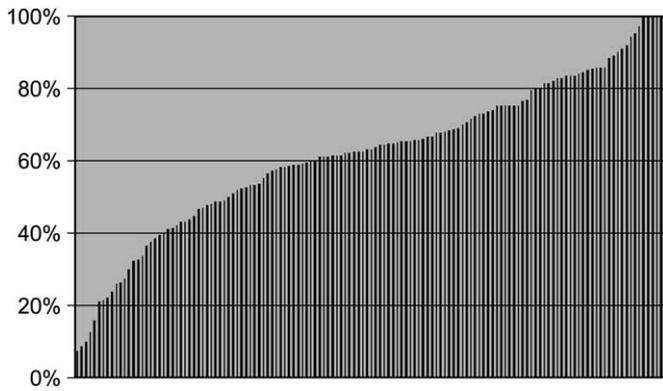


Figure 3. Percentage of patients with weight below the 5th percentile receiving supplemental nutritional feedings at each CF care center with >50 patients. Each vertical bar represents one CF center. Centers with <50 pediatric patients are not shown. The mean for all centers is 61.9% ± 21.3%.

different CF care centers, and those sites with the highest median age-adjusted pulmonary function generally monitor patients more consistently and prescribe more courses of intravenous antibiotics than other centers.¹⁵

The CF Registry provides other examples to illustrate this point. High calorie nutritional supplements are of proven benefit for improving weight gain in pancreatic-insufficient patients with CF.¹⁶ Yet, centers' reported rate of use of nutritional supplements in patients who are below the 5th percentile for weight varies from 7% to 100% (Figure 3). It is not surprising that this variability in the use of dietary supplements is mirrored by variation in nutritional outcomes: Some CF centers have very few children below the 5th percentile for weight, and others have a prevalence in excess of 40% (Figure 4). It is important to point out that these differences in weight are not explained by case severity mix. Center performance can be adjusted for the prevalence of patients with high-risk characteristics, but when this is done, the variability in outcomes remains wide and the relative center performance changes minimally.¹⁷ Furthermore, there is no evidence that centers with better outcomes have greater knowledge of CF care than others. All of the centers represented in the figures are CFF-accredited care centers with subspecialty physician directors supervising a knowledgeable multidisciplinary specialty team as mandated by the CFF. Furthermore, centers that might be expected to have greater expertise, either because they are large and have broader experience or because they perform more CF-related research and thus might be considered more "academic," do not necessarily stand out as superior performers in the CF Registry.¹⁷

Clinicians who care for children with a devastating illness such as CF are passionately committed to providing the best care possible, and the suggestion that this might not be the case is disconcerting. A major value of the CF Registry is that the data are good quality and representative of the entire CF population at each center, thus making it relatively easy to counter the initial defensive protests that data problems account for the observed variation. Furthermore, data are

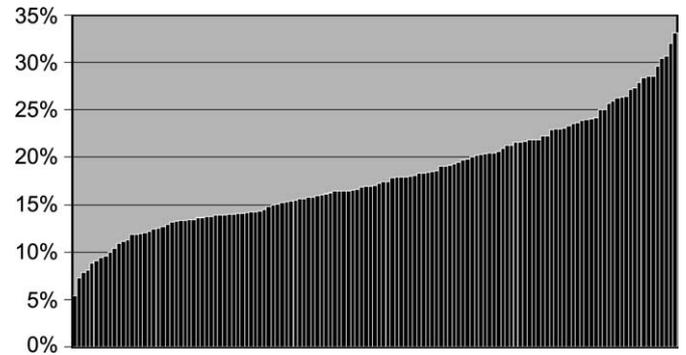


Figure 4. Percentage of patients below the 5th percentile for weight at each CF care center with >50 patients. Each vertical bar represents one CF center. Centers with <50 pediatric patients are not shown. The mean for all centers is 18.0% ± 5.6%.

supplied by center clinicians, who thus bear responsibility for the accuracy and are motivated to maintain it at a high level. Longitudinal analysis of CF Registry data shows that patients with CF cared for at certain centers consistently have short-term and long-term outcomes that are significantly better than the national average (unpublished data). The implication is that if the methods used at these centers were adopted by others, the result would be a dramatic and relatively rapid improvement in life expectancy and quality of life for all patients with CF. Although the response among CF health-care providers has been mixed, most have accepted this as a call to action, and the CFF has begun actively testing methods of accomplishing this goal.

Application of Methods for Improving Outcomes

Traditional CME activities focus on individual clinicians attending didactic sessions, in the belief that knowledge will somehow lead to improvements in practice and consequently to improved patient outcomes. Studies of the effectiveness of such efforts confirm that they rarely achieve their intended goal.^{18,19} Multifaceted, health care systems-oriented approaches to changing the process of care delivery at multiple levels are more effective in improving outcomes than passive approaches.^{19,20} Several recent, randomized trials have demonstrated the efficacy of teaching provider teams continuous quality improvement methods to adapt evidence to their local practice setting.^{21,22}

Recognizing this, the CFF has begun to establish an infrastructure to promote the development and spread of quality improvement methods within the CF community and to train centers in their application. The foundation is funding its own "Learning and Leadership" collaborative projects involving care centers from around the country, as well as two major external initiatives: the Northern New England CF Consortium, and a "Breakthrough Learning Collaborative"²³ supported by the University of North Carolina's Center for Children's Healthcare Improvement (NC CHI) and the National Initiative for Children's Healthcare Quality (NICHQ). The CFF is also working with Cincinnati Children's Hospital Medical Center, which is the recipient of a "Pursuing Perfection" grant from the

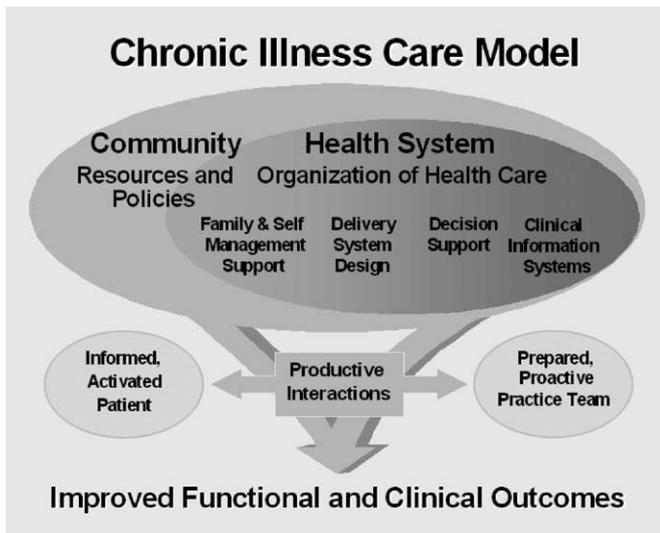


Figure 5. Wagner's chronic care model envisions provider teams and patients interacting in an environment where community resources and policies exist alongside and foster a healthcare delivery system that provides self-management support, an efficient delivery system design, decision support for providers, and a clinical information system that allows tracking of healthcare data on the individual patient and also on the aggregate population served by the provider team.

Robert Wood Johnson Foundation to improve care throughout the institution, with CF as one of the targeted conditions.

These projects all have their own specific approaches that may have differing emphases, but all build on the following theoretical and methodological principles of quality improvement.²⁴

1. *Appreciate that changes must be made to the system of healthcare delivery.*

The first step, and one that is often the most difficult for physicians, is to understand that simply working harder within a nonsupportive system will not yield the results desired. We depend on the functioning of a healthcare delivery system whose complexity has increased exponentially as growth in technology has accelerated, and chronic disease care comprises an increasing proportion of our clinical activities. The archetype of the individual physician who by force of intellect and will establishes the correct diagnosis and prescribes the appropriate therapy to cure a patient is anachronistic and inappropriate to the contemporary realities of providing care for children with chronic disease. Multiple caregivers must communicate and integrate a complex set of data and then prescribe therapy, based on the appropriate use of that data. Although it is incumbent on the system to ensure that providers are knowledgeable regarding ideal (or best) practices, it further needs to support consistent application of those interventions that the providers know to be optimal. Variation in outcomes (when adjusted for variation in risk) is then due to variation in the system's ability to provide this support in a consistent manner.¹

2. *Work with an appropriate model of chronic care delivery.*

The current healthcare system evolved out of one that was initially established to provide acute, episodic care. At this time, chronic conditions affect almost half of the US population and 18% of children,^{1,25} and are the main focus of pediatric subspecialty care. Yet, there remains a dearth of clinical programs with the infrastructure required to provide the full complement of services needed by children with chronic disease.²⁶ Physician groups, hospitals, and other health care organizations often provide care with incomplete information about the patient's condition, medical history, services provided in other settings, or medications prescribed by other clinicians. To optimize the care of children with chronic disease, it is useful to conceptualize and work toward instituting an idealized system of healthcare delivery that is composed of several interdependent components inside and outside the practice setting. Furthermore, patient visits should be considered within a long-term continuum and not as isolated and independent events. Wagner's chronic illness care model provides a useful framework for such care²³ (Figure 5). A more detailed explication of this model may be found at <http://www.improvingchroniccare.org>, but the following highlights are important:

a. *Community Resources*

Medical center-based subspecialists should partner with community organizations and primary care providers to supply needed services to patients. In addition, providers should publicly advocate for social policies that improve access to healthcare resources.

b. *Overall Health Delivery System*

Organizations should create a permeating culture that promotes safe, high quality care. There should be an open and systematic approach to reducing errors and incentives rewarding high quality care. Care should be coordinated within and across organizations.

c. *Patient and Family Self-Management*

When patients and families are informed and empowered as partners in care, they become an enormous resource for assessment, goal setting, and treatment planning. Furthermore, patients' input should be sought in reconfiguring delivery system design to make it optimally effective.

d. *Delivery System Design*

Delivery system design includes the structure and function of the clinic, from the telephone to the reception area to the examination room. Team members should have clearly defined roles and responsibilities and ensure that clinic flow is optimized, patient visits are planned to accomplish specific goals, and appropriate follow-up is ensured.

e. *Decision Support*

Decision support promotes the application of evidence-based care at the provider-patient interface. This is accomplished through the use of guidelines and algorithms, clinical tools to ensure that reliance on rote memory is minimized, and intended care is actually prescribed.

f. *Clinical Information Systems*

Clinical information systems function at two levels. For individual patient care, the system should provide ready access to data relevant to care decisions, provide timely reminders regarding routine interval care, and facilitate sharing of data to coordinate care. At the clinic-wide population level, the system should help to identify relevant subpopulations for proactive care and allow providers to monitor performance of the practice team. It is the lack of the latter data that keeps many providers in the dark regarding the true effectiveness of their care.

When informed patients take an active role in managing their health and providers feel prepared and supported with time and resources, their interaction is likely to be much more productive.

3. *Test small changes sequentially and then spread the effective ones.*

An effective organizational change strategy is an essential component of improvement work. Without a disciplined approach, practitioners who are newly aware of the extent of their system's deficiencies will often attempt immediate, dramatic changes that either fail in their planning stage because they get bogged down in endless preparatory meetings, or self-destruct in their implementation phase because of the number of unanticipated problems encountered. Use of the Plan/Do/Study/Act (PDSA) cycle is an approach of proven effectiveness.²⁷ To implement the process, the first step is to plan the details of a small test of change [plan]. The planned change is then carried out [do]. Once the change is attempted on a small scale, data on its effectiveness is gathered [study]. After discussion of what was learned by the initial endeavor, the change strategy is then modified and reattempted [act]. The repeated use of PDSA cycles provides a scientific basis for testing theories and identifying effective methods that accomplish meaningful improvements in care. The essential key to the success of this approach is the use of small changes that are easily accomplished, followed by the analysis of data to evaluate the impact of the intervention.

4. *Use data to get feedback on the effectiveness of the work.*

The use of data on performance is essential to recognize where opportunities for improvement exist and to garner feedback on what changes truly result in improved outcomes. Once an organization decides to implement specific actions to improve outcomes, it needs to track the consistency with which those actions are taken. Improved performance on these process measures can be measured as a preliminary step to improvement in the outcome measures that are the true goal of the work. Process measures should be selected to be sensitive reflectors of whether effective change is taking place. Feedback must be provided promptly and on a regular basis, and data should be reported visually in a way that can be understood and used by members of the care team as well as interested outsiders.

Table. Specific goals of the collaborative

Nutrition

- Process goals: At >95% of visits
 - ◆ Nutritional status classification is verified
 - ◆ Self-management goals regarding diet and use of pancreatic enzymes are reviewed
 - ◆ Patients with less than satisfactory nutritional status are documented to have received appropriate evaluation and intervention as described in the 2002 Consensus guidelines
- Outcome goals
 - ◆ 50% reduction in the proportion of children with less than satisfactory nutritional status
 - ◆ 30% increase in centers' median weight percentile

Environmental tobacco smoke

- Process goals: At >95% of visits
 - ◆ Parents' smoking status is documented
 - ◆ Patients receive counseling on elimination of environmental tobacco smoke exposure
 - ◆ If a smoking parent is present, caregivers utilize the NCI 5A model to help promote cessation
- Outcome goals
 - ◆ 95% of patients' families report a clear no smoking policy in their environments
 - ◆ 20% of smoking parents quit

5. *Collaborate, and "steal" good ideas shamelessly.*

The synergy that derives from collaboration among workers investigating the same problem is well known to scientific researchers, the most successful of whom are typically embedded in networks of cooperating laboratories within and outside their home institutions. This strategy is equally effective for the development and spread of innovations for improvement in the delivery of health services. The most commonly used cooperative model is one that seeks to identify "best practices" as a means of finding ideas that can be adapted from providers whose outcomes are the best within their field. However, novel, effective ideas for how to accomplish certain specific goals exist even at centers whose overall performance is average, especially if they are actively striving to improve their outcomes. Thus, collaboration among various centers and healthcare workers who are trying to accomplish the same or similar goals is an important and effective strategy to accelerate change.

One Example: The "Breakthrough Learning Collaborative" to Improve CF Care

Collaboration and data sharing underlie the recent development of "breakthrough series" collaborative learning methods, in which multidisciplinary teams from various sites assemble to work together on a problem of common interest.^{22,28-30} Teams review the evidence for recommended care practices, are provided with decision support tools, study changes that have proven effective at other sites, and receive training in the quality improvement methods outlined above.

Teams set measurable targets, track their performance, and compare results to gain insights about potentially useful changes. Participants are provided with performance feedback and help in its interpretation and receive ongoing support from medical specialists and experts in medical system improvement. The key aspect is the sharing and collaboration that takes place among sites that are working simultaneously on the same goal: When an effective strategy is discovered by one, it is immediately shared and others have the opportunity to adapt and build on it. The eventual goal is the development of techniques that may then be disseminated throughout the provider community.

The NC CHI/NICHQ CF collaborative chose to focus on improving nutrition and eliminating environmental tobacco smoke exposure in our patients. These goals were chosen because there is clear and convincing evidence that their achievement would improve lung function, the major cause of morbidity and mortality in CF,^{7,31-34} and because interventions of proven effectiveness to meet those goals are currently used in an inconsistent manner.^{16,35-44} These two goals differ significantly, however, regarding their familiarity to CF care providers. In the case of nutrition, all CF centers have traditionally emphasized its importance and have considerable expertise and experience in its promotion. However, very few have previously considered the importance of intervening to reduce environmental tobacco smoke exposure. Most pediatricians are unfamiliar with smoking cessation counseling and ambivalent about their role in supporting it, particularly because of the need to develop a therapeutic relationship with the smoking parents rather than the patient.

With funding and assistance from the CFF, interested CF care centers from around the country were solicited for participation in this project, and 15 centers joined in the collaborative. This group is diverse in relation to geographic distribution, size of clinic population, and academic and research orientation and baseline performance on nutritional measures. Teams have been trained in the key strategies at "learning sessions," supplemented by regular conference calls and a listserv that allows ongoing discussion. The specific goals of the collaborative are shown in the Table. Significant progress is being made, as reported in preliminary form at NACF meetings.^{8,45}

CONCLUSIONS

In its report, *Crossing the Quality Chasm*,¹ the Institute of Medicine identified problems in the system of health care delivery rather than deficiencies in individual physicians' practice as the major impediment to attaining quality health care for all Americans. Effective interventions are available to slow or reverse the progress of many chronic diseases of childhood, and our patients are best served by ensuring that they consistently receive indicated treatment. Variations in disease outcome are a reflection of inconsistency in the application of evidence-based therapies that should be received by all patients.

Although this perspective represents a significant break with the traditional view, it should allow physicians to feel

liberated rather than threatened. If a system is in place that ensures that intended routine treatments are reliably provided, then physicians can focus their attention and creativity on the more challenging diagnostic and management problems for which they may currently have insufficient time. Furthermore, methods that ensure the consistent provision of evidence-based therapies for patients with currently incurable diseases such as CF will typically lead to significant improvements in outcomes based on current clinical science while patients and their physicians await future advances in care provided by biomedical research.

The authors thank the faculty of the NC CHI/NICHQ collaborative for their guidance and input: Carlos E. Milla, MD, Marianna M. Sockrider, MD, DrPH, Lori Stark, PhD, Elisabeth Luder, PhD, Jonathan Winickoff, MD, MPH, Lisa White, MPH, and Divvie Powell, RN. Thanks also to the CF Foundation for its support, and especially to Bruce Marshall, who also provided helpful comments on this manuscript. Finally, we thank the Journal's reviewers of the original manuscript, whose suggestions significantly improved this paper.

REFERENCES

1. Institute of Medicine Committee on Quality Health Care in America. *Crossing the Quality Chasm: A new health system for the 21st century.* Washington, DC: National Academy Press; 2001.
2. Leatherman S, McCarthy D. *Quality of Health Care for Children and Adolescents: A Chartbook.* New York: The Commonwealth Fund; 2004.
3. Horbar JD, Rogowski J, Plsek PE, Delmore P, Edwards WH, Hocker J. Collaborative quality improvement for neonatal intensive care. NIC/QProject Investigators of the Vermont Oxford Network. *Pediatrics* 2001;107:14-22.
4. National Cancer Policy Board. In: Hewitt M, Wiener S, Simone JV, eds. *Childhood Cancer Survivorship: Improving Care and Quality of Life.* Washington, DC: National Academies Press; 2003. p. 206.
5. Davis PB, Drumm M, Konstan MW. Cystic fibrosis: state of the art. *Am J Respir Crit Care Med* 1996;154:1229-56.
6. Marshall BC, Samuelson WM. Basic therapies in cystic fibrosis: does standard therapy work? *Clin Chest Med* 1998;19:487-504.
7. Schoni MH, Casaulta-Aebischer C. Nutrition and lung function in cystic fibrosis patients: review. *Clin Nutr* 2000;19:79-85.
8. Schechter MS. Non-genetic influences on cystic fibrosis lung disease: the role of sociodemographic characteristics, environmental exposures, and healthcare interventions. *Semin Resp Crit Care Med* 2003;24:639-52.
9. Cystic Fibrosis Foundation. *Cystic Fibrosis Foundation Patient Registry 2002 Annual Data Report.* Bethesda, Maryland, 2003.
10. Anonymous Outcomes Review & Research Updates. 2001, 2004.
11. FitzSimmons SC. The changing epidemiology of cystic fibrosis. *J Pediatr* 1993;122:1-9.
12. Graub E, Graub M. Origin and development of the Cystic Fibrosis Foundation. In: Doershuk CF, ed. *Cystic Fibrosis in the 20th Century.* Cleveland, Ohio: AM Publishing, Ltd; 2001. p. 149-63.
13. Doershuk CF. Growth of the foundation's medical program. In: Doershuk CF, ed. *Cystic Fibrosis in the 20th Century.* Cleveland, Ohio: AM Publishing, Ltd; 2001. p. 218-38.
14. Konstan MW, Butler SM, Schidlow DV, Morgan WJ, Julius JR, Johnson CA. Patterns of medical practice in cystic fibrosis, I: evaluation and monitoring of health status of patients: Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. *Pediatr Pulmonol* 1999;28:242-7.
15. Johnson C, Butler SM, Konstan MW, Morgan W, Wohl ME. Factors influencing outcomes in cystic fibrosis: a center-based analysis. *Chest* 2003; 123:20-7.
16. Jelalian E, Stark LJ, Reynolds L, Seifer R. Nutrition intervention for weight gain in cystic fibrosis: a meta analysis. *J Pediatr* 1998;132:486-92.
17. Schechter MS. Demographic and center-related characteristics associated with low weight in pediatric CF patients. *Pediatr Pulmonol* 2002;Suppl 22:156-7.

18. Davis D, O'Brien MA, Freemantle N, Wolf FM, Mazmanian P, Taylor-Vaisey A. Impact of formal continuing medical education: do conferences, workshops, rounds, and other traditional continuing education activities change physician behavior or health care outcomes? *JAMA* 1999; 282:867-74.
19. Davis DA, Thomson MA, Oxman AD, Haynes RB. Changing physician performance: a systematic review of the effect of continuing medical education strategies. *JAMA* 1995;274:700-5.
20. Mazmanian PE, Davis DA. Continuing medical education and the physician as a learner: guide to the evidence. *JAMA* 2002;288:1057-60.
21. Margolis PA, Lannon CM, Stuart JM, Fried BJ, Keyes-Elstein L, Moor DE Jr. Practice based education to improve delivery systems for prevention in primary care: randomised trial. *BMJ* 2004;328:388.
22. Horbar JD, Carpenter JH, Buzas J, Soll RF, Suresh G, Bracken MB, et al. Timing of initial surfactant treatment for infants 23 to 29 weeks' gestation: is routine practice evidence based? *Pediatrics* 2004;113:1593-602.
23. Wagner EH, Glasgow RE, Davis C, Bonomi AE, Provost L, McCulloch D, et al. Quality improvement in chronic illness care: a collaborative approach. *J Comm J Qual Improv* 2001;27:63-80.
24. Deming WE. *Out of Crisis*. Cambridge, Mass: MIT, Center for Advanced Engineering Study; 1986.
25. Newacheck PW, Strickland B, Shonkoff JP, Perrin JM, McPherson M, McManus M, et al. An epidemiologic profile of children with special health care needs. *Pediatrics* 1998;102:117-23.
26. Wagner EH, Austin BT, Von Korff M. Improving outcomes in chronic illness. *Manag Care Q* 1996;4:12-25.
27. Langley G, Nolan K, Nolan T, Norman C, Provost L. *The improvement guide: a practical approach to enhancing organizational performance*. San Francisco, Calif: Jossey-Bass; 1996.
28. Horbar JD, Plsek PE, Leahy K. NIC/Q 2000: establishing habits for improvement in neonatal intensive care units. *Pediatrics* 2003;111: e397-410.
29. Ovretveit J, Bate P, Cleary P, Cretin S, Gustafson D, McInnes K, et al. Quality collaboratives: lessons from research. *Qual Saf Health Care* 2002;11: 345-51.
30. Kilo CM. Improving care through collaboration. *Pediatrics* 1999;103: 384-93.
31. Konstan MW, Butler SM, Wohl ME, Stoddard M, Matousek R, Wagener JS, et al. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. *J Pediatr* 2003;142:624-30.
32. Peterson ML, Jacobs DR Jr, Milla CE. Longitudinal changes in growth parameters are correlated with changes in pulmonary function in children with cystic fibrosis. *Pediatrics* 2003;112:588-92.
33. Steinkamp G, Wiedemann B. Relationship between nutritional status and lung function in cystic fibrosis: cross sectional and longitudinal analyses from the German CF quality assurance (CFQA) project. *Thorax* 2002;57: 596-601.
34. Zemel BS, Jawad AF, FitzSimmons S, Stallings VA. Longitudinal relationship among growth, nutritional status, and pulmonary function in children with cystic fibrosis: analysis of the Cystic Fibrosis Foundation National CF Patient Registry. *J Pediatr* 2000;137:374-80.
35. Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2002;35: 246-59.
36. Dalzell AM, Shepherd RW, Dean B, Cleghorn GJ, Holt TL, Francis PJ, et al. Nutritional rehabilitation in cystic fibrosis: a 5 year follow-up study. *J Pediatr Gastroenterol Nutr* 1992;15:141-5.
37. Shepherd RW, Holt TL, Thomas BJ, Kay L, Isles A, Francis PJ, et al. Nutritional rehabilitation in cystic fibrosis: controlled studies of effects on nutritional growth retardation, body protein turnover, and course of pulmonary disease. *J Pediatr* 1986;109:788-94.
38. Frankowski BL, Weaver SO, Secker-Walker RH. Advising parents to stop smoking: pediatricians' and parents' attitudes. *Pediatrics* 1993;91: 296-300.
39. Jaen CR, Crabtree BF, Zyzanski SJ, Goodwin MA, Strange KC. Making time for tobacco cessation counseling. *J Fam Prac* 1998;46:425-8.
40. Stein RJ, Haddock CK, O'Byrne KK, Hymowitz N, Schwab J. The pediatrician's role in reducing tobacco exposure in children. *Pediatrics* 2000; 106:E66.
41. Tanski SE, Klein JD, Winickoff JP, Avinger P, Weitzman M. Tobacco counseling at well-child and tobacco-influenced illness visits: opportunities for improvement. *Pediatrics* 2003;111:E162-7.
42. Wahlgren DR, Hovell MF, Meltzer SB, Hofstetter R, Zakarian JM. Reduction of environmental tobacco smoke exposure in asthmatic children. *Chest* 1997;111:81-8.
43. Winickoff JP, Hillis VJ, Palfrey JS, Perrin JM, Rigotti NA. A smoking cessation intervention for parents of children who are hospitalized for respiratory illness: the stop tobacco outreach program. *Pediatrics* 2003;111: 140-5.
44. Zapka JG, Fletcher K, Pbert L, Druker SK, Ockene JK, Chen L. The perceptions and practices of pediatricians: tobacco intervention. *Pediatrics* 1999;103:e65.
45. Schechter MS, Milla C, Sockrider M, Stark L, Luder E, White L, et al. Baseline characteristics do not predict early success by centers participating in a collaborative quality improvement project. *Pediatr Pulmonol* 2004;Suppl 27: 352.

COMBINING IMMUNOREACTIVE TRYPSINOGEN AND PANCREATITIS-ASSOCIATED PROTEIN ASSAYS, A METHOD OF NEWBORN SCREENING FOR CYSTIC FIBROSIS THAT AVOIDS DNA ANALYSIS

JACQUES SARLES, MD, PATRICE BERTHÉZÈNE, MSc, CHRISTIAN LE LOUARN, BSc, CLAUDE SOMMA, MD, JEAN-MARC PERINI, MD,
MICHAEL CATHELINE, MD, SOPHIE MIRALLIÉ, MD, KARINE LUZET, BSc, MICHAEL ROUSSEY, MD, JEAN-PIERRE FARRIAUX, MD,
JACQUES BERTHELOT, MD, AND JEAN-CHARLES DAGORN, PhD

Objectives To evaluate the performance of a strategy in which, after immunoreactive trypsinogen (IRT) determination, genetic analysis is replaced by a biological test, the pancreatitis-associated protein (PAP) enzyme-linked immunosorbent assay (ELISA).

Study design The French newborn screening program includes cystic fibrosis (CF) screening by the IRT/*CFTR* mutation strategy. PAP was assayed on screening cards, in parallel with IRT, in all newborns from 5 French regions (n = 204,749). Analysis of PAP values in CF and non-CF newborns with elevated IRT allowed direct comparison between the current strategy and the proposed IRT/PAP strategy.

Results A protocol in which newborns with IRT >50 ng/mL and PAP >1.8 ng/mL and those with IRT >100 ng/mL and PAP >1.0 ng/mL are directly recalled for sweat testing would have the same performance as the IRT/*CFTR* mutation strategy.

Conclusions The IRT/PAP strategy is an alternative for CF newborn screening, which avoids the drawbacks of genetic analysis and is cheaper and easier to implement than the current IRT/*CFTR* mutation strategy. (*J Pediatr* 2005;147:302-5)

Reports of beneficial outcomes of newborn screening for infants with cystic fibrosis (CF),¹ although limited,² have resulted in its implementation in a growing number of regions.³ The most widespread strategy, coupling immunoreactive trypsinogen (IRT) assay and *CFTR* mutation analysis,⁴ shows good sensitivity and specificity, but the use of genetic analysis raises questions. Discovery of healthy carriers and infants presenting with mild forms of CF is not the goal of neonatal screening, which is to recognize infants who need immediate treatment. Furthermore, providing information and counseling to families is difficult, but can be managed if the number of cases remains limited. However, the tendency to increase the number of tested mutations, which is ethically justified in countries with a large ethnic diversity,⁵ will improve screening performance only marginally while notably increasing the number of families requiring counseling. Finally, mass newborn screening using DNA analysis is problematic in countries where informed consent is requested.⁶

We have previously shown that the concentration of pancreatitis-associated protein (PAP), a stress protein synthesized by the diseased pancreas, is elevated in the blood of newborns with CF.⁷ But PAP elevation is not strictly specific to CF, and CF screening with PAP would have had performance similar to that of IRT alone. Yet analysis of populations of newborns with elevated PAP or IRT revealed that all newborns with CF show elevation of both IRT and PAP, whereas those without CF show elevation of IRT or PAP, but rarely of both.⁷ A small-scale study indicated that a screening strategy combining

See related articles, p 295,
p 306, p 312, p 316, p 321,
p 327, p 382, and p 402.

From Pediatrics and Nuclear Medicine Departments; Hôpital de la Timone, Marseille, France; Department of Pediatrics and Neonatal Screening Center, Lille, France; Children's Hospital, Nantes, France; Genetics Department, Angers, France; and INSERM U 264, Marseille, France.

Supported by a grant from the Caisse Nationale d'Assurance Maladie des Travailleurs Salariés.

J. C. Dagorn is a consultant for DYNABIO S.A., which produces the MucoPAP ELISA kits used in this study. None of the other authors has any personal or financial relationships to report that could cause a conflict of interest with this study.

Submitted for publication Oct 4, 2004; last revision received Apr 15, 2005; accepted May 6, 2005.

Reprint requests: Jacques Sarles, Service de Pédiatrie Multidisciplinaire, Hôpital d'Enfants de la Timone, F-13385 Marseille Cedex 05, France. E-mail: jacques.sarles@ap-hm.fr.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.05.017

CF	Cystic fibrosis	IRT	Immunoreactive trypsinogen
ELISA	Enzyme-linked immunosorbent assay	PAP	Pancreatitis-associated protein

IRT and PAP assays would ensure 100% sensitivity while being sufficiently specific to allow diagnosis by sweat testing.⁸

The aim of the present study was to compare, in the same population of newborns, the performance of the CF screening strategy currently in use in France (IRT/*CFTR* mutation analysis)⁶ with that of a strategy in which newborns with elevated IRT are tested for PAP instead of undergoing genetic analysis, with those with elevated PAP subjected to sweat testing.

METHODS

The study included all newborns from 5 French regional screening centers between November 2002 and December 2003 (n = 204,749). All of the newborns were screened for CF through the French national program started in April 2002. The screening strategy⁶ includes single IRT testing (CIS-Bio International, France or Perkin-Elmer, Finland) at day 3, followed by analysis for 20 *CFTR* mutations (CF20 Elucigene kit; Orchid Biosciences Inc, Abingdon, UK) for those found to have elevated IRT values (>50 ng/mL until February 2003 and >65 ng/mL thereafter). If 1 or 2 mutations are found, then the newborn is recalled for sweat testing. If no mutations are found, then a second blood spot is collected at day 21 to repeat the IRT, and a sweat test is conducted when IRT >45 ng/mL. Newborns with sweat test results ≥ 60 mEq/L are diagnosed as having CF. Those whose first sweat test is between 40 and 59 mEq/L are followed-up and checked as recommended at age 3, 6, and 12 months.⁹

PAP was assayed in all newborns by enzyme-linked immunosorbent assay (ELISA) (MucoPAP; DYNABIO S.A., Marseille, France), following the manufacturer's recommendations. Samples (3-mm diameter) were punched from the screening cards, and dried blood was eluted in 150 μ L of phosphate-buffered saline. Assays were conducted in duplicate, concomitantly with IRT. IRT and PAP assays were carried out locally, and data were transmitted to our center before the diagnosis was known.

RESULTS

Of the 204,749 newborns included in this study, 1177 (0.58%) had elevated IRT. These newborns were submitted to *CFTR* mutation analysis. No mutation could be detected in 1028 of them (86%), and these newborns were recalled at day 21 for a second IRT. Forty-five neonates carried 2 mutations of the *CFTR* gene, and 116 carried 1 mutation. Three of these 116 turned out to be affected. The incidence of the disease in that population was therefore 1/4266, which is close to the overall incidence in France for the same period (1/4890). Among the 48 babies screened as having CF, 43 presented with symptoms compatible with CF or abnormal sweat test results (≥ 60 mEq/L), but 5 were classified as having a borderline form of CF because they exhibited no symptoms, had normal sweat test results (<60 mEq/L), and mild mutations [R117H, TG12-T5(IVS8), S1251N, L997F, R347H], and they did not evolve toward CF status (appear-

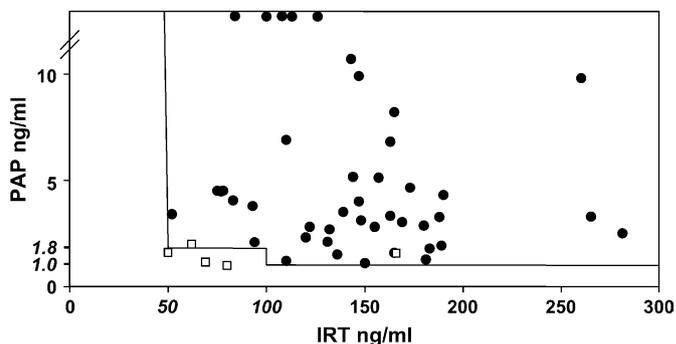


Figure 1. CF newborns screened in the study population. For each newborn, the IRT concentration in blood (ng/mL) is given as a function of PAP concentration (ng/mL). The black line represents the suggested thresholds in the IRT/PAP screening strategy described in Figure 2. Five cases with PAP values > 12 ng/mL were arbitrarily plotted as PAP = 12 ng/mL for the sake of clarity. Black dots represent genuine CF newborns. Open squares indicate mild forms of CF. Threshold values (50 and 100 ng/mL for IRT; 1.0 and 1.8 ng/mL for PAP) are indicated.

ance of clinical symptoms or elevation of sweat test) after more than 1 year of follow-up.

The lowest IRT value for a newborn with typical CF ($\Delta F508/\Delta F508$) was 52 ng/mL. (This child, who was identified before the change in the IRT threshold, would have been missed if he had been born after the change.) The lowest PAP value in the affected newborns was 1.1 ng/mL (Figure 1). Hence thresholds of 50 ng/mL for IRT and 1.0 ng/mL for PAP would confer 100% sensitivity to an IRT/PAP screening. However, the percentage of newborns to be recalled for sweat testing (0.72%) would be too high to allow easy management. A closer look at the results revealed that among the newborns with CF with moderately elevated IRT (50 to <100 ng/mL), 10 had genuine forms of the disease, their genotypes being $\Delta F508/\Delta F508$ (n = 6), $\Delta F508/P574H$ (n = 1), $\Delta F508/G542X$ (n = 1), $\Delta F508/G149R$ (n = 1), or $\Delta F508/?$ (with 110 mEq/L sweat chloride), whereas 4 had borderline forms with sweat chloride <60 mEq/L. All 10 of those with genuine forms had PAP concentrations >2 ng/mL; 3 of the 4 with borderline forms had PAP <1.8 ng/mL. Hence none of the newborns with IRT 50 to <100 ng/mL and PAP <1.8 ng/mL would require detection if it were agreed that borderline forms of the disease should not be screened.

On that basis, it was proposed that the IRT/PAP strategy should select for sweat testing newborns with IRT ≥ 50 ng/mL and PAP ≥ 1.8 ng/mL and those with IRT ≥ 100 ng/mL and PAP ≥ 1.0 ng/mL (Figure 1). The sensitivity of such a strategy would be 100% (Figure 1; Table I), given that exclusion of borderline forms is intended. But if, in contrast, the screening policy stated that borderline forms of CF need to be identified, then the sensitivity of the proposed strategy would decrease to 94%. Specificity will depend on the protocol chosen for IRT (Table I). The simplest protocol would be that a single IRT assay determines whether a PAP assay should be conducted. In that case, the proposed strategy would recall 0.24% of the neonates for sweat testing, with 8.6% of them

Table I. Performance of IRT/DNA and IRT/PAP strategies

	IRT/DNA		IRT/PAP
Babies screened	204.748		204.748
IRT day 3-positive	1.177*		3,890*
CFTR genotypes			
2 mutations	45 (incl 5 borderline [†])		
1 mutation	116 (3 CF)		
0 mutation	1028		—
IRT day 21-positive	111 (0 CF)		
		IRT single [‡]	IRT duplicate [‡]
No. of sweat tests	224 [§]	501 [¶]	329 [¶]
CF (total n in population)	48 (incl. 5 borderline [†])		48 (incl. 5 borderline [†])
PPV	21.4 % ^(a) or 4% ^(b)	8.6% [#]	13% [#]
CF not detected	2** (1 asymptomatic ^{***})		3 (all asymptomatic ^{***})

*IRT thresholds at 65 ng/mL for IRT/CFTR mutation and 50 ng/mL for IRT/PAP.

†Borderline = asymptomatic with normal sweat test (<60 mEq/L) but 2 CFTR mutations.

‡Two protocols are proposed in which the first step, IRT testing, is performed either once or twice.

§Newborns with 1 or 2 mutations, or 0 mutations but IRT day 21 above threshold.

¶Newborns with IRT > 50 ng/mL and PAP > 1.8 ng/mL, or IRT > 100 ng/mL and PAP > 1.0 ng/mL, are recalled for sweat testing.

||The PPV of the IRT/DNA strategy can be calculated considering that “affected babies” are newborns with 2 CFTR mutations and/or abnormal sweat test and “suspected babies” are either (a) those requiring sweat testing for diagnosis (1 or 0 mutations and elevated IRT at day 21) or (b) those whose parents had some sort of notification of an abnormal test result, that is, newborns with 1 mutation and those recalled for blood collection at day 21.

#The PPV of the IRT/PAP strategy was calculated considering that affected newborns were those with abnormal sweat test results (n = 43).

**The “putative” false-negative case (IRT = 52) is described in Results.

***Normal sweat test results; no symptoms after 18 months.

Table II. Estimated cost of IRT/DNA and IRT/PAP strategies

Step	Unit price (€)	IRT/DNA		IRT/PAP*	
		n (% of population)	Total k€	n (% of population)	Total k€
IRT	2.5	100,000 (100%)	250.0	100,000 (100%)	250.0
CFTR analysis	120	580 (0.58%)	69.6	22 (0.022%) [†]	2.6
PAP	4.5	—	—	4,000 (2%)	18.0
Sweat testing	46	110 (0.11%) [‡]	5.0	250 (0.25%)	11.5
Recall day 21	23	500 (0.5%)	11.5	—	—
Follow-up HZ	400	42 (0.4%) [§]	16.8	—	—
Total			352.9		282.1

*Costs were estimated for the strategy in which only 1 IRT is performed; for samples with IRT higher than threshold, PAP is performed in duplicate.

†CFTR analysis of newborns with CF for genetic counselling.

‡Newborns with 1 or 2 mutations, or 0 mutation but IRT day 21 higher than threshold.

§The French procedure requires for carriers (and newborns with CF) genetic counseling of the family and testing of all members for CFTR mutations.

confirmed as having CF. Another possibility would be to verify IRT values >50 ng/mL by a second assay, with the mean value compared with the threshold. This protocol, similar to the current protocol for selecting newborns who need genetic analysis, is more demanding of resources, but would decrease the percentage of recalled newborns to 0.16%, with CF diagnosis confirmed in 13% of them.

Table II gives a preliminary comparison of the costs of the IRT/CFTR mutation and IRT/PAP strategies. The cost of the initial IRT step is the same in both strategies. Interestingly, the cost of the subsequent steps appears significantly lower with the IRT/PAP strategy. However, an

accurate comparison would require that the IRT/PAP strategy be implemented sufficiently long to collect actual costs.

DISCUSSION

We compared the performance of 2 strategies for CF screening, the IRT/CFTR mutation strategy and the IRT/PAP strategy. This comparison could not be conducted prospectively, because CF screening by the IRT/CFTR mutations is mandatory in France. Under these conditions, setting threshold values a priori for PAP was purposeless. In agreement with the Caisse Nationale d'Assurance Maladie,

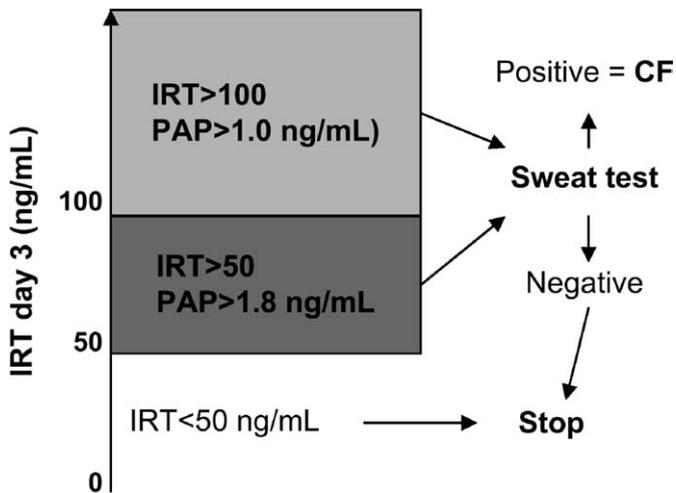


Figure 2. Suggested IRT/PAP strategy for CF screening. All newborns are tested for IRT. Newborns with IRT > 50 ng/mL are tested for PAP. Those with PAP > 1.8 ng/mL and those with PAP > 1.0 ng/mL and IRT > 100 ng/mL are recalled for sweat testing.

which manages newborn screening in France and which sponsored this study, we gathered data on more than 200,000 newborns, obtained from 5 independent centers in which PAP and IRT assays were conducted simultaneously for each newborn. The results were recorded in anonymous files and transmitted before diagnosis.

The proposed strategy with 2 thresholds (Figure 2) was initially suggested by 1 of the participating centers and was subsequently validated by the other centers. The sensitivity, apparently 100%, should be equal to or better than that of the IRT/CFTR mutation strategy, because the proposed IRT threshold is lower. The expected false-positive rate (<0.25%) is considered acceptable, because the delay between recall and diagnosis by sweat testing can be kept very short to reduce parents' stress. From a practical standpoint, the IRT/PAP strategy is simple to manage; the 2 steps are conducted in the same laboratory, and the PAP assay is a classical ELISA. Its main advantage is that it does not require *CFTR* mutation analysis, thereby avoiding all of the drawbacks of molecular

biology (ie, need for informed consent, unwarranted detection of heterozygotes, and detection of borderline forms of CF).

Because financial issues are important in mass screening, we compared the costs of the 2 strategies (Table II). Although available data allowed only rough estimates, the IRT/PAP strategy seems significantly cheaper because of the absence of DNA testing and genetic counseling, with an expected savings of about 0.7€ per screened baby. Together, these results suggest that the IRT/PAP strategy is an interesting alternative to strategies involving DNA analysis, especially for states or countries about to add CF to their screening programs.

We thank the Association Française pour le Dépistage et la Prévention des Handicaps de l'Enfant (AFDPHE). We also thank Ms. C. Bartoll and Ms. S. Orain for their technical assistance.

REFERENCES

- Farrell PM, Kosorok MR, Rock MJ, Laxova A, Zeng L, Lai HC, et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. *Pediatrics* 2001;107:1-13.
- Farrell PM, Li Z, Kosorok MR, Laxova A, Green CG, Collins J, et al. Bronchopulmonary disease in children with cystic fibrosis after early or delayed diagnosis. *Am J Respir Crit Care Med* 2003;168:1100-8.
- Southern K. Newborn screening for cystic fibrosis: the practical implications. *J R Soc Med* 2003;97:1-4.
- Wilcken B, Wiley V. Newborn screening methods for cystic fibrosis. *Paediatr Respir Rev* 2003;4:272-7.
- Comeau AM, Parad RB, Dorkin HL, Dovey M, Gerstle R, Haver K, et al. Population-based newborn screening for genetic disorders when multiple mutation DNA testing is incorporated: a cystic fibrosis newborn screening model demonstrating increased sensitivity but more carrier detections. *Pediatrics* 2004;113:1573-81.
- Farriaux JP, Vidailhet M, Briard ML, Belot V, Dhondt JL. Neonatal screening for cystic fibrosis: France rises to the challenge. *J Inherit Metab Dis* 2003;26:729-44.
- Sarles J, Barthelémy S, Ferec C, Iovana J, Roussey M, Farriaux JP, et al. Blood concentrations of pancreatitis-associated protein in neonates: relevance to neonatal screening for cystic fibrosis. *Arch Dis Child Fetal Neonatal* 1999; 80:F118-22.
- Barthelémy S, Maurin N, Roussey M, Ferec C, Murolo S, Berthézène P, et al. Evaluation of 47,213 infants in neonatal screening for cystic fibrosis, using pancreatitis-associated protein and immunoreactive trypsinogen assays. *Arch Pediatr* 2001;8:275-81.
- Massie J, Gaskin K, Van Asperen P, Wilcken B. Sweat testing following newborn screening for cystic fibrosis. *Pediatr Pulmonol* 2000;29:452-6.

NEWBORN SCREENING FOR CYSTIC FIBROSIS IS ASSOCIATED WITH REDUCED TREATMENT INTENSITY

ERIKA J. SIMS, PHD, JONATHAN MCCORMICK, MRCPCH, GITA MEHTA, MA MPhil, AND ANIL MEHTA, FRCPCH FRCP (EDIN)

Objectives To determine whether the improved clinical status after newborn screening (NBS) for cystic fibrosis (CF) segregates with increased therapeutic intervention compared with presentation by clinical diagnosis (CD).

Study design In 2002, two populations (1 to 9 years of age) who presented (excluding meconium ileus) by NBS ≤ 3 months of age or by CD were compared in an observational, cross-sectional design. NBS and CD populations (184 and 950 patients, respectively) were divided into 3-year age groups (1 to 3, 4 to 6, and 7 to 9 years). Therapies of duration >3 months were compared together with *Pseudomonas aeruginosa* infection status.

Results NBS patients ≤ 6 years of age received significantly fewer and less demanding therapies not explained by age, genotype, geography, or social deprivation. In 7- to 9-year-olds, significantly fewer NBS patients received intravenous antibiotics. NBS patients without *P aeruginosa* infection received significantly fewer therapies, but no differences were found between intermittently or chronically infected NBS and CD populations. Comparable results were found in $\Delta F508/\Delta F508$ subpopulations.

Conclusions CF populations diagnosed by NBS are associated with reduced treatment compared with age- and genotype-matched CD control subjects. (*J Pediatr* 2005;147:306-11)

Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disease in whites, affecting approximately 1 in 3500 births.¹ In the United Kingdom, regional newborn screening (NBS) programs result in $\sim 12\%$ of patients being identified by NBS, with the remainder diagnosed clinically (clinical diagnosis, CD). This permitted a pragmatic comparison of outcomes between cohorts of NBS and CD populations, as reported recently.² In these cohorts, in agreement with outcomes from the Wisconsin Cystic Fibrosis Neonatal Screening Study Group³⁻⁵ and others,⁶⁻¹⁰ we showed that NBS is associated with significantly improved height and a lower prevalence of lung infection but no difference in lung function compared with CD control subjects.² It is unknown whether the improved growth and infection outcomes were due to early identification and hence prompt treatment, or more intense therapy irrespective of symptoms. The symptoms of CF vary and in the United Kingdom; this is addressed by national treatment guidelines based on consensus documents from experienced clinical committees within the CF Trust.¹¹ These stratify patients into mild, moderate, and severe disease and recommend appropriate therapies. The current study used our earlier cohorts² to determine whether improved outcomes from NBS programs could be explained by differences in the intensity of therapy relative to age-matched CD control subjects.

We also addressed potential geographic confounders. UK CF centers are not always geographically congruous with NBS programs. CF centers located in England receive referrals from both NBS and CD patients. This factor, coupled with the large English population (~ 50 million), results in most of the NBS patients being diagnosed from this region of the United Kingdom. In contrast, the relatively sparsely populated areas of Wales

See related articles, p 295,
p 312, p 316, p 321,
p 327, p 332, p 396,
p 399, and p 405.

From United Kingdom Cystic Fibrosis Database, Division of Maternal and Child Health Sciences, Ninewells Hospital and Medical School, University of Dundee, Dundee, United Kingdom, on behalf of the UK CF Database Steering Committee.

Supported by the UK Cystic Fibrosis Trust, the National Health Service Division of the National Health Service (Scotland), and the Scottish Higher Education Funding Council (J.M.C. and A.M.).

E.J.S. and G.M. are employed by the University of Dundee.

Submitted for publication Oct 26, 2004; revision received Apr 22, 2005; accepted May 27, 2005.

Reprint requests: Anil Mehta, FRCPCH, FRCP (Edin), United Kingdom Cystic Fibrosis Database, Division of Maternal and Child Health Sciences, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK, DD1 9SY.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.05.034

CF	Cystic fibrosis	UKCFD	United Kingdom Cystic Fibrosis Database
NBS	Newborn screening	IMD	Index of multiple deprivation score
CD	Clinical diagnosis	PERT	Pancreatic enzyme replacement therapy

(~3 million) and Northern Ireland (~1.7 million) have geographically matched NBS and CF treatment services and thus receive almost all referrals through NBS. At the time of the study, Scotland (~5 million) had no NBS program. To control for CF center referral bias within the English centers, we additionally matched NBS and CD patients within those CF centers that treated referrals by both NBS and CD patients.

We focussed on all CF diagnoses after 1994 that would have received CF specialist care to limit any cohort effect that is a known confounder in succeeding generations of patients with CF.¹² We compared treatment data for NBS and CD CF populations 1 to 9 years of age in 2002 to determine whether NBS was associated with a higher intensity of therapy.

METHODS

UK CF Database (UKCFD) data were collected, verified, and error-checked from 41 CF centers and 12 smaller CF clinics in the years 2001 to 2002, as described recently,^{2,13} and at www.cystic-fibrosis.org.uk. All procedures were compliant with multicenter research ethics protocols and UK legislation on patient confidentiality. The study population was identical to that detailed in Sims et al² and is summarized in the flow diagram in Figure 1 (available online at www.jpeds.com). Study patients ages 1 to 9 years were divided into two populations (NBS/CD) by mode of diagnosis: NBS presented by neonatal screening within 3 months of birth and CD presented at any time by clinical diagnosis (with no family history of CF in any relative). Neonatal meconium ileus was excluded from both groups. Where numbers of patients were sufficient, the NBS and CD populations were subgrouped by age (1 to 3, 4 to 6, and 7 to 9 years) and by genotype, and median long-term therapy requirements were ascertained.

In the UKCFD, a long-term therapy is defined as one prescribed for at least 3 months.¹³ Therapies were pragmatically divided into low intensity (inhaled therapies or oral antibiotics) or medium intensity (nebulized therapies or oral corticosteroids), based on the simplicity of administration, potential for side effects, and systemic impact (Table I; available online at www.jpeds.com). Separately, a third category of intravenous antibiotic administration was defined as the number of patients receiving at least one course of intravenous therapy per year. The proportions of patients requiring low intensity, medium intensity, or courses of intravenous antibiotics was also determined. Chronic *Pseudomonas aeruginosa* was defined as ≥ 3 positive cultures in the previous 12 months. Intermittent *P aeruginosa* infection was defined as 1 or 2 positive cultures over the same period.

To match for genotype, we repeated the analyses for homozygous $\Delta F508$ NBS and CD populations. We also attempted to correct for referral bias by matching NBS and CD patients within those (English) CF centers that received between 15% and 85% of referrals by either NBS or CD. Our numbers were only sufficient for statistical analysis when such centers were grouped, and trends are reported where numbers were insufficient.

Confounding by Deprivation

As expected for a complex disease such as CF, social deprivation has been associated with poor clinical outcome.¹⁴ To determine whether our results could have been so confounded, a predetermined Index of Multiple Deprivation (IMD) score¹⁵ was compared for each NBS and CD population. IMD scores are derived for each postcode by the Office of the Deputy Prime Minister (ODPM) for the United Kingdom. They are a composite of seven domains: income, employment, health, education, skills/training, housing, and environment/crime. The score is weighted by geographic areas defined by groups of postcodes corresponding to the smallest defined census area (census output area of around 125 households). To protect confidentiality, each census output area is further aggregated into a lower super output area, which has an associated IMD score. Because CF centers with both NBS and CD patients were available mainly from England, we restricted our IMD-based deprivation analysis to the larger English population. This had the further advantage that IMD scores for the English population were available by using a common ODPM-derived, England-based formula.¹⁵

Statistics

Analyses were performed with the use of Microsoft Access and Excel (Microsoft Corporation, Redmond, WA), and graphs were created with the use of SigmaPlot (SigmaPlot for Windows version 4.01; SPSS Inc, Chicago, IL) and MINITAB version 13.1 (Minitab Inc, State College, PA). Unless stated otherwise, data were not normally distributed, and median scores were compared. Mann-Whitney two-sample rank tests were used to determine statistically significant differences between population medians. For the comparison of proportions of NBS and CD populations, the Central Limit Theorem was applied.¹⁶ To account for subdivision of populations, a value of $P \leq .01$ was considered to be significant for 3-year age group comparisons; otherwise, for comparison of total populations, the α -error was set at 0.05. No adjustment was made for multiple comparisons.

RESULTS

Study Population

Our study populations of NBS and CD patients (of all genotypes, ages 1 to 9 years and with clinical data) contained 184 and 950 patients, respectively (Figure 1; available online at www.jpeds.com). Of these, 98 and 531, respectively, were homozygous for $\Delta F508$. We tested whether these study populations were representative, and there was no significant difference in median age at diagnosis for our NBS ($n = 184$) and CD ($n = 950$) study populations when compared with their respective parent registered populations of NBS ($n = 284$) and CD ($n = 1126$) 1- to 9-year-olds.² Similar results were observed for the equivalent homozygous $\Delta F508$ subpopulations (data not shown). In addition, the number of $\Delta F508$ -homozygous patients in each study subpopulation and their age at presentation were as expected from previous calculations on the parent UKCFD data set.¹⁷

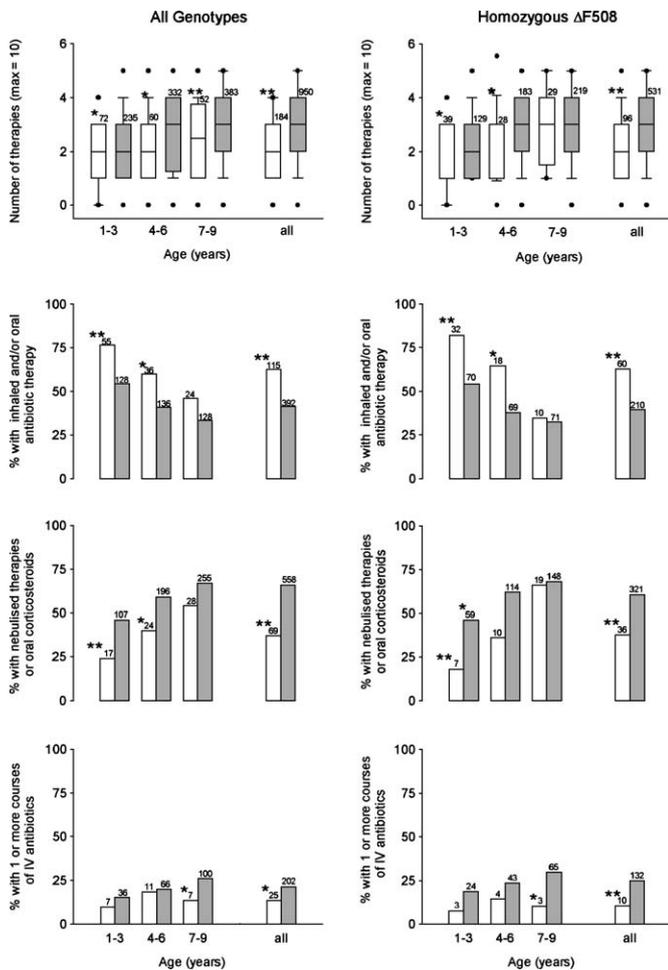


Figure 2. Comparison of therapeutic intensity. *Top left and right panels:* Box plots of number of long-term therapies by age group with median, interquartile range; dots show 5th to 95th percentiles for this and subsequent figures. Remaining panels (from top to bottom) show proportion of patients receiving long-term inhaled therapies and/or oral antibiotics as sole therapy; nebulized therapies and/or oral corticosteroids (in addition to long-term inhaled therapies and/or oral antibiotics and intravenous antibiotics additional to other therapies above). *Open and closed boxes and bars* indicate results for NBS and CD patients, respectively. Left/right columns show, respectively, outcomes for all genotypes and the homozygous $\Delta F508$ subpopulation. * $P < .01$ and ** $P < .001$. Number of patients in each age group is shown.

As expected, the proportion of NBS patients taking pancreatic enzyme replacement therapy (PERT) was significantly smaller (89%) compared with CD patients (95%). To test for phenotypic variation within the homozygous $\Delta F508$ NBS and CD study populations, we compared the prevalence of pancreatic insufficiency. No significant differences in proportions receiving PERT were present in the homozygous $\Delta F508$ subgroup (99% for both). Although drug replacement doses for pancreatic insufficiency may be variable,¹⁸⁻²⁰ this was not found within our genetically matched homozygous $\Delta F508$ study subpopulations (data not shown).

We assessed the degree of deprivation (IMD) for those patients living in England. We found no significant difference in the median IMD scores between NBS and CD patients

either in total (1.5; 95% CI, -1.23 to 4.35), for each age group (1 to 3 years: -1.45; 95% CI, -6.25 to 3.11; 4 to 6 years: 5.01; 95% CI, -0.51 to 11.35 and 7 to 9 years: 1.30; 95% CI, -3.10 to 6.14) or in a genetically homogeneous ($\Delta F508/\Delta F508$) subpopulation (3.24; 95% CI, -0.68 to 7.18). These analyses suggest bias in deprivation status would be an unlikely confounder between NBS and CD cohorts.

Long-term Therapies

We analyzed whether NBS patients received more treatment than CD control subjects in four different ways, as illustrated in Figure 2 (left column). First, NBS patients (open box plots) received a significantly smaller number of long-term therapies (Figure 2, left and right top panels). Second, a significantly higher proportion of NBS patients received only low intensity therapies in all age groups, except for 7- to 9-year-olds (compare open and closed bars, second panel, Figure 2). Third, and conversely, in all age groups except for 7- to 9-year-olds, a smaller proportion of NBS patients were receiving medium intensity therapies (third panel, Figure 2). Finally, at all ages, a smaller proportion of NBS patients received intravenous antibiotics compared with the CD population, although the trend only reached statistical significance for the 7- to 9-year-olds and for the total population (bottom panel, Figure 2).

NBS and CD populations might have different genetic profiles. This was considered to be a possible confounding factor.^{21,22} We therefore compared the homozygous $\Delta F508$ NBS subpopulation with equivalent CD control subjects (Figure 2, right column). Results were found comparable to that of the mixed genotype population, with the exception that we report almost identical numbers of long-term therapies for the 7- to 9-year-olds (compare the uppermost right panel of Figure 2 with the equivalent left panel). Similarly, no significant differences were found in therapeutic intensity in the oldest cohort of $\Delta F508$ homozygous 7- to 9-year-olds for either the low or medium intensity therapies. However, in agreement with the mixed genotype population, significantly fewer $\Delta F508$ homozygous NBS patients received courses of intravenous antibiotics compared with the CD population, despite an identical genotype.

English CF centers have different proportions of patients diagnosed by NBS. To control for a geographic bias, we aggregated data from seven English CF centers that received both NBS and CD referrals and whose spectrum of NBS diagnoses lay between 15% and 85%. Analysis of clinical outcomes and treatment trends from this aggregate of 115 NBS and 169 CD patients is shown in Table II. Similar trends were seen when matching NBS and CD patients within each center, but the numbers were too small for statistical analysis (data not shown).

We stratified NBS and CD populations according to *P aeruginosa* status into free, intermittent, and chronic subgroups (Figure 3; available online at www.jpeds.com). The NBS population free of *P aeruginosa* infection (~70%) were receiving a significantly lower number of long-term therapies compared with their equivalent (~60%) *P aeruginosa*-free CD

Table II. Benefits of an NBS program at centers receiving both NBS and CD referrals: Comparison of median values and percentages for NBS versus CD patients from CF centers with 15% to 85% NBS patients

Clinical measure	1 to 3 y NBS vs CD	4 to 6 y NBS vs CD	7 to 9 y NBS vs CD	All ages NBS vs CD
Height z-score (SD)	-0.44 vs -0.30	-0.41 vs -0.86	-0.41 vs -0.90	-0.41 vs -0.81*
Weight z-score (SD)	-0.11 vs -0.38	-0.27 vs -0.35	-0.42 vs -0.51	-0.26 vs -0.49
Northern CXR score	3 vs 4*	5 vs 4	5 vs 5	4 vs 5†
Shwachman score	95 vs 90*	89 vs 90	89 vs 85*	90 vs 88†
FVC (% predicted)	N/A	N/A	N/A	87.0 v 86.2
FEV ₁ (% predicted)	N/A	N/A	N/A	87.6 v 85.2
No. of long-term therapies	1.5 vs 2	2 vs 2	2 vs 3	2 vs 3†
% Receiving only low intensity therapies	82 vs 68	59 vs 46	42 vs 39	65 vs 47†
% Receiving no IV antibiotics	80 vs 58*	62 vs 71	85 vs 62*	75 vs 64 P = .06
% Receiving no nebulized therapies	82 vs 68	59 vs 46	42 vs 41	65 vs 47†
% Receiving ≥2 nebulized therapies	0 vs 3	13 vs 12	19 vs 30	9 vs 19*

Results are shown for 1- to 3-year, 4- to 6-year, and 7- to 9-year age groups and for the combined ages. For FEV₁ and FVC, results shown are for patients ages 5 to 9 years.

N/A, not applicable.

*P = .05.

†P = .005.

control subjects (one versus two therapies, respectively, a difference of -1 95% CI, -1.0 to -0.0001; $P < .001$; Figure 3, left column). This difference was not confounded by genotype or age and is quantified in the middle and lower panels of Figure 3, respectively. On further analysis, a significantly greater proportion of NBS patients were receiving oral antibiotics as sole therapy (39%) compared with CD (23%; $P = .031$), whereas only 14% of NBS patients were receiving nebulized therapies compared with 37% of CD patients ($P < .001$). For those with intermittent and chronic *P aeruginosa* infection, no significant differences in the number of long-term therapies were found between NBS and CD populations (Figure 3, top panel) despite further stratification by a common genotype (homozygous $\Delta F508$; Figure 3, middle panel) or age (within 12 months) (Figure 3, bottom panel).

Attendance at clinic could be an additional indication of differences in severity. However, we found no significant difference in either the distribution profiles of annual attendances for NBS or CD populations (median number of visits, 5 per annum for each) or between age groups, irrespective of stratification of *P aeruginosa* infection (data not shown). Comparable results were also found for the homozygous $\Delta F508$ subpopulations (data not shown).

DISCUSSION

Whether screening for CF provides long-term benefit remains controversial, given that no improvement in pulmonary outcome has been observed. We recently demonstrated that NBS for CF segregates with some clinical benefit with better median height and lower chest radiography scores as surrogate measures of disease severity for up to 6 years.² Further, in 3-year, age-matched and genetically homogeneous (for $\Delta F508/\Delta F508$ genotype) subpopulations, we also found

better clinical outcomes in NBS patients.² However, in common with other studies, we could not demonstrate better percent predicted FEV₁, a surrogate marker of death.⁵ The current study was prompted by the notion that reported pulmonary outcomes take no account of the intensity of treatment needed to achieve a given pulmonary response. Thus, if more treatment is needed to achieve a given FEV₁ in a CD compared with a comparable NBS patient, for example, this could lead to the erroneous conclusion that NBS is of no benefit. We report that similar lung function can be achieved after NBS despite a significantly lower number of long-term therapies compared with CD controls. Conversely, a greater number of therapies are needed to maintain a given lung function in CD patients. Our results are consistent with those of Connett and Yeatman,²³ who showed for a single UK CF center that patients identified at an earlier age at diagnosis required a lower number of long-term therapies compared with age- and genotype-matched ($\Delta F508/\Delta F508$), late-diagnosed control subjects. However, the extended duration over which their data was collected could have resulted in a possible cohort effect that can confound outcome data in CF.¹²

A potential risk in NBS programs is the inappropriate "out-of-protocol" initiation of therapies to asymptomatic patients after NBS.²⁴ Thus, therapies that would normally be prescribed after symptom development or positive culture might be initiated in an attempt to prevent the long-term decline in clinical outcome associated with CF disease progression. However, our data do not support this potential concern because for up to 6 years after NBS, we found proportionally fewer NBS children treated with nebulized and intravenous antibiotic therapy. We observed a rise in utilization of such treatment with increasing age and disease severity (ie, chronic infection by *P aeruginosa*), with a similar rise in the

frequency of attendance at the CF center in both NBS and CD populations (unpublished data). Our results, in agreement with Baumann et al,²⁵ also showed that an increasing number of therapies was associated with age and *P aeruginosa* infection status. We therefore cannot conclude that our observed better clinical outcomes associated with NBS result from more treatment than for matched CD cohorts. Indeed, the converse is the case.

This lower intensity of therapy might be explained by a reduced inflammatory status in the NBS CF lung that is not only treated prophylactically to prevent chronic staphylococcal infection for up to 2 years in the United Kingdom but is also intensively monitored for the earliest signs of disease. In contrast, after CD, treatment is aimed at reducing further loss of lung function incurred during the prediagnosis period. Whether current therapies can adequately suppress the proinflammatory state of the CF lung remains an unsolved clinical problem.²⁶ The higher prevalence of chronic *P aeruginosa* infection in the CD group² is consistent with this notion and with their requirement for extra intravenous therapy. A suggested benefit of the NBS program is the ability to treat at the earliest indications of lung infection and therefore possibly prolong the period free of chronic lung infection during a time of critically important lung growth. Indeed, the data we report here and in conjunction with the reduction in *P aeruginosa* prevalence in the same NBS cohort² suggest that the lower number of long-term therapies observed in the NBS population was at least in part attributable to the smaller proportion of patients intermittently or chronically colonized with *P aeruginosa*. This would further suggest that NBS patients in this study were treated according to protocol, based on symptoms or colonization status rather than in a preemptive manner.

Despite the rarity of childhood deaths in CF in the United Kingdom (unpublished data, UKCFD), the results presented here could be influenced by ascertainment bias resulting from patients registered with the UKCFD but without returned clinical data. However, we found no significant differences in the age at diagnosis of such registered patients (ages 1 to 9 years and Figure 1 of online supplementary material) when compared with those with returned clinical data for 2002. Registered and actively seen patients were similar when analyzed in terms of all patients, homozygous $\Delta F508$, and for NBS- and CD-matched populations. If such bias is present, it is not due to age at diagnosis. Additionally, we minimized the potential for a cohort effect by 3-year age matching. This period is unlikely to associate with a double-digit decline in lung function because this is estimated to be approximately 2% to 3% per annum.²⁷ Further, we observed similar interpopulation deprivation scores. Thus, social circumstances,²⁸ which may influence adherence, are likely to affect the two populations equally. The magnitude of our observed difference in outcomes could also be confounded by differences in treatment concordance. Failure to take treatment is likely to reduce the observed differences between the two populations, thus negating the potential benefits of NBS. Because the frequencies of attendance for the CD and NBS

populations were similar (data not shown), we do not believe that differences in the frequency of follow-up can account for our findings. We also report less intense treatment after NBS within a $\Delta F508$ subpopulation despite no differences in the proportion receiving PERT between these genetically homogeneous NBS and CD subpopulations. This makes it unlikely that age, social status, genotype, or disease variability/severity could significantly confound our results.

Variable prescribing practices between CF physicians also could have influenced our data. CF Trust guidelines indicate that all patients 2 years of age or younger should be prescribed oral flucloxacillin as prophylactic antistaphylococcal therapy.¹¹ In addition, all patients chronically infected with *P aeruginosa* should receive long-term nebulized antibiotics and/or DNase therapy. Our unpublished data show that 95% of UKCFD patients received prophylactic antistaphylococcal therapy for the first 2 years of life, in accordance with guidelines, and for patients 1 to 9 years of age, 90% of patients were prescribed appropriate protocol-determined¹¹ nebulized therapies for treatment of chronic *P aeruginosa* colonization. Allergy or hypersensitivity to nebulized antibiotics,²⁹ social circumstances making use of nebulized therapies at home inappropriate, and refusal to take nebulized therapy could be responsible for the remainder.

Overall, our data suggest that in the United Kingdom, NBS is associated with a lower number of long-term therapies compared with age- and genotype-matched CD control subjects. This adds further weight to the argument that NBS generates "more good than harm."³⁰ CF specialists have long argued that instead of managing the disease after complications arise, as in CD populations, it would be more appropriate to take a preventative approach to improve concordance and simultaneously extend the infection-free duration during a critical period of lung development.³¹ Our data provide evidence for a 6-year period during which NBS patients receive a significantly lower number of drugs. This finding has implications for calculations of the economic impact of NBS programs on health care budgets while simultaneously demonstrating that NBS coupled with clinical vigilance provides the opportunity for early intervention before complications arise.

The authors thank M. Fraser and S. Krawczyk for their expert data validation, and the directors and data managers at specialist CF centers and CF clinics throughout the United Kingdom that contributed data to the UK CF Database. For expert critical review, the authors thank Professor David Stone, University of Glasgow.

REFERENCES

1. Kosorok MR, Wei WH, Farrell PM. The incidence of cystic fibrosis. *Stat Med* 1996;15:449-62.
2. Sims EJ, McCormick J, Mehta G, Mehta A. Neonatal screening for cystic fibrosis is beneficial even in the context of modern treatment. *J Pediatr* 2005;147:306-12.
3. Farrell PM, Kosorok MR, Laxova A, Shen G, Kosciak RE, Bruns WT, et al. Nutritional benefits of neonatal screening for cystic fibrosis: Wisconsin Cystic Fibrosis Neonatal Screening Study Group. *N Engl J Med* 1997;337:963-9.

4. Farrell PM, Kosorok MR, Rock MJ, Laxova A, Zeng L, Lai HC, et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth: Wisconsin Cystic Fibrosis Neonatal Screening Study Group. *Pediatrics* 2001;107:1-13.
5. Farrell PM, Li Z, Kosorok MR, Laxova A, Green CG, Collins J, et al. Bronchopulmonary disease in children with cystic fibrosis after early or delayed diagnosis. *Am J Respir Crit Care Med* 2003;168:1100-8.
6. Dankert-Roelse JE, te Meerman GJ. Long term prognosis of patients with cystic fibrosis in relation to early detection by neonatal screening and treatment in a cystic fibrosis centre. *Thorax* 1995;50:712-8.
7. Mastella G, Zanolla L, Castellani C, Altieri S, Furnari M, Giglio L, et al. Neonatal screening for cystic fibrosis: long-term clinical balance. *Pancreatology* 2001;1:531-7.
8. Merelle ME, Schouten JP, Gerritsen J, Dankert-Roelse JE. Influence of neonatal screening and centralized treatment on long-term clinical outcome and survival of CF patients. *Eur Respir J* 2001;18:306-15.
9. Siret D, Bretaudeau G, Branger B, Dabadie A, Dagorne M, David V, et al. Comparing the clinical evolution of cystic fibrosis screened neonatally to that of cystic fibrosis diagnosed from clinical symptoms: a 10-year retrospective study in a French region (Brittany). *Pediatr Pulmonol* 2003;35:342-9.
10. Waters DL, Wilcken B, Irwing L, Van Asperen P, Mellis C, Simpson JM, et al. Clinical outcomes of newborn screening for cystic fibrosis. *Arch Dis Child* 1999;80:F1-7.
11. Littlewood JM, Bevan A, Connett G, Conway S, Govan J, Hodson M, et al. Antibiotic Treatment for Cystic Fibrosis: Report of the UK Cystic Fibrosis Trust Antibiotic Group. 2nd edition. 2002. Cystic Fibrosis Trust, Bromley, Kent, UK.
12. Corey M. Requirements for assessing possible benefits of screening—fundamental problems of comparing screened and unscreened groups of cystic fibrosis patients. In: Travert G, Wursteisen B, eds. *Neonatal Screening for Cystic Fibrosis*. Caen: Presses Universitaires de Caen; 1999. p. 289-99.
13. Mehta G, Sims EJ, Culross F, McCormick J, Mehta A. Potential benefits of the UK Cystic Fibrosis Database. *J R Soc Med* 2004;97:60-71.
14. Schechter MS, Margolis PA. Relationship between socioeconomic status and disease severity in cystic fibrosis. *J Pediatr* 1998;132:260-4.
15. Noble M, Wright G, Dibben C, Smith GAN, McLennan D, Anntila C, et al. *The English Indices of Deprivation*. 2004. Wetherby, West Yorkshire, UK, ODPM Publications.
16. Bland M. *An Introduction to Medical Statistics*. Oxford University Press; 1990.
17. McCormick J, Green MW, Mehta G, Culross F, Mehta A. Demographics of the UK cystic fibrosis population: implications for neonatal screening. *Eur J Hum Genet* 2002;10:583-90.
18. Gaskin K, Gurwitz D, Durie P, Corey M, Levison H, Forstner G. Improved respiratory prognosis in patients with cystic fibrosis with normal fat absorption. *J Pediatr* 1982;100:857-62.
19. Kristidis P, Bozon D, Corey M, Markiewicz D, Rommens J, Tsui LC. Genetic determination of exocrine pancreatic function in cystic fibrosis. *Am J Hum Genet* 1992;50:1178-84.
20. Modolell I, Alvarez A, Guarner L, de Gracia J, Malagelada JR. Gastrointestinal, liver, and pancreatic involvement in adult patients with cystic fibrosis. *Pancreas* 2001;22:395-9.
21. Cystic Fibrosis Genotype-Phenotype Consortium. Correlation between genotype and phenotype in patients with cystic fibrosis. *N Engl J Med* 1993; 329:1308-13.
22. Zielenski J. Genotype and phenotype in cystic fibrosis. *Respiration* 2000; 67:117-33.
23. Connett GJ, Yeatman SL. Delayed diagnosis in cystic fibrosis patients homozygous for the delta F508 mutation results in increased treatment to maintain health in childhood. *Pediatr Pulmonol* 2002;24S: A407.
24. Castellani C. Evidence for newborn screening for cystic fibrosis. *Paediatr Respir Rev* 2003;4:278-84.
25. Baumann U, Stocklossa C, Greiner W, Graf von der Schulenburg JM, von der Hardt H. Cost of care and clinical condition in paediatric cystic fibrosis patients. *J Cystic Fibrosis* 2003;2:84-90.
26. Ratjen F, Doring G. Cystic fibrosis. *Lancet* 2003;361:681-9.
27. Davis PB, Byard PJ, Konstan MW. Identifying treatments that halt progression of pulmonary disease in cystic fibrosis. *Pediatr Res* 1997;41: 161-5.
28. Schechter MS, Shelton BJ, Margolis PA, FitzSimmons SC. The association of socioeconomic status with outcomes in cystic fibrosis patients in the United States. *Am J Respir Crit Care Med* 2001;163: 1331-7.
29. Ramesh S. Antibiotic hypersensitivity in patients with CF. *Clin Rev Allergy Immunol* 2002;23:123-41.
30. Farrell MH, Farrell PM. Newborn screening for cystic fibrosis: ensuring more good than harm. *J Pediatr* 2003;143:707-12.
31. Schidlow DV. Maintaining the horizontal line: early intervention and prevention of CF lung disease. *J Cystic Fibrosis* 2004;3:63-6.

CYSTIC FIBROSIS BIRTH RATES IN CANADA: A DECREASING TREND SINCE THE ONSET OF GENETIC TESTING

ANNIE DUPUIS, PHD, DAVID HAMILTON, PHD, DAVID E. C. COLE, MD, PHD, AND MARY COREY, PHD

Objective To estimate cystic fibrosis (CF) birth rates in Canada from 1971 to 2000 and to assess the population impact of genetic testing in families with a history of CF, after identification of the CF transmembrane conductance regulator gene in 1989.

Study design Age-at-diagnosis data were obtained from the Canadian Cystic Fibrosis Foundation Patient Data Registry and Canadian births for the corresponding years from Canadian Vital Statistics. Estimates of the CF birth rate in each year were based on a nonparametric model that allows the birth rate to vary across the years and adjusts for censoring of currently undiagnosed patients.

Results The overall CF birth rate from 1971–1987 was 1/2714 with no increasing or decreasing trend. Beginning in 1988, 1 year before identification of the CF transmembrane conductance regulator gene, estimated CF birth rates followed a linear decline to an estimated rate of 1/3608 in 2000. CF birth rates may have stabilized in the last few years, but further decline may occur with implementation of carrier screening in the general population.

Conclusions These results demonstrate the temporal association of genetic testing and declining CF birth rates in Canada. They may assist in decisions relating to the allocation of resources for prenatal and neonatal CF screening programs. (*J Pediatr* 2005;147:312-5)

Cystic fibrosis (CF), the most common autosomal recessive life-shortening disorder in the white population,¹ is caused by mutations of the CF transmembrane conductance regulator (CFTR) gene. Since its discovery in 1989,^{2,3} more than 1200 CFTR alleles have been identified.⁴ The most frequent mutation throughout the world, $\Delta F508$, accounts for 71% of mutations found among Canadian patients with CF.⁵⁻⁷ However, the allelic frequency of this and other mutations varies across ethnic groups and geographic regions.⁸

Accurate estimates of CF birth rates are important in evaluating epidemiologic trends and predicting the future burden of disease. Such estimates are difficult to obtain because, although CFTR mutations are present at birth, delayed diagnosis or late onset of symptoms results in a later age-at-diagnosis in a substantial proportion of patients. The Canadian CF Foundation's (CCFF) Patient Data Registry Report for 2000⁷ notes that 40% of patients alive in 2000 were diagnosed after the first year of age, 9.6% after their tenth birthday, and 2% were diagnosed after age 30, consistent with reports for the CF population in the United States.⁹

To estimate CF birth rates, methods have been developed that do not depend on the age-at-diagnosis distribution. For example, heterozygote frequencies of the principal CF mutations can be obtained in women undergoing antenatal testing and in newborn infants. By adjusting for the relative frequencies of those mutations among patients with CF, estimated population-based incidence rates can be calculated from the Hardy-Weinberg equation. However, this does not reflect the reduction in CF births that result from terminated pregnancies or spontaneous antenatal losses. Incidence rates have also been estimated from statistical modeling of the age-at-diagnosis distribution of patients with

See related articles, p 295, p 302, p 306, p 316, p 327, p 332, p 396, p 399, and p 402.

From The Hospital for Sick Children and University of Toronto, Toronto, Ontario, and Dalhousie University, Halifax, Nova Scotia, Canada.

Supported by CCFF, CIHR, NSERC, Genome Canada.

Submitted for publication Feb 25, 2005; last revision received Jun 3, 2005; accepted Jun 22, 2005.

Reprint requests: Mary Corey, PhD, Population Health Sciences, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada, M5G 1X8. E-mail: mary.corey@sickkids.ca. 0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.06.043

CCFF	Canadian Cystic Fibrosis Foundation	CFTR	Cystic fibrosis transmembrane conductance
CF	Cystic fibrosis		regulator

CF.¹⁰ Such models adjust for censoring because of delay in diagnosis so that estimates of the number of CF births in a given year include patients not yet diagnosed.

Prenatal testing and genetic testing for CF are possible. With the localization of the CFTR gene to chromosome 7, a reliable approach based on closely linked restriction fragment length polymorphisms was developed and used to genotype fetal DNA from chorionic villus biopsy specimens.¹¹ Although population screening for CF mutations has not been widely endorsed, carrier screening of large at-risk populations is now being advocated; some have recommended that screening be offered to all women as an integral part of prenatal care.¹²

In this report, national registry data enumerating all known patients with CF in Canada born between 1971 and 2000 were used to obtain accurate trends in CF birth rates over time.

METHODS

Data

A table of age-at-diagnosis by birth year for patients born and diagnosed between 1971 and 2000 was obtained from the CCFF Patient Data Registry. The registry collects data annually from 38 specialized CF clinics throughout Canada. Because of the single-payer government health care system in Canada, virtually all patients diagnosed with CF are seen in these specialized clinics. Canadian births were obtained from the federal demographics database, Canadian Vital Statistics, for the corresponding years.

Statistical Analysis

By adjusting for censoring of currently undiagnosed patients, CF birth rates are derived that are estimates of the actual proportion of infants born in a given year and destined to have CF. Estimates of the age-at-diagnosis distribution and predictions of the number of CF patients yet to be diagnosed are also derived, using 2 similar models that assume that the number of cases diagnosed at each age in each year-cohort follow a Poisson distribution. The first is a variant of the nonparametric method described by Kalbfleisch and Lawless¹³ that allows the birth incidence to vary across the years. The second is an extension of the method of Chong et al¹⁰ that assumes that the birth rates follow a segmented linear model with constant birth incidence up to 1987 followed by a linear decrease. The breakpoint was selected to maximize the log likelihood for the model. Standard errors for the birth rates are obtained from the information matrix, and confidence intervals are calculated using the normal assumption. The age-of-diagnosis distribution and rate of undetected CF deaths are assumed to be stable over the study period, and sibling diagnoses are considered as independent. To assess the stability of the age at diagnosis distribution, the segmented linear model was extended to allow for change in this distribution. A test for significance of the change is based on the improvement in fit given by this extension.

Some diagnosed patients born late in any given calendar year are not included in the censoring year, in this case 2000.

To avoid bias from this systematic under-reporting, diagnosis data from the 2001 database were used to update values at each censored age. For example, those born in 2000 and diagnosed under 1 year in 2001 were added to those born and diagnosed in 2000, and a patient born in 1971 and diagnosed at age 29 in 2001 would be added to the number diagnosed at age 29 in the censoring year 2000.

RESULTS

Between 1971 and 1987, there were no significant trends in the estimates of the CF birth rates obtained from the nonparametric Poisson model (Figure). Although estimated annual rates fluctuated considerably through the 1970s and 1980s, the overall CF birth rate obtained from the segmented linear Poisson model was 1/2714, with no increasing or decreasing trend. A decline in CF birth rates was observed from 1988 to 2000, yielding an estimated birth rate for year 2000 of 1/3608, a 25% decrease over the 12-year period. Estimated birth rates in the final years of the study period suggest that rates may be stabilizing at a new level, but this conclusion remains tentative because these later estimates are associated with large standard errors due to the shorter period of observation and the smaller birth cohort sizes. The breakpoint for the segmented linear Poisson model was selected to maximize the log likelihood and corresponds to 2 years before the identification of the CFTR gene, bringing with it an increased potential for genetic testing and counseling. Differences in likelihood for breakpoints ranging from the years 1986 to 1990 were so slight as to suggest a rounded shoulder rather than an instantaneous decline in rates.

To assess our assumption of stable age-at-diagnosis distribution, we fitted an extra term to our model allowing the distribution to vary. A test of this term gave $P = .07$, which is suggestive of a change but not conclusive. The direction of the change was toward a somewhat earlier diagnosis. Birth rate estimates for recent years were therefore somewhat lower for the extended model, and the presented model thus gives a conservative estimate of the decreasing incidence over that time.

The cumulative age-at-diagnosis distribution derived from the model yields an estimate of 59% for the proportion of all patients diagnosed before age 30 who are identified within a year of birth. By age 10, this proportion has increased to 90%. Even after adjusting these figures to include an estimated 2% of diagnoses that occur after age 30, the resulting estimates for proportions of patients diagnosed by age 1 (58%) and age 10 (88%) are comparable to those reported for patients alive in 2000 (60% and 90.4%, respectively), as noted in the CCFF Patient Data Registry Report for 2000.⁷ Interestingly, the estimated number of patients with CF born in the entire period 1971–2000 who were still undiagnosed by the end of 2001 was 316.

DISCUSSION

Determining an accurate and unbiased estimate of CF birth rates has been an issue ever since registries and large

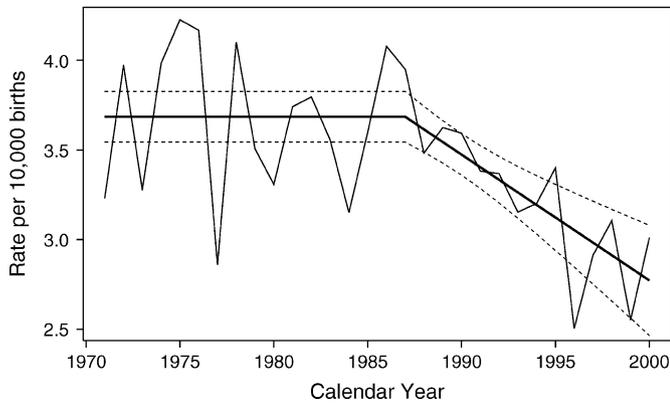


Figure. Non-parametric (fluctuating solid line) and segmented linear (heavy line) Poisson model estimates of the CF birth rates in Canada, 1971-2000 with 95% confidence interval (dashed line).

population surveys of the disorder became available. Gregg et al¹⁴ used data from the Wisconsin CF newborn screening program for the period of April 1985 to June 1991 to estimate the birth prevalence rate of CF. Newborns with serum immunoreactive trypsinogen levels ≥ 180 ng/mL on screening were then being diagnosed at 6 weeks of age by sweat chloride determinations after pilocarpine iontophoresis. On the basis of data from 220,865 newborn screens, an estimated incidence of 1/3431 live births among whites was obtained, and a CF carrier frequency of 1 in 30 was calculated. This agreed closely with a carrier frequency estimate of 1 in 31 derived from the relative frequencies of $\Delta F508$ mutations in 1531 normal newborn samples and 171 patients with CF.

Kosorok et al¹⁵ estimated the CF birth incidence using data from the CF Foundation Patient Registry in the United States for the 2-year interval of 1989 to 1991. Using a semi-parametric model that adjusts for “competing risks” (death before diagnosis) and censoring of patients who remained undiagnosed at the end of the study period, they estimated the incidence of CF among infants born to be 1/2906 among US whites and 1/10,338 among non-whites. Their model was adjusted for 15% under-reporting to the CF Patient Registry, as suggested by FitzSimmons.¹⁶ When under-reporting was excluded from the model, the estimated national incidence among whites was estimated to be 1/3419, which is very close to the incidence reported by Gregg et al¹⁴ and suggests that under-reporting to the registry may not be as important an issue as previously believed.

In Nova Scotia, Canada, a statistical model was applied by Chong et al¹⁰ to data from the IWK Grace Health Centre CF registry for the Canadian Maritime Provinces over the 20-year period of 1971 to 1990, and a CF birth rate of 1/2436 was derived for this predominantly northern European population. In that model, a constant birth prevalence rate was assumed.

Using data from the United Kingdom (UK) patient registry for the years 1968–1994, Dodge et al¹⁷ observed a consistent decline in incidence from 1989 to 1994, which they attributed to unreliable data in the final years of the study period because of delay in diagnosis. Our model, which adjusts

for this delay, identifies a decline in Canadian birth prevalence beginning in 1988 with a possible stabilization of rates beginning in 1996, both trends that are quite consistent with the UK estimates.

The 2% of patients in the 2000 Canadian Registry who were diagnosed after the age of 30 is enriched by the diagnosis of older atypical subjects in the most recent decade. These adults were identified largely through research projects targeting patient groups with CF-like single-organ symptoms, such as congenital bilateral absence of the vas deferens, idiopathic pancreatitis, or late-onset lung disease. Whether these conditions, linked to variant CFTR alleles but lacking classic multi-system involvement, should be labeled CF or something else entirely is still being debated.¹⁸ However, it is worth noting that our analyses are based on Poisson models that assume all subjects with CF are diagnosed by age 30 and therefore are not affected by these atypical individuals.

The close temporal relationship between the onset of testing and the decline in rates does not constitute a clear demonstration of cause and effect. Other demographic trends may have been influential, including the general decline in family size, although this demographic trend would be expected to increase rather than decrease the CF birthrate, because prenatal genetic testing is least likely to have occurred in firstborn CF pregnancies during this period in Canada.

Green et al¹⁹ reported a steady decline in CF birth rates for the East Anglia region of the UK between 1981 and 1990, corresponding to a period when neonatal screening along with genetic counseling, and later prenatal diagnosis, was established in the region. However, the 7.5% average yearly decline in the incidence of CF could not be fully explained by screening, and other factors, such as incomplete ascertainment, reduction in the rate of consanguinity, and population migration, were mentioned as possible co-contributors.

Similarly, in northwestern France, the decline in CF birth prevalence rate from 1/2364 in the 1980s to 1/3055 in the 1990s could not be fully explained by the screening program in place.²⁰ In a more recent study of the same population,²¹ terminated CF pregnancies could be identified and correlated with reduction of CF birth rates from 1992 to 2001. Terminations among couples related to a clinically diagnosed child resulted in a 9.6% reduction in CF births, compared with 15.7% among couples related to a screened child. Overall, family history of CF was associated with a 22.6% reduction in CF births. By adjusting these figures to reflect eventual diagnosis through clinical symptoms, they estimated that the reduction caused by prenatal diagnosis that occurred as the result of screening only was 6.1%. Similarly, the reduction in CF births resulting from prenatal diagnosis of couples related to a clinically diagnosed child was 18.5% whereas 12.8% was related to prenatal diagnosis after the detection of an echogenic bowel. The total of all the separate percent reductions described by Scotet et al²¹ exceeds the overall change they observed because each estimate was calculated assuming all other factors were in place, thereby reducing the denominator used in the calculations.

Our rates were not adjusted for ethnicity, but a rough estimate of the effect of changing ethnicity can be computed from national data.²² In 1986, 91% of Canadian births were to mothers born in Canada or Europe and only 9% to mothers born in Asia or elsewhere. Assuming a 1/2500 risk of CF in the former and 10-fold smaller risk (1/25,000) in the latter, the overall CF birthrate estimate would be 1/2720, virtually the same as our model estimate. By 2001, however, the proportion of babies born to mothers born in Asia or elsewhere increased to 17%, which leads to an estimated 7.8% decrease in CF birthrate (1/2952), or less than one third of the decline we report here. Direct study of these sub-populations suggest that such estimates will overstate the impact of immigration from Asia on CF birth rates in Canada. CF prevalence among Canadian children of South Asian origin is similar to that for the population of European origin living in the same geographic region.²³

The negligible differences observed in the model likelihood estimates for breakpoints ranging from 1986 to 1990 may well reflect a gradual implementation of precise genetic diagnosis and progressively enhanced reliability of prenatal testing methods in the years after localization of the CFTR gene to chromosome 7. The efficacy of genetic testing has improved steadily over the past decade as an increasing number of mutations have been identified. Canada does not currently have a national CF genetic screening program in place, which may explain in part the apparent stabilization of CF birth rates, especially if it is true that the individuals most likely to seek out and benefit from genetic testing, (ie, families with a history of CF) are now making regular use of prenatal diagnosis services. More widespread screening of couples in the general population has the potential to extend the decline in CF birth prevalence rates even further. However, increasingly effective treatment and improved survival of patients with CF may eventually reverse this trend.

We could not measure the uptake rate for genetic testing and counseling services on a national basis since the discovery of the CF gene, but we speculate that the onset of the decline in CF birth prevalence, coinciding as it does with the discovery of the CF gene, points to increased use of carrier screening and prenatal diagnosis services. Follow-up is necessary to establish whether the birth rates are stabilizing at a second plateau or are continuing to decline as genetic testing programs expand to include population-wide screening. This could have important implications for the allocation of resources for prenatal and neonatal CF programs.

We thank Dr. J. Buchanan for helpful editorial suggestions.

REFERENCES

1. Welsh MJ, Ramsey BW, Accurso F, Cutting GR. Cystic fibrosis. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The metabolic and molecular bases of inherited disease*. 8th ed. New York: McGraw-Hill; 2001. p. 5121-88.

2. Rommens JM, Iannuzzi MC, Kerem B, Drumm ML, Melmer G, Dean M, et al. Identification of the cystic fibrosis gene: chromosome walking and jumping. *Science* 1989;245:1059-65.
3. Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, et al. Identification of the cystic fibrosis gene: genetic analysis. *Science* 1989;245:1073-80.
4. Cystic Fibrosis Genetic Analysis Consortium (CFGAC). 2002. www.genet.sickkids.on.ca/cftr/. Accessed in April 2005.
5. Kristidis P, Bozon D, Corey M, Markiewicz D, Rommens J, Tsui LC, et al. Genetic determination of exocrine pancreatic function in cystic fibrosis. *Am J Hum Genet* 1992;50:1178-84.
6. Rozen R, De Braekeleer M, Daigneault J, Ferreira-Rajabi L, Gerdes M, Lamoureux L, et al. Cystic fibrosis mutations in French Canadians: three CFTR mutations are relatively frequent in a Quebec population with an elevated incidence of cystic fibrosis. *Am J Med Genet* 1992;42:360-4.
7. Canadian Cystic Fibrosis Foundation. Canadian Patient Data Registry National Report, 2000. Canadian Cystic Fibrosis Foundation; Toronto 2001.
8. Bobadilla JL, Macek M Jr, Fine JP, Farrell PM. Cystic fibrosis: a worldwide analysis of CFTR mutations—correlation with incidence data and application to screening. *Hum Mut* 2002;19:575-606.
9. Cystic Fibrosis Foundation. Patient Registry 2000 Annual Data Report. Bethesda (MD): Cystic Fibrosis Foundation; 2001.
10. Chong MY, Hamilton DC, Cole DEC. Retrospective estimation of the birth prevalence for delayed onset disorders: application to cystic fibrosis in Nova Scotia. *Stat Med* 2000;19:743-51.
11. Farrall M, Law HY, Rodeck CH, Warren R, Stanier P, Super M, et al. First-trimester prenatal diagnosis of cystic fibrosis with linked DNA probes. *Lancet* 1986;1:1402-5.
12. Khoury MJ, McCabe LL, McCabe ER. Population screening in the age of genomic medicine. *N Engl J Med* 2003;348:50-8.
13. Kalbfleisch JD, Lawless JF. Inference based on retrospective ascertainment: an analysis of the data on transfusion-related AIDS. *J Am Stat Assoc* 1989;84:360-72.
14. Gregg RG, Benjamin SW, Farrell PM, Laxova A, Hassemer D, Mischler EH. Application of DNA analysis in a population-screening program for neonatal diagnosis of cystic fibrosis (CF): comparison of screening protocols. *Am J Hum Genet* 1993;52:616-26.
15. Kosorok MR, Wei WH, Farrell PM. The incidence of cystic fibrosis. *Stats Med* 1996;15:449-62.
16. FitzSimmons SC. The changing epidemiology of cystic fibrosis. *J Pediatr* 1993;122:1-9.
17. Dodge JA, Morison S, Lewis PA, Coles EC, Geddes D, Russell G, et al. Incidence, population, and survival of cystic fibrosis in the UK, 1968-95. *Arch Dis Child* 1977;77:493-6.
18. Knowles MR, Durie PR. What is cystic fibrosis? *N Eng J Med* 2002;347:439-42.
19. Green MR, Weaver LT, Heeley AF, Nicholson K, Kuzemko JA, Barton DE, et al. Cystic fibrosis identified by neonatal screening: incidence, genotype, and early natural history. *Arch Dis Child* 1993;68:464-7.
20. Scotet V, Gillet D, Duguépéroux I, Audrézet M-P, Bellis G, Garnier B, et al. Spatial and temporal distribution of cystic fibrosis and of its mutations in Brittany, France: a retrospective study from 1960. *Hum Genet* 2002;111:247-54.
21. Scotet V, Audrézet M-P, Roussey M, Rault G, Blayau M, DeBraekeleer M, et al. Impact of public health strategies on the birth prevalence of cystic fibrosis in Brittany, France. *Hum Genet* 2003;113:280-5.
22. Belanger A, Gilbert S. The fertility of immigrant women and their Canadian-born daughters. In: Report on the demographic situation in Canada. Current demographic analysis. Ottawa: Alain Belanger Ministry of Industry; 2003. p. 127-51.
23. Mei-Zahav M, Durie P, Zielenski J, Solomon M, Tullis E, Tsui L-C, et al. The prevalence and clinical characteristics of cystic fibrosis in South Asian Canadian immigrants. *Arch Dis Child* 2005;90:675-9.

GESTATIONAL AND NEONATAL CHARACTERISTICS OF CHILDREN WITH CYSTIC FIBROSIS: A COHORT STUDY

FILIPPO FESTINI, RN, BA, BSN, GIOVANNI TACCETTI, MD, TERESA REPETTO, MD, MARIA FRANCESCA REALI, MD, SILVIA CAMPANA, DSC, GIANFRANCO MERGNI, BSc, LORE MARIANELLI, MD, AND MAURIZIO DE MARTINO, MD

Objective To examine whether the birth weight (BW) and the risks of being pre-term, low birth weight (LBW), and small for gestational age (SGA) of children with cystic fibrosis (CF) are different from nonaffected children.

Study design Retrospective cohort study. We examined all the children with CF born in Tuscany, Italy, from 1991 to 2002 (n = 70) comparing them to the entire population of non-CF-affected children born in the same period (n = 290,059).

Results The mean BW of newborns with CF was 246.2 g lower than the mean BW of the non-CF neonatal population ($P = .0003$). Children with CF had a higher risk of being born pre-term (RR 2.62, $P = .001$), LBW (RR 2.66, $P = .0009$), and SGA (RR = 1.74, $P = .04$) than the non-CF-affected children. The mean BW of term newborns with CF was 205.7 g lower than that of term non-CF-affected babies ($P = .0002$).

Conclusions Our data show an association between CF and reduced BW and show a greater risk of being pre-term for babies with CF. (*J Pediatr* 2005;147:316-20)

It is well documented that cystic fibrosis (CF) has a negative effect on the growth of children whether this is because of accompanying lung infections or because of the status of malnutrition. Little is known, however, of the influence CF has on the intrauterine development of the fetus and on the course of pregnancy itself.

About 60% of children with show pancreatic insufficiency (PI) at birth, which often determines poor growth and malnutrition in the first few weeks of life.¹ A group of non-CF-affected newborns with low birth weight (LBW) for their gestational age (GA) had reduced pancreatic function in comparison with the newborns with an adequate birth weight (BW) for GA, thus suggesting a link between impaired pancreatic function and reduced weight at birth.²

Other studies have shown that the cystic fibrosis transmembrane regulator (CFTR) protein is present in the apical membrane of the placental tissue^{3,4} and have suggested a role for altered CFTR in ionic transport at the placental level,⁵ leading to the hypothesis that an alteration in the CFTR may cause functional insufficiency of the fetal part of the placenta and inadequate placental exchange.

Some studies have reported a reduced BW in newborns with CF compared with control groups of healthy babies, siblings, or international neonatal standards.⁶⁻¹¹ The GA of newborns affected by CF was compared with that of healthy children in one study performed 45 years ago.⁷

To obtain accurate epidemiological data, it is necessary to perform studies over a long period of time based on well-defined entire populations belonging to defined geographical areas.¹² In particular, with CF, it is very important to identify cases through neonatal screening¹² to avoid a selection bias owing to the diagnosis of the disease made only on the basis of symptoms. In fact, neonatal screening allows us to identify cases of CF even in

See related articles, p 295, p 306, p 312, p 321, p 327, p 332, p 396, p 399, and p 402.

From the Cystic Fibrosis Center of Tuscany, Pediatric Infectious Diseases Department, Meyer Pediatric Hospital, University of Florence, Italy.

Supported by Telethon Italy's Research Grant EC 1208/2000.

Presented as a poster at the 17th North American Cystic Fibrosis Conference (New Orleans, October 2002) and published as an abstract in the Congress proceedings.

Submitted for publication Aug 4, 2004; last revision received Feb 9, 2005; accepted Apr 13, 2005.

Reprint requests: Dr Filippo Festini, Meyer Pediatric Hospital, University of Florence, via L. Giordano 13, Florence 50132, Italy. E-mail: f.festini@meyer.it. 0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.04.031

BW	Birth weight	LBW	Low birth weight
CF	Cystic fibrosis	PI	Pancreatic insufficiency
CFRT	Cystic fibrosis transmembrane regulator	PS	Pancreatic sufficiency
GA	Gestational age	SGA	Small for gestational age
IRT	Immunoreactive trypsin		

preclinical phases and to detect the milder forms of CF that would otherwise not be diagnosed. The objectives of this study were to verify if the mean BW of an overall population of children with CF born in a given geographical region, in a specific period of time, and diagnosed through screening differs from the BW of all other newborns not subject to the disease. We also wished to verify if children with CF have a different risk of being pre-term, LBW, and small for gestational age (SGA), in comparison to all the other newborns in the same area and in the same period.

METHODS

This was a retrospective, observational cohort study. Since 1982, the Regional Center for CF, in the Meyer Hospital of Florence, has conducted a neonatal screening program for CF in Tuscany, an administrative and geographical region of Italy with 3.5 million inhabitants. Since 1991, the program has involved the entire region, covering 99.8% of newborns.¹³ Starting from that year the screening has been carried out according to a two-stage immunoreactive trypsin protocol (IRT/IRT) on blood spot samples, with a complementary lactase test on meconium. When a newborn has a positive test, the family is contacted by the 45th day of life and invited to the Regional CF Center for a sweat test according to the Gibson and Cooke method.¹⁴ If the test is positive, the child is taken into the care of the CF Center, where a genetic test for CFTR mutations is immediately given to the newborn and the parents (currently, oligonucleotide ligation assay combined with polymerase chain reaction method for 31 mutations, plus denaturing high performance liquid chromatography for exon 17). A test of exocrine pancreatic function also is carried out immediately after a positive or borderline sweat test. Pancreatic function is tested by measuring chymotrypsin in feces (colorimetric method Chymo Roche, cutoff: 13.2 U/g [Chymo, Roche Diagnostics GmbH, Mannheim, Germany]). If the sweat test result is borderline, the child is followed-up to clarify the clinical status. Since February 2001, genetic testing on 31 mutations has been included in our screening protocol for all newborns positive on the first IRT test. The sensitivity and specificity of the screening program were 96.4% and 99.7%, respectively, with the IRT/IRT+meconium method, and 100% and 98.8%, respectively, after the introduction of the genetic test.

We studied all children with CF born in Tuscany from July 1, 1991 to June 30, 2002. The diagnosis of CF in Tuscany is centralized in our unit, the only center where the sweat test is performed and where a follow-up program is conducted for all patients with CF and, given that 2 years have passed from the end of the period under examination, we are confident that we have studied the entire population of children with CF born in Tuscany in that period. In the period of study, the incidence of CF was 1 per 4144, which is similar to reported Tuscan and Italian data.¹⁵⁻¹⁷ The BWs and GAs of the newborn children were determined from obstetric records.

We also examined the whole neonatal population in Tuscany during that period. To this purpose we used the

information contained in the database of the neonatal screening program, on the basis of the records accompanying the blood and meconium samples sent by each maternity unit of the region, or by each obstetrician practitioner, to the CF Center. These records hold the name, sex, BW, and GA—in full weeks—of each newborn but not length at birth. The file is written out by the maternity unit doctor, obstetrician, or nurse responsible for the newly born child. If a newborn is transferred from the maternity unit to a neonatal intensive care unit immediately after birth, the staff of the neonatal intensive care unit collect the samples and the information. Information on GA is reported on the basis of: either the last menstruation, as reported by the mother; ultrasonography scanning during pregnancy; physical examination of the newborn; or on more than one of these elements. However, the regional screening protocol provides that if GA is not certain, the GA box in the newborn's clinical chart sent to the screening Center must not be filled in. To avoid the possibility of missing children, every 3 months the CF neonatal screening staff double-check the names of babies whose blood and meconium samples are received by the CF Center, comparing them to the list of all the newborn babies born in each maternity unit.

After having excluded data of all newborns for whom there was neither BW nor GA and those for whom the GA was >43 or <24 weeks, we provisionally separated those for whom either only BW or only GA was reported, and we divided the remaining babies into groups according to sex and GA, in order to check the data quality. Examining visually these groups of data, we realized that for some GA the weight distributions were overbalanced toward the higher weight values, which in some cases were clearly excessive for the GA. We hypothesized that this might be because of the mixing of two distinct populations: those with a correct GA and those erroneously assigned to that GA through a transcription error, or an error in determining the date of the mother's last menstruation. Therefore, we excluded as nonplausible for their GA, newborns whose BW exceeded two interquartile ranges, above 75th and below 25th percentile of each group of GA and sex.^{18,19} In another article the percentiles of BW on the basis of GA and sex of the population of newborns in the period 1991 to 2002, in Tuscany, were presented.²⁰ After having excluded newborns with CF, we then calculated the mean BW per sex and overall, as well as the number of LBW babies and the relative percentages. For these two calculation, we included in the analysis also the newborns whose BW was known but not the GA. Finally, we calculated the number of pre-term babies and the relative percentages. For this calculation, we considered also the newborns whose GA was reported but not the BW.

Subsequently, we calculated the average BW per sex of newborns with CF. In addition, we determined the risk of newborns with CF being pre-term, LBW, and SGA in the same area and time period. We finally calculated the relative risk in comparison to the population of newborns not affected by CF.

The resulting differences between the different groups were tested with Student's *t* test. The statistical associations for the dichotomous qualitative variables were tested with the

Table I. Mean BW of children with CF compared with that of children without CF (males, females, and overall); 95% CI of the difference between means; t test P values

	Newborns with CF, mean BW (±SD)	Newborns without CF, mean BW (±SD)	Difference (CI 95%)	t test P value
Males	3082.9 g (±505.2)	3344.1 g (±501.6)	261.2 g (112.9, 409.4)	.0005
n	44	147,486		
Females	2945.3 g (±576.3)	3207.5 g (±481.3)	262.2 g (77.1, 447.2)	.005
n	26	138,339		
Overall	3031.8 g (±532.8)	3278 g (±496.6)	246.2 g (129.8, 362.5)	.0003
n	70	285,825		

χ^2 test. A level of statistical significance of 95% was established and P values were determined. The software Epi Info 2002, rev.1 (Centers for Disease Control, Atlanta, GA) and PHStat for Excel 97 (Prentice Hall, Pearson Education, Upper Saddle River, NJ) were used to process the data and for the statistical analysis.

For the purpose of this study we have used the following definitions: Adequate for GA: newborns whose BW falls between the 10th and 90th percentile for GA and sex; SGA: newborns whose BW falls below the 10th percentile for both GA and sex; LBW: newborns whose BW is <2500 g; pre-term: newborns whose GA is <37 weeks.

RESULTS

In the period examined 290,129 children (149,848 males and 140,281 females) were born in Tuscany, of whom 70 had CF (44 males and 26 females). We excluded 1105 babies (0.38%) whose BW and GA were both missing, 170 babies (0.05%) whose reported GA was >43 or <24 weeks, and 935 babies (0.32%) with a BW nonplausible for their GA, according to the method described above. Of the remaining 287,849 non-CF-affected children, 262,321 (91.1%) had complete data (both BW and GA), 2024 (0.7%) had only GA, and 23,504 (8.1%) had only BW.

Of those with CF, 67 were diagnosed by screening and two, who were negative at screening, were diagnosed for symptoms at 4 and 11.5 months. One newborn positive to screening was diagnosed postmortem by genetic screening.

Characteristics of Newborns with CF

It was not possible to determine the GA for only one of the 70 newborns with CF. Of the remaining 69, 10 were pre-term.

Five newborn babies with CF (7.1%) had meconium ileus. Their mean BW (3016 g, SD ± 264 g) was not significantly different from that of children with CF without MI (3033.1 g, SD ± 549.3 g).

At the time of diagnosis 42 children (61.8%) suffered from PI, whereas 26 (38.2%) had pancreatic sufficiency (PS). The pancreatic status of the newborn baby diagnosed post-mortem is not known. Of the two children diagnosed through symptoms, it is not known whether one had PI or PS at birth, and the other child had PS at diagnosis, so he was PS also at

birth. No statistically significant differences were found between the mean BW of babies with PI and that of babies with PS, as well as between their proportions of LBW, SGA, and pre-term births.

Of the 70 newborns with CF observed, nine had a $\Delta F508$ homozygous genotype, 38 a compound $\Delta F508$ heterozygous genotype, three were homozygous for stop mutations, and 15 had a compound stop mutation heterozygous genotype. No statistically significant differences were found between these four groups, as far as the mean BW and the proportion of LBW and pre-term infants are concerned.

Comparison between Newborns with and without CF

Table I illustrates the differences of BW of children with CF in comparison with the nonaffected neonatal population, and Table II compares the risk of being born LBW and pre-term between CF newborns and non-CF-affected children, and indicates the relative risk.

From the comparison of the percentiles of BW for GA and sex developed from the entire population of newborns in this period,²⁰ we found that 17.3% of babies with CF were SGA compared with 10% of the whole population (RR = 1.74, CI 95% 1.04, 2.91, χ^2 P value = .04).

Among the pre-term children with CF, two suffered from MI, eight had PI at birth, and four were LBW at birth. All pre-term newborns with CF had an adequate for GA weight at birth with respect to BW percentiles of Tuscany. In our population of babies with CF, all SGA newborns belong to the group of those born at term.

Table III illustrates the differences in BW between pre-term newborns with and without CF and between children born at term with and without CF.

DISCUSSION

Our study shows that in an entire population of newborns from an Italian region over a period of 11 years, the mean BW of newborns with CF was significantly lower in comparison with nonaffected children. Furthermore, for the first time, we observe in a cohort of children with CF a significantly greater risk of being born pre-term, weighing <2500 g at birth, and being SGA, in comparison to all the nonaffected newborns belonging to the same population.

Table II. Risks of being born LBW and pre-term among newborns with CF and newborns without CF; relative risks with 95% confidence intervals; χ^2 P values

		Newborns with CF		Newborns without CF		Relative Risk (CI 95%)	χ^2 P value
		n	Risk	n	Risk		
LBW	yes	10	14.2%	15,320	5.36%	2.66 (1.5, 4.7)	0.0009
	no	60		270,505			
Pre-term	yes	10	14.4%*	14,592	5.52%	2.62 (1.4, 4.6)	0.001
	no	59		249,753			

*One missing value.

Table III. Mean BW of pre-term and term newborns with CF compared with pre-term and term newborns without CF; 95% CI of the difference between means; t test P values

	Newborns with CF ^(*)		Newborns without CF ^(**)		Difference (CI 95%)	t test P value
	n	mean BW (\pm SD)	n	mean BW (\pm SD)		
Pre-term	10	2434 g (\pm 712.9)	14,428	2352.2 g (\pm 601.1)	-81.8 g (-454.5, 290.9)	ns
GA 37 weeks or more	59	3126.1 g (\pm 430.3)	247,893	3331.8 g (\pm 431.9)	205.7 g (95.4, 315.9)	.0002

*Missing data for one child.

**Missing data for 25,528 children (missing either BW or GA).

Previous studies have examined the neonatal characteristics of children with CF. Boyer⁶ compared a group of CF newborns with a random healthy control group and noted a significantly lower weight in both male and female babies with CF. Hsia⁷ studied a group of American newborns with CF and, although statistical tests were not performed, demonstrated a lower BW in children with CF in comparison with their healthy siblings and the standards elaborated for an English neonatal population. Even De Angelis et al⁸ detected a lower BW among newborns with CF in comparison with their siblings. He did not, however, differentiate between males and females, nor did he detect any statistically significant difference compared with random healthy controls. Mearns⁹ and Marcus et al¹⁰ also noted, in both male and female newborns with CF, a BW about 200 g lower than national standards. More recently, Muller et al¹¹ evidenced a difference in BW between a group of newborns with CF and a random healthy control group. Hsia⁷ did not detect differences in the GA of children with CF in comparison with healthy newborns; however, his study was carried out 45 years ago when there was a very different approach to the obstetrical-gynecological follow-up of pregnancies and when resuscitation techniques and perinatal care, which now enable the success of many pregnancies, were less widespread.

It has been hypothesized that in children with CF fetal growth is altered owing to an inadequate functioning of the exocrine pancreas,^{8,11} which determines reduced intrauterine nutrition and thus lower BW. Research carried out with animal models showed that the amniotic fluid supplies 10% to 14% of the nutritional needs of the fetus,²¹ a quantity that would be missing in the case of PI.

Some researchers have detected a lower BW in newborns with CF affected by MI in comparison with other

babies with CF.²² Others, however, came to the opposite results: Marcus et al hypothesized that there may be an artificial increase in BW owing to an accumulation of plugged meconium.¹⁰ Instead, in our study, we did not detect any significant difference in the BW of newborns with CF and MI.

Other studies have hypothesized that the difference in BW of newborn children with CF may be caused by maternal factors.^{6,8,9,11} Boyer's figures (though not statistically significant) point to the role of the placenta in determining the lower BW of newborns with CF. In fact, a group of mothers subjected to a special hypercaloric diet gave birth to babies with CF of a higher BW in comparison with those mothers who were not on such a diet.

The expression of the CFTR protein on the maternal part of the placenta has been demonstrated;^{3,4} there also is evidence from case studies that this protein, if changed, determines an alteration of placental ionic exchange,⁵ with the possible result of reducing fetal nutrition. Some mutations of the CFTR gene have been associated with more severe clinical manifestations of CF than others.²³ If, therefore, the CFTR is expressed on the placenta, it could be hypothesized that the type of maternal or fetal mutation may influence its function and, as a consequence, may influence the duration of the pregnancy and the weight of the newborn.

Some of the findings of our study are particularly interesting and deserve further examination. First, we noticed that in our study SGA newborn children with CF were all concentrated among those born at term, whereas pre-term babies all had an adequate BW for their GA. Moreover, the mean BW of pre-term newborns with CF did not differ significantly from that of nonaffected pre-term infants. On the contrary, term newborns with CF had a significantly lower BW in comparison with term babies not subject to the disease. Moreover, the

relative risk that newborns with CF be SGA does not seem as high as that of being LBW or pre-term. These factors, in our opinion, suggest that CF may cause premature birth but the gap in growth compared with nonaffected newborns comes about in the final period of gestation of term babies.

In the group of non-CF-affected children we had to exclude 0.75% of the subjects because the data reported in the database of the screening program were missing, implausible, or clearly wrong. Another 8.8% of the records reported only either the BW or the GA, but these data were included to calculate, respectively, the mean BW and the proportion of LBW babies, and the proportion of pre-term babies. This percentage of incomplete, missing, or wrong data has kept substantially stable over the last 13 years in our neonatal screening program. Other authors reported similar figures with regard to anthropometric data coming from neonatal population datasets.^{24,25}

One possible limit of the present study lies in the number of newborns with CF observed. Although the differences observed are statistically significant, and we have considered an entire cohort of babies with CF born in a given area, and in a specific period, the small number of infants with CF may reduce the meaning of our findings. It is hoped that multicenter studies involving a larger number of newborn babies will be carried out.

In conclusion, our study confirms a link between CF and reduced BW and shows, for the first time, a greater risk for babies with CF of being born pre-term. Further studies are necessary to explain the mechanisms that cause the phenomena observed.

REFERENCES

1. Bronstein MN, Sokol RJ, Abman SH, Chatfield BA, Hammond KB, Hambidge KM, et al. Pancreatic insufficiency, growth, and nutrition in infants identified by newborn screening as having cystic fibrosis. *J Pediatr* 1992;120:533-40.
2. Kolacek S, Puntis JW, Lloyd DR, Brown GA, Booth IW. Ontogeny of pancreatic exocrine function. *Arch Dis Child* 1990;65:178-81.
3. Mylona P, Glazier JD, Greenwood SL, Sides MK, Sibley CP. Expression of the cystic fibrosis (CF) and multidrug resistance (MDR1) genes during development and differentiation in the human placenta. *Mol Hum Reprod* 1996;2:693-8.
4. Faller DP, Egan DA, Ryan MP. Evidence for location of the CFTR in human placental apical membrane vesicles. *Am J Physiol* 1995;269:C148-55.
5. Davis B, Shennan DB, Boyd CA. Chloride transport in cystic fibrosis placenta. *Lancet* 1985;1:392-3.
6. Boyer PH. Low birth weight in fibrocystic disease of the pancreas. *Pediatrics* 1955;16:778-84.

7. Hsia DY. Birthweight in cystic fibrosis of the pancreas. *Ann Hum Genet* 1959;23:289-99.
8. De Angelis M, Brinciotti R, Bravo E, Antonelli M. Low weight at birth in cystic fibrosis and its relationship to insufficiency of the exocrine pancreas. *Minerva Pediatr* 1983;35:437-9.
9. Mearns MB. Growth and development. In: Hodson ME, Norman AP, Batten JC, eds. *Cystic Fibrosis*. London: Balliere Tindall; 1983. p. 183-96.
10. Marcus MS, Sondel SA, Farrell PM, Laxova A, Carey PM, Langhough R, et al. Nutritional status of infants with cystic fibrosis associated with early diagnosis and intervention. *Am J Clin Nutr* 1991;54:578-85.
11. Muller AE, Thamm B, Lietz T, Handrick W, Walter S. Cystic fibrosis: a cause of reduced birth weight? *Eur J Pediatr* 1999;158:264.
12. Lewis PA. The epidemiology of cystic fibrosis. In: Hodson ME, Geddes DM, eds. *Cystic Fibrosis*. London: Arnold; 2000. p. 13-25.
13. Marianelli L, Taccetti G, Campana S, Procopio E, Pelo E, Minuti B, et al. Neonatal screening of the Tuscan population for cystic fibrosis using immunoreactive trypsinogen test molecular analysis on blood spot samples and measurements of lactase activity on meconium. Telethon Foundation, Italy; Grant n. EC1208. Proceedings of Telethon Scientific Convention; November 12-14, 2000; Rimini, Italy.
14. Gibson LE, Cooke RE. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilising pilocarpine by iontophoresis. *Pediatrics* 1959;22:545-9.
15. Festini F, Taccetti G, Cioni ML, Repetto T, de Martino M. High incidence of cystic fibrosis in children born in Italy to Albanian immigrants. *Thorax* 2003;8:93.
16. Festini F, Repetto T, Taccetti G, Campana S, Mergni GF, Di Bilio C, et al. Distribution of the incidence of CF within Tuscany (Italy): are geographical factors relevant? *J Cystic Fibrosis* 2002;1(suppl 1):S158.
17. Bossi A, Casazza G, Padoan R, Milani S. What is the incidence of cystic fibrosis in Italy? Data from the National Registry (1988-2001). *Hum Biol* 2004;76:455-67.
18. Tukey JW. *Exploratory data analysis*. Don Mills, Ontario: Addison-Wesley; 1977. p. 27-56.
19. Arbuckle TE, Wilkins R, Sherman GJ. Birth weight percentiles by gestational age in Canada. *Obstet Gynecol* 1993;81:39-48.
20. Festini F, Procopio E, Taccetti G, Repetto T, Cioni ML, Campana S, et al. Birthweight-for-gestational-age percentiles of Tuscany. *J Matern Fetal Neonatal Med* 2004;15:411-7.
21. Mulvihill SJ, Stone MM, Debas HT, Fonkalsrud EW. The role of amniotic fluid in fetal nutrition. *J Pediatr Surg* 1985;20:668-72.
22. Kerem E, Corey M, Kerem B, Durie P, Tsui LC, Levison H. Clinical and genetic comparisons of patients with cystic fibrosis, with or without meconium ileus. *J Pediatr* 1989;114:767-73.
23. McKone EF, Emerson SS, Edwards KL, Aitken ML. Effect of genotype on phenotype and mortality in cystic fibrosis: a retrospective cohort study. *Lancet* 2003;361:1671-6.
24. Gagliardi L, Macagno F, Pedrotti D, Coraiola M, Furlan R, Agostinis L, et al. Weight, length, and head circumference at birth of a North-eastern Italian population. Report of the ad hoc committee of the Italian Society of Neonatology. *Riv Ital Pediatr* 1999;25:159-69.
25. Di Lallo R, Bertollini R, Papini P, Perucci A. Percentiles of birth weight computed using a birth registry: methodological issues and comparison with other standards. *Riv Ital Pediatr* 1991;17:567-75.

SEX DIFFERENCES IN HABITUAL PHYSICAL ACTIVITY AND LUNG FUNCTION DECLINE IN CHILDREN WITH CYSTIC FIBROSIS

J. SCHNEIDERMAN-WALKER, MSc, D. L. WILKES, MSc, L. STRUG, PhD, L. C. LANDS, MDCM, PhD, S. L. POLLOCK, MSc, MD, H. C. SELVADURAI, MD, PhD, J. HAY, PhD, A. L. COATES, BEng, MDCM, AND M. COREY, PhD

Objectives To evaluate the feasibility of measuring habitual physical activity (HPA) in children with cystic fibrosis (CF) and to assess the relation between HPA and the rate of decline in FEV₁ over a period of 2 years.

Study design At regular clinic visits, 109 patients (7 to 17 years; 56 girls) performed pulmonary function testing and completed the Habitual Activity Estimation Scale (HAES). Patients were divided into quartiles, based on activity levels derived from the HAES.

Results Girls in the two lowest activity quartiles had a more rapid rate of decline FEV₁ (−3.40% and −3.05% predicted, respectively) than girls in the two highest activity quartiles (−0.93% and +1.17% predicted, respectively) ($P = .02$). In boys, the rate of decline of FEV₁ was similar in all activity quartiles (−1.95% predicted). Patients reported significantly more activity in summer compared with spring, winter, and fall ($P < .0001$), and boys reported greater activity than girls (6.5 ± 2.9 vs 5.4 ± 2.5 h/d, $P < .05$).

Conclusions The annual rate of change of FEV₁ was related to activity quartile in girls but not in boys. This research suggests that an inactive lifestyle may partially explain the poorer survival of female patients with CF. The HAES is a feasible tool for routine follow-up of HPA in our CF clinic. (*J Pediatr* 2005;147:321-6)

It is widely accepted that forced expiratory volume in one second (FEV₁) is the best predictor of survival in cystic fibrosis (CF).^{1,2} As a result, preserving lung function for as long as possible is central to the management of CF in both treatment and research. Patients with CF are encouraged to be physically active to help mobilize mucous secretions and enhance breathing capacity; short-term exercise intervention studies have documented benefits from training.³⁻⁵ Results of a 3-year, randomized, controlled trial to evaluate the effect of a home exercise training regimen on rate of pulmonary function decline suggested a slower rate of decline in the exercise group compared with the control group.⁶ Although this training program was successful within the controlled conditions of a research study, the resources required to routinely administer such a program are probably not feasible in most CF clinics. Instead, we shifted our focus to habitual physical activity (HPA) as it is reflective of the level of activity incorporated into daily life and reasoned that benefits of an altered HPA level would be more feasible to maintain once an intervention was completed.⁷

Methods of monitoring HPA in children have included motion-sensing devices (accelerometers,^{8,9} pedometers¹⁰), videotape,¹¹ activity diaries,^{12,13} and questionnaires.^{14,15} Although several studies have quantified HPA in children with CF,¹⁴⁻¹⁶ the relation of HPA with lung function over time has not been investigated.

The Habitual Activity Estimation Scale (HAES) was developed to measure HPA in children with chronic disorders, following a recognized need for a clinically feasible tool to quantify usual physical activity.¹⁷ The HAES has been previously validated against an

See editorial, p 281, and related articles, p 295, p 302, p 306, p 312, p 316, p 327, p 396, p 399, and p 402.

From the Divisions of Respiratory Medicine and Population Health Sciences, Hospital for Sick Children, Research Institute, Toronto, Ontario, Canada; the Departments of Paediatrics and Public Health Sciences, University of Toronto, Toronto, Ontario, Canada; the Division of Respiratory Medicine, Montreal Children's Hospital, Montreal, Quebec, Canada; the Division of Respiratory Medicine, The Children's Hospital at Westmead, New South Wales, Australia; and the Faculty of Applied Health Sciences, Brock University, St. Catharines, Ontario, Canada.

Submitted for publication Nov 3, 2004; last revision received Jan 26, 2005; accepted Mar 16, 2005.

Reprint requests: Mary Corey, PhD, Population Health Sciences, Hospital for Sick Children, 555 University Ave, Toronto, Ontario, M5G 1X8 Canada.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.03.043

AD	Activity diary	HSC	Hospital for Sick Children
CF	Cystic fibrosis	MCH	Montreal Children's Hospital
HAES	Habitual Activity Estimation Scale	WD	Weekday
HPA	Habitual physical activity	TA	Total activity

accelerometer in fourth (9 years) and seventh (12 years) graders¹⁸ and successfully used as a measurement tool in both chronically ill and healthy populations.^{14,19-22} A high compliance rate was demonstrated for the HAES in a pilot study conducted at the Hospital for Sick Children (HSC) CF clinic over a 4-month period.²³

The activity diary (AD) is complementary to the HAES in that it provides additional information on type of activity. Originally designed to estimate energy expenditure and validated in 15-year-olds against doubly labeled water,¹² the AD has since been modified and used to measure HPA in 10- to 50-year-olds.^{13,24}

The purposes of this investigation were (1) to evaluate the relation between HPA and the rate of decline in pulmonary function as measured by FEV₁ over a 2-year period and (2) to assess the feasibility of routinely measuring HPA in children with CF.

METHODS

Subject Selection

Patients 7 to 17 years of age who had reported participating in their "typical habitual" activity during the past week were recruited from the HSC and Montreal Children's Hospital (MCH) CF clinics. Children arriving at the clinic unwell, displaying symptoms such as an increased cough, purulent sputum, malaise, fever, and/or inability to participate in regular habitual physical activity, were recruited at a later visit. The Research Ethics Boards of HSC and MCH approved the study protocol, and written informed consent was obtained from all participants.

Data Collection

Data were scheduled for collection for all study patients at each quarterly clinic visit over the 2-year period. If a patient was not well enough to participate in their regular habitual physical activity, their data collection was postponed until the visit that HPA had resumed. As a result, the number of data points ranged from 4 to 8 and varied between patients for the study period.

Anthropometric Measures

Height (standard stadiometer with heel plate) and weight (SR Instruments; model 555, Tonawanda, NY) were measured, and percentage of ideal weight for height was calculated according to CDC 2000 standards.²⁵ Skinfold thickness was measured at the biceps, triceps, subscapular, and suprailiac areas, using Harpenden skinfold calipers. Lean body mass (LBM) and percent fat were then calculated according to Durnin and Rahaman.²⁶

Pulmonary Function Testing

Full spirometry was done, and FEV₁ (SensorMedics VMax20 Pulmonary Spirometry Instrument, Yorba Linda, CA) was determined according to standard spirometric techniques.²⁷ Values were expressed as a percentage of predicted

value for height and sex, based on previously developed standards,²⁸ which have recently been shown to be indistinguishable from more recent data sets generated elsewhere.²⁹

HAES Questionnaire

At each quarterly clinic visit, study patients completed the HAES questionnaire for a typical weekday (Tuesday, Wednesday, or Thursday) and Saturday of the previous week. Parents or research study staff aided patients younger than 12 years in completing the HAES (if needed). Percentage of time awake was documented in each of 4 activity categories: inactive (lying down), somewhat inactive (SI, sitting down), somewhat active (SA, walking), and very active (VA, those activities that make the subject "breathe hard and sweat"). The use of wake-up and bedtimes as well as meal times and durations allowed the calculation of the total number of hours per day spent in each of the 4 activity categories. Total activity (TA) was calculated as SA + VA for each day. In addition, data were categorized by season, according to calendar date.

Activity Diary

Patients were sent home from the clinic with a 3-day (2 weekdays, 1 Saturday) AD¹³ approximately once every 6 months, the timing of which was adjusted to capture 1 AD per season for each patient, over the study period. Type and intensity of activity were recorded every 15 minutes on a scale ranging from 1 (lying down) through 9 (maximal intensity activity), for the three 24-hour periods. Activity levels of the two weekdays were averaged per category to create one weekday score and were reported along with the one Saturday score. Moderate (Mod) activity was calculated as hours per day spent in intensity categories 4 to 5 (low to moderate intensity) and vigorous (Vig) activity calculated from intensity categories 6 to 9 (vigorous to maximal intensity). TA was calculated as the sum of moderate and vigorous activity (Mod + Vig). Patients were instructed to return the AD by mail.

Aerobic Cycle Ergometer Test

Patients were scheduled to perform an annual maximal incremental cycling test on an electrically braked cycle ergometer (Rodby Elektronik AB, Enhorna, Sweden). One-minute work increments were chosen according to sex, height, and physical activity level.³⁰ Oxygen consumption, carbon dioxide production, tidal volume, and respiratory exchange ratio were measured continuously on-line through an automated exercise-testing program developed for use at HSC and MCH, as previously reported.⁶ Due to limited follow-up, only initial exercise test results are included in this report.

Data Analysis

FEV₁. Mixed model regression analysis (Laird and Ware, 1982) was used (Splus Insightful Corp, 2000) to evaluate the effect of activity level on the rate of decline in FEV₁. The importance of activity level and sex and the most suitable covariance structure were determined through Likelihood Ratio Testing of nested models.

Table I. Baseline description of 109 patients

Characteristic	Girls n = 56	Boys n = 53
Age (y)	12.2 ± 2.9	12.4 ± 2.7
Height (cm)	146 ± 13.2	149 ± 15.6
Height z-score	-0.43 ± 0.98	-0.52 ± 0.95
Weight (kg)	40.3 ± 12.1	40.4 ± 13.6
Weight z-score	-0.29 ± 1.09	-0.52 ± 1.01
Body mass index z-score	-0.08 ± 0.91	-0.33 ± 0.83
Percent fat (%)	23.4 ± 4.0	20.0 ± 5.6*
Lean body mass (kg)	30.6 ± 7.5	33.7 ± 11.4
Percentage of ideal weight for height (%)	103 ± 14.0	100 ± 10.1
FEV ₁ (% predicted)	83.9 ± 18.0	83.9 ± 16.6
Average total activity (weekday; h/d)	5.4 ± 2.5	6.5 ± 2.9 ^a
Average very active (weekday; h/d)	2.1 ± 2.0	2.8 ± 2.3
VO ₂ peak (mL/kg per min)	37.1 ± 6.5 ^a	43.3 ± 6.9 ^b
Work rate max (% predicted)	86 ± 16	82 ± 16

Values are mean ± SD.

**P* < .05.

^a*n* = 46.

^b*n* = 48.

Habitual Activity Estimation Scale

Linear regression was used to calculate the individual rate of change of TA over the course of the study. *t* tests illustrated that TA levels remained constant for that period; therefore the averaged value of TA was used in subsequent analysis. A categorical variable, Q, was computed for TA, based on quartiles of the average TA values of male and female subjects combined. Q1 represents the 25% of patients with the lowest TA values, and Q4 represents the 25% with the highest.

Correlation analysis was used to assess the relation of average TA and exercise testing variables, peakVO₂ and peak work rate (percent predicted). Mixed model analysis of variance was used to compare activity levels in four seasons. For all analyses, a nominal level of *P* < .05 was taken to indicate statistical significance.

RESULTS

Of the 153 eligible children from the HSC and MCH CF clinics who were approached to participate in the study, 116 agreed to participate (*n* = 103 HSC; *n* = 13 MCH). Reasons for nonparticipation included enrollment in other studies, irregularity of visits to the clinic, inadequate cognitive function, or lack of interest.

Since mean values and frequencies of baseline characteristics such as sex, initial FEV₁, and age were found to be comparable in the two centers, all analyses are reported for the combined cohort. Of those recruited, 5 patients chose not to continue after 1 or 2 visits, and 2 transitioned to the adult clinic before 4 visits. The data presented here are for 109 patients (56 girls) who have a minimum of four study visits.

Table II. Activity quartile distribution

Quartile	WDTA (h/d)	Boys (n)	Girls (n)
1	<3.7	8	20
2	3.8 to 4.8	17	10
3	4.9 to 6.1	16	11
4	>6.2	12	15

After 2 years of follow-up, 68 patients completed 8 study visits, 9 patients transferred to other CF clinics, and the remaining 32 have a reduced number of visits due to illness.

Baseline characteristics of the study patients appear in Table I. The boys and girls were comparable in age, growth parameters, and lung function. Average weekday total activity was higher for male subjects. Genetically, 50% of study participants were homozygous for ΔF508, 41% were heterozygous for ΔF508, and 9% were other genotypes. Four of 109 patients (3.6%) were positive for *Burkholderia cepacia* in their sputum. Five of 109 patients (4.5%) were pancreatic sufficient. There were no significant differences between the 37 patients who declined participation and those recruited into the study with respect to any of the above parameters (data not shown).

Habitual Physical Activity

All study patients who arrived at the clinic for their regularly scheduled visit completed the HAES. Although weekend and weekday scores were similar, weekend measurements exhibited much greater variability and thus were not used in the HPA measurement for each patient. Twenty-four (12 boys and 12 girls) were under the age of 12 years and received varying degrees of help to complete the questionnaire. Preliminary analysis revealed that although there was a tendency for the boys' reported WDTA hours to slightly decline over the course of the study period, this was entirely due to somewhat higher reported values on the first visit. Therefore, the average WDTA for each subject was used as the measure of HPA in all analyses. Table II describes the breakdown of WDTA into quartiles and the number of boys and girls in each.

Seasonal averages (±SD) of WDTA were 7.13 (±3.2), 4.53 (±2.7), 4.86 (±2.6), and 4.81 (±2.4) hours per day for summer, fall, winter, and spring, respectively (*P* < .0001) in the first year. There was no difference in weekday very active (WDVA) across seasons (average range, 1.8 to 2.5 h/d; SD range, ±1.4 to 2.3).

FEV₁ and Habitual Physical Activity

The average rate of decline in FEV₁ was -1.77% ± 5.37% predicted per year and was similar for male and female subjects. Activity quartile rather than average activity hours resulted in the strongest association with FEV₁ and was significantly dependent on sex (*P* = .02). Because of this significant interaction of sex and activity in the model of FEV₁ over time, separate models were estimated for male and female subjects, as illustrated in Table III. WDTA quartiles were

Table III. Mixed-model estimates of slope and intercept of rates of decline in FEV₁ by quartile

Model group	Intercept (FEV ₁ initial)	Slope
Girls Q1	79.9 ± 3.96	-3.40 ± 1.20
Girls Q2	77.7 ± 5.65	-3.05 ± 1.75
Girls Q3	91.4 ± 5.33	-0.93 ± 1.54
Girls Q4	89.7 ± 4.52	1.17 ± 1.27
Boys	84.8 ± 2.16	-1.95 ± 0.71

Values are mean ± SEM.

significantly related to rate of decline in FEV₁ in girls ($P = .02$) but not in boys ($P = .86$). The covariance structure for the random coefficients (slope and intercept) was explored in all models to determine the most suitable model assumptions. In the final model, which included activity category, likelihood ratio testing indicated that for both boys and girls, individual subjects' slope and intercept were uncorrelated; in other words, a subject's pulmonary function at the beginning of the study period was not associated with his or her rate of decline ($P = .3$ and $P = .9$ for boys and girls, respectively). In girls, an assumption of different variances within each activity quartile was better than a common variance assumption ($P = .03$), reflecting less variability of FEV₁ in the highest activity quartile than in the other quartiles.

Estimated mean rates of decline in FEV₁ for girls in the lowest two activity quartiles (Q1, Q2) were steeper than those in Q3. Girls in the highest activity quartile, Q4, had a positive rate of change of FEV₁. Girls in Q1 and Q2 also had lower intercepts representing lower mean initial FEV₁ than those in Q3 and Q4. Unlike the girls, the mixed-model estimates of the intercepts and slopes for boys were constant across WDTA quartiles. When analysis was repeated by using sex-specific activity quartiles, the same trends were seen.

Activity Diary

The total return rate for all diaries throughout the study was 56%. The return rate of first diary, on enrollment in the study, was 81%. As in the HAES, reported weekday and weekend scores were similar, but weekday scores were used in all analyses because of greater variability of weekend scores.

The most commonly reported types of activities were walking and unstructured play in the moderate and vigorous categories, respectively, regardless of season. Types of activities were similar for male and female subjects. From the AD, children reported average WDTA (h/d, ±SD) of 5.30 (±2.36), 3.10 (±1.71), 2.79 (±1.48), and 3.67 (±1.50) in the summer, fall, winter, and spring, respectively. There was a significant correlation between the AD and HAES for total activity in the summer only ($r = 0.62$, $P < .002$).

Exercise Testing

During the 2-year time frame of this study, we were able to collect one complete set of exercise test results. WDTA was

correlated only with peak VO₂ ($r = 0.24$, $P = .02$). Activity data was not related to any other exercise variable.

DISCUSSION

This longitudinal study investigated the relation between habitual activity and lung function decline in children with CF. Mixed-model regression analysis showed that the rate of decline of FEV₁ was related to the level of habitual physical activity in girls but not in boys. Female subjects in the lower two activity quartiles (Q1, Q2) were characterized by much steeper rates of decline than those in Q3 and Q4. This relation of FEV₁ and activity quartile persisted even when the quartiles were created separately for boys and girls, giving equal numbers in each sex-specific quartile. The overall mean rate of decline of FEV₁ was -1.77% predicted per year, similar in boys and girls and similar to that reported previously.²⁸ The association of lower initial FEV₁ with lower activity in girls but not boys suggests that previous decline in girls may have led to or may be the result of lower activity, but boys are more likely to maintain their activity level regardless of their declining health.

Of the 56 girls in the study, 30 (53%) were in Q1 and Q2, the activity quartiles with the steepest rates of decline of FEV₁. The finding of a larger percentage of girls in the lowest quartile and their lower average hours per day of total activity than boys is consistent with comparisons of healthy girls' and boys' activity levels by others.^{31,32} However, it may be that the consequence of lower or decreasing activity among girls with CF is more dramatic than in their non-CF peers. In CF, an FEV₁ value <30% predicted has been shown to be a grave indicator of the risk of death within the next 2 years.² Therefore, a more rapid rate of decline of FEV₁ may result in an FEV₁ <30% predicted sooner than a slower rate of decline. The challenge is to see if increasing the levels of activity of young female subjects may retard the rate of decline in FEV₁ and improve the poorer survival data seen in adolescent and young female adults compared with young male adults.

There were not sufficient numbers in the specific age groups for us to distinguish changes in activity related to puberty or the transfer from primary to high school. Continuing follow-up will provide the data to answer these important questions and support targeted intervention strategies.

In healthy populations, parents and teachers have lower physical activity expectations for girls than for boys and, as a result, girls with CF may well have even lower activity expectations.³³ This might result in an acceptance of a physically inactive lifestyle with less promotion of physical activity for girls. Boys, on the other hand, as recipients of higher physical activity expectations by parents, teachers, and peers, may have a greater promotion of physical activity.³³

A typical breakdown of reported total activity was 30 to 60 minutes of gym class, 30 to 45 minutes of vigorous activity at recess, and 60 minutes of vigorous extracurricular activity. The remainder of TA was composed of somewhat active, low-intensity exercise (SA). In summer, mean total activity increased from approximately 5 to 7 h/d, whereas vigorous

activity remained unchanged. This suggests that the time spent sitting in the classroom was substituted by increased time spent in low-intensity activities. Since activity levels for children were higher in summertime, the other three seasons may represent target areas for future strategies to promote physical activity to those in the lower activity quartiles.

Children with CF have been reported to have a lower¹⁵ or similar¹⁴ level of activity compared with healthy children. Comparison of the current data to children with CF and healthy children may be difficult if the season of data collection is not reported. Boucher et al¹⁴ reported TA in boys and girls as 8.7 h/d and 7.9 h/d, respectively, which were subsequently confirmed to be summer values (Dr. Larry Lands, July 2004, Montreal Children's Hospital). Currently reported WDTA values for summer (7.13 h/d) and spring (4.8 h/d) are also similar to values reported in the pilot work of Pollock et al.²³

We determined that the HAES is a clinically feasible tool to quantify HPA in children with CF. The HAES had a 100% completion rate, required 10 minutes to complete (with assistance from parent if necessary), and could be done while waiting for clinical appointments. This questionnaire could easily be implemented into the regular follow-up of patients with CF.

The overall return rate of 56% for the AD was poor compared with the 100% completion of the HAES and therefore limits our ability to study the true relation between these two instruments. Patients reported some ADs lost, a reluctance to fill out forms when at home, and a greater time and inconvenience to complete than the HAES. Similar to the HAES, the AD was able to capture an increase in TA in the summer. WDTA (HAES) was correlated to WDTA (AD) only in the summer. This may reflect a greater ease of completion of the AD when unburdened by daily demands of school routines in addition to their disease.

As reported by others^{10,11,34} the lack of significant correlation (except summer) between the HAES and AD suggests that these two instruments are capturing different aspects of HPA. Whereas self-report measures clearly have their limitations, motion sensors, widely considered by some to be the criterion reference for quantifying habitual activity, also have shortcomings,³⁵ especially for the unstructured play of children. The advantage of the HAES is that it is a feasible instrument for use in a clinical setting as it captures data at a defined point in time.

The most commonly reported activities in this population were walking and unstructured play. Others have found a decreased involvement of children with CF in vigorous activity compared with their healthy peers.³⁶ It is possible that given the daily treatment demands imposed on the family of the child with CF, the burden of disease may simply limit the degree of involvement in structured activities compared with families without CF.

WDTA was related to initial VO_2 peak only and no other exercise variables in our study. Comparisons of WDTA and changes in exercise variables over time will be possible with more exercise testing in a longer follow-up, allowing us to determine how these measures are related to HPA.

Other benefits of regular habitual activity for children with CF may include improved muscle function, improved mucus clearance, and improved potential difference, possibly leading to better mucus hydration.³⁷ A continued follow-up of this cohort of patients with CF will allow us to address the "chicken and egg" question of which comes first: the decline of FEV_1 , changes in habitual activity patterns, or exercise capacity.³⁶ Our findings support use of the HAES as a feasible tool to collect habitual activity data on children with CF in a clinical setting. Low activity in girls with CF was associated with steeper rates of decline in their FEV_1 over the 2-year study period. Longitudinal follow up will reveal whether maintaining or increasing high levels of habitual physical activity can influence the rate of lung function decline. Results from the AD data will be used in future modification of the HAES to capture additional information on types of activity, to determine which may be most beneficial to patients with CF.

REFERENCES

1. Rosenfeld M, Davis R, FitzSimmons S, Pepe M, Ramsey B. Gender gap in cystic fibrosis mortality. *Am J Epidemiol* 1997;145:794-803.
2. Kerem E, Reisman JJ, Corey ML, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med* 1992;326:1187-91.
3. Zach M, Oberwaldner B, Hausler F. Cystic fibrosis: physical exercise versus chest physiotherapy. *Arch Dis Child* 1982;57:587-9.
4. Keens TG, Krastius IRB, Wannamaker EM, Levison H, Crozier DN, Bryan C. Ventilatory muscle endurance training in normal subjects and patients with cystic fibrosis. *Am Rev Respir Dis* 1977;116:853-60.
5. Orenstein DM. Exercise conditioning and cardiopulmonary fitness in cystic fibrosis: the effects of a 3-month supervised running program. *Chest* 1981;80:392-8.
6. Schneiderman-Walker J, Pollock SL, Corey ML, Wilkes DD, Canny GJ, Pedder L, et al. A randomized controlled trial of a three-year home exercise program in cystic fibrosis. *J Pediatr* 2000;136:304-10.
7. Bar-Or O. Home-based exercise programs in cystic fibrosis: are they worth it? *J Pediatr* 2000;136:279-80.
8. Puyau MR, Adolph AL, Vohra FA, Butte NF. Validation and calibration of physical activity monitors in children. *Obesity Res* 2002;10:150-7.
9. Trost SG, Pate RR, Sallis JF, Freedson P, Taylor WC, Dowda M, et al. Age and gender differences in objectively measured physical activity in youth. *Med Sci Sports Exerc* 2002;34:350-5.
10. O'Connor J, Ball EJ, Steinbeck KS, Davies PSW, Wishart C, Gaskin KJ, et al. Measuring physical activity in children: a comparison of four different methods. *Pediatr Exerc Sci* 2003;15:202-15.
11. Tremblay MS, Inman JW, Willms JD. Preliminary evaluation of a video questionnaire to assess activity levels of children. *Med Sci Sports Exerc* 2001;33:2139-44.
12. Bratteby L-E, Sandhagen B, Fan H, Samuelson G. A 7-day activity diary for the assessment of daily energy expenditure validated by the doubly labelled water method in adolescents. *Eur J Clin Nutr* 1997;51:585-91.
13. Bouchard C, Tremblay A, Leblanc C, Lortie G, Savard R, Theriault G. A method to assess energy expenditure in children and adults. *Am J Clin Nutr* 1983;37:461-7.
14. Boucher GP, Lands LC, Hay JA, Hornby L. Activity levels and the relationship to lung function and nutritional status in children with cystic fibrosis. *Am J Phys Med Rehabil* 1997;76:311-5.
15. Nixon PA, Orenstein DM, Kelsey JL. Habitual physical activity in children and adolescents with cystic fibrosis. *Med Sci Sports Exerc* 2001;33:30-5.
16. Stanghelle JK, Hjeltnes N, Michalsen H, Bangstad H, Skyberg D. Pulmonary function and oxygen uptake during exercise in 11-year old patients with cystic fibrosis. *Acta Paediatr Scand* 1986;75:657-61.

17. Hay JA. Development and testing of the habitual activity estimation scale. Proceedings of the XIXth International Symposium of the European Group of Pediatric Work Physiology 1997;2:125-9.
18. Molgaard C, Thomsen BL, Michaelsen KF. The influence of calcium intake and physical activity on bone mineral content and bone size in healthy children and adolescents. Osteoporos Int 2001;12:887-94.
19. Hay J. Development of a 24 hour recall measure (abstract). Canadian Association of Sport Sciences Annual Conference, 1991.
20. Hay J. The stability of children's self-perceptions regarding activity: a five-year follow-up (abstract). Proceeding of the Ninth North American Society for Pediatric Exercise Medicine, 1994.
21. Atkinson SA, Halton J, Hay J, Gordon C, Webber C. Normative values for lumbar spine bone mass in children in relation to age, gender, and physical activity (abstract). J Bone Miner Res 1991;6[A196]:S132.
22. Halton J, Hay J, Atkinson S, Webber C, Barr RD. Physical activity and bone mineralization in children during treatment for acute lymphoblastic leukemia (abstract). Proceedings of the American Society of Pediatric Hematology/Oncology 1993;2:22.
23. Pollock SL, Schneiderman-Walker J, Reisman JJ, Kopec J, Corey M. Pediatric activity patterns and the association with disease severity and exercise performance in cystic fibrosis (abstract). Pediatr Pulmonol Suppl 1999;19:290-1.
24. Eisenmann JC, Katzmarzyk PT, Theriault G, Song TMK, Malina RM, Bouchard C. Physical activity and pulmonary function in youth: the Quebec family study. Pediatr Exerc Sci 1999;11:208-17.
25. Growth charts for healthy children. 2003. Available from www.cdc.gov/growthcharts/. Accessed on April 21, 2005.
26. Durnin JVGA, Rahaman MM. The assessment of the amount of fat in the human from measurement of skinfold thickness. Br J Nutr 1967;21:681-9.
27. American Thoracic Society. Standardization of spirometry: 1994 update. Am J Respir Crit Care Med 1995;152:1107-36.
28. Corey M, Levison H, Crozier DN. Five- to seven-year course of pulmonary function in cystic fibrosis. Am Rev Respir Dis 1976;114:1085-92.
29. Subbarao P, Lebecque P, Corey M, Coates AL. Comparison of spirometric reference values. Pediatr Pulmonol 2004;37:515-22.
30. Godfrey S, Davies CTM, Wozniak ER, Barnes C. Cardio-respiratory response to exercise in normal children. Clin Sci Mol Biol 1971;40:419-42.
31. Klentrou P, Hay J, Plyley M. Habitual physical activity levels and health outcomes of Ontario youth. Eur J Appl Physiol 2003;89:460-5.
32. Vincent SD, Pangrazi RP, Raustorp A, Tomson LM, Cuddihy TF. Activity levels and body mass index of children in the United States, Sweden and Australia. Med Sci Sports Exerc 2003;35:1367-73.
33. Hay J, Donnelly PM. Sorting out the boys from the girls: teacher and student perceptions of student physical ability. Avante 1996;2:36-51.
34. Sallis JK, Buono MJ, Roby JJ, Micale FG, Nelson JA. Seven-day recall and other physical activity self-reports in children and adolescents. Med Sci Sports Exerc 1993;25:99-108.
35. Campbell KL, Crocker PRE, McKenzie DC. Field evaluation of energy expenditure in women using TriTrac accelerometers. Med Sci Sports Exerc 2002;34:1667-74.
36. Nixon PA, Orenstein DM, Kelsey SF, Doerschuk CF. The prognostic value of exercise testing in patient with cystic fibrosis. N Engl J Med 1992;327:1785-8.
37. Hebestreit A, Kersting U, Basler B, Jeschke R, Hebestreit H. Exercise inhibits epithelial sodium channels in patients with cystic fibrosis. Am J Respir Crit Care Med 2001;164:443-6.

ON THE MOVE?

Send us your new address at least six weeks ahead

Don't miss a single issue of the journal! To ensure prompt service when you change your address, please photocopy and complete the form below.

Please send your change of address notification at least six weeks before your move to ensure continued service. We regret we cannot guarantee replacement of issues missed due to late notification.

JOURNAL TITLE:

Fill in the title of the journal here. _____

OLD ADDRESS:

Affix the address label from a recent issue of the journal here.

NEW ADDRESS:

Clearly print your new address here.

Name _____

Address _____

City/State/ZIP _____

COPY AND MAIL THIS FORM TO:

Subscription Customer Services
Elsevier Inc.
6277 Sea Harbor Dr
Orlando, FL 32887

OR FAX TO:

407-363-9661

OR E-MAIL:

elspcs@elsevier.com

OR PHONE:

800-654-2452

Outside the U.S., call

407-345-4000

MILD TO MODERATE CYSTIC FIBROSIS IS NOT ASSOCIATED WITH INCREASED FRACTURE RISK IN CHILDREN AND ADOLESCENTS

ALISHA J. ROVNER, BA, BABETTE S. ZEMEL, PHD, MARY B. LEONARD, MD, MSCE, JOAN I. SCHALL, PHD, AND VIRGINIA A. STALLINGS, MD

Objectives To determine whether children and adolescents with cystic fibrosis (CF), pancreatic insufficiency (PI), and mild-to-moderate lung disease have an increased risk of fracture compared with concurrent healthy control subjects.

Study design A lifetime fracture history questionnaire was administered to 186 subjects (ages 6 to 25 years) with CF, PI and mild-to-moderate lung disease and 427 healthy white control subjects (ages 4 to 25 years).

Results A fracture was reported by 24% of subjects with CF and 23% of healthy control subjects. Average age of first fracture was similar between the groups (8.3 years for subjects and 8.8 years for controls). The radius/ulna was the most common fracture site in both groups. Risk of fracture, adjusted for sex and age, was not greater in the CF group compared with the control group (hazard ratio: 0.96, 95% CI: 0.68, 1.30, $P = .82$).

Conclusion Children and adolescents with CF, PI, and mild-to-moderate lung disease were not at an increased risk of fracture. (*J Pediatr* 2005;147:327-31)

Improved medical and nutritional therapy has increased the median life expectancy of individuals with cystic fibrosis (CF) to 33 years in the United States.¹ Increased survival has been accompanied by previously uncommon complications including diabetes,^{2,3} liver disease,⁴ and osteopenia and osteoporosis.⁵

Individuals with CF and pancreatic insufficiency (PI) have several risk factors for low bone mass, including poor growth, delayed puberty, malabsorption of calcium and vitamin D, decreased weight-bearing physical activity, and use of corticosteroid medications. In 1979, Mischler et al⁶ described low bone mass in 27 children and young adults with CF. Since this observation, investigators have examined bone mineral content (BMC) and bone mineral density (BMD) in children and adults with CF, reporting conflicting results.⁷⁻¹³ The variability in study results is likely due to differences in measurement techniques, illness severity, sample size, sampling strategy, reference data,¹⁴ and varied strategies to adjust for impaired growth and delayed maturation. Thus the nature and magnitude of bone mineral deficits in children with CF remains to be determined.

The clinical significance of low BMD and BMC during childhood is failing to attain optimal peak bone mass and having an increased risk of sustaining a fracture. There have been case reports of fracture in both children^{15,16} and adults with CF.^{17,18} Two studies have suggested that people with CF may be at increased risk of fracture.^{19,20} Both compared fracture rates of subjects with CF to historical control data from the National Center for Health Statistics National Health Interview Survey (NHIS), a 1970–1977 nationwide survey of the noninstitutionalized population conducted by household interview.²¹ Fracture rates in healthy children vary according to age and sex, and by geographic location and time period^{22,23}; therefore concurrent control fracture data are preferable for assessing fracture risk in a population. The purpose of this study was to estimate fracture rates and risk of fracture in children and adolescents with CF, PI, and mild-to-moderate lung disease, compared with a concurrent, sample of healthy control subjects.

See related articles, p 295,
p 306, p 312, p 316, p 321,
p 332, p 396, p 399,
and p 402.

From the Divisions of Gastroenterology and Nutrition and Nephrology, The Children's Hospital of Philadelphia, Department of Pediatrics, Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pa, and the Center for Human Nutrition at Johns Hopkins Bloomberg School of Public Health, Baltimore, Md.

Supported in part by the National Institute of Health (ROIHL57448, K08-DK02523), Cystic Fibrosis Foundation and the General Clinical Research Center (M01-RR00240) and Nutrition Center at The Children's Hospital of Philadelphia.

Submitted for publication Aug 23, 2004; last revision received Mar 7, 2005; accepted Apr 4, 2005.

Reprint requests: Virginia A. Stallings, MD, Joseph Stokes Research Institute, University of Pennsylvania School of Medicine, 3615 Civic Center Blvd, Philadelphia, PA 19104. E-mail: stallingsv@email.chop.edu.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.04.015

BMI	Body mass index	FEV ₁	Forced expiratory volume in 1 second
BMC	Bone mineral content	NHIS	National Health Interview Survey
BMD	Bone mineral density	PI	Pancreatic insufficiency
CF	Cystic fibrosis		

Table I. Characteristics of subjects with CF and healthy control subjects

	Subjects with CF	Healthy control subjects	P value
N	186	427	
Age, years	12.4 ± 4.1	11.4 ± 3.9	.007
Sex	93 males, 50%	193 males, 45%	NS
Height for age z-score	-0.6 ± 1.0	0.2 ± 0.9	<.01
Weight for age z-score	-0.5 ± 1.1	0.3 ± 0.9	<.01
BMI z-score	-0.3 ± 1.0	0.2 ± 0.9	<.01
FEV ₁ , %predicted	85 ± 17%		

METHODS

Subjects

Subjects with CF aged 6 to 25 years were recruited from 14 CF centers throughout the eastern United States to participate in 1 of 2 studies of growth and bone health in people with CF. Inclusion criteria were diagnosis of CF by clinical signs, sweat test >60 mEq/L or genotype analysis, and PI. Exclusion criteria were: Forced expiratory volume in 1 second (FEV₁) < 40% predicted, CF-related diabetes (CFRD), pulmonary colonization with *Burkholderia cepacia*, or any other medical illness (independent of CF) known to affect growth or bone health.

Healthy subjects (n = 538) aged 4 to 25 years were recruited from the greater Philadelphia area using several recruitment strategies. These included newspaper ads, recruitment from primary care pediatrics and adolescent practices throughout Pennsylvania, Delaware, and New Jersey affiliated with The Children's Hospital of Philadelphia, and flyers distributed throughout the Home and School Associations in schools in Pennsylvania and New Jersey. These subjects volunteered for a study to develop a contemporary reference data set for growth, body composition, and bone measurements. Exclusion criteria were any disease or medication known to affect growth, nutritional status, or bone health. In this sample of healthy children there was an ethnic distribution (white and black) that was similar to that reported in the US census. Also, there was a similar prevalence of obesity in this sample compared with children in the US. For the purposes of this study, control subjects were restricted to the 427 white subjects since 97% of the enrolled subjects with CF were white, and this was representative of the US CF population.¹ The Institutional Review Board at The Children's Hospital of Philadelphia and all other participating institutions approved the protocol. Informed consent was obtained from the parent or guardian of each subject, and assent was obtained from children over 7 years of age.

Fracture History Questionnaire

A lifetime fracture history questionnaire was administered to subjects (when age appropriate) and their parents by a trained member of the research team. Subjects or their parents were asked whether they had sustained any fractures in their life, the skeletal site, date of the fracture, and the treatment.

Anthropometry

Body weight was measured with an electronic scale (Scaltronix Inc., Wheaton, Ill) accurate to 0.1 kg, and standing height with a stadiometer (Holtain, Crymych, England) by standard research techniques accurate to 0.1 cm.²⁴ Age- and sex-specific weight, height and body mass index (weight/height²) (BMI) z-scores were calculated by using year 2000 growth data from the National Center for Health Statistics, Center for Disease Control.²⁵

Pulmonary Function

Pulmonary disease was evaluated in subjects with CF by standard pulmonary function methods. Forced expiratory volume in 1 second (FEV₁) was compared with reference values and reported as the percentage of the predicted value (FEV₁ % predicted).²⁶

Statistical Analyses

Means and standard deviations were used to summarize continuous variables, and proportions for categorical variables. Subjects with CF and control subjects were compared using *t* tests and χ^2 tests, as appropriate. Fracture incidence rates (events/person-years of life) were calculated for all fractures within group (CF vs control), sex, and age categories. Age categories representing age at fracture (0 to 4, 5 to 9 and 10 to 14 years) were selected on the basis of a recently published population-based study of incidence of distal forearm fractures.²³ Fracture rates were also calculated using the age categories from the NHIS because those categories were used in a previous study of fracture rates in people with CF.¹⁹ Initial analyses compared time to first and time to second fracture. A Cox proportional hazard regression model with time dependant covariates was used to compare the hazard (or risk) of fracture in subjects with CF compared with control subjects.²⁷ Time 0 was the date of birth. Among those who did not experience a fracture, observations were censored at the age when the questionnaire was administered. A conditional risk set model was used that took into account time from prior fracture because a subject could have had more than one fracture (event), and the order of the fracture was important (ie, timing of the occurrence of a second fracture could only occur after a first fracture).²⁸ Data were analyzed with STATA 8.0 (College Station, Texas).

RESULTS

One hundred eight-six subjects with CF and PI (50% male) and 427 healthy subjects (45% male) participated in the study (Table I). As a group, the subjects with CF had

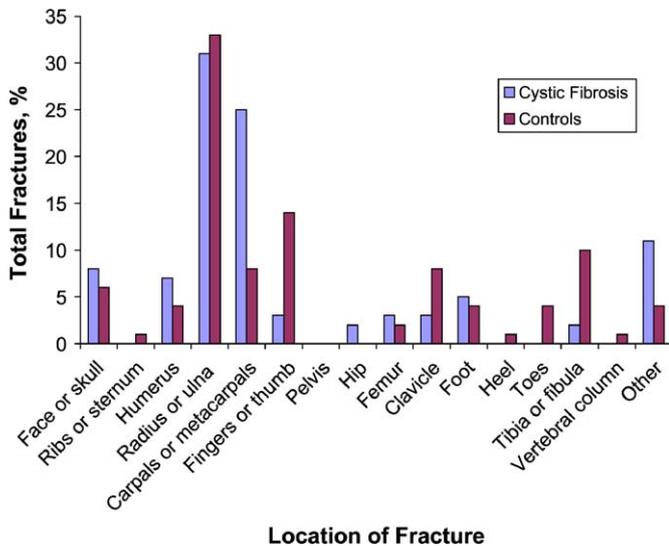


Figure. Fracture sites for all fractures in subjects with CF and healthy control subjects.

mild-to-moderate lung disease with a mean FEV₁ of 85 ± 17% (range 47 to 125% predicted FEV₁).

Rates and Site of Fracture

Forty-three subjects with CF (24%) had a history of 61 fractures, and 96 control subjects (23%) had a history of 134 fractures. Of the subjects with CF who sustained a first fracture, 30% sustained a second fracture, and 1% sustained a third fracture. Of the 96 control subjects who sustained a first fracture, 30% and 2% sustained second and third fractures, respectively. The average age of a first fracture was similar between the 2 groups (8.3 years in subjects with CF vs 8.8 years in control subjects, $P = .49$). The average age of a second fracture was 10.1 years in subjects with CF and 10.4 years in control subjects ($P = .77$).

The sites of fracture were similar between the subjects with CF and the control subjects (Figure). The most common site of fracture for both groups was the radius/ulna (31% in subjects with CF vs 33% in control subjects). Hand fractures (including carpal, metacarpal, finger, and thumb) were the next most common fracture site for both groups.

The rates of fracture were stratified by age and sex (Table II). Fracture rates were not statistically significantly different between subjects with CF and control subjects in any age strata. Fracture rates were calculated by the age categories that the NHIS used (0 to 5 and 6 to 16 years of age) to compare with data from fracture data published by Henderson et al¹⁹ (Table III).

Risk of Fracture

A Cox regression model was used to compare the risk of fracture in the subjects with CF to the control subjects. Factors that were included in the model were group, age, and sex. The relative risk of fracture for the CF group after controlling for covariates was 0.96 (95% CI: 0.68, 1.30, $P = .82$), indicating no difference between groups.

Table II. Fracture rates per 100 person years

	All fractures	Person years*	Fractures/100 person years [†]
Birth to 4 years			
Male controls	11	962	1.1
Male CF	5	465	1.1
Female Controls	11	1168	0.9
Female CF	2	465	0.4
5 to 9 years			
Male Controls	22	685	3.2
Male CF	12	396	3.0
Female Controls	30	895	3.3
Female CF	15	406	3.7
10 to 14 years			
Male Controls	19	285	6.7
Male CF	12	148	8.1
Female Controls	28	408	6.9
Female CF	9	129	7.0

*There were too few person years in any age categories above 10-14 to calculate rates.

[†]There were no significant differences between patients with CF and control subjects for any of the age groups.

DISCUSSION

As the life expectancy of people with CF has increased, so has the concern that this population is at increased risk for low bone mass and fracture. Mischler et al⁶ initially described low bone mass in children and young adults with CF over 20 years ago. Since this initial study, some studies have found decreased BMD and BMC,⁷⁻¹⁰ whereas others have not.¹¹⁻¹³ Most published studies on bone health in people with CF have used dual-energy x-ray absorptiometry. There are challenges in the interpretation of densitometry results in children because BMC and BMD are strongly influenced by bone size. Thus BMD may be underestimated in children with short stature. CF is associated with poor linear growth¹; therefore earlier studies that did not adjust for stature may have overestimated the magnitude of bone deficits. More recent studies of people with CF have adjusted for stature²⁹ or have used bone mineral apparent density, a model that addresses the problem of bone density being underestimated in children with smaller bones.¹⁰

The concern with low BMD and BMC during childhood is failure to attain age-appropriate and then optimal peak bone mass, which may result in an increased risk of sustaining a fracture. Two studies have reported fracture rates in children and adults with CF compared with historical control data from the 1970 to 1977 NHIS.²¹ Henderson et al¹⁹ examined the history of fractures in 150 children and young adults with CF ages 5 to 22 years. The only group that had a fracture rate higher than the healthy control subjects was the 6- to 16-year-old females (4.9 vs 3.0 per 100 patient-years). In a study of fractures in adults with late-stage CF awaiting lung transplantation, significant increases in fracture rates were found for males ages 25 to 45 years (8.5 vs 2.8 per 100 patient-years)

Table III. Fracture rates per 100 person years (NHIS age categories)

	Present study	Henderson study*
Birth to 5 years		
Male Controls	1.2	1.7
Male CF	1.2	2.2
Female Controls	0.9	0.8
Female CF	0.4	0.7
6 to 16 years		
Male Controls	4.0	4.3
Male CF	3.8	3.8
Female Controls	3.5	3.0
Female CF	4.2	4.3

*Reference 19 (Control data from this study was from the NHIS).

and females 17 to 34 years (3.7 vs 1.7).²⁰ This study examined an older, very ill cohort (mean FEV₁%: males 34% and females 33%), so the results are not generalizable to children, adolescents, and young adults with better pulmonary and nutritional status. Moreover, both studies used the NHIS fracture data described above as the comparison group. First, fracture rates not only vary by age and sex in children, but secular trends suggest increasing fracture rates in healthy children.^{22,23} Therefore the comparison of fracture data from 30 years ago may overstate fracture risk in recent CF subjects. Also, the incidence of fracture peaks around 15 years of age in males and 12 years of age in females,^{30,31} so grouping children ages 6 to 16 within a single category may mask important age effects.

Studies of adults with CF awaiting lung transplantation have uniformly reported osteoporosis and fractures.³²⁻³⁴ People with CF whose lung status requires consideration for lung transplantation likely have a history of reduced physical activity, malnutrition, increased inflammatory cytokines, and glucocorticoid medication use, all of which have a negative impact on bone health. Several additional studies found a positive correlation of BMD with FEV₁ and with BMI,^{20,35-37} suggesting an association between nutritional status and bone health.

Using a hazard model, our current study did not find an increased risk of fracture in subjects with CF with mild to moderate lung disease and PI. These subjects had mild growth and nutritional status abnormalities and were generally representative of people with CF in the US.¹ In the US, 96% of children and 77% of adults with CF have normal to moderate lung disease as indicated by FEV₁.¹ By design, those with more advanced lung disease and those with other CF-related complications, such as CFRD or liver disease, were excluded. These complications, although quite serious, only affect a minority of people with CF (CFRD, 12%; and liver disease, 6%).¹

Two strengths of this study were the statistical approach used to analyze multiple fractures and the use of a contemporary control group. Previous studies have collapsed fracture

data into 2 categories: a fracture group and a no-fracture group.³⁸ This method ignores relevant information such as time to fracture and the occurrence of multiple fractures. One approach to analyzing multiple failure data is to examine the time to first event (fracture), but this also ignores potential relevant information because it is not uncommon for children to sustain more than one fracture.³⁹ Therefore we used a Cox proportional hazard model, which takes into account the time when an event occurs, rather than simply whether an event occurs.

A limitation of this study was that the fracture events were self-reported (subject and parental) and were not confirmed by radiographs; therefore recall bias was possible. Studies have been conducted on the validity of self-reports of fractures in adults, but to our knowledge there are no similar studies in children. Validity studies in adults showed that self-report of a distal forearm fracture, which is the most common site of childhood skeletal injury, is relatively accurate.^{40,41} In a study of women (47 to 56 years), sensitivity of self-report of fracture was 78% for all fractures and 95% for wrist fracture, and the respective specificities were 96% and 99%. Because this was retrospective data, we did not have information on subjects at the time of the fracture such as nutritional status, Tanner Stage, and use of steroids. Another limitation of this study is that lifetime patterns of physical activity were not assessed, so it is not known whether both groups had comparable exposure to behaviors that put them at risk for fractures. One possible reason that the risk of fracture was not greater in the CF group compared with the control subjects is that people with CF may not engage in as many high-impact activities as healthy people. Also, in the older male groups, there was not enough power to detect a difference if one actually existed.

Results from this study suggest that individuals with CF, mild-to-moderate lung disease and PI up to 16 years of age do not have increased rates of fractures. Increased risk of fracture, as previously reported in the literature, is a complication of CF that likely occurs as the disease manifestations advance, corticosteroid use increases, and physical activity decreases. Future studies are needed to identify clinical characteristics, in addition to having end-stage lung disease or being a lung transplant recipient, associated with fracture risk in people with CF. In the absence of these more specific data, CF care should continue to support bone health objectives with normal growth and development, weight-bearing physical activity, and optimal intake of calcium, vitamin D and vitamin K.

We are grateful to the participants and their families, the participating CF centers, and Dr. Charles Scott in the Division of Biostatistics at The Children's Hospital of Philadelphia for his assistance in data analysis. We also thank the General Clinical Research Center staff and the Nutrition and Growth Laboratory at The Children's Hospital of Philadelphia. We would also like to thank the Center Directors and staff at the 14 Cystic Fibrosis Centers from which the children were recruited for this study: Albany Medical Center (Albany, NY); Children's Hospital of Buffalo (Buffalo, NY); Children's National Medical Center (Washington, DC); Emory University (Atlanta, Ga); Hershey Medical Center (Hershey, Pa); Johns Hopkins Children's

Center (Baltimore, Md); Long Island College Hospital (Brooklyn, NY); The Children's Medical Center (Dayton, Ohio); The Children's Hospital of Philadelphia (Philadelphia, Pa); The Hospital of the University of Pennsylvania (Philadelphia, Pa); Schneider Children's Hospital of Long Island (New Hyde Park, NY); St. Christopher's Hospital for Children (Philadelphia, Pa); State University New York at Stony Brook (Stony Brook, NY); and University of Florida (Gainesville, Fla).

REFERENCES

1. Cystic Fibrosis Foundation. 2003 Annual Report. 2002 Patient Registry. Bethesda, MD: Cystic Fibrosis Foundation; 2003.
2. Cucinotta D, Arrigo T, Di Benedetto A, Scoglio R, Magazzu G, De Luca F. A long-term, prospective evaluation of factors affecting diabetes mellitus onset in cystic fibrosis. *Diabetes* 1999;48:A63-4.
3. Hardin DS, Moran A. Diabetes mellitus in cystic fibrosis. *Endocrinol Metab Clin N Am* 1999;28:787-800.
4. Sokol RJ, Durie PR. Recommendations for management of liver and biliary tract disease in cystic fibrosis. Cystic Fibrosis Foundation Hepatobiliary Disease Consensus Group. *J Pediatr Gastroenterol Nutr* 1999;28(Suppl 1):S1-13.
5. Aris RM, Merkel PA, Bachrach LK, Borowitz DS, Boyle MP, Elkin SL, et al. Guide to bone health and disease in cystic fibrosis. *J Clin Endocrinol Metab* 2005;90:1888-96.
6. Mischler EH, Chesney PJ, Chesney RW, Mazess RB. Demineralization in cystic fibrosis detected by direct photon-absorptiometry. *Am J Dis Child* 1979;133:632-5.
7. Laursen EM, Molgaard C, Michaelsen KF, Koch C, Muller J. Bone mineral status in 134 patients with cystic fibrosis. *Arch Dis Childhood* 1999; 81:235-40.
8. Henderson RC, Madsen CD. Bone mineral content and body composition in children and young adults with cystic fibrosis. *Pediatr Pulmonol* 1999;27:80-4.
9. Bhudhikanok GS, Lim J, Marcus R, Harkins A, Moss RB, Bachrach LK. Correlates of osteopenia in patients with cystic fibrosis. *Pediatrics* 1996; 97:103-11.
10. Bhudhikanok GS, Wang MC, Marcus R, Harkins A, Moss RB, Bachrach LK. Bone acquisition and loss in children and adults with cystic fibrosis: a longitudinal study. *J Pediatr* 1998;133:18-27.
11. Gronowitz E, Mellstrom D, Strandvik B. Normal annual increase of bone mineral density during two years in patients with cystic fibrosis. *Pediatrics* 2004;114:435-42.
12. Mortensen LA, Chan GM, Alder SC, Marshall BC. Bone mineral status in prepubertal children with cystic fibrosis. *J Pediatr* 2000;136:648-52.
13. Salamoni F, Roulet M, Gudinchet F, Pilet M, Thiebaud D, Burckhardt P. Bone mineral content in cystic fibrosis patients: correlation with fat-free mass. *Arch Dis Childhood* 1996;74:314-8.
14. Leonard MB, Propert KJ, Zemel BS, Stallings VA, Feldman HI. Discrepancies in pediatric bone mineral density reference data: potential for misdiagnosis of osteopenia. *J Pediatr* 1999;135:182-8.
15. Mitchell EA, Elliott RB. Spontaneous Fracture of the Sternum in A Youth with Cystic Fibrosis. *J Pediatr* 1980;97:789-90.
16. Yen D, Hedden D. Multiple vertebral compression fractures in a patient treated with corticosteroids for cystic fibrosis. *Can J Surg* 2002;45:383-4.
17. Lim AY, Isopescu S, Thickett KM, Gumery LB, Darby AJ, Honeybourne D, et al. Bilateral fractured neck of the femur in an adult patient with cystic fibrosis. *Eur J Intern Med* 2003;14:196-8.
18. Haworth CS, Freemont AJ, Webb AK, Dodd ME, Selby PL, Mawer EB, et al. Hip fracture and bone histomorphometry in a young adult with cystic fibrosis. *Eur Resp J* 1999;14:478-9.
19. Henderson RC, Specter BB. Kyphosis and fractures in children and young adults with cystic-fibrosis. *J Pediatr* 1994;125:208-12.
20. Aris RM, Renner JB, Winders AD, Buell HE, Riggs DB, Lester GE, et al. Increased rate of fractures and severe kyphosis: sequelae of living into adulthood with cystic fibrosis. *Ann Intern Med* 1998;128:186-93.
21. Frazier KL. The frequency of occurrence, impact and cost of musculoskeletal conditions in the United States, Chicago. *J Pediatr Orthoped* 1997; 6:79-83.
22. Wilkins KE. The Incidence of Fractures in Children. In: Rockwood CA, Wilkins KE, Beaty JH, eds. *Fractures in Children*, 4th edition. Philadelphia: Lippencott-Raven Publishers; 1996. p. 3-17.
23. Khosla S, Melton LJ, Dekutoski MB, Oberg AL, Riggs BL. Incidence of childhood distal forearm fractures over 30 years—A population-based study. *JAMA* 2003;290:1479-85.
24. Lohman T, Roche AR, Martorell R. *Anthropometric standardization reference manual*. Champaign, Ill: Human Kinetics; 1988.
25. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, et al. CDC growth charts: United States. *Adv Data* 2000;1-27.
26. Morris A, Kanner RE, Crapo R, Gardner RM. *Clinical pulmonary function testing: a manual of uniform laboratory procedures*. Salt Lake City: Intermountain Thoracic Society; 1984. p. 1-24.
27. Fisher LD, Lin DY. Time-dependent covariates in the Cox proportional-hazards regression model. *Annu Rev Public Health* 1999;20:145-57.
28. Kelly PJ, Lim LLY. Survival analysis for recurrent event data: an application to childhood infectious diseases. *Stat Med* 2000;19:13-33.
29. Hardin DS, Arumugam R, Seilheimer DK, LeBlanc A, Ellis KJ. Normal bone mineral density in cystic fibrosis. *Arch Dis Child* 2001;84: 363-8.
30. Landin LA. Fracture patterns in children. *Acta Orthopaedica Scandinavica* 1983;54:1-109.
31. Cooper C, Dennison EM, Leufkens HG, Bishop N, van Staa TP. Epidemiology of childhood fractures in Britain: a study using the general practice research database. *J Bone Min Res* 2004;19:1976-81.
32. Donovan DS, Papadopoulos A, Staron RB, Adesso V, Schulman L, McGregor C, et al. Bone mass and vitamin D deficiency in adults with advanced cystic fibrosis lung disease. *Am J Respir Crit Care Med* 1998;157: 1892-9.
33. Aris RM, Neuringer IP, Weiner MA, Egan TM, Ontjes D. Severe osteoporosis before and after lung transplantation. *Chest* 1996;109: 1176-83.
34. Tschoop O, Boehler A, Speich R, Weder W, Seifert B, Russi EW, et al. Osteoporosis before lung transplantation: association with low body mass index, but not with underlying disease. *Am J Transplant* 2002;2:167-72.
35. Elkin SL, Fairney A, Burnett S, Kemp M, Kyd P, Burgess J, et al. Vertebral deformities and low bone mineral density in adults with cystic fibrosis: a cross-sectional study. *Osteoporosis Int* 2001;12:366-72.
36. Conway SP, Morton AM, Oldroyd B, Truscott JG, White H, Smith AH, et al. Osteoporosis and osteopenia in adults and adolescents with cystic fibrosis: prevalence and associated factors. *Thorax* 2000;55:798-804.
37. Gibbens DT, Gilsanz V, Boechat MI, Dufer D, Carlson ME, Wang CI. Osteoporosis in cystic fibrosis. *J Pediatr* 1988;113:295-300.
38. Ma DQ, Jones G. Clinical risk factors but not bone density are associated with prevalent fractures in prepubertal children. *J Paediatr Child Health* 2002;38:497-500.
39. Goulding A, Jones IE, Williams SM, Grant AM, Taylor RW, Manning PJ, et al. First fracture is associated with increased risk of new fractures during growth. *J Pediatr* 2005;146:286-8.
40. Ismail AA, O'Neill TW, Cockerill W, Finn JD, Cannata JB, Hoszowski K, et al. Validity of self-report of fractures: results from a prospective study in men and women across Europe. EPOS Study Group. European Prospective Osteoporosis Study Group. *Osteoporosis Int* 2000;11:248-54.
41. Honkanen K, Honkanen R, Heikkinen L, Kroger H, Saarikoski S. Validity of self-reports of fractures in perimenopausal women. *Am J Epidemiol* 1999;150:511-6.

FIRST BACTERIAL INFECTION AS AN ALTERNATIVE CLINICAL END POINT FOR REGULATORY APPROVAL OF AGENTS TARGETING THE PRIMARY CYSTIC FIBROSIS DEFECT

DONALD R. VANDEVANTER, PHD

Considerable effort is being expended to discover and develop therapeutic agents capable of correcting or compensating for (ie to “cure”) the primary cystic fibrosis (CF) defect in the lung. Therapeutic strategies include improving the processing or functioning of mutant cystic fibrosis transmembrane regulator (CFTR) protein,¹ up- or down-regulating alternative ion channels,² and introducing exogenous DNA sequences capable of producing functional CFTR protein.³

In spite of substantial investment in strategies to mitigate the effects of the primary CF defect, less progress has been made with respect to methods to adequately demonstrate clinical safety and efficacy of resulting therapies to obtain regulatory approval for marketing. Ideally, a therapy targeting the primary defect would be administered *in infants before significant disease progression*. This simple concept presents a substantial challenge for drug developers because there is no precedent for the development and regulatory approval of a “curative” therapy in symptom-free people with CF. In 1992 a consensus conference sponsored by the US Cystic Fibrosis Foundation identified the following end points as appropriate for demonstrating tangible benefit of a new therapeutic agent in patients: decreased frequency of pulmonary exacerbations, stable or improved pulmonary function, improved quality of life measures, and for younger patients, improved growth.⁴

The 2 therapies that have been approved by regulatory agencies for management of CF lung disease, recombinant human dornase alpha (rhDNase) and tobramycin inhalation solution (TIS), were studied and are now approved for use in people with CF and some degree of lung disease. Their approval was obtained through demonstration of an improvement in pulmonary function and a reduction in the incidence of acute exacerbations. Unfortunately, neither lung function benefit nor reduced hospitalization incidence are very robust clinical end points in individuals with CF who have not experienced a certain amount of pulmonary disease progression, as studies of rhDNase and TIS in subjects with mild lung disease have both demonstrated.^{5,6}

A study of a curative therapy conducted in subjects under 6 years of age, subjects who are symptom free, or subjects who have very mild lung disease would require many hundreds of subjects, years of observation, or both to demonstrate statistical significance if difference in lung function were the clinical end point.⁷ The risk and expense associated with such a path for regulatory approval is daunting. Alternatively, if an approval strategy comparable to that of rhDNase or TIS were used for a curative therapy, clinicians would not be provided with safety or efficacy data for patients early in the disease process. In the absence of such data, developers would expect a very slow expansion of product use into milder and milder CF disease segments, and expansion would require significant additional investment of both time and resources for additional clinical trials.⁸

Given the inadequacy of effect on pulmonary function as an end point for regulatory approval of a curative CF therapy, an alternative clinical end point more directly related to the primary CF defect is needed. In addition to being measurable in infants with CF, the clinical end point should also be methodologically tractable (in that the measure is relatively unambiguous and reproducible within and between subjects), statistically robust (where differences in incidence or magnitude of the measure between individuals with and without CF can be demonstrated using relatively modest sample sizes), clinically valid (in that clinicians would consider a statistically significant change in the incidence or magnitude of the measure as clinically meaningful with respect to risk of disease progression), and mechanistically sound (in that the measured end point can be linked back to the primary defect). Although CF is a multi-organ disease, a new end point should ideally be linked to pulmonary disease progression because most therapies in development to target CFTR are intended for topical delivery to the lung, and loss of lung function is the predominant cause of death.

See related articles, p 295,
p 306, p 312, p 316,
p 327, p 396,
p 399, and p 402.

Chiron Corporation Seattle, WA 98119.

Reprint requests: Donald R. VanDevanter, PhD, Chiron Corporation, 201 Elliott Ave W, Seattle, WA 98119. E-mail: Enigmaster@comcast.net.

J Pediatr 2005;147:332-4.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.06.046

CF	Cystic fibrosis	rhDNase	Recombinant human deoxyribonuclease
HRCT	High-resolution computerized tomography	TIS	Tobramycin inhalation solution
NPD	Nasal potential difference		

Nasal potential difference (NPD) is a relatively noninvasive measure that can be obtained in infants, but that lacks key features of a viable end point for approval. NPD is directly linked to ion movement across the epithelium, and a change in NPD can be used to demonstrate therapeutic mitigation of the CF defect.³ A variation of NPD has recently been proposed in which potential differences are measured with a bronchoscope in the distal airways in young children.⁹ Unfortunately, the magnitude to which an individual's potential difference deviates from a normal value does not appear to be particularly predictive of the ultimate severity of their CF lung disease progression,¹⁰ and there is no algorithm for correlating change in potential difference to change in disease progression.

High-resolution computerized tomography (HRCT) of the lung can be used to obtain data on lung disease progression in infants and before significant disease progression.^{11,12} HRCT has the advantages that it can be performed in younger subjects and can identify anatomic events that ultimately lead to loss of pulmonary function, but HRCT does not overcome a limitation of lung function as an end point: there can be variability in the measure, and lung disease does not develop predictably early in the life of an infant with CF. In addition, there is no data set with which a clinician (or regulator) can extrapolate from an early change in HRCT global scoring over time to a risk of CF disease progression or survival, and serial HRCT in infants is not without risk because of cumulative radiation exposure.

Risk of early respiratory tract infection by bacterial pathogens associated with CF has not been explored as an end point for regulatory approval, but it appears to possess key attributes of a robust clinical surrogate for CF disease progression. Respiratory tract infection is readily measurable by either serum antibody analyses or throat swab cultures.^{13,14} Infants with CF are prone to opportunistic respiratory tract infection with pathogens including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia* at dramatically higher incidences than the general population, with cross-sectional incidences ranging from 20% to 50% (depending on the pathogen) in infants with CF less than 2 years of age in the US.¹⁵ Longitudinal analyses of infant cohorts have demonstrated respiratory tract infection with *P aeruginosa* of about 50% (depending on detection method) by age 2 years¹⁴ and 70%¹⁴ to greater than 95%¹³ by age 3 years. Respiratory tract *P aeruginosa* infection in infants is a strong predictor of subsequent progression of pulmonary disease,^{14,16,17} and progression of pulmonary disease is the primary cause of death in CF.¹⁵ Surveillance for respiratory tract infection is routinely performed by CF clinicians today, with intervention often after a change in infection status. A clinical trial end point of reduced incidence of respiratory tract infection in infants should therefore prove clinically meaningful to clinicians, provided that the test agent has no intrinsic antibiotic activity.

Because the incidence of bacterial respiratory tract infection in infants with CF is fairly high, a statistically significant treatment effect can be demonstrated with reasonably modest sample sizes. Sample sizes required to assure

Table. Sample sizes required for 90% statistical power as a function of infection incidence

Control infection incidence	40%	30%	20%	10%
Treatment infection incidence	20%	15%	10%	5%
Treatment effect odds ratio	0.375	0.412	0.444	0.474
Sample size required per arm*	98	144	237	513

*Alpha = 0.05; 1-sided 2-group continuity-corrected χ^2 test of equal proportions.

90% power for studies seeking a 50% treatment effect (ie in which the incidence of infection is reduced 50% over a given period by treatment) are provided as a function of control arm infection incidence in the Table. Note that these power calculations are *independent* of the bacterial pathogen studied or the method used to identify infection.

If first bacterial infection is to be used as a study end point, several methodologic and epidemiologic hurdles will need to be cleared. Clinical/scientific consensus will be required regarding which method(s) should be used to define infection and which particular organism(s) (eg, *S aureus*, *P aeruginosa*, or both?) will be studied. The most simple, prevalent, and clinically useful detection method in use today, throat swab culture, may be less reproducible and more prone to operator error than detection of elevated serum antibacterial antibody titers by a central laboratory. In contrast, the lack of standardized reagents, protocols, and definitions of bacterial infection using antibody analyses has led to contradictory reports of the incidence and timing of antibody detection in CF infection. After agreement on a definition and method for confirming early bacterial infection in CF, fundamental data will need to be collected on the incidence and rate of bacterial infections in CF and unaffected pediatric populations (with attention to the effect of CF patient cohorting on infection rates) to further validate the end point and allow adequate powering of pivotal trials.

If a cure for CF is to be approved, all interested parties (patients, clinicians, sponsors, and regulators) will have to accept some level of compromise. There is no precedent for regulatory approval of a CF cure, and clinical end points used for the approvals of rhDNase and TIS are not well suited to the task. Effect on incidence of respiratory tract bacterial infection appears to be both a scientifically valid and commercially viable efficacy end point, but, regardless of what end point is eventually agreed on, it is not too early for clinicians, sponsors, and regulators to begin addressing this challenge.

I thank Dr Xin Yu of Chiron Corporation for support with statistical analyses, and Drs Arnold Smith and Michael Konstan for critical reading of this manuscript.

REFERENCES

1. Dormer RL, Derand R, McNeilly CM, Mettey Y, Bulteau-Pignoux L, Metaye T, et al. Correction of delF508-CFTR activity with benzo(c)quinolizinium compounds through facilitation of its processing in cystic fibrosis airway cells. *J Cell Sci* 2001;114:4073-81.

2. Kellerman D, Evans R, Mathews D, Shaffer C. Inhaled P2Y2 receptor agonists as a treatment for patients with cystic fibrosis lung disease. *Adv Drug Deliv Rev* 2002;54:1463-74.
3. Konstan MW, Davis PB, Wagener JS, Hilliard KA, Stern RC, Milgram LJ, et al. Compacted DNA nanoparticles administered to the nasal mucosa of cystic fibrosis subjects are safe and demonstrate partial to complete cystic fibrosis transmembrane regulator reconstitution. *Hum Gene Ther* 2004;15:1255-69.
4. Ramsey BW, Boat TF. Outcome measures for clinical trials in cystic fibrosis. Summary of a Cystic Fibrosis Foundation consensus conference. *J Pediatr* 1994;124:177-92.
5. Quan JM, Tiddens HA, Sy JP, McKenzie SG, Montgomery MD, Robinson PJ, et al. Pulmozyme Early Intervention Trial Study Group. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr* 2001;139:813-20.
6. Murphy TD, Anbar RD, Lester LA, Nasr SZ, Nickerson B, VanDevanter DR, et al. Treatment with tobramycin solution for inhalation reduces hospitalizations in young CF subjects with mild lung disease. *Pediatr Pulmonol* 2004;38:314-20.
7. Davis PB, Byard PJ, Konstan MW. Identifying treatments that halt progression of pulmonary disease in cystic fibrosis. *Pediatr Res* 1997;41:161-5.
8. VanDevanter DR, Wagener JS, Konstan MW, Smith AL, Yu X. Implications of unique adverse events for clinical trials conducted in asymptomatic CF subjects. *Pediatr Pulmonol* 2003;25S:254.
9. Davies JC, Davies M, McShane D, Smith S, Chadwick S, Jaffe A, et al. Potential difference measurements in the lower airway of children with and without cystic fibrosis. *Am J Respir Crit Care Med* 2005;171:1015-9.
10. Fajac I, Hubert D, Guillemot D, Honore I, Bienvenu T, Volter F, et al. Nasal airway ion transport is linked to the cystic fibrosis phenotype in adult patients. *Thorax* 2004;59:971-6.
11. Marchant JM, Masel JP, Dickinson FL, Masters IB, Chang AB. Application of chest high-resolution computer tomography in young children with cystic fibrosis. *Pediatr Pulmonol* 2001;31:24-9.
12. Brody AS, Klein JS, Molina PL, Quan J, Bean JA, Wilmott RW. High-resolution computed tomography in young patients with cystic fibrosis: distribution of abnormalities and correlation with pulmonary function tests. *J Pediatr* 2004;145:32-8.
13. Burns JL, Gibson RL, McNamara S, Yim D, Emerson J, Rosenfeld M, et al. Longitudinal assessment of *Pseudomonas aeruginosa* in young children with cystic fibrosis. *J Infect Dis* 2001;183:444-52.
14. West SE, Zeng L, Lee BL, Kosorok MR, Laxova A, Rock MJ, et al. Respiratory infections with *Pseudomonas aeruginosa* in children with cystic fibrosis: early detection by serology and assessment of risk factors. *JAMA* 2002;287:2958-67.
15. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation patient registry 2003 annual data report. Bethesda, MD: Cystic Fibrosis Foundation; 2004.
16. Demko CA, Byard PJ, Davis PB. Gender differences in cystic fibrosis: *Pseudomonas aeruginosa* infection. *J Clin Epidemiol* 1995;48:1041-9.
17. Li Z, Kosorok MR, Farrell PM, Laxova A, West SE, Green CG, et al. Longitudinal development of mucoid *Pseudomonas aeruginosa* infection and lung disease progression in children with cystic fibrosis. *JAMA* 2005;293:581-8.

A CONTROLLED TRIAL OF A TRAINING COURSE FOR PARENTS OF CHILDREN WITH SUSPECTED AUTISM SPECTRUM DISORDER

HELEN MCCONACHIE, MA, MPhil, PhD, VAL RANDLE, BSc, PhD, DONNA HAMMAL, BSc, MSc,
AND ANN LE COUTEUR, BSc, MBBS, FRCPsych, FRCPCH

Objective To evaluate a training course for parents, designed to help them understand autism spectrum disorder and to facilitate social communication with their young child.

Study design Controlled trial for 51 children aged 24 to 48 months, whose parents received either immediate intervention or delayed access to the course. Outcome was measured 7 months after recruitment in parents' use of facilitative strategies, stress, adaptation to the child; and in children's vocabulary size, behavior problems, and social communication skills.

Results Taking into account scores at recruitment, child's level of ability, diagnostic grouping, and the interval between assessments, a significant advantage was found for the intervention group in parents' observed use of facilitative strategies and in children's vocabulary size.

Conclusions The training course is well received by parents and has a measurable effect on both parents' and children's communication skills. (*J Pediatr* 2005;147:335-40)

Recent increase in the awareness of autism spectrum disorders (ASD) among the general public, primary care teams, pediatricians, and other health care professionals has led to a rise in the numbers of very young children being referred to community child health and mental health services for assessment, diagnosis, and support.¹⁻³ Epidemiologic studies suggest that the rate of ASD in preschool age children is 6 per 1000.⁴⁻⁶

Much research activity in recent years has been directed toward early identification of the features that are characteristic of autism to inform the development of appropriate early intervention strategies.^{7,8} Joint attention and imitation ability are positively associated with later development of language and with fewer social communication deficits.⁹ Problems in joint attention are likely to make pleasurable interaction difficult for parents to sustain, with consequent stress and feelings of failure.¹⁰ Therefore intervention strategies are required that aim to improve interaction through alerting parents to ways of facilitating their child's shared attention to activities. Such intervention strategies potentially have direct benefits for children and indirect benefits through changing parents' knowledge and confidence.¹¹

There is limited research evidence concerning the effectiveness of early intervention approaches that involve parents. Most researchers have not used randomized group comparison designs because of the practical and ethical difficulties in randomly assigning children and families to treatment groups.¹²⁻¹⁴

The More Than Words program was recently developed by the Hanen Centre in Canada for families of children with ASD.¹⁵ The group training program aims to facilitate parents' skills in social interaction with their child and to build successful communication through enhancing parents' ability to observe, to engage the child in structured routines (such as action songs with the child), and to use natural opportunities such as household and child-care tasks for joint attention during the day. Parent involvement as cotherapists for

See editorial, p 283.

From the School of Clinical Medical Sciences, University of Newcastle, Sir James Spence Institute, Royal Victoria Infirmary, Newcastle, United Kingdom.

Funded by the Community Fund (National Lottery Charities Board) through a collaboration between Children North East (Director: Joy Higginson) and the University of Newcastle upon Tyne. The NHS Executive R & D Northern and Yorkshire Region funded the training of the course leaders.

Submitted for publication Aug 19, 2004; last revision received Feb 1, 2005; accepted Mar 30, 2005.

Reprint requests: Helen McConachie, University of Newcastle, Sir James Spence Institute, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, United Kingdom. E-mail: h.r.mcconachie@newcastle.ac.uk.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.03.056

ADI-R	Autism Diagnostic Interview-Revised	MCDI	MacArthur Communicative Development Inventory
ADOS	Autism Diagnostic Observation Schedule	NCA	Not core autism
ASD	Autism spectrum disorder	PFQ	Parent Feelings Questionnaire
BSQ	Behavior Screening Questionnaire	QRS-F	Questionnaire on Resources and Stress-Friedrich short form
CI	Confidence interval		
JAFA	Joy and Fun Assessment		

their autistic child, with positive outcomes both for communication and behavior, has a considerable history^{16,17} but may also involve potential risk for parents if the child does not improve as anticipated.¹⁸ An understanding of the coping strategies of parents of young disabled children suggests that social support is of high importance,¹⁹ and interventions that involve groups of parents working together have the potential to lead to parents developing continuing support networks.^{20,21} Therefore the independent evaluation of parent group training programs such as More Than Words should incorporate measurement of outcomes that include specific child behaviors such as social communication skills, parent-child interaction strategies, and broader outcomes for parents.¹⁴

METHOD

Hypothesis

Parents who attend a More Than Words course will use more facilitative interaction strategies and be less stressed, and their children will have better language and communication skills, and fewer behavior problems, than parents who have not attended this course.

Design

The study compared the outcomes for parents of preschool-aged children with suspected ASD who either started on a 3-month More Than Words course shortly after recruitment (immediate intervention) or had to wait for a course because one was not available at the time their child's difficulties were identified (delayed control). Thus the design makes use of a naturally occurring opportunity for controlled comparison. Outcome measures were taken at recruitment (time 1) and approximately 7 months later (time 2). (Children were followed up on 2 further occasions, but this article reports only the immediate outcomes.)

Participants

Fifty-one preschool-aged children and their parents were included in the study. Courses offer 2 places for parents, or 1 parent and another care giver; however, for the research the main care giver was chosen as the parent to be filmed interacting with their child (49 mothers, 2 fathers). Inclusion criteria: child identified by the local community pediatrician or speech and language therapist as having language delay and some aspect of concern about social behavior that raised the suspicion of ASD; aged between 24 and 48 months; parent(s) agreed to attend a More Than Words course. A firm diagnosis was not required, thus allowing the intervention to be offered as soon as the child's difficulties were identified. Exclusion criteria: serious organic medical disorder; about to start an intensive home program.

Over a 2-year period (1999 to 2001), course leaders in 6 local authorities of the North East of England approached 108 families whose child met the first inclusion criterion and offered them a place in a More Than Words course, along with support services to increase equity of access to the courses.

Twenty families turned down the offer. Of the 88 remaining, 32 did not consent to participate in the research, citing reasons such as not wanting more professionals making home visits, and too much stress around the time of diagnosis (unpublished). Of the 56 families recruited, 5 children did not have assessments at Time 2 (2 moved away, 1 started an intensive intervention, 2 withdrew consent).

Intervention

The format of the More Than Words course is weekly sessions (total 20 hours) of group instruction and practice of facilitative strategies, with the aim of increasing fun interactions between parent and child. In addition there are 3 home visits for individual discussion and feedback. The course brings together approximately 8 sets of parents/care givers of preschool-age children who are likely to be experiencing similar difficulties and who train together as a group. This provides an opportunity for mutual support and sharing of information. The course content aims to teach parents to structure the child's environment to motivate them to communicate, to create structured routines with opportunities for their child to initiate or respond, and to use visual cues to aid the child's comprehension (Table I; available online at www.jpeds.com).

Courses developed by the Hanen Centre for parents of children with communication difficulties (such as "It Takes Two to Talk"), with adaptations for children with ASD, have been running in North East England since 1995. Before the start of the project, the course leaders attended an additional "More Than Words" training course with a Hanen Centre trainer. Throughout the study the course leaders continued to meet at 4-month intervals to ensure that a common protocol for delivery of the courses was maintained. Courses were offered in each authority at 6- to 9-month intervals.

Child Descriptive Measures (At Time 1)

ABILITY. The Vineland Adaptive Behavior Scales²² is a parent interview about the child's abilities in socialization, communication, daily living skills, and motor skills. The adaptive behavior composite is a standard score with mean of 100 (sd 15).

DIAGNOSTIC GROUP. A detailed interview with parents, the Autism Diagnostic Interview (ADI-R),²³ was undertaken at recruitment. The Autism Diagnostic Observation Schedule (ADOS)²⁴ was administered to the child. This is a semi-structured play-based assessment undertaken by a trained examiner, who presents the child with a series of materials and play activities, using a variety of social presses, and makes ratings of the child's communication, social interaction, imagination, and repetitive behaviors. Algorithm scores were calculated for the ADI-R and ADOS and compared with published cut-offs for Autism (and ASD, ADOS only). A "best-estimate" clinical diagnosis was then agreed on by the senior authors (HM, ALC), blind to study group allocation, drawing on all available clinical and research information including all time 1 research assessments. Several of the

children did not have a confirmed clinical diagnosis at recruitment, although they had been referred for assessment for suspected ASD. The children were grouped as “Autism” where they met all criteria for a Diagnostic and Statistical Manual diagnosis of core autism (29), and “NCA” (not core autism) where the best-estimate clinical diagnosis included pervasive developmental disorder not otherwise specified (17) or other early childhood developmental disorder such as specific language disorder (5).

Child Outcome Measures (At Time 1 and 2)

VOCABULARY. The MacArthur Communicative Development Inventory (MCDI)²⁵ is a checklist of words and phrases, marked by the parent to indicate which the child understands and produces. The total speech production score was used.

SOCIAL COMMUNICATION SKILLS. The ADOS was developed primarily as a diagnostic tool for ASD. However, it has been used recently as a measure of change with intervention.^{26,27} The standardized diagnostic algorithm score for reciprocal social interaction and communication was used in analysis, with lower scores representing better skills. Interrater reliability for total ADOS item ratings was maintained for the duration of the study at more than 75% agreement.

BEHAVIOR PROBLEMS. The Behavior Screening Questionnaire (BSQ)²⁸ is a parent interview about 12 areas of behavioral difficulties in preschool-age children, such as sleep, activity level, and compliance. The score range is from 0 to 24.

Parent Outcome Measures (At Time 1 and 2)

PARENT’S USE OF FACILITATIVE STRATEGIES. The Joy and Fun Assessment (JAFA) (unpublished) was created for this study. It is an observational checklist of the extent to which parents use the positive strategies taught in the More Than Words course, rated from a 5-minute video of toy-based interaction between parent and child. Nine parent strategies are rated: use of fun words (to attract attention, such as “wheee!”), simplified language (parentese), musicality of speech, fun physical contact, praise, pretend games, smiles and laughter, turn-taking routines, and imitations and expansions. The total score has a maximum of 36. Interrater reliability on a 15% sample of tapes was $r = 0.88$.

STRESS. The Questionnaire on Resources and Stress (QRS-F)²⁹ has been used extensively in research on parental stress in children with disabilities. It measures 4 components of parental perceptions: parent and family problems, pessimism, child characteristics and physical incapacity. The last was excluded in this study, as well as 3 items of child characteristics that were inappropriate for the preschool-age group. The score range for the adapted questionnaire is 0–43, with higher scores representing more stress. The scale had good internal reliability, with a Cronbach’s alpha of .91.

ADAPTATION TO THE CHILD. The Parent Feelings Questionnaire (PFQ) is an adaptation of the Judson scale,³⁰

a 22-item, 7-point scale used as an outcome measure in several studies of families of young children with disabilities.³¹ For this study, 8 items were added relevant to parent-child communication, and the salience of diagnosis (eg, “It’s easy to play with my child.....It’s difficult to play with my child”). The total score range is 30–210, with higher scores representing more adaptation. The scale had good internal reliability with a Cronbach’s alpha of .88.

Process Measures

ATTENDANCE. The percentage of the group sessions attended by the primary care giver.

OTHER INTERVENTIONS. At time 2, the parent was asked about their child’s attendance at mainstream and specialist educational programs over the preceding months since recruitment. A “substantial ASD-specific” program was defined as a minimum of 6 hours per week in a class or unit for children with ASD, or in a specialist school for children with severe learning disabilities, over the 3 months before time 2.

Procedure

The study was approved by the Northern and Yorkshire Multi-centre Regional Ethical Committee and all relevant Local Ethics Committees. Informed consent to take part in the study was obtained by the course leaders at the time of offering the More Than Words course to the parents. Support with child care and transport was offered to parents in conjunction with a local voluntary organization.

Children were seen for assessment in their own homes, with 1 research worker (VR, developmental psychologist) conducting all but 3 of the ADOS assessments. Before the ADOS was carried out, parents were provided with a standard set of toys, including a ball, a tea-set, 2 tambourines, a push-and-go truck, and a toy typewriter, and asked to play as they normally would with their child for at least 5 minutes. This interaction was video-recorded for later rating of parent strategies (JAFA), conducted by trained psychologists blind to group allocation or time. The ADOS was also video-recorded for later rating and reliability checks. Parents were interviewed about adaptive behavior and behavior problems, and 3 questionnaires (MCDI, PFQ and QRS-F) were given to parents with a stamped addressed envelope for later completion and return.

The time 2 assessments were conducted approximately 7 months after time 1, 4 months after the end of a course. The gap between assessments therefore varied where the start dates of some “immediate” courses were unavoidably delayed.

Analysis

Analysis of covariance was performed to compare time 2 outcome measures between immediate intervention and delayed control groups, making adjustment for the time 1 scores for each outcome measure, the time interval between assessments, the adaptive behavior level and the diagnosis of the child. The statistical package Stata 8.0 was used for the analysis.

Table II. Characteristics of the intervention and control groups

	Intervention (n = 26)	Control (n = 25)
Number of boys	21	21
Child mean age in months (SD)	38.12 (6.54)	34.96 (6.68)
Diagnostic group		
Autism	17	12
NCA	9	13
Vineland Adaptive Behavior Scale composite (SD)	66.42 (11.44)	67.76 (9.81)
Interval between assessments in months (SD)	8.65 (1.50)	5.16 (1.31)

RESULTS

There was no significant difference between the characteristics of children in the immediate intervention and the delayed control groups (Table II). However, a greater proportion of children in the intervention group met criteria for a diagnosis of core autism. The groups were significantly different in terms of the interval between assessments.

The parents in the intervention group on average attended 90.5% of the course sessions. All of the children had attended some kind of playgroup or educational program concurrently with the More Than Words course, varying from 2 hours to 30 hours a week. Seventeen children in the intervention group and 16 in the delayed control group had received some specialist provision in the previous 7 months. However, this amounted to "substantial ASD-specific" provision for only 8 children in the intervention group and 3 in the control. Thus use of other services did not differ significantly between the groups.

Taking into account scores at time 1, child's level of adaptive behavior, diagnostic grouping, and the interval between assessments, a significant difference was found at time 2 between intervention and control groups in terms of children's vocabulary size (MCDI). The autism control group reported on average -50.3 (95% CI: $-92.0, -8.6$) words less than the intervention group ($P = .019$), and the NCA control group on average -114.6 (95% CI: $-160.6, -68.6$) words less than the intervention group ($P < .001$). Children's vocabulary progress was not significantly related to having been in substantial ASD-specific educational provision ($t = 1.273, P = .210$) (Table III).

There were no significant group differences found for the social-communication algorithm score (ADOS) nor for child behavior problems (BSQ). For the parents, a significant advantage was found for the intervention group in parents' use of facilitative strategies (JAFA). The group comparison for the children with autism shows that the control group parents had a significantly lower score at time 2 (mean

difference -3.6 , 95% CI: $-7.2, 0, P = .05$) than the intervention group parents; however, the group comparison was not significant for the parents of children with NCA (mean difference 1.4 , 95% CI: $-2.5, 5.3, P = .47$) (Table IV). There were no significant differences in the regression model for parental stress (QRS-F), nor for adaptation (PFQ) between intervention and controls, for either diagnostic group.

DISCUSSION

This short-term controlled study aimed to determine effects for parents and for children with ASD of parents' attendance at a More Than Words course. There were 2 main study findings. First, parents are able to learn the interaction strategies that are likely to be facilitative for their children's development of communication, particularly the parents of children with a clear diagnosis of autism. Second, the children whose parents attended a course had larger reported vocabulary, whatever the child's diagnostic grouping. Because the More Than Words course lasted for 3 months, and the time 2 assessment was undertaken around 4 months after the course ended, it can be suggested that parents' enhanced strategies had a positive effect on their children's development of vocabulary, although a causal link cannot be proved with the current study design.

However the study and its findings have some limitations. First, the sample of children and parents involved in the study is around half of the potential population identified. The research group is slightly but significantly more economically advantaged than the "refusers" (unpublished). The extent of the bias that this might exert on the results is not known, particularly because intervention studies in autism almost never describe the socioeconomic characteristics of the population from which their samples are drawn.^{12,32} Second, the group allocation was not randomized. The groups did not differ in parental willingness to take part, because the More Than Words courses were part of on-going services in the various authorities, and timing was solely determined by the availability of the next course. The groups differed significantly only in regard to the interval between research assessments, although the distribution of diagnostic groupings approached significance. These differences were taken into account by the regression model used in the statistical analysis; however, other unknown sources of bias cannot be completely ruled out. Third, the follow-up time reported in this article is necessarily short, because the controlled part of the study design used the natural opportunity of parents having to wait for a course to begin. Fourth, the delayed control group were receiving some degree of individual services from their speech and language therapists while waiting, that is, they were not a "no intervention" control group. This may have reduced the power of the study to detect differences. However, it is a truer reflection of "real life" in provision of services and so indicates the extent of added value of the course.

Finally, the child outcome measure that showed a significant effect of intervention (MCDI) relies on parental report. The direct measure of children's skills (ADOS) did not.

Table III. Comparison of time 1 and time 2 child measures between intervention and control groups

Child	Intervention		Control	
	Autism n = 17 Mean (SD)	NCA n = 9 Mean (SD)	Autism n = 12 Mean (SD)	NCA n = 13 Mean (SD)
Expressive vocabulary MCDI				
T1	34.65 (62.74)	188.22 (159.18)	30.75 (54.35)	77.54 (79.22)
T2	72.6 (100.07)	271.38 (148.43)	38.92 (54.89)	131.54 (114.7)
Social-communication ADOS				
T1	17.35 (2.45)	4.33 (2.78)	17.17 (3.76)	7.15 (5.24)
T2	14.82 (6.47)	6.00 (3.87)	14.00 (6.45)	7.69 (5.84)
Behavior BSQ				
T1	11.59 (4.70)	9.33 (4.21)	12.42 (3.94)	9.31 (3.71)
T2	12.50 (5.05)	8.44 (3.40)	12.92 (4.10)	9.23 (3.98)

Significant difference at time 2 in bold, taking into account time 1 scores.

Table IV. Comparison of time 1 and time 2 parent measures between intervention and control groups

Parent	Intervention		Control	
	Autism (n = 17) Mean (SD)	NCA (n = 9) Mean (SD)	Autism (n = 12) Mean (SD)	NCA (n = 13) Mean (SD)
Interaction JAJFA				
T1	11.18 (4.30)	10.89 (2.98)	10.83 (3.86)	12.85 (3.91)
T2	13.94 (4.68)	11.11 (3.44)	11.58 (4.54)	13.77 (3.49)
Stress QRS-F				
T1	19.53 (9.50)	18.44 (9.88)	19.60 (5.32)	15.08 (8.63)
T2	21.93 (7.58)	16.33 (14.50)	17.30 (7.92)	13.08 (7.72)
Adaptation PFQ				
T1	145.00 (20.40)	150.33 (26.06)	134.92 (14.43)	155.39 (28.66)
T2	145.92 (20.69)	161.88 (27.45)	146.36 (18.35)	159.31 (22.36)

Significant difference at time 2 in bold, taking into account time 1 scores.

Although the ADOS was originally designed as a diagnostic tool, the social-communication algorithm score has been used to measure change successfully in one study at 12-month follow-up in children with core autism receiving individual language-based intervention.²⁷ The children in this study had a wider range of levels of impairment and a shorter duration of follow-up. Further detailed analysis being undertaken in this study indicates that specific groupings of ADOS ratings are sensitive to change over a longer follow-up time, indicating a specific positive effect of the intervention on child skills (unpublished).

The JAJFA was developed to be a measure of parents' use of facilitative strategies in interaction relevant to the More Than Words course content but also to other early communication interventions for parents of young children with impairments. On average at time 1, parents were equally able to use fun strategies with their children whatever their severity of impairment in social communication, yet only the parents of children with core autism changed significantly by time 2. Because children in both diagnostic groupings improved in vocabulary when their parents attended a course, this raises the

possibility that the JAJFA is less sensitive to change where children are more able and more likely to take the initiative in interaction. This possibility will be clearer in follow-up analysis of findings for the whole group after intervention. However, it seems likely that the impact of the course may indeed be greater for parents of children with core autism, where the strategies introduced are particularly empowering, after they have struggled to capture the attention of their child, have found their child's self-directed behavior hard to interpret as communication, and so may have felt unable to interact or play with their child.

This study adds to the small evidence base concerning useful early interventions for children with ASD. Nevertheless, future studies need to be multicenter to use randomized designs, to have greater power, and ideally to allow comparison between alternative programs for families and children.^{13,14} The More Than Words course is well received by families in terms of consistent attendance, and their comments when interviewed.³³ Nevertheless, it is a short-term intervention, with a total of 11 group and individual contacts over 3 months. It did not have a significant

effect (either positive or negative) on parental stress or adaptation to the child and perhaps should not have been expected to given its brevity and specific focus; children with ASD pose a range of challenges to their parents. However, *More Than Words* does enable parents to build a foundation of positive communication strategies with their child.

We are very grateful to the parents and children who took part in the research, and who welcomed us into their homes. The research progress depended on the dedication and cooperation of the course leaders: Jan Raine, Alyson Eggett, Val Dean, Lynne Bennett, Beryl Downing, Marie Sowter, Linda Dixon, Judith Booth, Judy Crow, Diana Finlay and Bev Wilson. The Hanen Centre (Director: Elaine Weitzman) gave encouragement for the research. Fern Sussman conducted the training with the course leaders, and Anne McDade, UK and Ireland Hanen representative, was an invaluable member of the project Steering Group. Barry Ingham and Emma Honey did detailed work on three of the measures.

REFERENCES

1. Charman T, Baird G. Practitioner review: diagnosis of autism spectrum disorder in 2- and 3-year-old children. *J Child Psychol Psychiatry* 2002;43:289-305.
2. Filipek PA, Accardo PJ, Baranek GT, Cook EH, Dawson G, Gordon B, et al. The screening and diagnosis of autistic spectrum disorders. *J Autism Dev Disord* 1999;29:439-84.
3. Le Couteur A. National Autism Plan for Children. London: National Autistic Society, Royal College of Psychiatrists, Royal College of Paediatrics and Child Health, and the All Party Parliamentary Group on Autism; 2003.
4. Baird G, Charman T, Baron-Cohen S, Cox A, Swettenham J, Wheelwright S, et al. A screening instrument for autism at 18 months of age: a 6 year follow-up study. *J Am Acad Child Adolesc Psychiatry* 2000;39:694-702.
5. Centers for Disease Control and Prevention Prevalence of Autism in Brick Township, New Jersey, 1998. Atlanta, Ga: Centers for Disease Control and Prevention; 2000. Community Report. Available at: www.cdc.gov/ncbddd/dd/rptoc.htm. Accessed June 14, 2005.
6. Chakrabarti S, Fombonne E. Pervasive developmental disorders in preschool children. *JAMA* 2001;285:3093-9.
7. Charman T, Swettenham J, Baron-Cohen S, Cox A, Baird G, Drew A. Infants with autism: an investigation of empathy, pretend play, joint attention and imitation. *Developmental Psychol* 1997;33:781-9.
8. Mundy P, Sigman M, Kasari C. Joint attention, developmental level, and symptom presentation in autism. *Dev Psychopathol* 1994;6:389-401.
9. Charman T. Why is joint attention a pivotal skill in autism? *Philosophical Transactions of the Royal Society of London. Series B: Biological sciences*; 2003;358:315-24.
10. Travis LL, Sigman M. Social deficits and interpersonal relationships in autism. *Ment Retard Dev Disabil Res Rev* 1998;4:65-72.
11. Kaiser AP, Hancock TB. Teaching parents new skills to support their young children's development. *Infants Young Child* 2003;16:9-21.
12. Diggle T, McConachie H, Randle V. Parent implemented early intervention for young children with autism spectrum disorder. In: *The Cochrane Library*, Issue 1. 2003. Oxford: Update Software.
13. National Research Council. *Educating Children with Autism*. Committee on Educational Interventions for Children with Autism. Division of Behavioral and Social Sciences and Education. Washington, DC: National Academy Press; 2001.
14. Charman T, Howlin P, Aldred C, Baird G, Degli Espinosa F, Diggle T, et al. Research into early intervention for children with autism and related disorders: methodological and design issues. *Autism* 2003;7:217-25.
15. Sussman F. *More Than Words: helping parents promote communication and social skills in children with autism spectrum disorder*. Toronto: Hanen Centre; 1999.
16. Schopler E, Reichler RJ. Parents as cotherapists in the treatment of psychotic children. *J Autism Childhood Schizophrenia* 1971;1:87-102.
17. Howlin P, Rutter M. *Treatment of autistic children*. Chichester: John Wiley; 1987.
18. Robbins FR, Dunlap G, Plienis AJ. Family characteristics, family training and the progress of young children with autism. *J Early Intervent* 1991;15:173-84.
19. McConachie H. Implications of a model of stress and coping for services to families of young disabled children. *Child Care Health Dev* 1994;20:37-46.
20. Cox AD. Befriending young mothers. *Br J Psychiatry* 1993;163:6-18.
21. Shields J. The NAS EarlyBird program: partnership with parents in early intervention. *Autism* 2001;5:49-56.
22. Sparrow SA, Balla DA, Cicchetti DV. *Vineland Adaptive Behavior Scales*. Circle Pines, Minn: American Guidance Services; 1984.
23. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview—Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord* 1994;24:659-85.
24. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, DiLavore P, et al. The Autism Diagnostic Observation Schedule—Generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord* 2000;30:205-23.
25. Fenson L, Dale PS, Reznick JS, Thal D, Bates E, Hartung JP, et al. *MacArthur Communicative Development Inventories: user's guide and technical manual*. San Diego: Singular Publishing Group; 1993.
26. Owley T, McMahon W, Cook EH, Lauthere T, South M, Mays LZ, et al. Multisite, double-blind, placebo-controlled trial of porcine secretin in autism. *J Am Acad Child Adolesc Psychiatry* 2001;40:1293-9.
27. Aldred C, Green J, Adams C. A new social communication intervention for children with autism: pilot randomized controlled treatment study suggesting effectiveness. *J Child Psychol Psychiatry* 2004;45:1420-30.
28. Richman N, Graham P. A behavioral screening questionnaire for use with three-year-old children. Preliminary findings. *J Child Psychol Psychiatry* 1971;12:5-33.
29. Friedrich WN, Greenberg MT, Crnic K. A short-form of the questionnaire on resources and stress. *Am J Ment Deficiency* 1983;88:41-8.
30. Judson SL, Burden RL. Towards a tailored measure of parental attitudes: an approach to the evaluation of one aspect of intervention projects with parents of handicapped children. *Child Care Health Dev* 1980;6:47-55.
31. Sloper P, Turner S. Risk and resistance factors in the adaptation of parents of children with severe physical disability. *J Child Psychol Psychiatry* 1993;34:167-88.
32. Smith T. Outcome of early intervention for children with autism. *Clin Psychol Sci Pract* 1999;6:33-49.
33. Ashley K, Le Couteur A. It's a family affair. Paper presented at the 14th Annual Durham International Conference on Autism, April 2003.

VARIABLES ASSOCIATED WITH THE EARLY FAILURE OF NASAL CPAP IN VERY LOW BIRTH WEIGHT INFANTS

AMER AMMARI, MB, BS, MANDHIR SURI, MD, VLADANA MILISAVLJEVIC, MD, RAKESH SAHNI, MD, DAVID BATEMAN, MD,
ULANA SANOCKA, MD, CARRIE RUZAL-SHAPIRO, MD, JEN-TIEN WUNG, MD, AND RICHARD A. POLIN, MD

Objective To identify risk factors and neonatal outcomes associated with the early failure of “bubble” nasal continuous positive airway pressure (CPAP) in very low birth weight (VLBW) infants with respiratory distress syndrome (RDS).

Study design Following resuscitation and stabilization at delivery, a cohort of 261 consecutively inborn infants (birth weight ≤ 1250 g) was divided into three groups based on the initial respiratory support modality and outcome at 72 hours of age: “ventilator-started” group, “CPAP-failure” group, and “CPAP-success” group.

Results CPAP was successful in 76% of infants ≤ 1250 g birth weight and 50% of infants ≤ 750 g birth weight. In analyses adjusted for postmenstrual age (PMA) and small for gestational age (SGA), CPAP failure was associated with need for positive pressure ventilation (PPV) at delivery, alveolar-arterial oxygen tension gradient (A-a DO₂) >180 mmHg on the first arterial blood gas (ABG), and severe RDS on the initial chest x-ray (adjusted odds ratio [95% CI] = 2.37 [1.02, 5.52], 2.91 [1.30, 6.55] and 6.42 [2.75, 15.0], respectively). The positive predictive value of these variables ranged from 43% to 55%. In analyses adjusted for PMA and severe RDS, rates of mortality and common premature morbidities were higher in the CPAP-failure group than in the CPAP-success group.

Conclusion Although several variables available near birth were strongly associated with early CPAP failure, they proved weak predictors of failure. A prospective controlled trial is needed to determine if extremely premature spontaneously breathing infants are better served by initial management with CPAP or mechanical ventilation. (*J Pediatr* 2005;147:341-7)

Respiratory distress syndrome (RDS) is an important cause of morbidity and mortality in preterm infants.¹⁻³ Intermittent positive pressure ventilation (PPV) and prophylactic administration of replacement surfactant are the standard treatments for infants with moderate or severe disease.³ However, mechanical ventilation is invasive and has the potential to injure the airways and lung parenchyma. Ventilator-induced lung injury may be associated with alveolar structural damage, pulmonary edema, inflammation, and fibrosis.⁴ Avoidance of mechanical ventilation is an effective way to reduce the incidence of chronic lung injury.

Gentle ventilation strategies have been suggested as a way to improve pulmonary outcomes for very preterm infants.⁵⁻⁶ Although nasal continuous positive airway pressure (CPAP) has been associated with a lower incidence of newborn chronic lung disease (CLD) when used as the initial respiratory support modality in very low birth weight (VLBW) infants with RDS,^{1,7} not all extremely premature infants with RDS are candidates for initial treatment with CPAP, and not all those who are given CPAP can be successfully managed with this modality. Infants who fail CPAP may suffer the consequences of delayed surfactant administration and other adverse outcomes that may be related to early CPAP failure.

We undertook this retrospective analysis of the hospital course of inborn, VLBW infants ≤ 1250 g at our institution to try to answer the following questions: (1) Are there perinatal/neonatal variables that distinguish infants who are successfully managed with

See editorial, p 284.

From the Division of Neonatology-Department of Pediatrics and the Division of Pediatric Radiology, College of Physicians and Surgeons, Columbia University, New York, New York.

Submitted for publication Jul 22, 2004; last revision received Apr 5, 2005; accepted Apr 26, 2005.

Reprint requests: Dr Richard A. Polin, Division of Neonatal-Perinatal Medicine, Department of Pediatrics, College of Physicians and Surgeons, Columbia University, 3959 Broadway BHS-115, New York, NY 10032-3702. E-mail: rap32@columbia.edu.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.04.062

A-a DO ₂	Alveolar-arterial oxygen tension gradient	PPROM	Preterm premature rupture of membranes
CLD	Chronic lung disease	PPV	Positive pressure ventilation
CPAP	Continuous positive airway pressure	RDS	Respiratory distress syndrome
IVH	Intraventricular hemorrhage	ROP	Retinopathy of prematurity
PDA	Patent ductus arteriosus	SGA	Small for gestational age
PMA	Postmenstrual age	VLBW	Very low birth weight

CPAP from those who fail CPAP? and (2) Can we predict which infants are likely to fail CPAP?

METHODS AND DESIGN

“Bubble” nasal CPAP is routinely used at the Children’s Hospital of New York, Columbia University as an initial respiratory support modality in spontaneously breathing VLBW infants with RDS. Following resuscitation (if needed) and stabilization at delivery, VLBW infants are immediately carried to the transitional nursery within the delivery suite, where CPAP is applied to those with spontaneous respiratory effort within 5 to 10 minutes of birth.¹ The initial respiratory support modality for infants without spontaneous respiratory effort, including those who have required prolonged PPV at birth and those with severe cardiorespiratory instability, is mechanical ventilation via an endotracheal tube. Administration of exogenous surfactant (Survanta®) is not routine with either modality of ventilatory support. When used as late rescue it is reserved for infants with endotracheal intubation requiring a fraction of inspired oxygen (FIO₂) >0.60 to maintain arterial oxygen tension between 50 and 70 mmHg or oxygen saturation between 90% and 95%.

We performed a retrospective analysis of the prenatal histories, clinical courses, and laboratory data of all inborn admissions to the neonatal intensive care unit between June 1999 and July 2002, to determine which variables might be associated with failure of bubble nasal CPAP in VLBW infants ≤1250 g at birth. Data sources included maternal and infant medical records, laboratory data, procedure logs, and initial chest radiographs.

Respiratory Care Groups

Infants were categorized into one of three respiratory care groups based on the respiratory care modality used during the first 72 hours of life. Respiratory modalities used during delivery room resuscitation and stabilization, although noted, were not included in the categorization scheme. Categorization was as follows: infants were first divided into two groups, the “ventilator-started” group included infants whose initial respiratory support modality at birth was endotracheal intubation and mechanical ventilation; the “CPAP-started” group consisted of infants begun on nasal CPAP following delivery. This designation was made during stabilization in the transitional nursery and usually (but not always) corresponded to management within the delivery room. Infants in the CPAP-started group were subsequently subdivided into a “CPAP success” group that included infants who were successfully treated with CPAP for at least 72 hours and a “CPAP failure” group that included those who required endotracheal intubation for respiratory failure within the first 72 hours of life. For the purpose of the study, “failure” of CPAP occurred when oxygenation was worsening (FIO₂ requirement exceeded 0.6) or ventilation was inadequate (arterial pH dropped below 7.20 and PaCO₂ exceeded 65 mmHg) or infants had frequent episodes of apnea requiring repeated stimulation or bag-and-mask ventilation despite

adequate CPAP delivery and oxygenation during the first 72 hours of life. CPAP failure beyond 72 hours of age is uncommon and rarely related to the initial respiratory disease or to severe recurrent apnea. Infants failing CPAP received endotracheal intubation and mechanical ventilation with or without surfactant.

The maternal variables examined included multiple birth, pregnancy-induced hypertension, diabetes mellitus, preterm premature rupture of membranes (PPROM) >18 hours, cesarean section, fetal distress, meconium-stained amniotic fluid, maternal medications (corticosteroids, indomethacin, magnesium sulfate, antibiotics, and terbutaline), and clinical chorioamnionitis (defined as the presence of fever with one or more of the following: maternal leukocytosis >15,000/mm³, uterine tenderness, fetal tachycardia, or foul-smelling amniotic fluid).⁸

Infant variables included birth weight, postmenstrual age (PMA), presence of small for gestational age (SGA; weight for PMA below 10th Lubchenko percentile),⁹ Apgar scores, delivery room management (PPV via a bag and mask or via an endotracheal tube), indices of severity of the respiratory distress (severity of RDS on the initial chest x-ray, PaO₂/FIO₂ ratio, alveolar-arterial oxygen tension gradient [A-a DO₂] at the time of the first arterial blood gas [ABG]), the duration of oxygen therapy, and neonatal morbidities: pneumothorax, patent ductus arteriosus (PDA; by echocardiography), germinal matrix-intraventricular hemorrhage (IVH; by cranial ultrasonography typically performed at 24-48 hours, 7 days, 3-4 weeks, and 6-8 weeks of age), severe IVH (grades III-IV), presence of retinopathy of prematurity (ROP; any grade by 32 weeks PMA with weekly or bi-weekly follow-up), severe ROP (requiring photocoagulation), necrotizing enterocolitis (clinical and surgical diagnoses), CLD, moderate-severe CLD, and mortality. For the purposes of these comparisons, CLD was defined according to the new classification, which differentiated three groups of preterm infants with CLD <32 weeks gestation.^{10,11} Mild CLD was defined as the treatment with supplemental oxygen for ≥28 days but not at 36 weeks PMA; moderate CLD was defined as treatment with supplemental oxygen for ≥28 days and treatment with <30% oxygen at 36 weeks PMA, and severe CLD was defined as treatment with supplemental oxygen for at least 28 days and treatment with >30% oxygen and/or positive pressure (PPV or nasal CPAP) at 36 weeks PMA. The severity of RDS on the initial chest x-ray was graded as mild, moderate, or severe according to standard classification by our pediatric radiologist (CR-S) who was blinded to failure as an outcome.¹²

Clinical and laboratory data included the ABG and FiO₂ at the time of admission and at the time of CPAP failure. Only about half of the study infants had umbilical venous cord gas results available for analysis; results of these did not differ among groups. Indices of severity of RDS (PaO₂/FIO₂ ratio, arterial to alveolar oxygen tension ratio, and A-a DO₂) were calculated at the time of first blood gas. Rates of neonatal morbidities (see above) were calculated only for those infants whose duration of survival placed them at risk for that particular morbidity; otherwise the data were treated as missing.

Table I. Distribution of infants (n (%)) into respiratory care groups by birth weight

Respiratory care group/Birth weight (g) [no. of infants]	<500 [14]	500-599 [23]	600-699 [42]	700-799 [31]	800-899 [34]	900-999 [25]	1000-1099 [34]	1100-1199 [37]	1200-1250 [21]	≥1250 [261]
Ventilator-started (% of total)	7 (50)	9 (39)	5 (12)	6 (19)	3 (9)	1 (4)	0 (0)	1 (3)	0 (0)	32 (12)
CPAP-started (% of total)	7 (50)	14 (61)	37 (88)	25 (81)	31 (91)	24 (96)	34 (100)	36 (97)	21 (100)	229 (88)
CPAP-failure (% of CPAP-started)	3 (43)	8 (57)	21 (57)	8 (32)	5 (16)	3 (13)	4 (12)	2 (6)	1 (5)	55 (24)
CPAP-success (% of CPAP-started)	4 (57)	6 (43)	16 (43)	17 (68)	26 (84)	21 (87)	30 (88)	34 (94)	20 (95)	174 (76)

STATISTICAL ANALYSIS

To characterize the risks for early CPAP failure, three comparisons were made based on the infant's initial and eventual respiratory care group: ventilator-started versus CPAP-started; ventilator-started versus CPAP failure; and CPAP failure versus CPAP success. Because many of the variables used are not normally distributed, median values and their corresponding 95% CI for each group are reported.¹³ *P* values for post hoc comparisons were obtained from individual comparisons using Mann-Whitney test. To compensate for multiple comparison artifacts in post hoc testing, we used a rejection *P* value of .019 for the individual comparisons, equivalent to an overall *P* value of .05 for the three comparisons being made for each variable.¹⁴

For multivariate analyses of possible associations between maternal variables and failure we used logistic regression with CPAP failure as the dichotomous dependent variable and adjusted for the effects of PMA, infant gender, and SGA. We also used logistic regression models to control for PMA, presence of SGA, and presence of severe RDS on initial chest x-ray to examine possible associations between mortality and morbidity indicators among the three groups. Nonsignificant terms were removed sequentially from logistic models and the results recalculated at each removal.

Prediction of Early CPAP Failure

We used three variables strongly associated with early CPAP failure (birth weight, PMA, and A-a DO₂), available at birth or immediately thereafter (when early management might be altered by their results) to construct models that might predict early CPAP failure. The variables were first dichotomized at the intersection point between the sensitivity and specificity of the test (CPAP failure vs birth weight at 100-g intervals, CPAP failure vs PMA at 1-week intervals, and CPAP failure vs A-a DO₂ at 100-mmHg intervals) yielding cut-points for birth weight (≤750 g), PMA (<26 weeks), and A-a DO₂ (>180 mmHg). We assessed the positive predictive value of these variables alone and in combination.

RESULTS

Respiratory Care Groups

Following initial resuscitation and stabilization in the delivery room and the transitional nursery, 229 (88%) infants

were placed on nasal CPAP (the CPAP-started group) and 32 (12%) infants were started on mechanical ventilation (the ventilator-started group) as initial respiratory support modalities. Of ventilator-started infants, 29 of 32 (91%) underwent endotracheal intubation in the delivery room; the remaining three infants underwent endotracheal intubation on admission to the transitional nursery. Five of 229 (2%) infants in the CPAP-started group (two CPAP successes and three CPAP failures), who needed endotracheal intubation and ventilation during initial resuscitation, had their endotracheal tubes removed on admission to the transitional nursery. Among the infants in the CPAP-started group, 174 (76%) infants were successfully treated with CPAP for at least 72 hours (the CPAP-success group), and 55 (24%) required the placement of an endotracheal tube for respiratory failure within the first 72 hours of life (the CPAP-failure group).

Maternal Risk Factors

In multivariate analyses controlled for PMA, SGA, and infant gender, none of the following maternal risk factors was associated with early CPAP failure: multiple birth, pregnancy-induced hypertension, diabetes mellitus, PPRM, clinical chorioamnionitis, cesarean section, fetal distress, meconium-stained amniotic fluid, and maternal medications (corticosteroids, indomethacin, magnesium sulfate, antibiotics, and terbutaline). In these analyses both PMA and SGA were significantly associated with early CPAP failure (adjusted odds ratio [95% CI] = 0.53 [0.43, 0.65] for every week's increase in gestational age and 2.77 [1.21, 6.34] when infants were SGA) and infant gender was not.

Infant Risk Factors and Characteristics

There was no significant difference between the number of male and female infants in each of the three respiratory support groups. Table I shows the distribution of infants by respiratory care groups in 100-g birth weight increments. Infants <500 g were included in this study (n = 14). Among infants with birth weight ≤750 g, 73.9% (68/92) were initially begun on CPAP and 50% (34/68) failed and required mechanical ventilation. The CPAP success rates for weight groups 751 to 1000 g (n = 77) and 1001 to 1250 g (n = 92) were 80% (56/70) and 92.3% (84/91), respectively. Among infants ≥26 weeks PMA, 2.8% (5/174) were initially begun on mechanical ventilation and 12.6% (22/169) of those started on

Table II. Distribution of infants (n (%)) into respiratory care groups by weeks of PMA

Respiratory care group/PMA (wk)	23	24	25	26	27	28	29	30	31	32	33	34	≤34
[no. of infants]	[13]	[35]	[39]	[39]	[26]	[41]	[31]	[15]	[8]	[7]	[5]	[2]	[261]
Ventilator-started (% of total)	7 (54)	10 (29)	10 (26)	2 (5)	2 (8)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	32 (12)
CPAP-started (% of total)	6 (46)	25 (71)	29 (74)	37 (95)	24 (92)	40 (100)	31 (100)	15 (100)	8 (100)	7 (100)	5 (100)	2 (100)	229 (88)
CPAP-failure (% of CPAP-started)	3 (50)	12 (48)	18 (62)	12 (32)	3 (13)	3 (8)	4 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	55 (24)
CPAP-success (% of CPAP-started)	3 (50)	13 (52)	11 (38)	25 (68)	21 (87)	37 (92)	27 (87)	15 (100)	8 (100)	7 (100)	5 (100)	2 (100)	174 (76)

Table III. Comparison of infant characteristics by respiratory care group (continuous variables)

	Median [95% Confidence Interval]*				Post hoc comparisons**		
	Ventilator-started A	CPAP-started B+C	CPAP-failure B	CPAP-success C	A:(B+C)	A:B	B:C
Gestational age (wk)	24 [23.1, 24.9]	27 [26.2, 27.8]	25 [24.5, 25.5]	28 [27.7, 28.3]	<.001	.004	<.001
Birth weight (g)	622.5 [457, 692]	900 [843, 957]	669 [610, 727]	973 [907, 1034.7]	<.001	.06	<.001
Apgar (1 min)	2 [0.4, 3.6]	6 [5.3, 6.7]	6 [5.0, 7.0]	7 [6.0, 8.0]	<.001	<.001	.002
Apgar (5 min)	7 [6.0, 8.0]	8 [8.0, 8.0]	8 [7.6, 8.4]	8 [8.0, 8.0]	<.001	<.001	.002
<i>First arterial blood gas values</i>							
pH	7.21 [7.17, 7.25]	7.29 [7.27, 7.31]	7.28 [7.26, 7.30]	7.30 [7.28, 7.32]	<.001	<.001	.20
pCO ₂	48 [40.9, 55.1]	47 [45.1, 48.9]	49 [46.7, 51.3]	46 [44.0, 47.9]	.11	.38	.39
pO ₂	63.5 [45.3, 78.7]	86 [77.2, 94.8]	87 [62.1, 111.9]	85.5 [75.6, 94.4]	<.001	.005	.08
Base excess (mmol)	-7 [-8.5, -5.5]	-3 [-3.6, -2.4]	-4 [-5.1, -2.9]	-3 [-3.5, -2.5]	<.001	<.001	.20
paO ₂ /FIO ₂	0.75 [0.42, 0.98]	2.25 [2.02, 2.48]	1.76 [1.34, 2.17]	2.45 [2.20, 2.68]	<.001	<.001	<.001
A-a DO ₂	559.5 [492, 627]	154 [133, 176]	235.5 [189, 281]	118 [98, 137]	<.001	<.001	<.001

*95% confidence intervals for median obtained using Maritz Jarrett estimate of standard error.

**P values for post hoc comparisons obtained using Mann-Whitney test. Rejection P value of .019, based on studentized critical values for the three comparisons made for each variable.

CPAP failed. There were no CPAP failures after 29 weeks gestation (Table II).

Infants who succeeded on CPAP were about 3 weeks more mature and weighed about 300 g more than those who failed (Table III). Median 1-minute Apgar scores were significantly lower in the ventilator-started group than in the CPAP-started group (2 vs 6) but median 5-minute scores were similar (7 vs 8). The decision to apply mechanical ventilation (vs starting nasal CPAP) was made during the first several minutes of life (probably within the first minute) and was based mainly on the degree of depression of the newborn rather than on size or maturity. Results of the first ABG, usually performed within the first hour of life, differed sharply between those who were initially ventilated and those who were started on CPAP but not between those who succeeded and those who failed CPAP. However, the level of respiratory support required to obtain these gases was not the same: the medians of

PaO₂/FIO₂ and A-a DO₂ differed significantly in a continuum between groups.

Ventilator-started infants were about 30 times more likely to have received positive pressure, via a bag and mask, at delivery than infants who were started on CPAP (91% vs 24%; OR = 29.9, 95% CI [8.8, 102]). Those who had endotracheal intubation and ventilation at delivery were overwhelmingly more likely to remain in the ventilator-started group (91% vs 2%, OR = 433, 95% CI [98, 1908]). The proportion of infants judged to have radiographic evidence of severe RDS was significantly higher for infants who were ventilator-started than for infants who were CPAP-started (63% vs 25%, OR = 4.9, 95% CI [2.3, 10.7]). Eighty-one percent (47/58) of cases of severe RDS in the CPAP-started group occurred among those who ultimately failed CPAP. The mean and median times to early CPAP failure were 18.4 hours (±SD 14.0 hours) and 16 hours, respectively. The mean and median

Table IV. Adjusted odds ratios for mortality and morbidities by respiratory care groups

Outcome factor	Ventilator-started: CPAP-failure		CPAP-failure: CPAP-success	
	AOR [95% CI]	P value	AOR [95% CI]	P value
Pneumothorax	2.06 [0.82, 5.15]	.06	5.23 [1.60, 17.12]	.003
CLD (any severity)	1.83 [0.85, 3.94]	.06	2.77 [1.50, 5.11]	<.001
CLD (moderate-severe)	0.83 [0.19, 3.68]	.91	2.32 [0.69, 7.83]	.09
PDA (Symptomatic)	0.40 [0.22, 0.75]	.002	0.95 [0.58, 1.57]	.42
PDA (ligation)	0.88 [0.39, 2.01]	.38	1.36 [0.71, 2.59]	.17
Necrotizing enterocolitis (clinical diagnosis)	0.82 [0.27, 2.47]	.36	1.35 [0.53, 3.45]	.27
ROP (All grades)	0.78 [0.32, 1.88]	.29	1.25 [0.68, 2.32]	.24
ROP (photocoagulation)	0.44 [0.10, 1.90]	.14	0.96 [0.36, 2.54]	.47
IVH (all grades)	1.83 [1.03, 3.47]	.03	1.79 [1.03, 3.12]	.02
IVH (grade III-IV)	2.71 [1.29, 5.67]	<.001	2.20 [1.03, 4.69]	.02
Death	4.50 [2.08, 9.71]	<.001	7.21 [2.55, 20.45]	.001

Only survivors to eligibility of complication included in counts. Logistic model of outcome factor regresses against respiratory support modality controls for PMA, SGA, and presence of severe RDS on initial chest x-ray. AOR, adjusted odds ratio.

FIO₂ requirement at the time of CPAP failure were 0.66 (SD 0.2) and 0.67, respectively. Mean ABG values at the time of failure for infants failing CPAP were pH = 7.15 (SD 0.10), PaCO₂ = 69 mmHg (SD 19), PaO₂ = 57 mmHg (SD 22). A blood culture taken at birth was positive in two infants successfully maintained on CPAP and two infants in the ventilator started group.

In a multivariate analysis controlling for PMA and SGA, the adjusted OR and 95% CI for association with early CPAP failure were 2.37 [1.02, 5.52] for PPV at delivery, 2.91 [1.30, 6.55] for A-a DO₂ >180 mmHg, and 6.42 [2.75, 15.0] for severe RDS on the initial chest x-ray.

Mortality and Morbidities

Death occurred in 21 of 32 (66%) of ventilator-started infants and 20 of 229 (9%) of CPAP-started infants. Mortality in the CPAP-failure group was 18 of 55 (33%), and the mortality in the CPAP-success group was 2 of 174 (1%). Periventricular leukomalacia was noted only in one survivor, an infant in the CPAP failure group. Among survivors, the median duration of oxygen therapy differed significantly between the ventilator-started and the CPAP-started groups (50 days [17, 83] vs 3.0 days [2.1, 3.9], respectively, *P* = .003) but not between the ventilator-started group and the CPAP failure group (35 days [20, 51], *P* = .863).

The adjusted OR for the logistic regression models with mortality and morbidity variables as outcomes are given in Table IV. The models were controlled for PMA, SGA, and presence of severe RDS on the initial chest x-ray. Only infants who survived to eligibility for the complication were included in the analyses. CLD and IVH (any grades) were progressively more likely to be associated with ventilator-started than CPAP-failing infants and CPAP-failing than CPAP-succeeding infants. PDA was more common among CPAP-started than ventilator-started infants. Significantly higher rates of mortality, pneumothorax, CLD (all grades), IVH (all grades and grades 3 and 4) were associated with CPAP failure compared with CPAP success.

Surfactant Administration

No infant who succeeded on CPAP in the study received replacement surfactant. The proportion of infants who received surfactant in the ventilator-started group was equal to that in the CPAP failure group (53% vs 51%, OR = 1.1, 95% CI [0.5, 2.6]). Those infants with severe RDS by chest x-ray were more likely to receive surfactant (OR = 4.5, 95% CI [1.8, 11.4]). Infants in the CPAP failure group who received surfactant were those who failed earlier (11.8 hours [SD 10.3] vs 25.1 hours [SD 14.3], *P* <.001). There was no positive or negative significant association between receipt of surfactant and any of the adverse outcomes, including mortality, pulmonary hemorrhage, PTX, CLD, PDA requiring ligation, IVH, severe IVH, ROP (any grade), severe ROP (requiring photocoagulation), necrotizing enterocolitis, or the duration of oxygen therapy. The power to detect possible associations between surfactant administration and any these complications within each respiratory care group was insufficient.

Prediction of Early CPAP Failure

The dichotomous variables birth weight ≤750 g, PMA <26 weeks, and A-a DO₂ >180 mmHg maximized the specificity and sensitivity of birth weight, PMA, and A-a DO₂ to predict early CPAP failure. Early CPAP failure rates for these variables were 50%, 55%, and 51%, respectively. Only 53% of CPAP-started infants with radiographic evidence of severe RDS failed CPAP. These failure rates are equivalent to the positive predictive values of the individual tests. There was no improvement in positive predictive values when these criteria were used in combination.

DISCUSSION

Progress in neonatal intensive care is closely related to improvements in the management of respiratory failure in small infants. Current modalities of ventilatory assistance range from CPAP to various modes of mechanical ventilation.

The advent of less invasive methods of delivering CPAP to infants with RDS is associated with reduced need for intubation and mechanical ventilation and a lower incidence of CLD.^{1,15-16} The clinical outcomes for infants who succeed on CPAP are excellent, with low rates of mortality, IVH, ROP requiring photocoagulation, and lower neurodevelopmental sequelae in school-age children who had been VLBW infants managed with respiratory strategy that minimizes ventilatory intervention.^{15,17-22} Although many retrospective studies attest to the effectiveness of bubble nasal CPAP in the management of RDS in preterm infants,^{6,17-19,23-28} no published randomized prospective controlled trial compares the use of CPAP with other management strategies applied at birth.

At the Children's Hospital of New York, bubble nasal CPAP delivered with Hudson[®] prongs (Hudson Respiratory Care Inc., Temecula, Calif) is the initial ventilatory support modality for all spontaneously breathing infants regardless of PMA or birth weight. In our study, 76% of spontaneously breathing VLBW infants (birth weight \leq 1250 g) were managed successfully with nasal CPAP. Even at the lowest PMA (23-26 weeks), CPAP was successful in about half of the infants.

Few studies have examined factors that might predict CPAP failure in VLBW infants. In a study from Malaysia of infants with moderate or severe RDS, septicemia and pneumothorax during CPAP therapy were found to be significantly associated with failure of CPAP in preterm infants <37 weeks.²⁹ More than half of infants in this study were on bubble nasal CPAP using Hudson[®] nasal prongs. In our study, we chose to examine data that could be collected as close as possible to the time of birth to attempt to predict failure and design alternative management strategies that could usefully be applied early in the course of the disease. We found that the factors associated with early CPAP failure were those related to the small birth size (birth weight \leq 750 g), immaturity (PMA <26 weeks), severity of RDS (as indicated by A-a DO₂ >180 mmHg and severe RDS on the initial chest x-ray) and need for PPV at delivery. These factors essentially define a "small, sick baby" who may be somewhat depressed at birth. Although each of these factors was strongly associated with early CPAP failure, none had a positive predictive value above 55%; all were relatively poor predictors of failure even in the lowest birth weight and gestation age ranges included in the study. Part of the difficulty with predicting CPAP failure may involve the difficulty in predicting severity of RDS at birth. The median failure time was 16 hours of age; perhaps if we had chosen a slightly later time (but one still early enough to give rescue surfactant effectively), for example, at 4 to 6 hours of age, to collect our data, the PPV of associated factors might have been higher. The higher morbidity/mortality among CPAP failures could reflect either the overall poor health condition of the infant that is associated with adverse sequelae or the stress of a CPAP trial that predisposes to poor outcomes.

Several small studies have demonstrated improved respiratory outcomes when surfactant administration has been followed by extubation to CPAP at birth,³⁰⁻³² and even when surfactant has been administered at a median age of 18 hours.²³

None of the infants in our study who succeeded on CPAP received surfactant; among those who failed CPAP, surfactant was given only after CPAP failure and treatment with mechanical ventilation, and only then if the oxygen requirement stabilized at FIO₂ \geq 0.60. The fact that only half of our inborn infants in the ventilator-started and CPAP failure groups received surfactant is at variance with generally accepted practice. Our practice of giving a trial of CPAP to all spontaneously breathing VLBW infants with respiratory distress regardless of their birth weight and length of gestation limited the use of early surfactant to those infants who received endotracheal intubation and mechanical ventilation at birth. However, two thirds of infants with severe RDS by x-ray received surfactant, and three quarters of the surfactant given was administered to this group. Although we found that surfactant receipt was not associated with any reduction in the rates of mortality or complications in the groups of infants who either failed CPAP or were initially ventilated, our observational study was not designed or powered to examine outcomes related to surfactant receipt. Nor is it possible to compare our surfactant-related outcomes with those of infants at other institutions who received different patterns of surfactant administration and ventilatory management.^{30,33} Whether or not infants at risk for early CPAP failure are better off being treated initially with mechanical ventilation and surfactant is a question that only a prospective, randomized controlled trial can settle. Such a trial might be performed in a group that has about equal odds of CPAP success and failure, that is, in infants with a birth weight \leq 750 g or PMA <26 weeks in our study.

It may be useful to discuss briefly the kind of questions that have been addressed by our study that a controlled trial will not need to answer. Given that essentially every infant who could have been possibly started on CPAP received this modality, our observational, retrospective study is adequate to examine the circumstances and outcomes of early CPAP failure. Our study also defines the "outer limits" of complication rates in the CPAP failure group. That is, if infants who failed CPAP fared worse in any important outcome category than the group of very small, very sick babies who required PPV/endotracheal intubation in the delivery room and subsequent mechanical ventilation, then it might be wrong to use CPAP in any infant with a reasonable chance of failure. We found that mortality and complication rates were significantly lower among those failing CPAP than among infants who were ventilator-started, controlling for gestation and initial severity of RDS, but worse than for infants who succeeded on CPAP. This is modest but essential reassurance.

We would like to acknowledge the editorial assistance of Dr. Karl Schulze.

REFERENCES

1. Polin RA, Sahni R. Newer experience with CPAP. *Semin Neonatol* 2002;7:379-89.
2. Goldsmith JP, Karotkin EH, eds. *Assisted Ventilation of the Newborn*. 3rd ed. WB Saunders; 1996.
3. Kallapur S, Ikegami M. The surfactants. *Am J Perinatol* 2000;17:335-43.

4. Attar MA, Donn SM. Mechanisms of ventilator-induced lung injury in premature infants. *Semin Neonatol* 2002;7:353-60.
5. Jobe AH, Ikegami M. Prevention of bronchopulmonary dysplasia. *Curr Opin Pediatr* 2001;13:124-9.
6. Jacobsen T, Gronvall J, Petersen S, Andersen GE. "Minitouch" treatment of very low-birth-weight infants. *Acta Paediatr* 1993;82:934-8.
7. Wung JT. Respiratory management for low-birth-weight infants. *Crit Care Med* 1993;21:S364-5.
8. Mark SP, Croughan-Minihane MS, Kilpatrick SJ. Chorioamnionitis and uterine function. *Obstet Gynecol* 2000;95:909-12.
9. Lubchenko LO, Hansman C, Dressler M, Boyd E. Intrauterine growth as estimated from liveborn birth-weight data at 24 to 42 weeks of gestation. *Pediatrics* 1963;32:793-800.
10. Bancalari E. Changes in the pathogenesis and prevention of chronic lung disease of prematurity. *Am J Perinatol* 2001;18:1-9.
11. Bancalari E, Claure N, Sosenko IR. Bronchopulmonary dysplasia: changes in pathogenesis, epidemiology and definition. *Semin Neonatol* 2003;8:63-71.
12. Kero PO, Makinen EO. Comparison between clinical and radiological classification of infants with the respiratory distress syndrome (RDS). *Eur J Pediatr* 1979;130:271-8.
13. Wilcox RR. Confidence intervals in the one sample case. In: Introduction to robust estimation and hypothesis testing. San Diego: Academic Press; 1997. p. 69-89.
14. Hsu JC. Multiple Comparisons: Theory and Methods. London: Chapman & Hall; 1996.
15. Gittermann MK, Fusch C, Gittermann AR, Regazzoni BM, Moessinger AC. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birth weight infants. *Eur J Pediatr* 1997; 156:384-8.
16. Lundstrom KE. Initial treatment of preterm infants: continuous positive airway pressure or ventilation? *Eur J Pediatr* 1996;155:S25-9.
17. Joris N, Sudre P, Moessinger A. Early application of CPAP in newborns with post-menstrual age below 34 weeks lowers intubation rate and shortens oxygen therapy without altering mortality and morbidity. *Schweiz Med Wochenschr* 2000;130:1887-93.
18. Espagne S, Hascoet JM. Noninvasive ventilation of premature infants. *Arch Pediatr* 2002;9:1100-3.
19. Narendran V, Donovan EF, Hoath SB, Akinbi HT, Steichen JJ, Jobe AH. Early bubble CPAP and outcomes in ELBW preterm infants. *J Perinatol* 2003;23:195-9.
20. Robertson NR. Early nasal CPAP reduces the need for intubation in VLBW infants. *Eur J Pediatr* 1998;157:438.
21. Sanocka U, Durkin M, Chiroboga C, Kuban K, Hinton V, VanMarter L, et al. Variations in respiratory management of VLBW infants: Effects on long-term outcomes. *Ped Res* 2002;51:289A.
22. Topp M, Uldall P, Greisen G. Cerebral palsy births in eastern Denmark, 1987-90: implications for neonatal care. *Paediatr Perinat Epidemiol* 2001;15: 271-7.
23. Verder H, Robertson B, Greisen G, Ebbesen F, Albertsen P, Lundstrom K, et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish Multicenter Study Group. *N Engl J Med* 1994;331:1051-5.
24. Kamper J, Wulff K, Larsen C, Lindequist S. Early treatment with nasal continuous positive airway pressure in very low-birth-weight infants. *Acta Paediatr* 1993;82:193-7.
25. De Klerk AM, De Klerk RK. Nasal continuous positive airway pressure and outcomes of preterm infants. *J Paediatr Child Health* 2001;37:161-7.
26. Guerrini P, Brusamento S, Rigon F. Nasal CPAP in newborns with birth weight under 1500 g. *Acta Biomed Ateneo Parmense* 2000;71: 447-52.
27. Jonsson B, Katz-Salamon M, Faxelius G, Broberger U, Lagercrantz H. Neonatal care of very-low-birth weight infants in special-care units and neonatal intensive-care units in Stockholm. Early nasal continuous positive airway pressure versus mechanical ventilation: gains and losses. *Acta Paediatr Suppl* 1997;419:4-10.
28. Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birth weight infants: spontaneous breathing or intubation? *Pediatrics* 1999;103:961-7.
29. Boo NY, Zuraidah AL, Lim NL, Zulfiqar MA. Predictors of failure of nasal continuous positive airway pressure in treatment of preterm infants with respiratory distress syndrome. *J Trop Pediatr* 2000;46:172-5.
30. Blennow M, Jonsson B, Dahlstrom A, Sarman I, Bohlin K, Robertson B. Lung function in premature infants can be improved: surfactant therapy and CPAP reduce the need of respiratory support. *Lakartidningen* 1999;96:1571-6.
31. Merran AT (IFDAS study group). Early nasal continuous positive airway pressure with prophylactic surfactant for neonates at risk of RDS. The IFDAS multi-center randomized trial. *Pediatr Res* 2002;51:379A.
32. Verder H, Albertsen P, Ebbesen F, Greisen G, Robertson B, Bertelsen A, et al. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. *Pediatrics* 1999;103:E24.

SHORT- AND LONG-TERM CARDIOVASCULAR EFFECTS OF MIXED AMPHETAMINE SALTS EXTENDED RELEASE IN CHILDREN

ROBERT L. FINDLING, MD, JOSEPH BIEDERMAN, MD, TIMOTHY E. WILENS, MD, THOMAS J. SPENCER, MD, JAMES J. MCGOUGH, MD, FRANK A. LOPEZ, MD, AND SIMON J. TULLOCH, MD ON BEHALF OF THE SLI381.301 AND .302 STUDY GROUPS

Objective To assess the short- and long-term cardiovascular effects of once-daily treatment with a mixed amphetamine salts extended-release formulation (MAS XR; Adderall XR[®]) in children age 6 to 12 years with attention-deficit/hyperactivity disorder (ADHD).

Study design Short-term cardiovascular effects were assessed during a 4-week, double-blind, randomized, placebo-controlled, forced-dose-titration study of once-daily 10, 20, and 30 mg MAS XR (n = 580). Long-term cardiovascular effects were assessed in 568 subjects during a 2-year, open-label extension study of MAS XR (10 to 30 mg/day). Resting sitting blood pressure and pulse were measured at baseline and weekly during the short-term study, then monthly during long-term treatment.

Results Changes in blood pressure, pulse, and QT interval corrected by Bazett's formula (QTcB) in children receiving MAS XR were not statistically significantly different than those changes seen in children receiving placebo during short-term treatment. Mean increases in blood pressure after 2 years of MAS XR treatment (systolic, 3.5 mm Hg; diastolic, 2.6 mm Hg) and pulse (3.4 bpm) were clinically insignificant, and there was no apparent dose-response relationship.

Conclusions Cardiovascular effects of short- and long-term MAS XR were minimal during short- and long-term MAS XR treatment at doses of ≤ 30 mg/day in otherwise healthy children. (*J Pediatr* 2005;147:348-54)

Attention-deficit/hyperactivity disorder (ADHD) is a serious neurobehavioral disorder and one of the most prevalent chronic health conditions in children, affecting up to 10% of school-age youth in the United States.^{1,2} Psychostimulant medications are known to reduce the core symptoms of hyperactivity, impulsivity, and inattention. Stimulants are considered among first-line medication therapy for ADHD.³⁻⁶ Many once-daily long-acting stimulant formulations have been developed to simplify the dosage regimen for subjects with ADHD. These include Adderall XR[®], a mixed amphetamine salts extended-release (MAS XR) formulation (50% immediate-release beads, 50% extended-release beads).

The available extended-release stimulant formulations each have unique pharmacokinetic and pharmacodynamic profiles, but all stimulants have sympathomimetic effects that can lead to increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) and pulse at therapeutic doses.⁷ However, the cardiovascular effects of immediate-release (IR) amphetamine and methylphenidate (MPH) formulations that have been documented in children and adolescents appear to be modest. In a scientific statement released in 1999, the American Heart Association recommended no specific cardiovascular monitoring for children and adolescents receiving IR stimulant medications (eg, dextroamphetamine, MPH, pemoline).⁷ Rapport and Moffit⁸ reviewed the cardiovascular effects of short-term treatment with MPH IR and reported pulse increases of 3 to 10 bpm,

See editorial, p 287.

From the University Hospitals of Cleveland, Cleveland, Ohio; Massachusetts General Hospital, Boston, Massachusetts; UCLA Neuropsychiatric Institute, Los Angeles, California; Children's Developmental Center, Maitland, Florida; and Shire Pharmaceutical Development Inc., Rockville, Maryland.

Presented in part at the 50th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, Miami Beach, Florida.

Drs. Findling, Biederman, Wilens, Spencer, McGough, and Lopez are consultants to Shire Pharmaceutical Development, Inc. Dr. Tulloch is an employee of Shire Pharmaceutical Development, Inc.

Submitted for publication Sep 21, 2004; last revision received Jan 28, 2005; accepted Mar 4, 2005.

Reprint requests: Robert L. Findling, MD, University Hospitals of Cleveland, 11100 Euclid Avenue, Cleveland, OH 44106-5080. E-mail: Robert.Findling@uhhs.com.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.03.014

ADHD	Attention-deficit/hyperactivity disorder	MAS XR	Mixed amphetamine salts extended-release formulation
AE	Adverse event		
ANOVA	Analysis of variance	MPH	Methylphenidate
DBP	Diastolic blood pressure	QTcB	QT interval corrected by Bazett's formula
ECG	Electrocardiogram	SBP	Systolic blood pressure
IR	Immediate release		

SBP increases of 3.3 to 8 mm Hg, and DBP increases of 1.5 to 14 mm Hg. In one of the largest studies systematically assessing the cardiovascular effects of stimulants in young people, clinically insignificant effects on blood pressure and pulse (increases of < 5 mm Hg and < 5 bpm) occurred with 5-, 10-, and 15-mg once-daily doses of mixed amphetamine salts (MAS) IR (Adderall®) and 5-, 10-, and 15-mg twice-daily doses of MPH IR.⁹ In the only published report of long-term cardiovascular effects associated with an extended-release (XR) stimulant formulation, Wilens et al¹⁰ reported small increases in blood pressure and pulse (increases < 3 mm Hg and < 4 bpm) during a 12-month study of osmotic-release MPH in children with ADHD.

Herein we present an analysis of cardiovascular data collected from 6- to 12-year-old children with ADHD, most of whom began MAS XR treatment during a large, well-controlled, short-term study of MAS XR and continued treatment in a 2-year, open-label extension study.^{11,12} We hypothesized that MAS XR would have no clinically significant effect on pulse or blood pressure during short- or long-term treatment.

METHODS

Subjects and Study Design

Subjects who participated in the open-label extension study were previously enrolled in 1 of 2 double-blind, placebo-controlled MAS XR studies. One was a 4-week (1-week placebo washout and 3 weeks of active treatment), multicenter, randomized, double-blind, parallel-group, placebo-controlled, outpatient study of once-daily MAS XR (10, 20, or 30 mg) or placebo in 580 children age 6 to 12 years with ADHD.¹¹ The other was a 6-week, randomized, double-blind, crossover analog classroom study of 3 doses of once-daily MAS XR (10, 20, and 30 mg), placebo, and an active control (MAS IR 10 mg) in 51 children age 6 to 12 years with ADHD.¹³ Of the 568 children who continued treatment in the 2-year long-term study, most (n = 525) participated in the outpatient study and 43 participated in the analog classroom study. Only cardiovascular data from the 4-week outpatient and the 2-year open-label extension studies are presented here.

To be eligible for the open-label extension study, subjects were required to complete either the analog classroom or outpatient study without any clinically relevant adverse events (AEs), or to have withdrawn from either study for reasons other than AEs. Subjects were boys and girls age 6 to 12 years with blood pressure and pulse in the normal range (as judged by the investigator) who satisfied the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria for a primary diagnosis of ADHD, combined or hyperactive-impulsive type,¹⁴ as required by the previous short-term studies.^{11,13} Subjects were required to be in good health. Children were recruited into the short-term studies using a combination of advertising and distribution of information about study participation at local outpatient clinics. All study procedures and informed consent/assent forms were approved by the

institutional review board at each participating research site. Parents or caregivers provided written consent for their child's enrollment after receiving both written information and an oral explanation of the study procedures, and subjects age 7 years and older provided written assent for study participation.

Children were ineligible to participate in the short- or long-term studies if they were incapable of following the study instructions or had a comorbid psychiatric diagnosis (eg, psychosis, bipolar illness, pervasive developmental disorder, severe obsessive-compulsive disorder, severe depressive or severe anxiety disorder), history of seizure, hypersensitivity to MAS, hyperthyroidism, or glaucoma. Prohibited concomitant medications in all studies included anticonvulsant drugs, clonidine, guanfacine, and any medications that may have affected blood pressure, pulse, or central nervous system performance.

Dosing

The short-term outpatient study design used a dose-escalation regimen for the MAS XR treatment groups in which subjects were assigned treatment to 1 of 4 arms: placebo, a 10-mg MAS XR group, a 20-mg MAS XR group, or a 30-mg MAS XR group. After a 1-week placebo washout, all children received MAS XR 10 mg for the first treatment week, those assigned to the 20-mg and 30-mg groups received 20 mg for the second week, and those assigned to the 30-mg group received 30 mg for the third week. Regardless of the dose received in previous short-term studies, MAS XR was initiated at 10 mg once daily every morning for the long-term open-label study. Upward dose adjustments were allowed weekly during the first month of the open-label study, then at any monthly clinic visit for the duration of the study. Dose adjustments were allowed in 10-mg increments (maximum dose, 30 mg/day) based on clinical judgments of optimal effectiveness and tolerability. For most subjects who continued in the long-term study (n = 568), the baseline visit was the final study visit of the previous 6-week analog classroom study or the 4-week outpatient study.

Cardiovascular Measures

Cardiovascular measures included resting sitting SBP and DBP and resting sitting pulse rate. Blood pressures were measured in the same arm by the same study personnel using the same cuff (either manual or automated), after the subject had been seated for at least 3 minutes at every study visit. Measurements were taken at baseline and weekly during the short-term study. During the long-term study, cardiovascular measurements were taken at baseline (or at the last visit of the short-term study), weekly during the first month, and then monthly up to 24 months. Blood pressure and pulse measurements preceded venipunctures in all studies. The timing of vital sign assessment relative to medication administration was not standardized; however, most clinic visits were likely to have occurred within 12 hours of the morning MAS XR dose.

Electrocardiogram (ECG) measurements were performed using a 12-lead ECG. For the short-term study,

Table I. Demographic and baseline characteristics for the subjects in the long-term study*

Characteristic	Safety population (n = 568)
Age, mean ± SD (years)	8.7 ± 1.8
6 to 8, n (%)	264 (46)
9 to 12+, n (%)	304 (54)
Gender, n (%)	
Boys	442 (78)
Girls	126 (22)
Race, n (%)	
White	412 (73)
Black	67 (12)
Hispanic	53 (9)
Other	24 (4)
Weight (kg), mean ± SD (range)	33.5 ± 11.5 (16.4–93.6)
Height (cm), mean ± SD (range)	134.4 ± 11.4 (104.1–170.2)
ADHD diagnosis, n (%)	
Combined	518 (91)
Hyperactive-impulsive	27 (5)
Inattentive (protocol deviation)	11 (2)
Comorbidity, n (%)	
Yes	168 (30)
No	388 (68)
ADHD treatment before enrollment in previous short-term studies, n (%)	
Stimulant	353 (62)
Amphetamine only	44 (8)
Methylphenidate only	79 (14)
Not specified	230 (40)
Other treatment	8 (1)
No prior medication treatment	177 (31)
None listed	30 (5)

SD, standard deviation.

Numbers may not add up to 100% because of missing data or rounding.

*525 of the 568 (92%) subjects enrolled in the long-term study had participated in the short-term study.

ECGs were completed at the screening or baseline visit (baseline ECG) and again at the final study visit (after 3 weeks of MAS XR treatment or at the final clinic visit if a participant withdrew from the study early). For the long-term study, the endpoint ECG from the short-term study was considered the baseline ECG; repeat ECGs were conducted at months 12, 18, and 24. A central laboratory was used to evaluate all ECG readings (Covance Central Diagnostics, Reno, Nev). If the central laboratory deemed an ECG abnormal, then the study investigator evaluated the abnormality for clinically significant changes from baseline. If the investigator considered the ECG abnormality to be clinically significant, then a pediatric cardiologist reviewed it. Bazett's formula was used to correct QT intervals for heart rate effect (QTcB).¹⁵ Blood pressure, pulse, and ECGs were not assessed with respect to time of medication dose administration or assessed in relation to peak blood levels of MAS in any study.

Statistical Analyses

All analyses were performed using SAS statistical software, version 6.12 or higher (SAS Institute, Cary, NC).¹⁶ A mixed-model analysis of variance (ANOVA) was conducted to determine the effect of MAS XR treatment and time on blood pressure and pulse in the short-term study. Group mean ECG interval measurements at endpoint were compared with baseline values using a 1-way ANOVA of MAS XR versus placebo. For the long-term study, monthly group mean changes in blood pressure and pulse were compared with baseline values using a 1-sample *t* test. Multiple linear regression analysis was used to explore the relationship between changes in vital signs and mean MAS XR dose (mg/kg) over time. Mean ECG interval measurements at 12, 18, and 24 months were compared with mean baseline measurements using a paired *t* test. Alpha was set at 0.05 for all analyses.

Categorical Analyses

For both the short- and long-term studies, a categorical analysis of blood pressure and pulse was completed to determine whether any blood pressure or pulse measurements exceeded normal values for age. Because no a priori limits were specified that would dictate withdrawal from the study or a change in MAS XR dose, limits of normality were defined post hoc. For pulse, values > 140 bpm are likely to be clinically significant.^{17,18} For blood pressure, the upper limits were defined by the 95th percentile values for 12-year-old children (> 130 mm Hg for SBP and > 90 mm Hg for DBP).¹⁹ Any QTcB value exceeding 500 msec was considered clinically significant.²⁰ Adverse event data were reviewed to determine whether any subjects discontinued from either study or required a change in MAS XR dose because of a cardiovascular AE.

RESULTS

Of the 568 subjects who continued MAS XR treatment in the long-term study, 525 (92%) participated in the short-term study (Table I).

Short-Term MAS XR Treatment

In the short-term study, 173 of 210 subjects (82%) randomized to receive placebo and 336 of 374 (90%) subjects randomized to receive MAS XR completed all 3 active treatment weeks. There were no serious cardiovascular AEs. Mean blood pressure and pulse for the placebo and 10-, 20-, and 30-mg MAS XR groups during the short-term study are presented by treatment week in Table II. The mixed-model ANOVA results indicate that short-term treatment with MAS XR 10, 20, or 30 mg/day had no statistically significant effect on SBP, DBP, or pulse rate. In addition, the ANOVA indicates no effect of MAS XR treatment over time. The number of subjects in the placebo group who had at least 1 SBP measurement > 130 mm Hg (n = 5) was similar to the number of subjects (n = 4) receiving any dose of MAS XR who had at least 1 potentially clinically important SBP measurement. Of these 4 subjects receiving MAS XR,

Table II. Blood pressure and pulse over time and by dose of MAS XR in the short-term study

Timepoint	Randomized treatment group			
	Placebo (n = 209) (mean ± SD)	MAS XR 10 mg (n = 129) (mean ± SD)	MAS XR 20 mg (n = 119) (mean ± SD)	MAS XR 30 mg (n = 123) (mean ± SD)
Baseline				
Diastolic BP (mm Hg)	63.2 ± 7.2	63.8 ± 7.5	64.4 ± 6.8	63.3 ± 7.8
Systolic BP (mm Hg)	103.4 ± 8.7	102.8 ± 10.6	103.0 ± 9.2	101.8 ± 10.4
Pulse (bpm)	86.7 ± 11.1	84.7 ± 11.2	86.6 ± 9.8	86.9 ± 11.8
Week 1				
Diastolic BP	64.3 ± 7.8	63.9 ± 7.2	64.2 ± 7.9	64.2 ± 7.3
Systolic BP	103.6 ± 9.8	101.6 ± 9.8	103.4 ± 10.4	103.2 ± 10.0
Pulse	86.4 ± 10.9	85.7 ± 11.8	84.5 ± 9.1	86.4 ± 11.2
Week 2				
Diastolic BP	62.7 ± 6.8	63.7 ± 7.0	64.2 ± 7.2	64.2 ± 7.4
Systolic BP	102.2 ± 8.4	103.3 ± 11.3	103.5 ± 9.6	102.3 ± 9.8
Pulse	86.4 ± 10.2	86.7 ± 11.4	85.2 ± 10.3	85.5 ± 11.6
Week 3				
Diastolic BP	62.7 ± 8.0	63.7 ± 7.6	63.6 ± 8.3	64.7 ± 7.2
Systolic BP	103.2 ± 10.6	103.1 ± 10.5	103.9 ± 9.5	103.9 ± 9.8
Pulse	86.0 ± 10.6	85.8 ± 10.2	85.5 ± 11.0	86.5 ± 11.8
ANOVA results				
	Treatment effect		Time effect	
Diastolic BP	$F_{3, 1610} = 1.29, P = .2765$		$F_{3, 1610} = 0.71, P = .5461$	
Systolic BP	$F_{3, 1610} = 0.28, P = .8399$		$F_{3, 1610} = 2.01, P = .1107$	
Pulse	$F_{3, 1606} = 0.63, P = .5925$		$F_{3, 1606} = 0.19, P = .9019$	

1 received 10 mg, 1 received 20 mg, and 2 received 30 mg. Most of the SBP measurements > 130 mm Hg ranged from 131 to 139 mm Hg; these measurements were sporadic and appeared to resolve spontaneously. Only 3 of the 9 subjects had more than 1 SBP measurement > 130 mm Hg; the highest recorded SBP was 152 mm Hg. No subjects had a DBP > 90 mm Hg or a pulse > 140 bpm during the short-term study. No subjects required a change in MAS XR dose or were discontinued from the short-term study because of cardiovascular AEs.

One-way ANOVA revealed no statistically significant differences between group mean ECG interval measurements for the MAS XR group compared with placebo. The change in mean QT interval at endpoint was 4.5 ± 24.9 msec for the placebo group, compared with 0.9 ± 27.3 msec for the MAS XR group ($P = .1244$). For ECG pulse, the mean change at endpoint was -1.0 ± 10.2 bpm for the placebo group, compared with 0.3 ± 11.7 bpm for the MAS XR group ($P = .2127$). The mean change at endpoint for the QTcB was 2.5 ± 20 msec for the placebo group, compared with 2.1 ± 18.8 msec for the MAS XR group ($P = .8244$). Mild ECG abnormalities were observed in 10 subjects at endpoint. The findings for 5 children ($n = 1$ in the placebo group, $n = 2$ in the 10-mg group, $n = 1$ in the 20-mg group, and $n = 1$ in the 30-mg group) were deemed clinically insignificant or a normal age-dependent variant by a pediatric cardiologist. In the other

5 cases, the following abnormalities were noted on initial ECG: nonspecific T-wave abnormality ($n = 1$), minor R-wave intraventricular conduction delay and a nonspecific T-wave abnormality ($n = 1$), P-wave terminally negative in V_1 and an R-on-T variant ($n = 1$), nonspecific ST-segment abnormality ($n = 1$), and premature atrial systole ($n = 1$). For these 5 subjects, a repeat ECG (interpreted by a pediatric cardiologist) was normal. No subject had a QTcB interval measurement > 500 msec during short-term treatment.

Long-Term MAS XR Treatment

Of the 568 subjects who enrolled in the extension study, 277 completed 2 years of MAS XR treatment. Changes in mean blood pressure (Figure 1) and pulse (Figure 2) during up to 2 years of MAS XR treatment were modest and not clinically significant. Some monthly mean blood pressure and pulse values were statistically significantly different than mean baseline values ($P < .05$), but the magnitude of mean changes from baseline and from month to month were very small. The initial MAS XR dose for all subjects enrolled in the long-term study was 10 mg/day, and the mean dose ranged from 20 mg/day at 3 months to 22 mg/day at 24 months. Most subjects received 20 mg/day for the duration of the long-term study.

The correlation between height and skeletal age has been found to be stronger than the correlation between height and chronological age; also, physical maturation, not

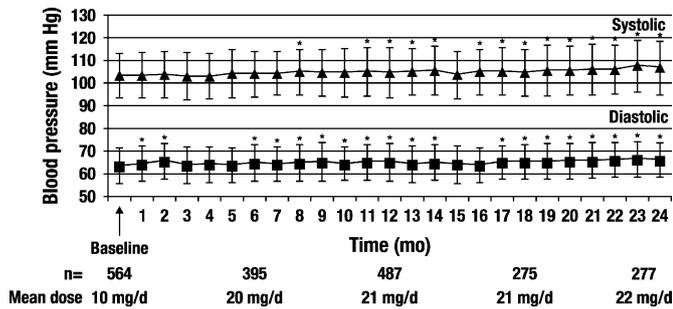


Figure 1. Change in mean blood pressure (± 1 standard deviation) over time during long-term MAS XR treatment. * $P < .05$ compared with mean baseline value by 1-sample t test.

chronologic age, has been found to be the most powerful determinant of normal blood pressure.²¹ The implication of these findings is that physical characteristics such as height and skeletal maturation are more consistent predictors of BP than is chronologic age. Therefore, we analyzed the relationship between vital signs and both mg/kg dose and height over time during this 2-year study. The mean MAS XR dose was 0.62 mg/kg at month 12, 0.59 mg/kg at month 18, and 0.58 mg/kg at month 24. There was no relationship between the weight-corrected dose of MAS XR and change in either blood pressure or pulse. For DBP, a model that included mg/kg dose and height accounted for much of the variation in DBP over time ($R^2 = .76$; $P = .0009$), but the modest increase in DBP over time was affected by the increase in height ($P = .0057$) and not by the magnitude of the mg/kg dose ($t = 1.10$, $P = .3351$). Results were similar for SBP ($R^2 = .74$; $P = .0012$), and the small increase in SBP over time was related to increased height ($P = .0026$) but not to weight-adjusted dose ($P = .1075$). As might be expected,²² a model including height and mg/kg dose did not explain much of the variation in pulse over time ($R^2 = .38$; $P = .0888$); there was no relationship between pulse and height ($P = .8200$) or pulse and mg/kg dose ($P = .3474$).

Clinically important blood pressure and pulse measurements were sporadic and appeared to resolve spontaneously during long-term MAS XR treatment. Only 2% (11/568) of the subjects in the long-term study had a DBP measurement > 90 mm Hg at any visit during up to 2 years of MAS XR treatment. Of these 11 subjects, only 1 had 2 DBP measurements > 90 mm Hg (98 and 95 mm Hg); the other 10 subjects had only 1 measurement > 90 mm Hg. The highest recorded DBP during long-term MAS XR treatment was 98 mm Hg. Less than 10% of subjects had a SBP measurement > 130 mm Hg ($n = 50$). Of these 50 subjects, most were in the range of 131 to 139 mm Hg; only 6 subjects (1%) had more than 5 SBP measurements > 130 mm Hg throughout the long-term study. One SBP measurement in the 140 to 149 mm Hg range was recorded for 4 subjects, 1 measurement > 150 mm Hg was recorded for 3 subjects, and the highest SBP measurement (166 mm Hg) was recorded for 1 subject on 1 occasion. No subjects had a pulse > 140 bpm at any clinic visit during long-term treatment. The mean MAS XR dose for the 517 subjects (91%) with no potentially

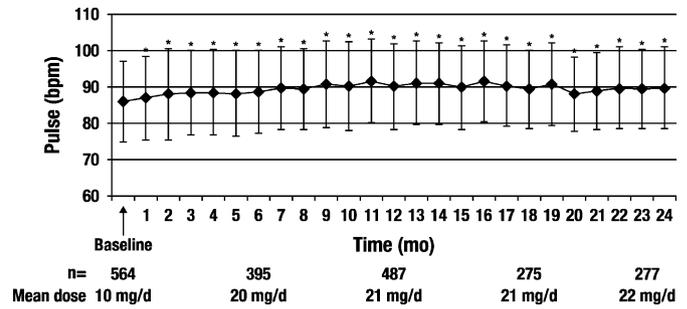


Figure 2. Change in mean pulse (± 1 standard deviation) over time during long-term MAS XR treatment. * $P < .05$ compared with mean baseline value by 1-sample t test.

clinically important blood pressure or pulse measurements was 19 mg/day, and this dose was similar to the mean dose for subjects with 1 or more clinically important SBP (20 mg/day) or DBP (24 mg/day) measurements.

There were no serious cardiovascular AEs during long-term treatment with MAS XR. Study medication was discontinued because of cardiovascular AEs for only 4/568 subjects (0.7%) during long-term MAS XR treatment. Of these 4 subjects, 1 subject experienced tachycardia (108 bpm at baseline, 101 to 121 bpm during long-term treatment) that was considered both moderate in severity and related to MAS XR 20 mg/day. Two subjects experienced intermittent chest pain that resolved and was considered mild in severity and possibly related to MAS XR 20 mg/day for both subjects. One of the subjects with intermittent chest pain was receiving MAS XR for 9 months; sinus bradycardia was noted on baseline ECG but was not considered clinically significant, and premature ventricular contractions were noted at the end-of-study ECG. There is no follow-up ECG for this subject. The other subject with intermittent chest pain was receiving MAS XR 20 mg for 12 months; sinus arrhythmia and sinus bradycardia were noted at the baseline ECG, and sinus bradycardia for age was noted at the end-of-study ECG. A fourth subject experienced hypertension (130/90 mm Hg after 12 months) that was considered of moderate severity by the investigator and possibly related to MAS XR 10 mg/day; sinus arrhythmia was noted on baseline ECG, and sinus bradycardia (pulse 63 bpm) was noted on end-of-study ECG. This subject was not hypertensive at baseline and had no past medical history or any medical comorbidities indicating a predisposition to hypertension. At a 1-month follow-up visit, this subject's blood pressure was 115/80 mm Hg. MAS XR was discontinued for these 4 subjects, and all were withdrawn from the long-term study.

Group mean QTcB values were not statistically significantly different from baseline after 12, 18, and 24 months of MAS XR treatment. The changes in the mean QT interval from baseline of -9.4 ± 28.1 msec at month 12 and -6.0 ± 27.5 msec at month 24 are statistically significant at $P < .001$, but are not clinically important and are likely explained by the slight increases in pulse at months 12 and 24 (Table III). No subject had a QTcB interval measurement > 500 msec during long-term treatment. The most common ECG abnormalities

Table III. Summary of ECG measurements during long-term treatment with MAS XR

ECG measurement (mean ± SD)	Timepoint in long-term study			
	Baseline (n = 565)	Month 12 (n = 409)	Month 18 (n = 277)	Month 24 (n = 276)
QT interval (msec)	343.2 ± 27.8	333.4 ± 28.5 (P < .001)	339.0 ± 28.6 (P = NS)	337.2 ± 28.3 (P < .001)
Pulse (bpm)	82.7 ± 11.7	87.0 ± 11.9 (P < .001)	85.2 ± 12.1 (P = NS)	86.7 ± 11.5 (P < .001)
QTcB interval (msec)	400.1 ± 17.2	398.5 ± 16.4 (P = NS)	400.9 ± 17.1 (P = NS)	402.4 ± 17.1 (P = NS)

NS, not statistically significant compared with baseline value by the paired *t* test; SD, standard deviation.

recorded after 24 months of MAS XR treatment included sinus arrhythmia (n = 25), ST-T wave abnormalities (n = 5), and poor anterior R-wave progression (n = 4), none of which were considered clinically significant.

DISCUSSION

Previous investigations of the cardiovascular effects of IR stimulants in youth with ADHD indicated clinically insignificant increases in blood pressure and pulse that were typically dose related. In a systematic comparison of the cardiovascular effects of equipotent doses of MPH IR and MAS IR in 195 youths, Findling et al⁹ observed a linear dose-response relationship between blood pressure and pulse and MAS IR or MPH IR dose during short-term treatment. The changes in blood pressure and pulse during long-term MAS XR treatment were similar in magnitude to changes previously reported for MAS IR and MPH IR treatment, but no dose-response relationship was apparent during short- or long-term MAS XR treatment. The lack of a dose-response relationship in the MAS XR studies may be attributable to differences in timing between dosing and cardiovascular measurements in the studies, or to differences between IR and XR formulations. Findling et al⁹ instructed participants to ingest the dose of MAS IR or MPH IR approximately 2 hours before each clinic visit, whereas participants in the MAS XR studies were instructed to take the medication once daily in the morning regardless of scheduled clinic visits. The MAS XR capsule contains a 1:1 ratio of IR beads, which release the first half of the dose on ingestion, and XR beads, which begin to release the second half of the dose 4 hours later. However, interindividual variations of the pharmacokinetic properties of MAS XR have been reported,²³ and variation in peak stimulant blood levels may affect both blood pressure and pulse. In addition, blood pressure and pulse of children and adolescents are affected by circadian rhythms, so precision is lost if measurements are not qualified by the time of day,²⁴ and pulse values vary widely in all age groups.²²

The cardiovascular effects of short- and long-term MAS XR appear to be similar both in magnitude and lack of a dose-response relationship to the effects of long-acting MPH formulations in children with ADHD. An analog classroom comparison of osmotic-release MPH (Concerta[®]) and MPH XR capsules (Metadate[®] CD) evaluated changes in pulse and

BP and found no dose-response relationship for BP or pulse changes during a 3-week study.²⁵ No statistically significant changes in DBP occurred during the 12-hour analog classroom day; the mean increase in SBP was 5.2 mm Hg for osmotic-release MPH at 7.5 hours postdose (mean decrease of 0.6 mm Hg in the MPH XR group); and the mean increase in pulse was ~9 bpm for both medications 1.5 hours postdose. In a 1-year open-label extension study of osmotic-release MPH in 432 children age 6 to 13 years, mean changes in blood pressure and pulse were strikingly similar to the changes observed during long-term MAS XR treatment. Osmotic-release MPH treatment produced statistically significant, but clinically insignificant, changes in SBP (3.3 mm Hg), DBP (1.5 mm Hg), and pulse (3.9 bpm) at endpoint compared with off-drug baseline values, but there was no clear dose relationship despite a 25% increase in mean dose from month 1 to month 12 (from 1.0 to 1.25 mg/kg/day).¹⁰

The results presented here are from a post hoc analysis of short- and long-term studies that were designed to demonstrate the overall safety and efficacy of MAS XR. Subjects enrolled in the short-term study (and who continued in the long-term study) were required to have normal blood pressure and pulse on study entry, and subjects with hypertension or any other cardiovascular disorder were excluded from participation. The effects of short- or long-term use of MAS XR in subjects with significant cardiovascular dysfunction or blood pressure abnormalities are unknown. The study population included only children age 6 to 12 years who were not receiving any other medications that could affect blood pressure or pulse. The lack of standardization in the timing of medication administration and assessment of vital signs could have resulted in measurements after the medication effects had worn off, but this is unlikely given that few clinic visits would have occurred more than 12 hours after dosing.

The pattern of blood pressure, pulse, and ECG changes observed during both short- and long-term studies indicates that MAS XR has an acceptable cardiovascular safety profile in healthy children. The cardiovascular effects of MAS XR appear minimal, and because the effects are similar to those reported for IR stimulants and the American Heart Association recommendation that routine cardiovascular monitoring is not indicated for IR formulations, it appears that specific cardiovascular monitoring during either short- or long-term MAS XR treatment also is not indicated.

REFERENCES

1. American Academy of Pediatrics, Committee on Quality Improvement and Subcommittee on Attention-Deficit/Hyperactivity Disorder. Clinical practice guideline: diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. *Pediatrics* 2000;105:1158-70.
2. Rowland AS, Umbach DM, Stallone L, Naftel J, Bohlig M, Sandler DP. Prevalence of medication treatment for attention deficit-hyperactivity disorder among elementary school children in Johnston County, North Carolina. *Am J Public Health* 2002;92:231-4.
3. Bradley C. The behavior of children receiving benzedrine. *Am J Psychiatry* 1937;94:577-85.
4. American Academy of Pediatrics, Committee on Quality Improvement and Subcommittee on Attention-Deficit/Hyperactivity Disorder. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. *Pediatrics* 2001;108:1033-44.
5. American Academy of Child and Adolescent Psychiatry. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. *J Am Acad Child Adolesc Psychiatry* 2002;41:26S-49S.
6. Zito JM, Safer DJ, dosReis S, Gardner JF, Magder L, Soeken K, et al. Psychotropic practice patterns for youth: a 10-year perspective. *Arch Pediatr Adolesc Med* 2003;157:17-25.
7. Gutgesell H, Atkins D, Barst R, Buck M, Franklin W, Humes R, et al. AHA Scientific Statement: cardiovascular monitoring of children and adolescents receiving psychotropic drugs. *J Am Acad Child Adolesc Psychiatry* 1999;38:1047-50.
8. Rapport MD, Moffitt C. Attention deficit/hyperactivity disorder and methylphenidate: a review of height/weight, cardiovascular, and somatic complaint side effects. *Clin Psychol Rev* 2002;22:1107-31.
9. Findling RL, Short EJ, Manos MJ. Short-term cardiovascular effects of methylphenidate and Adderall. *J Am Acad Child Adolesc Psychiatry* 2001;40:525-9.
10. Wilens TE, Biederman J, Lerner M, and the Concerta® Study Group. Effects of once-daily osmotic-release methylphenidate on blood pressure and heart rate in children with attention-deficit/hyperactivity disorder: results from a one-year follow-up study. *J Clin Psychopharmacol* 2004;24:36-41.
11. Biederman J, Lopez FA, Boellner SW, Chandler MC. A randomized, double-blind, placebo-controlled, parallel-group study of SLI381 (Adderall XR) in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2002;110:258-66.
12. McGough JJ, Biederman J, Wigal SB, Lopez FA, McCracken JT, Zhang Y, et al. Long-term tolerability and effectiveness of once-daily mixed amphetamine salts (Adderall XR®) in children with ADHD. *J Am Acad Child Adolesc Psychiatry* 2005;44(6): in press.
13. McCracken JT, Biederman J, Greenhill LL, Swanson JM, McGough JJ, Spencer TJ, et al. Analog classroom assessment of a once-daily mixed amphetamine formulation, SLI381 (Adderall XR), in children with ADHD. *J Am Acad Child Adolesc Psychiatry* 2003;42:673-83.
14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington, DC: American Psychiatric Association; 1994.
15. Bazett H. An analysis of time relations of electrocardiogram. *Heart* 1920;7:353-70.
16. SAS Institute, Inc. SAS/STAT software: changes and enhancements through release 6.12. Cary, NC: SAS Institute, Inc.; 1997.
17. Garson A, Bricker JT, McNamara DG. The science and practice of pediatric cardiology. Philadelphia: Lea & Febiger; 1990.
18. Park MK, ed. Pediatric cardiology for practitioners. Chicago: Year Book Medical Publishers; 1998.
19. Gunn VL, Nechyba C, eds. The Harriet Lane handbook: a manual for pediatric house officers. 16th ed. Philadelphia: Mosby; 2002.
20. Committee for Proprietary Medicinal Products. The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. London: The European Agency for the Evaluation of Medicinal Products, Human Medicines Evaluation Unit; December 17, 1997. (Report no. CPMP/986/96).
21. Rosner B, Princeas RJ, Loggie JMH, Daniels SR. Blood pressure nomograms for children and adolescents, by height, sex, and age, in the United States. *J Pediatr* 1993;123:871-86.
22. Davignon A, Rautaharju P, Boisselle E, Soumis F, Megelas M, Choquette A. Normal ECG standards for infants and children. *Ped Cardiol* 1979/80;1:123-31.
23. McGough JJ, Biederman J, Greenhill LL, McCracken JT, Spencer TJ, Posner K, et al. Pharmacokinetics of SLI381 (Adderall XR), an extended-release formulation of Adderall. *J Am Acad Child Adolesc Psychiatry* 2003;42:684-91.
24. Massin MM, Macyns K, Withofs N, Ravet F, Gérard P. Circadian rhythm of heart rate and heart rate variability. *Arch Dis Child* 2000;83:179-82.
25. Swanson JM, Wigal SB, Wigal T, Sonuga-Barke E, Greenhill LL, Biederman J, et al. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study). *Pediatrics* 2004;113(3 pt 1):e206-16. Available at <http://pediatrics.org/cgi/content/full/113/3/e206>.

REGIONAL VARIATION IN ICU CARE FOR PEDIATRIC PATIENTS WITH ASTHMA

SUSAN L. BRATTON, MD, MPH, FOLAFOLUWA O. ODETOLA, MD, JAMIE MCCOLLEGAN, BS, MICHAEL D. CABANA, MD, MPH, FIONA H. LEVY, MD, MBA, AND HEATHER T. KEENAN, MDCM, PHD

Objective To determine adherence to guidelines for severe asthma care and evaluate regional variability in practice among pediatric intensive care units (PICU).

Study design A retrospective cohort study of children treated for asthma in a PICU during 2000 to 2003.

We utilized the Pediatric Health Information System (PHIS) database to identify patients and determine use of asthma therapies when patients did not improve with standard therapy (inhaled β -agonists and systemic corticosteroids).

Results Of 7125 children studied, 59% received inhaled anticholinergic medications. Use of other therapies included systemic β -agonists (n = 1841 [26%]), magnesium sulfate (n = 1521 [21%]), methylxanthines (n = 426 [6%]), inhaled helium-oxygen gas mixture (heliox) (n = 740 [10%]), and endotracheal intubation with ventilation (n = 1024 [14%]). Use of therapies varied by census region. Over half the patients (n = 524) who received ventilation did so for ≤ 1 day. Adjusted for severity of illness, use of mechanical ventilation varied significantly by census division; however, much of the variation was among children ventilated for ≤ 1 day.

Conclusion Adherence to national guidelines for use of inhaled anticholinergics among critically ill children is low, and marked variation in use of invasive ventilation exists. More explicit guidelines regarding indications for invasive ventilation may improve asthma care. (*J Pediatr* 2005;147:355-61)

Asthma remains the most common cause of hospitalization for children <15 years of age¹ and is a common reason for admission to a pediatric intensive care unit (PICU).² Acute care costs for asthma have been estimated to range from 35% to 78% of all asthma-related charges.^{3,4} Improved asthma diagnosis and management are recognized as both a national and international imperative.^{5,6} Strategies to alleviate the impact of asthma on patients and the healthcare system have included asthma self-management education, improved access to healthcare, and improved healthcare delivery through use of care guidelines.⁷

The Global Initiative for Asthma (GIA) with endorsements by the World Health Organization and the National Heart Lung and Blood Institute (NHLBI) issued the *Pocket Guide for Asthma Management and Prevention in Children*⁶ that includes a treatment flowchart for hospital-based care of asthma exacerbations. Although this guideline includes more potential treatments reserved for patients unresponsive to usual therapy and criteria regarding need for intensive care compared with prior NHLBI guidelines, the recommendations remain somewhat vague for treatment of the most severely ill patients.⁵

GIA recommendations regarding therapies for a severe exacerbation of asthma include inhaled β -agonists, inhaled anticholinergics, and intravenous glucocorticoids, with consideration of systemic administration of β -agonists and intravenous methylxanthines for children who are not improving. Finally mechanical ventilation is listed as a therapy to consider; however, no criteria are given for when it is appropriate to implement this support.

See related article, p 362.

From the University of Utah School of Medicine, Department of Pediatrics, Salt Lake City, Utah; the University of Michigan Health System, Department of Pediatrics; St Louis Children's Hospital Quality Management, St. Louis, Missouri; and the University of Texas Southwestern School of Medicine, Department of Pediatrics.

Submitted for publication Jan 12, 2005; last revision received Mar 9, 2005; accepted May 5, 2005.

Reprint requests: Dr Susan L. Bratton, 295 Chipeta Way, P.O. Box 581289, Salt Lake City, UT 84158-0289. E-mail: susan.bratton@hsc.utah.edu.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.05.008

APR-DRG	All patient refined-diagnostic related groups	NHLBI	National Heart Lung and Blood Institute
CHCA	Child Health Corporation of America	PICU	Pediatric intensive care unit
CMI	Case mix index	PHIS	Pediatric Health Information System
heliox	Inhaled helium-oxygen gas mixture	PRISM III	Pediatric risk of mortality
GIA	Global Initiative for Asthma	RRR	Relative risk ratio

To better understand national practice regarding therapies for severe asthma, we examined an administrative database, determining the therapies used in the management of patients with asthma admitted to a group of PICUs in the United States for patients who did and did not receive mechanical ventilation.

METHODS

Data Source

This study utilized data from a large, multi-institutional administrative database, the Pediatric Health Information System (PHIS). The PHIS database is maintained by the pediatric hospital members of the Child Health Corporation of America (CHCA), which currently includes 41 member hospitals.⁸ CHCA is a business alliance of pediatric hospitals that provides a range of products and services designed to reduce cost, increase revenue, and enhance the competitiveness of children's hospitals. The database contains member-specific standardized data on demographics, diagnoses, procedures, interventions, and outcomes for all pediatric patients admitted to each participating pediatric institution. Available data elements are abstracted and coded by the collaborating medical records departments using PHIS data quality guidelines including the following: standard demographic data, dates of service, and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).⁹ Data quality checks occur at member hospitals and again at the data coordination center. Routine monthly meetings occur to resolve discrepancies and prevent data errors. For this study, we extracted data for patients discharged from 2000 to 2003 who had been admitted to a PICU for treatment of acute asthma. Patients were included if they had had a primary diagnosis of acute asthma (ICD-9 code of 493.0-493.9) and had been charged for at least 1 day of PICU care. PHIS captures therapies and medications that generate charges to the patient. We included all children admitted to a PICU for treatment of acute asthma from 2000 to 2003.

Variables

Data on patient age, gender, race, payer, use of asthma medications and therapies, as well as charges and outcome were examined. Duration of invasive ventilation was calculated in calendar days and length of PICU, and hospital stay was based on daily census at midnight. Severity of illness was assessed by the case mix index (CMI) and all patient refined-diagnostic related groups (APR-DRG).^{10,11} APR-DRGs are the most widely used method for severity-of-illness and risk-of-mortality adjustment. Elements that determine the score include diagnosis and procedure codes, age, gender, status at discharge, and days on the ventilator. The CMI is based on primary and secondary diagnoses as well as procedures, including mechanical ventilation.

Outcome

We analyzed the use of specific medications (eg, inhaled ipratropium bromide, intravenous magnesium sulfate,

systemic administration of terbutaline, aminophylline, or theophylline, as well as the use of specific mechanical support heliox, noninvasive ventilation, or endotracheal intubation with invasive mechanical ventilation).¹²⁻¹⁶ The analysis focused on these medications and supportive therapies as they are typically utilized when patients do not improve in response to standard treatment of inhaled β -agonist and systemic corticosteroids. Both the presence of the given asthma therapy and duration of use in days were recorded.

Analysis

Hospitals were grouped into geographic regions based on US Census divisions ([Appendix](#)). The Pacific census division hospitals had the lowest use of mechanical ventilation and were used as the reference group. Rates of mechanical ventilation were determined, and compliance with recommendations for acute care management based on the GIA pathway⁶ was assessed for patients who received and those who did not receive invasive mechanical ventilation.

All statistical analyses were conducted using the Statistical Package of the Social Sciences, version 12.0 for Windows (SPSS Inc, Chicago, Ill). Data were expressed as medians (with 25th and 75th quartiles) or percentages. Data were compared using the χ^2 unadjusted relative risk ratio (RRR) with 95% CI and the Kruskal-Wallis H test with a Bonferroni adjustment for multiple pairwise comparisons. Binomial logistic models were analyzed to assess differences in OR for use of invasive ventilation by census division adjusting for factors including asthma therapies, APR-DRG severity category, and other potential confounding factors such as age, presence of infection, black race, and Medicaid insurance.^{2,16-18} Asthma therapies were coded as dichotomous variables. The data did not allow a determination of the sequence of asthma therapies; models that did not include asthma therapies also were assessed, and the estimates by census division were not substantially altered. Need for ventilation >1 day and ventilation \leq 1 day were separately evaluated with the same models to assess differences between census divisions for short duration of mechanical ventilation. Statistical significance was defined as $P < .05$.

RESULTS

Of 87,875 pediatric patients treated for asthma in a participating hospital during the study period, 7125 (8%) received care in a PICU. Selected demographic features of the PICU patients are shown in [Table I](#). One thousand twenty-four children (14%) received invasive ventilation. Use of mechanical ventilation differed by area of the country, as did severity of illness assessed by APR-DRG (highest severity score). Use of mechanical ventilation varied from 6% in the Pacific census division children's hospitals to 27% in the East North Central census division children's hospitals, whereas APR-DRG extreme severity of illness ranged from 4% in the West North Central to 22% in the Mountain division. Nineteen percent of patients with extreme

APR-DRG severity of illness grading received mechanical ventilation.

Compliance with the GIA pathway⁶ was assessed, stratified by use of invasive ventilation (Table II). Among patients who were not invasively ventilated, 3445 (57%) received inhaled anticholinergic medications. In addition to systemic corticosteroids and inhaled β -agonists, inhaled anticholinergic therapy is recommended as standard care of children with severe exacerbations.⁶ Among patients who received invasive ventilation, 748 (73%) received inhaled anticholinergic therapy, which was almost twice as likely compared with children not receiving invasive ventilation (RRR 1.9, 95% CI 1.7-2.2).

The GIA pathway recommends *consideration* of methylxanthines, systemic administration of β -agonists and magnesium sulfate for patients with severe exacerbations not improving from treatment with inhaled β -agonists, systemic corticosteroids, and inhaled anticholinergic therapy.⁶ Among non-intubated patients, 4% received methylxanthines, 26% received systemic administration of β -agonists, and 20% were treated with magnesium sulfate. There was significant variation by region for use of the medications (Table II). Among children who received invasive ventilation, 17% received methylxanthines, 23% were treated with systemic β -agonists, and 32% received magnesium sulfate. Use of methylxanthines or magnesium sulfate was approximately twice as high among children treated with invasive ventilation (RRR 2.1; 95% CI [1.8-2.4] and RRR 1.7; 95% CI [1.5-2.0], respectively); the use of systemic β -agonists however, did not differ significantly between children who received invasive mechanical ventilation and those who did not. Among children who received invasive mechanical ventilation, only 404 (40%) received one additional therapy recommended for consideration by the GIA pathway when patients were not improving with first line therapy. One hundred forty-eight (15%) received two therapies, and 14 (0.8%) received all three. Children not treated with invasive mechanical ventilation received significantly fewer of these therapies: 2272 (37%) received one, 368 (6%) were treated with two, and 16 (0.3%) got all three.

The use of heliox or noninvasive ventilation for severe asthma exacerbations are not addressed in the GIA pathway. Nevertheless, five hundred and fifty-three (9%) children who were not intubated received heliox gas, and 142 (2%) received noninvasive ventilation (Table II). One-hundred eighty-seven patient received heliox and invasive ventilation. The database does not distinguish patients who received heliox via the ventilator; however, clinical experience suggests this is a rare event given concerns regarding errors in measured tidal volume with heliox gas mixtures,¹⁹ suggesting that the vast majority likely received heliox via a mask rather than an endotracheal tube. Forty-three children received both noninvasive and invasive ventilation. The order for mechanical support cannot be determined for children who received both methods of ventilation on the same day. Seventy-seven percent of the children who received noninvasive ventilation did not go on to require invasive ventilation.

Table I. PICU patients with acute asthma

	N = 7125 n (%)
Males	4279 (60)
Age (years)	5.9 (2.4, 10.7 years)
(median, 25 th and 75 th quartiles)	
Race	
White	3483 (49)
Black	2926 (41)
Other	543 (8)
Missing	173 (2)
Medicaid Insurance	3471 (49)
Region of United States	
Mid Atlantic	352 (5)
South Atlantic	939 (13)
East North Central	1362 (19)
East South Central	709 (10)
West North Central	776 (11)
West South Central	873 (12)
Mountain	120 (2)
Pacific	1994 (28)
HMO	35% (26, 44%)
(median, 25 th and 75 th quartiles)	
Length of PICU stay (days)	1 (1, 2)
(median, 25 th and 75 th quartiles)	
Length of hospital stay (days)	3 (2, 5)
(median, 25 th and 75 th quartiles)	
Hospital charges (\$)	11,900 (7725, 19,615)
(median, 25 th and 75 th quartiles)	
Hospital Outcome	
Discharged alive	7056 (99)
Transferred	43 (0.6)
Died	24 (0.3)

HMO, health maintenance organization.

The GIA pathway states that use of sedative medications in the treatment of patients with asthma is contraindicated.⁶ Despite these recommendations, 218 (4%) non-intubated patients received ketamine, an anesthetic medication often selected for its bronchodilatory properties (Table II). The use of other sedative agents was not assessed. Among invasively ventilated patients 37% received ketamine sometime during the PICU stay, such use varying significantly by census division.

Among the 1024 patients who received mechanical ventilation, the median duration of ventilation was 1 day and the interquartiles are 1 and 4. Median charges were \$26,798 (25th and 75th quartile: \$13,909, 58,959, respectively) which was significantly greater than hospital charges among children who did not receive invasive ventilation (median \$10,909, 25th and 75th quartile: \$7323, \$17,141, respectively). The multivariate models regarding risk of invasive ventilation and US Census division are presented in Table III. Risk of mechanical ventilation varied significantly when hospitals were grouped by US Census division, despite adjustment for APR-DRG severity of illness and other confounding factors. The time

Table II. Regional variation in ICU therapies for asthma

	Patients Who Did Not Receive Mechanical Ventilation, N = 6101						
	N (%) Ip	N (%) Xanthine	N (%) Terbutaline	N (%) MagSO ₄	N (%) Heliox	N (%) Bipap	N (%) Ketamine
Mid Atlantic (n = 288)	241 (84)	5 (2)	45 (16)	40 (14)	137 (48)	0	23 (8)
South Atl (n = 780)	621 (80)	0	169 (22)	290 (37)	55 (7)	2 (0.3)	59 (8)
E N Central (n = 989)	765 (77)	70 (7)	215 (22)	162 (16)	106 (11)	108 (11)	39 (4)
E S Central (n = 612)	213 (35)	72 (12)	204 (33)	83 (14)	73 (12)	7 (1)	22 (4)
W N Central (n = 714)	397 (57)	55 (8)	146 (20)	66 (9)	8 (1)	1 (0.1)	5 (1)
W S Central (n = 751)	258 (35)	23 (3)	202 (27)	228 (30)	52 (7)	17 (2)	46 (6)
Mountain (n = 93)	83 (89)	22 (24)	18 (19)	11 (12)	2 (2)	0	3 (3)
Pacific (n = 1874)	867 (47)	13 (1)	604 (32)	313 (17)	120 (6)	7 (0.4)	21 (1)
Total	3445 (57)	260 (4)	1603 (26)	1193 (20)	553 (9)	142 (2)	218 (4)

	Patients Who Did Receive Mechanical Ventilation, N = 1024						
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Mid Atlantic (n = 64)	47 (73)	4 (6)	12 (19)	21 (33)	43 (67)	0	35 (55)
South Atl (n = 159)	129 (81)	1 (0.6)	33 (21)	67 (42)	48 (30)	1 (0.6)	72 (45)
E N Central (n = 373)	332 (89)	97 (26)	76 (20)	75 (20)	39 (11)	25 (7)	92 (25)
E S Central (n = 97)	40 (41)	33 (34)	28 (29)	34 (35)	6 (6)	11 (11)	38 (39)
W N Central (n = 62)	29 (47)	12 (19)	15 (24)	21 (34)	4 (7)	1 (2)	22 (36)
W S Central (n = 122)	73 (60)	7 (6)	30 (25)	56 (46)	8 (7)	2 (1)	63 (52)
Mountain (n = 27)	25 (93)	16 (59)	7 (26)	4 (15)	1 (4)	0	18 (67)
Pacific (n = 120)	73 (61)	6 (5)	37 (31)	50 (42)	38 (32)	3 (3)	41 (34)
Total	748 (73)	176 (17)	238 (23)	328 (32)	187 (18)	43 (4)	382 (37)

All therapies differed significantly by region except systemic terbutaline use among ventilated patients.

Atl, Atlantic; *Bipap*, bi-level positive airway pressure; *EN Central*, East North Central; *ES Central*, East South Central; *Heliox* = helium-oxygen gas mixture; *Ip*, ipratropium bromide; *MagSO₄*, magnesium sulfate; *WN Central*, West North Central; *WS Central*, West South Central; xanthine; aminophylline or theophylline.

course for institution of asthma therapies and their relationship to invasive ventilation could not be determined more finely than by calendar day, hence any association between the treatments and the risk of invasive ventilation cannot be evaluated in this analysis. The only therapy that was associated with a significantly lower risk of invasive mechanical ventilation was noninvasive ventilation, which appeared to decrease the risk (OR 0.5; 95% CI 0.3-0.8). However, the use of noninvasive ventilation was associated with substantial hospital charges, and median charges did not differ significantly from children who received invasive ventilation (median \$26,367, 25th and 75th quartile \$18,497, \$37,006, respectively).

Five hundred twenty-four (51%) patients received mechanical ventilation for ≤1 day, which suggested regional differences for relatively brief duration of mechanical ventilation. To evaluate this regional variation in duration of mechanical ventilation several comparison were made. First, children ventilated ≤1 day were compared with children who were not ventilated; then children ventilated >1 day were compared with those ventilated for ≤1 day (Table III). Comparison of the models regarding risk of invasive ventilation for >1 day showed that risk associated with census divisions was more similar, and greater regional variability in the risk of invasive ventilation was found among patients ventilated ≤1 day. For instance, the risk of invasive ventilation

for severe asthma in children's hospitals in the East North Central census division for ≤1 day was 11 times greater compared with the Pacific census division (OR 11.4; 95% CI [7.9-16.4]); however, use of ventilation >1 day was less than half (OR 0.4; 95% CI [0.2-0.7]).

Only 24 patients (0.3% of PICU patients) died. Factors significantly associated with death included older age and use of invasive mechanical ventilation (OR 20.4; 95% CI [6.9-59.9]). Region, use of other therapies, race, and Medicaid insurance were not significantly related to death.

DISCUSSION

Our study found large variability in use of asthma therapies for pediatric patients with severe exacerbations. Variability was noted in the administration of recommended medications such as inhaled anticholinergics as well as medications with less convincing evidence to support their use for severe exacerbations (eg, methylxanthines and systemic β-agonists). There was marked regional variation in the use of inhaled heliox, noninvasive mechanical ventilation, and invasive mechanical ventilation in the United States.

The use of inhaled anticholinergics and the avoidance of sedative agents are endorsed by the GIA.⁶ Surprisingly, >60% of children treated in two census divisions did not receive

Table III. Risk of invasive ventilation: ventilation 1 day and >1 day

	All Ventilation		Ventilation ≤ 1 day		Ventilation > 1 day	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)*
Region of Country						
Mid Atlantic	2.0	(1.3-3.0)	3.1	(1.8-5.5)	0.8	(0.4-1.6)
South Atlantic	2.8	(2.1-3.8)	2.9	(1.8-4.5)	1.3	(0.7-2.3)
East North Central	6.4	(4.9-8.3)	11.4	(7.9-16.4)	0.4	(0.2-0.7)
East South Central	2.7	(1.9-3.8)	5.7	(3.7-8.7)	0.3	(0.1-0.5)
West North Central	1.7	(1.1-2.4)	2.3	(1.4-3.7)	0.6	(0.3-1.2)
West South Central	2.2	(1.6-3.0)	1.4	(0.8-2.3)	2.7	(1.4-5.2)
Mountain	1.9	(1.0-3.3)	2.4	(1.1-45.0)	0.9	(0.4-2.5)
Pacific	1	reference	1	reference	1	reference

Models are adjusted for Medicaid insurance, African-American race, gender, presence of infection, age, APR-DRG (categorical 1-4), and use of asthma therapies.

Presence of infection was significantly associated with increased risk of “all” ventilation ($P < .0001$) and ventilation >1 day ($P < .0001$), whereas Black race was significantly associated with decreased risk of “all” ventilation ($P < .0001$) and ventilation ≤ 1 day ($P < .0001$) but not ventilation >1 day. Medicaid insurance was associated with increased risk of “all” ventilation ($P = .013$).

*The comparison group for this model is patients ventilated ≤ 1 day, whereas the comparison for the other two models are patients who are not ventilated.

inhaled anticholinergics for severe asthma exacerbations. Although adherence overall was not optimal, our results are similar to a report by Salmero et al among adult patients treated in French emergency departments for asthma.²⁰ Ketamine use among children not treated with mechanical ventilation was 3.6%. We did not evaluate use of other sedative and analgesic medications. Use of sedation among patients in respiratory distress should only occur in a well-monitored setting and only for select cases. As expected, use of ketamine among children receiving mechanical ventilation was significantly higher compared with non-intubated patients.

Systemic β-agonists were the most commonly used medications (26%) among therapies recommended for *consideration* among children not responding to treatment with inhaled β-agonists, inhaled anticholinergics, and systemic corticosteroids in the GIA pathway. However, use of systemic β-agonists was not more common among children treated with mechanical ventilation, although the endotracheal tube and ventilator circuit increase dead space and are known to severely limit delivery of inhaled medications.²¹⁻²³

Methylxanthines were used in only 6% of patients. The Cochrane meta-analysis concludes that addition of methylxanthines to asthma care for status asthmaticus improves asthma symptoms within the first 24 hours; however, use is limited by adverse effects such as nausea and vomiting.²⁴ One large randomized study of children with severe asthma showed that the addition of methylxanthines significantly decreased the risk of mechanical ventilation.²⁵ However, no large studies have shown whether systemic β-agonists or methylxanthines are more effective as an additional therapy for severe asthma.²⁶

There was remarkably low use of second tier therapies to prevent intubation and mechanical ventilation. Less than half of patients treated with mechanical ventilation received a second tier therapy, and only 15% received two. Mechanical ventilation for asthma severely limits delivery of inhaled medications and is fraught with potential complications thus

intensive efforts should be made to avoid invasive ventilation when possible.

Neither heliox nor noninvasive ventilation is recommended in the GIA pathway⁶; however, these supportive therapies were used to treat severe asthma exacerbations in a minority of cases (10% and 3%, respectively). Unlike methylxanthines and systemic β-agonists, heliox is nontoxic; however, helium’s effect on gas flow can be limited by hypoxia and need for higher concentrations of inspired oxygen. Trials regarding heliox have been small, and the beneficial effects appear to be most pronounced in the first hour of therapy.¹³ Heliox gas mixtures have been shown to improve aerosol delivery among both intubated and non-intubated patients.^{27,28}

Noninvasive ventilation was first described for use in adults with chronic obstructive pulmonary disease.²⁹ However, recent reports have shown that noninvasive ventilation can be used in both adults and children with asthma. It decreases subjective work of breathing,^{15,30} and aerosol therapy can be delivered via the mask.³¹ Use of noninvasive ventilation was not widespread in our study. Patient charges were similar to those who received invasive mechanical ventilation, which is not surprising given the need for attentive respiratory care services as well as ventilator charges. One of the study limitations is that we did not have conventional severity of illness scores other than the APR-DRG severity of illness, and likewise we did not have blood gas values to assess disease severity to adequately compare patients treated with noninvasive ventilation with similar patients who did not receive noninvasive ventilation. In most PICU settings, noninvasive ventilation is attempted before intubation; we assume that it was predominately used in this manner at the study hospitals. However, noninvasive ventilation also may be utilized to prevent respiratory failure after extubation.³² In the multivariate analysis, we found that use of noninvasive ventilation was significantly associated with decreased risk of

invasive ventilation; however, given our data limitations, this finding should be considered preliminary and deserves further study.

A striking finding pertained to the varied use of mechanical ventilation. The unadjusted rates of invasive ventilation ranged from 6% to 27% of patients with asthma treated in different census division PICUs. This may be explained by severity of illness and other processes of care such as the availability of respiratory step-down units. However, over half of the patients were ventilated ≤ 1 day, and after adjustment for severity of illness (APR-DRG) and other potential confounding factors, there were significant and large associations between risk of short use of invasive ventilation and census divisions. Our finding of large variation in practice mirrors a study by Roberts et al,² who found that among 14 PICUs the average use of mechanical ventilation for asthma patients was 17%; however, such use varied significantly by center with the use of mechanical ventilation ranging from 3% to 47%. After adjustment for worst respiratory rate, age, and pediatric risk of mortality (PRISM III) score,³³ children at high-use centers were two and a half times more likely to receive ventilation compared with low-use centers.

Our study finding that over half the patients who were intubated received ventilation for ≤ 1 day suggests either rapid improvement in clinical status or alternatively a lower clinical threshold for institution of invasive ventilation early in the patient's acute care. More detailed guidelines regarding clinical parameters that suggest need for intubation and invasive ventilation along with provider education may help decrease such large variation in practice. Preventing unnecessary intubation and invasive ventilation is important because it is potentially harmful and expensive.^{34,35} If neuromuscular blocking agents are required for a prolonged period, patients may develop myopathy.³⁶

Studies that utilize databases benefit from large sample size but have other limitations. We could not ascertain whether patients were intubated in the prehospital, emergency department or PICU setting: this knowledge would be helpful to target the appropriate group of providers for education regarding criteria for intubation among children with asthma. As therapies were recorded by date rather than time, we could not clearly determine the escalation order of asthma therapy in most cases. This makes inferences between therapies and risk of intubation impossible. Likewise we were unable to assess dose, so we can only report if a therapy was used, rather than if an optimal dose was utilized. Variability was reported by geographic region rather than hospital. Because one census region contained a single hospital we could not utilize a statistical model that adjusted for both hospital and region.

We did not have physiological data or standard risk of mortality scores such as PRISM or pediatric index of mortality³⁷ but rather had to rely on the APR-DRG severity of illness, which is increased in part by use of mechanical ventilation. Our findings mirror those of Roberts et al who did adjust for severity of illness with PRISM III.² Because of concern regarding use of the APR-DRG severity of illness (a 4-point classification of mild, moderate, severe, and extreme),¹⁰ models using the CMI

were evaluated, and the variability by census region remained and were of similar magnitude compared with the analysis with APR-DRG. We relied on charge information to capture medications and mechanical support. Therapies for which a charge was not generated would not be included and thus may be under reported. Finally we report on a sample of children's hospitals and thus the findings may not mirror care for all critically ill children with asthma. We report variability related to region that reflect hospital practices within that region; however, the point remains that asthma practice varies within the United States.

Our study shows large variability in asthma care for patients treated in PICUs at children's hospitals. Use of mechanical ventilation and noninvasive ventilation were associated with significantly greater costs, and half of patients who received invasive ventilation did so for ≤ 1 day. More detailed guidelines regarding escalation of therapy and when to initiate mechanical support may benefit this group of children. Many children who are treated with mechanical ventilation did not receive recommended inhaled anticholinergic therapy before intubation. There is need to clarify and better define asthma guidelines that relate to PICU care, particularly because adherence to asthma guidelines in outpatient settings has been shown to improve patient quality of life.^{38,39}

APPENDIX

United States Geographic Regions

New England: ME, NH, VT, MA, RI, CT

Mid Atlantic: NY, NJ, PA

South Atlantic: DE, MD, DC, VA, WV, NC, SC, GA, FL

East North Central: OH, IN, IL, MI, WI

East South Central: KY, TN, AL, MS

West North Central: MN, IO, MO, ND, SD, KS

West South Central: AR, LA, OK, TX

Mountain: MT, ID, WY, CO, NM, AZ, UT, NV

Pacific: WA, OR, CA, AK, HI

REFERENCES

1. McCormick MS, Kass B, Elixhauser A, Thompson J, Simpson L. Annual Report on Access to and Utilization of Health Care for Children and Youth in the United States: 1999. *Pediatrics* 2000;105:219-30.
2. Roberts JS, Bratton SL, Brogan TV. Acute severe asthma: differences in therapies and outcomes among pediatric intensive care units. *Crit Care Med* 2002;30:581-5.
3. Weiss KB, Gergen PJ, Hodgson TA. An economic evaluation of asthma in the United States. *N Engl J Med* 1992;326:469-73.
4. Lozano P, Fishman P, VonKorff M, Hecht J. Health care utilization and cost among children with asthma who were enrolled in a health maintenance organization. *Pediatrics* 1997;99:757-64.
5. National Heart Lung Blood Institute, National Asthma Education and Prevention Program. Practical guide for the diagnosis and management of asthma. [Based on the Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma]. Bethesda, MD: National Institutes of Health. US Department of Health and Human Services; 1997. Publ. No 97-4063.
6. Pocket Guide for Asthma Management and Prevention in Children, Global Initiative for Asthma. National Institutes of Health, 2003. p. 30. Available online at www.ginasthma.com (accessed October 9, 2004).

7. Lara M, Rosenbaum S, Rachelefsky G, Nicholas W, Morton SD, Emont S, et al. Improving childhood asthma outcomes in the United States: a blueprint for policy action. *Pediatrics* 2002;109:919-30.
8. Pediatric Health Information System (PHIS). Child Health Corporation of America. Available online at <http://www.chca.com/index.html> (accessed 10/12/04).
9. St Anthony's Softbound ICD-9 Code Book, 1997. Reston, VA: St Anthony Publishing; 1996.
10. 3M™ All Patient Refined DRG (APR-DRG) Software. Available online at http://www.3m.com/us/healthcare/his/products/coding/refined_drg.jhtml (accessed 12/31/04).
11. Description of methodologic and hospital specific factors affecting the calculation of a children's hospital DRG case mix index. NACHRI, Feb 6, 2001. Available online at <http://www.childrenshospitals.net/Template.cfm?Section=Search&Template=/Search/SearchDisplay.cfm> (accessed 11/21/04).
12. Rodrigo G, Pollack C, Rodrigo C, Rowe BH. Heliox for nonintubated acute asthma patients. *Cochrane Database Syst Rev* 2003;CD002884.
13. Ho AM, Lee A, Karmakar MK, Dion PW, Chung DC, Contardi LH. Heliox vs air-oxygen mixtures for the treatment of patients with acute asthma: a systematic overview. *Chest* 2003;123:882-90.
14. Kress JP, Noth I, Gehlbach BK, Barman N, Pohlman AS, Miller A, et al. The utility of albuterol nebulized with heliox during acute asthma exacerbations. *Am J Respir Crit Care Med* 2002;165:1317-21.
15. Thill PJ, McGuire JK, Baden HP, Green TP, Checchia PA. Noninvasive positive pressure ventilation in children with lower airway obstruction. *Pediatr Crit Care Med* 2004;5:408-9.
16. Bratton SL, Roberts JS, Watson RS, Cabana MD. Acute severe asthma: outcome and Medicaid insurance. *Pediatr Crit Care Med* 2002;3:234-8.
17. Brown R, Bratton SL, Cabana MD, Kaciroti N, Clark NM. Physician asthma education program improves outcomes for children of low income families. *Chest* 2004;126:369-74.
18. Altman DG. *Practical Statistics for Medical Research*. London: Chapman and Hall; 1992:410.
19. Tassaux D, Jolliet P, Thouret JM, Roesler J, Dorne R, Chevrolet JC. Calibration of seven ICU ventilators for mechanical ventilation with helium-oxygen mixtures. *Am J Respir Crit Care Med* 1999;160:22-32.
20. Salmeron S, Liard R, Elkharrat D, Muir J, Neukirch F, Ellrodt A. Asthma severity and adequacy of management in accident and emergency departments in France: a prospective study. *Lancet* 2001;25;358:629-35.
21. Crogan SJ, Bishop MJ. Delivery efficiency of metered dose aerosols given via endotracheal tubes. *Anesthesiology* 1989;70:1008-10.
22. Manthous CA, Hall JB. Administration of therapeutic aerosols to mechanically ventilated patients. *Chest* 1994;106:560-71.
23. Travers AH, Rowe BH, Barker S, Jones A, Camargo CA. The effectiveness of IV β -agonists in treating patients with acute asthma in the emergency department: a meta-analysis. *Chest* 2002;122L:1200-7.
24. Mitra A, Bassler D, Ducharme FM. Intravenous aminophylline for acute severe asthma in children over 2 years using inhaled bronchodilators. *Cochrane Database Syst Rev* 2001;CD001276.
25. Yung M, South M. Randomized controlled trial of aminophylline for severe acute asthma. *Arch Dis Child* 1998;79:405-10.
26. Roberts G, Newsom D, Gomez K, Raffles A, Saglani S, Begent J, et al. North West Thames Asthma Study Group. Intravenous salbutamol bolus compared with an aminophylline infusion in children with severe asthma: a randomised controlled trial. *Thorax* 2003;58:284-5.
27. Goode ML, Fink JB, Dhand R, Tobin MJ. Improvement in aerosol delivery with helium-oxygen mixtures during mechanical ventilation. *Am J Respir Crit Care Med* 2001;163:109-14.
28. Anderson M, Svartengren M, Bylin G, Philipson K, Camner P. Deposition in asthmatics of particles inhaled in air or helium-oxygen. *Am Rev Respir Dis* 1993;147:524-8.
29. Mehta S, Hill NS. Noninvasive ventilation. *Am J Respir Crit Care Med* 2001;163:540-77.
30. Meduri GU, Cook TR, Turner RE, Cohen M, Leeper KV. Noninvasive positive pressure ventilation in status asthmaticus. *Chest* 1996;110:767-74.
31. Chatmongkolchart S, Schettino GPP, Dillman C, Kacmarek RM, Hess DR. In vitro evaluation of aerosol bronchodilator delivery during noninvasive positive pressure ventilation: effect of ventilator settings and nebulizer position. *Crit Care Med* 2002;30:2515-9.
32. Meade M, Guyatt G, Sinuff T, Griffith L, Hand L, Toprani G, et al. Trials comparing alternative weaning modes and discontinuation assessment. *Chest* 2001;120(suppl 6):425S-37S.
33. Pollack MM, Patel KM, Ruttimann UE. The Pediatric Risk of Mortality III-Acute Physiology Score (PRISM III-APS): a method of assessing physiologic instability for pediatric intensive care unit patients. *J Pediatr* 1997;31:575-81.
34. Leatherman JW, Ravenscraft SA. Low measured auto-positive end-expiratory pressure during mechanical ventilation of patients with severe asthma: hidden auto-positive end-expiratory pressure. *Crit Care Med* 1996;24:541-6.
35. Williams TJ, Tuxen DV, Scheinkestel CD, Czarny D, Bowes G. Risk factors for morbidity in mechanically ventilated patients with severe asthma. *Am Rev Respir Dis* 1992;142:607-15.
36. Watling SM, Dasta JF. Prolonged paralysis in intensive care unit patients after use of neuromuscular blocking agents: a review of the literature. *Crit Care Med* 1994;22:884-93.
37. Slater A, Shann F, for the ANZICS Paediatric Study Group. The suitability of pediatric index of mortality (PIM), PIM2, the pediatric risk of mortality (PRISM), and Prism III for monitoring the quality of pediatric intensive care in Australia and New Zealand. *Pediatr Crit Care* 2004;5:447-54.
38. Committee on Quality of Health Care in America Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academy Press; 2001.
39. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJH, Pauwels RA, et al for the GOAL Investigators Group. *Am J Resp Crit Care Med* 2004;170:836-44.

PEDIATRICIANS' SCREENING URINALYSIS PRACTICES

COLIN M. SOX, MD, MS, AND DIMITRI A. CHRISTAKIS, MD, MPH

Objective To determine pediatricians' routine screening urinalysis practices.

Study design This was a survey of a nationally representative sample of pediatricians practicing in the U.S. regarding their screening urinalysis practices in childhood.

Results Of the 1502 pediatricians sampled, 653 eligible subjects participated, for an estimated response rate of 49.5%. The vast majority of participants (78%) routinely screen asymptomatic children with urinalysis in at least 1 age group. Pediatricians' screening urinalysis practice varies based on age group: 9% screen during infancy (<1 year), 60% screen during early childhood (1 up to 5 years), 55% screen during late childhood (5 to 12 years), and 58% screen during adolescence (13 to 20 years). The majority of pediatricians (58%) routinely screen more than 1 age group. Some 38% of the pediatricians surveyed believe that the overall health of children is improved by screening all asymptomatic children with urinalysis.

Conclusions Many pediatricians routinely conduct screening urinalysis during childhood, frequently at ages not recommended by the American Academy of Pediatrics. (*J Pediatr* 2005;147:362-5)

Office-based urinalyses can test urine for glucose, red blood cells, protein, and leukocytes. In the past, urinalysis was the most widely recommended screening test used for children in the United States.^{1,2} In both 1977 and 1992, the American Academy of Pediatrics (AAP) recommended that screening urinalysis be performed during 4 periods of a child's life: infancy, young childhood, late childhood, and adolescence.^{3,4} Debate about whether screening urinalysis should be routinely conducted on asymptomatic children⁵⁻⁷ led to a revision of these guidelines in 2000.⁸ The AAP now recommends that screening urinalyses be done routinely on 2 groups: 5-year-old children and sexually active adolescents.⁸

Given the recent attention that screening urinalysis has received, we were surprised to discover that little was known about pediatricians' routine screening urinalysis practices. Although it has been reported that pediatricians perform frequent screening urinalyses,^{5,6} to date no empirical study has examined pediatricians' routine practices or their beliefs about the importance of conducting screening urinalysis. Because attitudes toward a practice may influence clinicians' compliance with guidelines, we sought to determine both pediatricians' attitudes toward screening urinalysis and their routine screening urinalysis practices.

METHODS

Subjects

Seeking a random sample of pediatricians practicing general pediatrics in the United States, we recruited subjects from the American Medical Association (AMA) master file of licensed physicians. Compiled for the U.S. Department of Defense, this list is considered a complete collection of physicians' names, addresses, specialties, age, and sex, and is not limited to members of the AMA. From the 44,561 pediatricians with no secondary specialty listed in the master file in December 2001, 1502 were randomly selected for participation. We conducted this study using data collected with a questionnaire that we designed to address multiple research questions, including a trial investigating the effect of

See related article, p 355.

From the department of Ambulatory Care and Prevention, Center for Child Health Care Studies, Harvard Medical School and Harvard Pilgrim Health Care, Boston, Massachusetts and the Department of Pediatrics, University of Washington, Children's Hospital and Regional Medical Center and the Child Health Institute, Seattle, Washington.

Supported by funding from the Robert Wood Johnson Foundation and the Nesholm Family Foundation, Seattle, Washington.

Submitted for publication Nov 23, 2004; last revision received Feb 15, 2005; accepted May 5, 2005.

Reprint requests: Colin M. Sox, MD, MS, Center for Child Health Care Studies, Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, 133 Brookline Avenue, 6th Floor, Boston, MA 02115. E-mail: colin_sox@harvardpilgrim.org.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.05.009

AAP	American Academy of Pediatrics	USPSTF	United States Preventative Services Task Force
AMA	American Medical Association		

Table I. Subject characteristics

Variable	Number (total 653)	Percent (%)
Male	284	44
U.S. medical school graduate	516	80
Pediatric resident	100	16
Board certified in pediatrics	519	81
General pediatrician	521	80
Small primary practice	137	22
U.S. region	198	30
Northeast		
Southeast	119	18
Midwest	129	20
South	97	15
Mountain-Pacific	110	17

decision support on medical decision making (results to be reported separately). We chose a sample size of 1502 to ensure that the trial of decision support would be appropriately powered.

Survey Instrument

We developed a questionnaire and piloted it among a different group of 22 pediatricians. One of our goals for the questionnaire was to measure the subjects' reported practices and attitudes toward screening urinalysis. To measure practices, we asked all subjects to check the box next to each childhood age group for which they routinely conduct screening urinalysis on asymptomatic patients at least once: infancy (<1 year), early childhood (1 up to 5 years), older childhood (5 to 12 years), and/or adolescence (13 to 20 years). To measure attitudes, we asked subjects to check either "yes" or "no" in response to the following question: "Do you think that the overall health of children is improved by screening all children with urinalysis?" These 2 questions were asked of all subjects and were not part of the trial of decision support.

To collect information on subjects' training, we asked whether they were board-certified in pediatrics, a graduate of a medical school located in the United States, and currently in a pediatric residency program. We defined "foreign medical school graduate" as a graduate of a medical school located outside of the United States.

To collect information about practice, we asked subjects to report the percent of clinical time spent in general pediatrics and whether they worked in a practice that had 1 or 2 pediatricians or more. We defined a "small primary practice" as one whose primary practices included 1 or 2 pediatricians. We defined a "general pediatrician" as one who reported spending more than 80% of his or her clinical time in general pediatrics. We categorized subjects' location by U.S. region using the state of practice and regional definitions used by the National Cancer Data Base: northeast (CT, ME, MA, NH, NJ, NY, PA, RI, VT), southeast (DE, FL, GA, MD, NC, SC, VA,

Table II. Pediatricians' screening urinalysis practices and beliefs

	Number (total 653)	Percent (%)
Routinely screen all asymptomatic children at least once in:		
Infancy (age <1 year)	51	9
Early childhood (age 1 to 5 years)	371	60
Late childhood (age 5 to 12 years)	335	55
Adolescence (age 12 to 20 years)	349	58

DC, WV), south (AL, AR, KY, LA, MS, OK, TN, TX), midwest (IL, IA, IN, KS, MI, MO, MN, MS, NE, ND, OH, SD, WI), and mountain-Pacific (AZ, CO, ID, MT, NV, NM, UT, WY, AK, CA, HI, OR, WA).⁹

We mailed each subject a 4-page questionnaire, a prepaid return envelope, a dollar bill as a token of appreciation, and a letter assuring that participation was voluntary and that responses would be kept confidential. We gave each subject the opportunity to decline participation. We sent each nonrespondent a replacement survey at 4-week intervals, for a maximum of 4 mailings per subject, and sent a reminder postcard after the second mailing. We contacted the institution of each subject who did not respond to confirm that the subject's mailing address was correct. The University of Washington Institutional Review Board approved the design of this study.

Statistical Analysis

We used the χ^2 test to investigate associations between a subject's characteristics and whether the subject conducts routine screening urinalysis in at least 1 childhood age group.

RESULTS

Of the 1502 potential subjects, we excluded 43 who did not currently practice general pediatrics in the United States and 106 whose questionnaires were returned by the Postal Service with no forwarding address. Of the 1353 remaining, 653 returned completed surveys and 59 actively refused to participate, leaving 641 potentially eligible nonresponders. The estimated response rate was 49.5%.¹ We found no statistically significant differences between responders and nonresponders by sex or age. Participants graduated from medical school a mean of 16.3 years before responding to the questionnaire (standard deviation, 11.7; median, 14; range, 1 to 55); other participant characteristics are presented in Table I.

The vast majority of participants (78%) routinely conduct screening urinalysis on asymptomatic children in at least 1 age group, and the majority (58%) routinely screen in more than 1 group. Pediatricians' screening urinalysis practices varies by child age, with 55% screening in the age group that includes 5-year-olds (Table II). More than 1/3 of subjects (38%) stated that they believe that the overall health of

children is improved by screening all asymptomatic children with urinalysis.

General pediatricians are more likely than pediatricians who spend less than 80% of their clinical time in general pediatrics to conduct screening urinalysis routinely at least once during childhood (82% vs 64%; $P < .001$). Foreign medical school graduates are more likely than U.S. medical school graduates to conduct screening urinalysis routinely at least once during childhood (91% vs 75%; $P < .001$). Pediatricians who have completed residency are more likely than residents to conduct screening urinalysis routinely at least once during childhood (81% vs 66%; $P = .001$). We found no significant regional variation in pediatricians' routine screening urinalysis practices (northeast, 79%; southeast, 78%; Midwest, 81%; south, 79%; mountain-Pacific, 73%; $P = .62$).

DISCUSSION

We found that the vast majority of pediatricians routinely screen asymptomatic children with urinalysis at some point during childhood. The AAP currently recommends urinalysis screening of all 5 year-old children,⁸ and we found that more than 50% of pediatricians routinely screen in the age group that includes this age. Because we did not specifically ask about screening children at age 5, we do not have a precise estimate of the proportion in compliance with the AAP guidelines; we can only say that no more than 55% of participants were in compliance with this guideline. We also found that many screen children at ages not recommended by the AAP (infancy, early childhood, and adolescence). We found an interesting inconsistency between pediatricians' beliefs and practices. Although a minority of participants believe that the overall health of children is improved by screening all children with urinalysis, the vast majority routinely screen asymptomatic children with urinalysis at some point.

Our findings that pediatricians' screening urinalysis practices are not compliant with the AAP recommendations is consistent with previous work that found that pediatricians frequently do not comply with clinical practice guidelines.¹⁰⁻¹² Given the paucity of evidence supporting screening urinalysis, it is interesting to note that many pediatricians screen so often. Perhaps pediatricians overscreen because they do not know that the AAP revised their guidelines in 2000 to advise that all children be screened only once, at age 5 years.⁸ Possibly adding to confusion over the guidelines, in the mid-1990s both the United States Preventative Services Task Force (USPSTF)¹³ and the Canadian Task Force on Preventative Health Care¹⁴ recommended against screening children for bacteriuria, and the 2004 USPSTF guidelines specified urinalysis screening recommendations only for adults, not for children.¹⁵

The reason for the disassociation between some pediatricians' screening urinalysis beliefs and practices is not clear. Perhaps some are aware of the poor quality of evidence supporting performing routine screening urinalysis to detect bacteriuria^{13,14} or significant renal disease,¹⁶⁻²⁰ whereas others may conduct screening urinalysis only to comply with requirements of insurance groups or for school entry.

Several limitations of the present study warrant comment. First, this study is subject to response bias, because the physicians who returned completed surveys might be different than those who did not. However, we were reassured that there were no significant sex or age differences between responders and nonresponders and that our response rate was similar to the mean response rates in previously published studies of physician surveys.^{21,22} Second, participants' stated screening urinalysis practices might not represent their actual clinical practices; however, there does not appear to be any obvious social response bias in answering our questions. Third, our question addressing attitudes toward screening urinalysis has not been externally validated; however, we feel that this question was posed in a straightforward manner and has face validity. Finally, we did not gather information on other factors that may influence screening behavior, such as requirements established by Medicaid or schools.

Our study confirms previous reports^{5,6} that pediatricians perform screening urinalyses frequently. These findings have important implications. Our findings that pediatricians report conducting screening urinalysis on groups of children for whom the AAP does not recommend screening is of concern,⁸ because screening children with urinalysis multiple times during childhood is costly.⁵ Educational interventions to improve this practice may be warranted. Perhaps such interventions should emphasize that inappropriate testing can lead to false-positive results, which frequently trigger a cascade of follow-up tests and related anxiety.

This work was conducted while Dr. Sox was a Robert Wood Johnson Clinical Scholar at the University of Washington. The Robert Wood Johnson Generalist Physician Faculty Scholar program supports Dr. Christakis. The opinions expressed herein are those of the authors and not of the Robert Wood Johnson Foundation.

REFERENCES

1. Council of American Survey Research Organizations. On the definition of response rates: a special report from the CASRO Task Force on Completion Rates. Port Jefferson, NY: Council of American Survey Research Organizations; 1982.
2. Bailey EN, Kiehl PS, Abram DS, Bailey EN, Kiehl PS, Akram DS, et al. Screening in pediatric practice. *Pediatr Clin North Am* 1974;21:123-65.
3. American Academy of Pediatrics. Screening school children for urologic disease. *Pediatrics* 1977;60:239-43.
4. American Academy of Pediatrics. Policy reference guide: a comprehensive guide to AAP policy statements published through December 1992. 6th ed. Elk Grove Village, IL: American Academy of Pediatrics; 1993.
5. Kaplan RE, Spring JE, Feld LG. Screening dipstick urinalysis: a time to change. *Pediatrics* 1997;100:919-21.
6. Hoekelman RA. Is screening urinalysis worthwhile in asymptomatic pediatric patients? *Pediatr Ann* 1994;23:459-60.
7. Mitchell N, Stapleton FB. Routine admission urinalysis examination in pediatric patients: a poor value. *Pediatrics* 1990;86:345-9.
8. American Academy of Pediatrics, Committee on Practice and Ambulatory Medicine. Recommendations for preventive pediatric health care. *Pediatrics* 2000;105:645-6.
9. Mettlin CJ, Murphy GP, Rosenthal DS, Menck HR. The national cancer data base report on prostate carcinoma after the peak in incidence rates in the U.S. *Cancer* 1998;83:1679-84.
10. Christakis DA RF. Pediatricians' awareness of and attitudes about four clinical practice guidelines. *Pediatrics* 1998;101:825-30.

11. Cabana MD RC, Powe NR, Wu AW, Wilson MH, Abboud PAC, Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282:1458-65.
12. Zerr DM DBM, Cummings P. Predictors of physician compliance with a published guideline on management of febrile infants. *Pediatr Infect Dis J* 1999;18:232-8.
13. U.S. Preventative Services Task Force. U.S. Preventative Services task force guide to clinical preventative services. 2nd ed. Baltimore: Williams & Wilkins; 1996.
14. Canadian Task Force on the Periodic Health Exam. The Canadian guide to clinical preventive health care. Ottawa: Health Canada; 1994.
15. U.S. Preventative Services Task Force. Screening for asymptomatic bacteriuria: recommendation statement. Rockville, MD: Agency for Healthcare Research and Quality; 2004.
16. Murakami M, Yamamoto H, Ueda Y, Murakami D, Yamauchi K. Urinary screening of elementary and junior high-school children over a 13-year period in Tokyo. *Pediatr Nephrol* 1991;5:50-3.
17. Vehaskari VM, Rapola J, Koskimies O, Savilahti E, Vilksa J, Hallman N. Microscopic hematuria in schoolchildren: epidemiology and clinicopathologic evaluation. *J Pediatr* 1979;95:676-84.
18. Ito K, Kawaguchi H, Hattori M. Screening for proteinuria and hematuria in schoolchildren: is it possible to reduce the incidence of chronic renal failure in children and adolescents? *Acta Paediatr Jpn* 1990; 32:710-5.
19. Feld LG, Meyers KE, Kaplan BS, Stapleton FB. Limited evaluation of microscopic hematuria in pediatrics. *Pediatrics* 1998;102:e42.
20. Hisano S, Kwano M, Hatae K, Kaku Y, Yamane I, Ueda K, et al. Asymptomatic isolated microhaematuria: natural history of 136 children. *Pediatr Nephrol* 1991;5:578-81.
21. Asch DA, Jedrzejewski MK, Christakis NA. Response rates to mail surveys published in medical journals. *J Clin Epidemiol* 1997;50: 1129-36.
22. Cummings SM, Savitz LA, Konrad TR. Reporting response rates to mailed physician questionnaires. *Health Serv Res* 2001;35:1347-55.

Receive tables of contents by e-mail

To receive the tables of contents by e-mail, sign up through our Web site at <http://www.us.elsevierhealth.com/jpeds>.

Choose E-mail Notification.

Simply type your e-mail address in the box and click the Subscribe button.

Alternatively, you may send an e-mail message to majordomo@mosby.com. Leave the subject line blank and type the following as the body of your message:

subscribe jpeds_toc

You will receive an e-mail to confirm that you have been added to the mailing list.

Note that table of contents e-mails will be sent out when a new issue is posted to the Web site.

REDUCED NOCTURNAL BLOOD PRESSURE DIP AND SUSTAINED NIGHTTIME HYPERTENSION ARE SPECIFIC MARKERS OF SECONDARY HYPERTENSION

TOMÁŠ SEEMAN, MD, PhD, DANIELA PALYZOVÁ, MD, Jiří DUŠEK, MD, PhD, AND JAN JANDA, MD PhD PROF

Objective To investigate with the use of ambulatory blood pressure (BP) monitoring whether nocturnal BP dip and nighttime BP values are different in children with untreated primary and secondary hypertension.

Study design Ambulatory BP monitoring studies from 145 children with untreated hypertension were retrospectively analyzed. Forty-five children had primary hypertension and 100 children had secondary hypertension.

Results Children with secondary hypertension had lower nocturnal BP dip for systolic and diastolic BP in comparison to children with primary hypertension ($8\% \pm 5\%$ vs $14\% \pm 4\%$ for systolic and $14\% \pm 7\%$ vs $22\% \pm 5\%$ for diastolic BP, $P < .0001$ for both). Eleven percent of children with primary hypertension were classified as nondipper (BP dip $<10\%$) for systolic BP and no child for diastolic BP; on the contrary, in children with secondary hypertension, 65% were nondippers for systolic and 21% for diastolic BP. Nocturnal systolic and diastolic BP loads were significantly greater in children with secondary hypertension than in those with primary hypertension.

Conclusions Reduced nocturnal BP dip and sustained nighttime BP elevation are specific markers of secondary hypertension in children with untreated hypertension. Children with blunted nocturnal BP dip or sustained nighttime hypertension should be thoroughly investigated searching for the underlying cause of hypertension. (*J Pediatr* 2005;147:366-71)

Ambulatory blood pressure monitoring (ABPM) has become a valuable method in the treatment of children with arterial hypertension.^{1,2} Hypertension in childhood can be secondary (caused mainly by renal, endocrine, or cardiovascular disorders) or primary, that is, without identified underlying disorder.^{3,4} Early differentiation between primary and secondary hypertension is of high diagnostic, therapeutic, and prognostic importance because it facilitates initiation of specific treatment for the underlying condition.

Ambulatory blood pressure monitoring is a potential tool for differentiation between these two forms of hypertension. There are several studies in adult patients showing that nocturnal blood pressure (BP) decrease (dip) is reduced in patients with secondary hypertension in comparison to patients with primary hypertension.⁵⁻¹¹ In children, only one study systematically investigated this issue.¹² Flynn¹² has shown in this study on 93 mostly treated hypertensive children that pediatric patients with secondary hypertension also have a blunted nocturnal BP dip compared with children with primary hypertension. He did not find any difference in nocturnal BP dip between these two groups when the subgroup of untreated children was considered; this is probably a result of the small number of untreated children.

The aim of our study was to investigate in a larger cohort of untreated hypertensive children whether nocturnal BP dip is different in patients with secondary hypertension compared with patients with primary hypertension and to identify further BP characteristics of children with secondary hypertension that could differentiate them from children with primary hypertension.

From the Department of Pediatrics, University Hospital Motol, 2nd School of Medicine, Charles University Prague, Prague, Czech Republic; and the Department of Pediatrics, University Hospital Královské Vinohrady, 3rd School of Medicine, Charles University, Prague, Czech Republic.

Supported by grant IGA Ministry of Health CR reg. No. NE/7629-3.

No conflicts of interest.

Submitted for publication Oct 11, 2004; last revision received Feb 21, 2005; accepted Apr 15, 2005.

Reprint requests: Tomáš Seeman, MD, Department of Pediatrics, University Hospital Motol, 2nd School of Medicine, Charles University Prague, V Úvalu 84, 15006 Prague 5, Czech Republic.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.04.042

ABPM	Ambulatory blood pressure monitoring	GFR	Glomerular filtration rate
BP	Blood pressure	NKF	National Kidney Foundation

METHODS

We retrospectively reviewed all ABPM studies obtained in our center between January 1995 and December 2002. Indications for ABPM studies were elevated clinic BP or an underlying disease (renal, endocrine, or cardiovascular) suggesting BP alterations regardless of clinic BP. The results of the ABPM studies were used for detection of sustained or white coat hypertension but were not used to classify the children as having either primary or secondary hypertension. Institutional review board approval was received for the study design.

Oscillometric monitors SpaceLabs 90207 or 90217 (SpaceLabs Medical, Redmond, WA) were used. An appropriate cuff¹³ was placed on the nondominant arm by a physician who also informed the child and parents in detail of the operation of the monitor. Monitors were programmed to measure BP automatically every 20 minutes during the day and every 30 minutes at night. According to the reference values by Soergel et al,¹⁴ data were analyzed by using standardized daytime (8 AM to 8 PM) and nighttime (12 AM to 6 AM) periods.

Mean systolic and diastolic BP at daytime and at nighttime were calculated. Nocturnal BP dip was calculated as a percentage of mean nighttime BP decline compared with mean daytime BP: [(mean daytime BP – mean nighttime BP): mean daytime BP] × 100. It is not yet known what is abnormal nocturnal BP decline in children¹⁵; therefore, reduced nocturnal BP dip was defined using adult criteria as systolic BP dip <10% and/or diastolic BP dip <10%.¹⁶ Children with reduced nocturnal systolic and/or diastolic BP fall were classified as nondippers. Blood pressure load for daytime and nighttime BP was calculated as a percentage of readings higher than the 95th percentile for healthy children.¹⁵

Inclusion criteria for the study were (1) abnormal ABPM recording defined as mean systolic and/or diastolic BP at daytime and/or nighttime ≥95th percentile values for healthy children, using the data from the study by Soergel¹⁴; (2) no antihypertensive medication (including diuretics); (3) no steroids, cyclosporine, or tacrolimus medication; (4) sufficient number of BP measurements during ABPM study (only recordings with a minimum of 40 readings and without breaks longer than 2 hours). Exclusion criteria for the study were (1) children with end-stage renal failure treated with dialysis; (2) children after renal transplantation.

Children were classified as having primary or secondary hypertension after a standardized comprehensive diagnostic evaluation recommended by the Working Group on Hypertension Control in Children and Adolescents that included appropriate clinical, laboratory, and radiographic studies, as recommended by this consensus group.¹³ This laboratory diagnostic evaluation included complete blood count, urinalysis, urine culture, serum electrolytes, blood urea nitrogen, creatinine, uric acid, cholesterol, triglycerides, renal ultrasound, and echocardiography in all children and hormonal studies and renoparenchymal or renovascular imaging in selected patients.

Table I. Clinical and anthropometric characteristics of children with primary and secondary hypertension

	Primary HT (n = 45)	Secondary HT (n = 100)	P value*
Age (years)	15.7 ± 3.4	11.8 ± 4.2	<.0001
Height (cm)	173 ± 17.4	147.5 ± 24.7	<.0001
Weight (kg)	73.6 ± 19.9	43.8 ± 19.6	<.0001
Weight (percentile)	82.0 ± 21.4	51.6 ± 34.9	<.0001
BMI (kg/m ²)	24.3 ± 4.8	19.1 ± 4.0	<.0001
BMI (percentile)	78.0 ± 23.7	53.0 ± 32.9	<.0001
Female sex (%)	13	34	<.0001

HT, indicates hypertension; BMI, indicates body mass index.

*Two-way, unpaired t test.

Statistical Analysis

Data are expressed as mean ± SD, or as percentages. Statistical analysis was performed by using the SPSS statistical program. The Mann-Whitney *U* test and unpaired 2-tailed *t* test were used to examine differences between groups. The Fisher 2-sided exact test was used to determine the difference in group proportions. Receiver operator curve analysis was used to evaluate sensitivity and specificity of nocturnal BP dip and BP load for predicting the presence of secondary hypertension. *P* values <.05 were considered statistically significant.

RESULTS

All 921 ABPM studies performed in our pediatric department between January 1995 and December 2002 were reviewed. Seven hundred seventy-six studies were excluded from the analysis, 372 (48 %) because of mean BP values <95th percentile (ie, normotension), 295 (38%) because of treatment with antihypertensive medications, diuretics, steroids, cyclosporine, or tacrolimus, 70 (9%) because of renal replacement therapy (dialysis or renal transplant), and 39 (5%) because of insufficient BP readings during the ABPM study.

A total of 145 ABPM studies from 145 different children fulfilled the inclusion criteria. Forty-five children had primary hypertension and 100 children had secondary hypertension. The underlying cause of secondary hypertension was renoparenchymal disease (n = 90; primary renal disease included glomerulonephritis in 22 children, reflux nephropathy in 20 children, obstructive uropathy in 11 children, congenital hypoplasia/dysplasia in 9 children, autosomal recessive polycystic kidney disease in 9 children, autosomal dominant polycystic kidney disease in 7 children, chronic tubulopathy in 7 children, and residual renal abnormalities after hemolytic uremic syndrome in 5 children); renal artery stenosis (n = 5) and endocrinopathy (n = 5; glucocorticoid-remediable aldosteronism in 2 children; and pheochromocytoma, Cushing syndrome, and congenital adrenal hyperplasia caused by deficiency of 11-β hydroxylase in 1 child each).

Renal function was normal according to the National Kidney Foundation (NKF) classification¹⁷ in all children with

Table II. Comparison of dipping status and likelihood of secondary hypertension with a non-dipping status

	Systolic BP dip	Diastolic BP dip	Non-dipping for systolic BP <10%	Non-dipping for diastolic BP <10%	Non-dipping for systolic BP <10% and diastolic BP <10%
Primary HT (n = 45)	14 ± 4	22 ± 5	11%	0%	0%
Secondary HT (n = 100)	8 ± 5	14 ± 7	65%	21%	19%
P value	<.0001 [†]	<.0001 [†]	<.0001 [‡]	= .0002 [‡]	<.0001 [‡]
Sensitivity	NA	NA	65%	21%	19%
Specificity	NA	NA	89%	100%	100%

HT, indicates hypertension; BP, indicates blood pressure; NA, indicates not applicable.

[†]unpaired 2-tailed t test.

[‡]Fisher exact test.

Table III. Comparison of blood pressure loads in children with primary and secondary hypertension

	Daytime systolic BP load	Daytime diastolic BP load	Nighttime systolic BP load	Nighttime diastolic BP load
Primary HT (n = 45)	65.9 ± 17.9	32.6 ± 19.4	43.4 ± 25.6	25.4 ± 19.9
Secondary HT (n = 100)	53.7 ± 30.6	41.0 ± 31.5	70.7 ± 28.1	59.4 ± 29.2
P value [†]	= .03	NS	<.0001	<.0001

HT, indicates hypertension; BP, indicates blood pressure; NS, indicates not significant.

[†]unpaired 2-tailed t test.

primary hypertension (mean calculated glomerular filtration rate [GFR], 132 ± 17 mL/min/1.73 m²; range, 106 to 159) and in all children with renovascular and endocrine forms of secondary hypertension; 20 children with renoparenchymal hypertension had mildly reduced renal function (GFR, 60 to 89 mL/min per 1.73 m²), and 8 children had moderately reduced renal function (GFR, 30 to 59 mL/min per 1.73 m²) according to the NKF classification (mean GFR in all children with secondary hypertension, 99 ± 43 mL/min per 1.73 m²; range, 30 to 227).

The mean time studied by ABPM was 24.5 ± 11.6 hours, the mean number of BP readings during this time was 59 ± 26, and ABPM was generally well tolerated by the children (93% of attempted readings were successful).

The demographic data of children with primary and secondary hypertension are shown in Table I. All were white. Children with primary hypertension were significantly older and heavier (according to absolute as well as relative body weight and body mass index) than children with secondary hypertension. Children with primary hypertension were less likely to be of female sex than children with secondary hypertension.

Children with secondary hypertension had significantly lower nocturnal BP dip for systolic as well as for diastolic BP in comparison to children with primary hypertension (Table II). Their nocturnal systolic and diastolic BP dip was also significantly lower than in healthy children (mean nocturnal dip in systolic BP 13% and in diastolic BP 23% in healthy children; data from Soergel et al¹⁴). On the contrary, children with primary hypertension had nocturnal BP dip not signif-

icantly different from healthy children. A subgroup of children with renovascular hypertension had higher systolic and diastolic BP dip (12% and 23%) than a subgroup of children with endocrine hypertension (3% and 11%, *P* < .05) and higher diastolic BP dip (23%) than a subgroup of children with renoparenchymal hypertension (14%, *P* < .05).

In children with primary hypertension, 11% were classified as nondippers for systolic BP, and none of them were nondipper for diastolic BP. In children with secondary hypertension, 65% were nondippers for systolic BP and 21% for diastolic BP. The specificity of nondipping phenomenon for predicting secondary hypertension was 89% for systolic BP dip and 100% for diastolic BP dip (Table II). The thresholds of nocturnal BP dip for predicting the presence of secondary hypertension with 100% specificity and the best sensitivity were found to be <5% for systolic and <13% for diastolic BP. These thresholds had sensitivity of 26% for systolic and 36% for diastolic BP for predicting secondary hypertension. The thresholds with the best specificity and sensitivity together for predicting secondary hypertension were found to be <10% for systolic and <16% for diastolic BP (receiver operator curve area 0.828 for systolic BP dip and 0.819 for diastolic BP; specificity and sensitivity index, 1.539 for systolic and 1.506 for diastolic BP dip).

Children with secondary hypertension revealed higher systolic as well as diastolic BP loads during the nighttime than children with primary hypertension (Table III). On the contrary, children with primary hypertension had higher systolic BP load during the daytime than children with secondary hypertension. Daytime diastolic BP load was

Table IV. Likelihood of secondary hypertension with an elevated blood pressure load

	Nighttime systolic BP load >85%	Nighttime diastolic BP load >60%	Nighttime systolic BP load >85% and nighttime diastolic BP load >60%
Primary HT (n = 45)	3 pts (6%)	1 pt (2%)	1 pt (2%)
Secondary HT (n = 100)	41 pts (41%)	47 pts (47%)	29 pts (29%)
P value [‡]	<.0001	<.0001	<.0001
Sensitivity	41%	47%	29%
Specificity	94%	98%	98%

HT, indicates hypertension; BP, indicates blood pressure; pts, indicates patients.

[‡]Fisher exact test.

not significantly different between these two groups (Table III).

Examination of the relation between BP load and the likelihood of secondary hypertension is summarized in Table IV. Based on the distribution of BP loads in the study population, cutoff values of 25% to 95% were tested as potential thresholds for the prediction of secondary hypertension. The most significant thresholds were found to be 60% for nighttime systolic BP load and 85% for nighttime diastolic BP load (Table IV). Both of these thresholds had a sensitivity of almost 50% and a specificity of more than 90%.

DISCUSSION

The most important indications for introducing ABPM in a pediatric patient are confirmation of sustained hypertension or detection of white coat hypertension^{18,19} and assessment of nighttime BP profile. There are several studies in adults showing that patients with secondary hypertension have more often disturbed circadian BP rhythm with nondipping BP pattern than patients with primary hypertension.⁵⁻⁹ We have found that children with reflux nephropathy have isolated elevation of nighttime BP with reduced BP dip.²⁰ In children, there is only one study that demonstrated that children with secondary hypertension, both untreated and treated, have blunted nocturnal BP dip and higher nighttime systolic and daytime diastolic BP loads than children with primary hypertension; however, having evaluated separately only untreated children, the difference in BP dipping status was no longer seen.¹² In Flynn's opinion, the failure to show any difference would have been caused by the small number of untreated children in this study.

In this study, we have retrospectively evaluated all ABPM studies in our pediatric center. During the last 8 years, we have performed ABPM in nearly 1000 children. Only ABPM studies that showed persistent hypertension in untreated children have been included to exclude possible influence of drugs on the BP level and circadian rhythm. Despite these hard exclusion criteria, the number of 145 children with untreated hypertension is more than 3 times greater than in the study done by Flynn. Our study demonstrated that untreated children with secondary hypertension had much lower nocturnal BP dip than children with primary hypertension.

Furthermore, the nondipping phenomenon for diastolic BP was found only in children with secondary hypertension and never in a child with primary hypertension. In other words, the specificity of diastolic nondipping in predicting secondary hypertension in an untreated child with hypertension was 100%. On the other hand, the low sensitivity of the nondipping phenomenon to predict secondary hypertension in children (only 21%) shows that more than three fourths of children with secondary hypertension have normal nocturnal dip of diastolic BP. The sensitivity of nondipping phenomenon in systolic BP to predict secondary hypertension was considerably higher (65%); however, the specificity reached only 89%. Overall, the nocturnal BP dip in children with secondary hypertension is on average approximately 2 times lower than in children with primary hypertension (Table II).

The thresholds of nocturnal BP dip with 100% specificity and the best sensitivity for prediction of secondary hypertension were found to be <5% for systolic and <13% for diastolic BP. It is not yet known how abnormal BP dipping should be defined in children,¹⁵ and therefore adult criteria (<10% for both diastolic and systolic BP) are usually used. We could speculate whether the use of cut-points that can differentiate between children with primary and secondary hypertension with 100% specificity should be used to define abnormal dipping in children. The use of adult criteria of nondipping also in pediatrics makes approximately 30% of healthy children nondippers for systolic BP according to the normative data by Soergel et al.¹⁴

The exact mechanism of diminished nocturnal BP fall in patients with secondary hypertension still needs to be examined, although it appears that different mechanisms are responsible for nondipping in different underlying disorders.¹ The possible mechanisms involved in the nondipper pattern in different disorders include impaired renal sodium excretion, high-salt diet, raised sympathetic tone, disassociation of BP with the autonomic nervous system, or the tendency to orthostatic hypotension during the day with normally functioning baroreflex.^{1,11}

We have further demonstrated that children with secondary hypertension have higher nocturnal BP loads for both systolic and diastolic BP than children with primary hypertension. As opposed to the study by Flynn, we have not found any significant differences in daytime diastolic BP

between these two groups and have found higher daytime systolic BP load in children with primary hypertension. One of the possible reasons that the results of our study differ from those of Flynn is that Flynn's study also included children with renal transplants who often have severe diastolic hypertension.

The best thresholds of the BP loads for predicting the presence of secondary hypertension were found to be the nighttime systolic BP load >85% and nighttime diastolic BP load >60%. Blood pressure loads greater than these thresholds were highly specific for predicting secondary hypertension (specificity, 98% and 94%), although the sensitivity was only approximately 50%. High nighttime BP loads can be also used as a sensitive predictor of secondary hypertension with similarly high specificity as the nondipping phenomenon.

The results of this study confirm that ABPM could be a useful initial investigation tool for children with elevated clinic BP values. It can be used not only for the classic indications such as confirmation of persistent hypertension and exclusion of white coat hypertension but it can provide also valuable information for differentiating primary and secondary hypertension. This is a very important task in pediatrics, where secondary hypertension is more common than in adults. An early clue for a diagnosis of secondary hypertension is of therapeutic significance because the physician is able to initiate specific treatment. The specificity of nondipping phenomenon and high nocturnal BP loads for predicting secondary hypertension are very high, reaching 89% to 100%. Therefore, all children with reduced nocturnal BP dip or sustained nocturnal hypertension have to be seen as highly suspicious of having secondary hypertension and have to be thoroughly evaluated for possible underlying renal or endocrine disorder.

As could be expected, the demographic and anthropometric data have demonstrated that children with primary hypertension were generally older and heavier than children with secondary hypertension. This was shown also in the study by Flynn¹² and is in agreement with the general concept, that primary hypertension is more prevalent in older children²¹ and that overweight and obesity is one of the major determinants of BP level and risk factor for developing hypertension in children.²²⁻²⁴ However, the demographic and anthropometric data were not as sensitive or specific in predicting primary or secondary hypertension; for example, 69% of children with primary hypertension were overweight but also 34% of children with secondary hypertension were overweight, making the specificity of overweight or obesity in predicting primary hypertension low.

Adult as well as pediatric patients with decreased renal function reveal higher prevalence of hypertension and more often blunted nocturnal BP dip than patients with normal renal function.²⁵⁻²⁷ In our study, 28% of children with secondary hypertension had decreased renal function according to the NKF criteria. We did not find any significant differences in nighttime BP loads or nocturnal BP dips between children with impaired renal function and children with normal renal function (data not shown). It is well known that children with end-stage renal failure or after renal

transplantation have often blunted nocturnal BP dip.^{28,29} We did not include any child with end-stage renal failure or after renal transplantation in our study (exclusion criterion), to improve the value of our data for a routine clinical practice in pediatric hypertension, where children with renal failure are not routinely treated. This could be one of the possible reasons for the failure to observe any differences in nighttime BP loads and nocturnal BP dips between children with normal and impaired renal function.

The reproducibility of nighttime BP values and dipper status remains unclear. Some studies have demonstrated a good reproducibility of ABPM values; however other have shown a limited reproducibility.³⁰⁻³² However, the very strong statistically significant differences in dipping status and nighttime BP loads between the groups of children with primary and secondary hypertension makes bias caused by poor reproducibility of the ABPM values unlikely.

The authors thank Marie Hladíková for performing the statistical analysis.

REFERENCES

1. Portman RJ, Yetman RJ. Clinical uses of ambulatory blood pressure monitoring. *Pediatr Nephrol* 1994;8:367-76.
2. Sorof JM, Portman RJ. Ambulatory blood pressure monitoring in the pediatric patient. *Pediatrics* 2000;136:578-86.
3. Wyszynska T, Cichock E, Wieteska-Klimczak A, Jobs K, Januszewicz P. A single pediatric center experience with 1025 children with hypertension. *Acta Pediatr* 1992;81:244-6.
4. Arar MY, Hogg RJ, Arant BS Jr, Seikaly MG. Etiology of sustained hypertension in the Southwestern United States. *Pediatr Nephrol* 1994;8: 186-9.
5. Schrader I, Person C, Pfertner U, Buhr-Schinner H, Schoel G, Warneke G, et al. Absence of nocturnal decrease in blood pressure in 24-hour blood pressure monitoring: an indication of secondary hypertension. *Klin Wochenschr* 1989;67:659-65.
6. Baumgart P, Walger P, Dorst KG, von Eiff M, Rahn KH, Vetter H. Can secondary hypertension be identified by twenty-four-hour ambulatory pressure monitoring? *J Hypertens* 1989;7(Suppl):S25-8.
7. Middeke M, Schrader J. Nocturnal blood pressure in normotensive subjects and those with white coat, primary, and secondary hypertension. *BMJ* 1994;308:630-2.
8. Polonia J, Santos AR, Gama GM, Barros H. Accuracy of twenty-four-hour ambulatory blood pressure monitoring (night-day values) for the diagnosis of secondary hypertension. *J Hypertens* 1995;13:1738-41.
9. Jensen LW, Pedersen EB. Nocturnal blood pressure and relation to vasoactive hormones and renal function in hypertension and chronic renal failure. *Blood Press* 1997;6:332-42.
10. Robles NR, Cancho B, Ruiz-Calero R, Angulo E, Sanchez-Casado E. Nighttime blood pressure fall in renal disease patients. *Ren Fail* 2003;25: 829-37.
11. Zelinka T, Štrauch B, Pecan L, Widimský J Jr. Diurnal blood pressure variation in pheochromocytoma, primary aldosteronism and Cushing's syndrome. *J Hum Hypertens* 2004;18:107-11.
12. Flynn JT. Differentiation between primary and secondary hypertension in children using ambulatory blood pressure monitoring. *Pediatrics* 2002;110: 89-93.
13. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. Update on the 1987 task force report on high blood pressure in children and adolescents: a working group report from the National High Blood Pressure Education Program. *Pediatrics* 1996;98:649-58.
14. Soergel M, Kirchstein M, Bush C, Danne T, Gellermann J, Holl R, et al. Oscillometric twenty-four-hour ambulatory blood pressure values in

healthy children and adolescents: a multicenter trial including 1141 subjects. *J Pediatr* 1997;130:178-84.

15. Lurbe E, Sorof JM, Daniels SR. Clinical and research aspects of ambulatory blood pressure monitoring in children. *J Pediatr* 2004;144:7-16.

16. Staessen JA, Bieniaszewski L, O'Brien E, Gosse P, Hayashi H, Imai Y, et al. Nocturnal blood pressure fall on ambulatory monitoring in large international database. *Hypertension* 1999;29:30-9.

17. Hogg RJ, Furth S, Lemley KV, Portman R, Schwartz GJ, Coresh J, et al. National kidney foundation's kidney disease outcomes quality initiative clinical practice guidelines for chronic kidney disease in children and adolescents: evaluation, classification, and stratification. *Pediatrics* 2003;111:1416-21.

18. Flynn JT. Impact of ambulatory blood pressure monitoring on the management of hypertension in children. *Blood Press Monit* 2000;5:211-6.

19. Sorof JM, Poffenbarger T, Franco K, Portman R. Evaluation of white coat hypertension in children: importance of the definitions of normal ambulatory blood pressure and the severity of casual hypertension. *Am J Hypertens* 2001;14:855-60.

20. Patzer L, Seeman T, Luck C, Wühl E, Janda J, Misselwitz J. Day- and night-time blood pressure elevation in children with higher grades of renal scarring. *J Pediatr* 2003;142:117-22.

21. Bartosh SM, Aronson AJ. Childhood hypertension: an update on etiology, diagnosis and treatment. *Pediatr Clin North Am* 1999;46:235-52.

22. Feld LG, Springate JE, Waz WR. Special topics in pediatric hypertension. *Semin Nephrol* 1998;18:295-303.

23. He Q, Ding ZY, Fong DY, Karlberg J. Blood pressure is associated with body mass index in both normal and obese children. *Hypertension* 2000;36:165-70.

24. Sorof JM, Lai D, Turner J, Poffenbarger T, Portman RJ. Overweight, ethnicity, and the prevalence of hypertension in school-aged children. *Pediatrics* 2004;113:475-82.

25. Covic A, Goldsmith D. Ambulatory blood pressure monitoring: an essential tool for blood pressure assessment in uraemic patients. *Nephrol Dial Transplant* 2002;17:1737-41.

26. Farmer CK, Goldsmith DJ, Quinn JD, Dallyn P, Cox J, Kingswood JC, et al. Progression of diabetic nephropathy: is diurnal blood pressure rhythm as important as absolute blood pressure level? *Nephrol Dial Transplant* 1998;13:635-9.

27. Mitsnefes M, Kimball TR, Daniels SR. Office and ambulatory blood pressure elevation in children with chronic renal failure. *Pediatr Nephrol* 2003;18:145-9.

28. Lingens N, Soergel M, Loirat C, Busch C, Lemmer B, Schärer K. Ambulatory blood pressure monitoring in paediatric patients treated by regular haemodialysis and peritoneal dialysis. *Pediatr Nephrol* 1995;9:167-72.

29. Lingens N, Dobos E, Witte K, Busch C, Lemmer B, Klaus G, et al. Twenty-four-hour ambulatory blood pressure profiles in pediatric patients after renal transplantation. *Pediatr Nephrol* 1997;11:23-6.

30. Lurbe E, Aguilar F, Gomez A, Tacons J, Alvarez V, Redon J. Reproducibility of ambulatory blood pressure monitoring in children. *J Hypertens* 1993;11(Suppl 5):S288-9.

31. Mochizuki Y, Okutani M, Dongfeng Y, Iwasaki H, Takusagawa M, Kohno I, et al. Limited reproducibility of circadian variation in blood pressure dippers and nondippers. *Am J Hypertens* 1998;11:403-9.

32. Stolarz K, Staessen JA, O'Brien ET. Night-time blood pressure: dipping into the future. *J Hypertens* 2002;20:2131-3.

Access to *The Journal of Pediatrics Online* is now reserved for print subscribers!

Full-text access to *The Journal of Pediatrics Online* is available for all print subscribers. To activate your individual online subscription, please visit *The Journal of Pediatrics Online*, point your browser to <http://www.us.elsevierhealth.com/jped>, follow the prompts to **activate online access here**, and follow the instructions. To activate your account, you will need your subscriber account number, which you can find on your mailing label (*note*: the number of digits in your subscriber account number varies from 6 to 10). See the example below in which the subscriber account number has been circled:

Sample mailing label

This is your subscription account number

*****3-DIGIT 001
SJ P1
FEB00 J009 C: 1 (1234567-89) U 05/00 Q: 1
J. H. DOE, MD
531 MAIN ST
CENTER CITY, NY 10001-001

Personal subscriptions to *The Journal of Pediatrics Online* are for individual use only and may not be transferred. Use of *The Journal of Pediatrics Online* is subject to agreement to the terms and conditions as indicated online.

SLEEP DISTURBANCE AND RAGE ATTACKS IN OPSOCLONUS-MYOCLONUS SYNDROME: RESPONSE TO TRAZODONE

MICHAEL R. PRANZATELLI, MD, ELIZABETH D. TATE, C-FNP, MN, WILLIAM S. DUKART, MD, MARY JO FLINT, MD,
MICHAEL T. HOFFMAN, MD, AND AMY E. OKSA, MD

Objectives Parents of children with opsoclonus-myoclonus syndrome (OMS) frequently describe poor sleep and rage attacks. We hypothesized that these manifestations are related and could result from underlying monoaminergic dysfunction.

Study design We clinically characterized the sleep and behavioral characteristics of 51 young children with OMS; 19 of those with the most disruptive sleep patterns were treated with trazodone, a soporific serotonergic agent.

Results Sleep disturbances, including prolonged sleep latency, fragmented sleep, reduced quantity of sleep, snoring, and nonrestorative sleep, were reported in 32 children, and frequent rage attacks were reported in 25. In 59% of the poor sleepers, parents felt that the problem was severe enough to warrant treatment. Children sleeping <10 hours/night had a higher rage frequency than those who slept more. Of the children who required trazodone, 84% were receiving corticosteroids or adrenocorticotrophic hormone (corticotrophin), compared with 37% in the subgroup with normal sleep. Trazodone (3.0 ± 0.4 mg/kg/day) improved sleep and behavior in 95% of the children, significantly increasing total sleep time by 72%, decreasing the number of awakenings by 76%, and reducing rage attacks by 33%.

Conclusions Children with OMS exhibited multiple types of sleep disturbances, which contributed to rage attacks. Trazodone was effective in improving sleep and decreasing rage attacks and was well tolerated, even in toddlers. (*J Pediatr* 2005;147:372-8)

Opsoclonus-myoclonus syndrome (OMS) is a neuroblastoma-associated paraneoplastic disorder with serious neuropsychiatric sequelae. Of all of the behavioral symptoms of OMS, such as cognitive impairment, attention deficit disorder (ADD), and obsessive-compulsive disorder, sleep disturbance and rage attacks are the most difficult for the family to cope with.¹ Reduced quality of sleep can also harm the developing child by impairing emotional development, learning, and growth.² Multiple pharmacologic interventions have been unsuccessful in children with OMS, because of a lack of efficacy or the propensity for paradoxical reactions to sedatives in this disorder.³

Trazodone hydrochloride, a sedating triazolopyridine derivative with some anxiolytic and hypnotic properties, was first marketed in the United States as an antidepressant in 1983. It is principally a serotonergic agent.⁴ In adults, the antidepressant effect occurs at doses of 300 to 600 mg, but in sub-antidepressant doses (50 to 100 mg), it also treats depression-associated sleep disorders.⁵ Although understudied in children under 12 years old, it is used in older children to treat migraine headaches,⁶ disruptive behavior,⁷ depression,⁸ and sleep disorders.⁹

We hypothesized a perturbation of monoaminergic neurotransmission to account for sleep disturbances and rage attacks in OMS. Abnormalities of cerebrospinal fluid (CSF) monoamine metabolites have been found in OMS¹⁰ and in disruptive behavioral disorders of children and adolescents.¹¹ Trazodone, with its serotonergic properties and good safety index, seemed like an ideal drug for sleeping problems in this population, and after seeing

From the Departments of Neurology and Pediatrics, Southern Illinois University School of Medicine, Springfield, Illinois; Greenbriar Physicians, Inc., Ronceverte, West Virginia; Pediatric Professional Association, Overland Park, Kansas; Elmhurst Clinic Pediatrics, Elmhurst, Illinois; and Dickinson Clinic, MedCenter One Health Systems, Dickinson, North Dakota.

Supported by funds from the Children's Miracle Network.

Submitted for publication Jan 4, 2005; last revision received Apr 6, 2005; accepted May 6, 2005.

Reprint requests: Dr. Michael R. Pranzatelli, National Pediatric Myoclonus Center, SIU School of Medicine, PO Box 19643, Springfield, IL 62794-9643. E-mail: mpranzatelli@siumed.edu.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.05.016

ACTH	Adrenocorticotrophic hormone (corticotropin)	5-HT	5-hydroxytryptamine
ADD	Attention deficit disorder	HVA	Homovanillic acid
ADHD	Attention deficit hyperactivity disorder	m-CPP	m-chlorophenylpiperazine
CSF	Cerebrospinal fluid	OMS	Opsoclonus-myoclonus syndrome
5-HIAA	5-hydroxyindoleacetic acid	REM	Rapid eye movement

Table I. Characteristics of subjects with sleep problems and response to trazodone

Characteristic	All OMS (from n = 51) %	Sleep problems (from n = 51)		Response to trazodone (from n = 19)	
		Yes %	No %	Yes % (n)	No % (n)
Age category					
Toddlers	43	33	10	37 (7)	5 (1)
Preschool	33	20	14	42 (8)	0
School-age	24	12	11	16 (3)	0
Gender					
Boys	43	25	18	42 (8)	0
Girls	57	39	18	53 (10)	5 (1)
Etiology					
No tumor found	59	31	26	53 (10)	5 (1)
Tumor found	41	33	10	42 (8)	0
Rage attacks					
Infrequent	51	29	22	42 (8)	0
Frequent	49	35	14	53 (10)	5 (1)
Attention problems/hyperactivity					
No	45	27	18	37 (7)	0
Yes	55	35	20	58 (11)	5 (1)
Current steroids or ACTH					
No	41	22	23	16 (3)	0
Yes	59	41	14	79 (15)	5 (1)
OMS motor severity category					
Mild	61	39	22	79 (15)	0
Moderate	25	14	12	5 (1)	0
Severe	14	12	1	11 (2)	5 (1)
OMS duration category					
Acute	12	10	2	5 (1)	5 (1)
Subacute	31	24	8	21 (4)	0
Chronic	57	31	25	69 (13)	0

“Problems sleeping” refers to >2 types of sleep disturbances. “Response to trazodone” indicates a “yes” response from parents to the question of whether trazodone improved their child’s sleep. Age category was defined as infant = <1.5 years; toddler = 1.5 to <3 years; preschool = 3 to <5 years; school age = ≥5 years. Rage attacks were designated as infrequent if <3/week. OMS severity category was based on total score as follows: mild = 0 to 12; moderate = 13 to 24; severe = 25 to 36. OMS duration category was defined as follows: acute = <3 months; subacute = 3 to 12 months; chronic = >12 months. Clinical characteristics had no statistically significant effects on problems sleeping or response to trazodone, except for current steroids or ACTH ($P = .0015$; Fisher’s exact test).

its benefit, we adopted it into our practice. We now report on the sleep and behavioral characteristics of children with OMS and a retrospective series on the response to trazodone as symptomatic therapy. Because many were being treated with corticosteroids or corticotropin (ACTH), which can modify sleep¹² and CSF monoamines,¹³ anti-inflammatory therapy was identified as an important variable.

METHODS

Subjects

Fifty-one children with OMS, who were recruited from 2001 to 2004 through the National Pediatric Myoclonus Center and its website (www.omsusa.org) or physician referrals, underwent comprehensive clinical data collection and neurologic evaluation under an Institutional Review Board-

approved protocol. Informed consent was obtained from the parents. Each child had been evaluated previously for occult neuroblastoma, and those with a tumor had undergone surgical resection. The clinical characteristics of the study population are presented in Table I. Mean age ± standard error of the mean for the entire cohort was 4.3 ± 0.5 years (range, 1.7 to 17 years).

Subjective Sleep Assessment

Parents had been interviewed as to whether their child regularly had trouble falling asleep (insomnia), could not sleep through the night (fragmented sleep), had fitful or restless sleep, habitual snoring, sleeptalking (somniloquy), or sleep-walking (somnambulism), or woke up tired and cranky (poor awakening quality, nonrestorative sleep). They were asked about the total number of hours that the child usually slept each

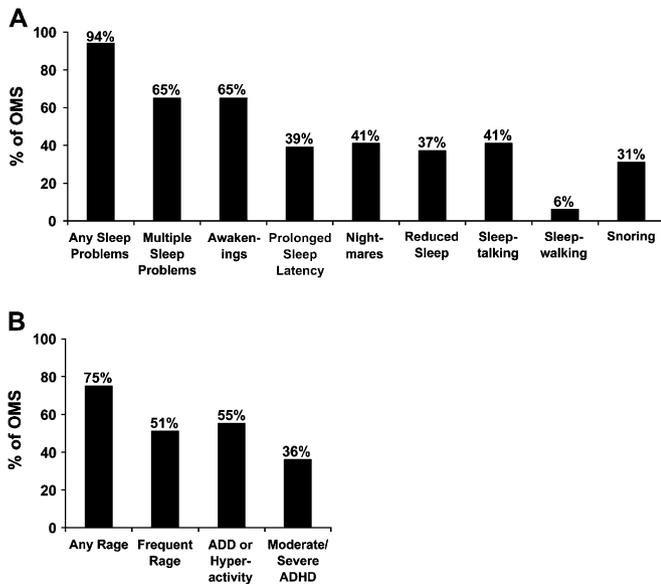


Figure 1. Percentages of various types of sleep problems (A) or rage and other behaviors (B) in 51 children with OMS. (A) “Multiple sleep problems” was defined as more than 2 types of problems sleeping. “Reduced sleep” was defined as <10 hours/night. All other designations are the result of yes/no answers. (B) “Frequent rage” was defined as rage score ≥ 3 . “ADD or hyperactivity” refers to symptoms of ADD/ADHD described to parents, who were then asked to rate them. Children with moderate or severe symptoms are represented by “moderate/severe ADHD.”

night and the number of nightly awakenings. Prolonged sleep latency was defined as taking more than 30 minutes to fall asleep, parents were well aware of it because they had to lie down with, hold, or otherwise console the child until sleep onset. Many of the children slept with their parents or went to their parents’ bed during the night when they woke up, so the parents had no problem providing the other information either.

Behavioral Assessment

Parents were questioned about rage attacks, which were described to them as extremely exaggerated temper tantrums. Rage was semiquantitated on a Likert scale from 0 to 5 as follows: 0 = none, 1 = 1 to 2 episodes/week, 2 = 3 episodes/week, 3 = 1 episode/day, 4 = 2 episodes/day, 5 = multiple episodes/day. Parents were also asked about aggressive behavior (eg, biting, kicking, hair pulling, shoving) and symptoms of ADD (eg, hyperactivity, distractibility, poor attention span).¹⁴

OMS Severity Assessment

The children were videotaped using a standardized format. A trained observer scored the videotapes using the OMS Evaluation Scale, a 12-item scale for assessing motor impairment.¹⁵ Each item was rated from 0 to 3, and subscores were tallied into a total score, which was used for subsequent comparisons.

Drug Administration

When parents had requested medication for their child’s sleep disturbance, trazodone had been started as a single oral

dose 1 hour before the desired bedtime. Toddlers were started on 25 mg, and the parents were instructed to increase the dose by 25 mg at 2-week intervals up to 100 mg if necessary to improve sleep and control of rage. For older children, the starting dose was 50 mg, with titration up to 150 mg as needed. Most parents were willing to increase the dose to achieve the desired effect, but some could not be persuaded to go above the starting dose.

Data Analysis

Statistical analysis was performed using Microsoft Excel and the Statistical Analysis System (SAS) as follows: comparisons of number of subjects by Fisher’s exact test or the χ^2 test, group means by 2-tailed *t*-tests or analysis of variance, trends in frequency by the Cochran-Armitage trend test, posttreatment changes in the percentage of subjects with sleep or behavioral problems by McNemar’s test, and posttreatment changes in means by paired *t*-tests. The level of significance was set at $P < .05$. Primary independent variables were key sleep characteristics (prolonged latency of sleep onset, number of nocturnal awakenings, sleep duration), behavior (rage and attention deficit symptoms), and ACTH or steroid treatment. Sleep duration, predetermined to be the most fundamental sleep variable, was used to divide the dataset into 3 groups based on reduced sleep time. A cutoff of 10 hours of sleep per night was chosen, based on a conservative estimate of the number of hours of sleep a child needs at age 4 years,³ the mean age of the children in our study.

RESULTS

Characterization of Sleep Disturbances

More than 90% of parents reported that their child had some difficulty sleeping, and 65% reported more than 2 sleep problems (Figure 1A). The percentage of affected children was highest for awakenings during the night (65%) and was otherwise similar for prolonged sleep latency, reduced sleep, nightmares, sleeptalking, and snoring (31% to 41%). Sleepwalking occurred infrequently.

In the prodromal phase of the illness, before opsoclonus or myoclonus, children exhibited extreme irritability, accompanied by sleeplessness or 15-minute sleep intervals. Some demanded to be held almost constantly. The parents reported feeling stressed and sleep-deprived.

Previously, several different drugs, including clonazepam, codeine, diazepam, diphenhydramine, lorazepam, and melatonin, had been tried unsuccessfully for sleep. Parents recalled that during the acute phase of OMS, intravenous morphine, fentanyl, or midazolam had been given in the hospital, with paradoxical reactions or lack of efficacy.

Characterization of Rage

Rage attacks were reported in 75% of the children (Figure 1B), with frequent attacks (at least 1 rage episode per day, or a rage score of ≥ 3) in as many as 49%. This percentage

Table II. Effect of sleep duration on other sleep variables and behaviors

Variable	Group 1	Group 2	Group 3	P value
	(n = 19) %	(n = 13) %	(n = 19) %	
Any sleep problem	83	92	100	.06
Two sleep problems	33	69	84	.0015*
Awakenings	55	85	100	.0007*
Prolonged sleep latency	28	46	53	.13
Nightmares	33	58	60	.12
Sleeptalking	33	46	47	.39
Sleepwalking	0	0	16	.042*
Snoring	28	46	42	.38
Any rage	56	92	84	.044*
Frequent rage	28	69	58	.07
Any ADD/ADHD symptoms	44	62	63	.25
More severe ADHD symptoms	18	54	44	.12

Ordered severity groupings were created by whether children slept ≥ 10 hours (normal sleep time; group 1), < 10 hours without parents requesting sleep medication (reduced sleep time; group 2), and < 10 hours with parents asking for sleep medication (reduced sleep time; group 3). Children with reduced sleep had multiple other sleep problems.

*Statistically significant trend across groups; Cochran-Armitage trend test.

was comparable to that for parent-reported symptoms of attention deficit hyperactivity disorder (ADHD).

Parents volunteered such terms as “meltdowns,” even “nuclear meltdowns,” to describe the episodes. These occurred as attacks of screaming, often brought on by the child not getting his or her way, but at other times with frustration or for no apparent reason. Attack duration was 20 minutes to several hours. During the episodes, the children were inconsolable. Aggression was directed toward other family members, often a specific parent. Parents and grandparents showed bruises or scars where they had been bitten. Children often bit themselves on the arms or banged their heads on the floor or wall during the attacks. Parents had no difficulty distinguishing these rage attacks from normal tantrums, which they thought of as being orders of magnitude less severe. After a rage attack, many children were remorseful, and the transition back to normal mood was “as if a switch had been thrown.” Multiple episodes in a day were not uncommon.

Rage attacks sometimes occurred in the clinic. Characteristics of these attacks included trivial provocations, sudden changes in mood, ear-piercing screaming, loss of self-control, and “shutting down.” Some children crawled under an office chair, getting close to the wall or corner, and engaged in head banging or hiding their faces while crying. Others kicked, hurled objects, threw back their heads, and slammed doors. One slapped his mother across the face and yanked her hair during the peak of crying.

Table III. Relation of reduced sleep to rage frequency

Group	N	Age (years)	Rage score	P values
1	18	4.3 \pm 0.7	1.7 \pm 0.5	—
2	13	4.7 \pm 1.0	3.4 \pm 0.5	.038*
3	19	4.1 \pm 0.8	3.2 \pm 0.5	.015*

Rage was scored on a scale from 0 to 5, with 3 representing 1 episode/day. There was a statistically significant main effect of group on rage frequency ($F = 3.5$; $P = .038$; analysis of variance).

*Rage score (an index of rage frequency/severity) was increased significantly in groups 2 and 3, compared to group 1 (2-tailed t test).

Relation of Clinical Variables

The only clinical or demographic variable that significantly affected sleep disturbance was current steroid or ACTH use (Table I). When OMS was classified on the basis of total sleep time (≥ 10 hours, normal sleep; < 10 hours, reduced sleep), 3 groups were created: normal sleep duration (group 1), reduced sleep duration for which parents did not seek treatment (group 2), and reduced sleep duration for which parents sought treatment (group 3). Steroids or ACTH were currently used in 37% of group 1 children, 54% of group 2 children, and 84% of group 3 children. The proportion of the combined steroid and ACTH-treated children increased with increasing sleep disturbances ($P = .01$; χ^2 test). Although the proportion of steroid-treated children remained unchanged, that of ACTH-treated children increased ($P = .001$). This represented a significant trend across the groups. In group 3, when ACTH dose was divided at the median into “low-dose” (< 10 U/m²/day) and “high dose” (≥ 10 U/m²/day), the number of hours of sleep was lower in the high-dose group (4.8 \pm 0.5) than in the low-dose group (7.1 \pm 0.8) ($P = .028$; 2-tailed t -test).

Statistically significant trends were found across the 3 groups (Table II). Children with reduced sleep also had multiple other sleep problems and more nighttime awakenings, sleepwalking, and rage. Although total motor score and OMS duration did not differ significantly between groups, rage score was significantly higher in groups 2 and 3 than in group 1 (Table III). The rage score was higher in children with symptoms of ADD (3.2 \pm 0.4) than in those without such symptoms (2.0 \pm 0.4) ($P = .044$; 2-tailed t -test). When group 3 was divided into infrequent rage (score < 3) and frequent rage (≥ 3), sleep latency was longer in those with frequent rage (41.7 \pm 8.8 min) than in those with infrequent rage (17.9 \pm 5.1 min) ($P = .049$; 2-tailed t -test).

Children in group 3 were more likely to have received multiple immunotherapies in the past than those in group 1 ($P = .007$; 2-tailed t -test). The same was true of immunotherapy during trazodone treatment ($P = .002$; t -test). In group 3, 8 of 10 children with ≥ 4 awakenings/night had tumors, compared with 0 of 7 with < 4 awakenings ($P = .002$; Fisher’s exact test).

When group 3 was divided into snoring and nonsnoring subgroups, there were no statistically significant differences in

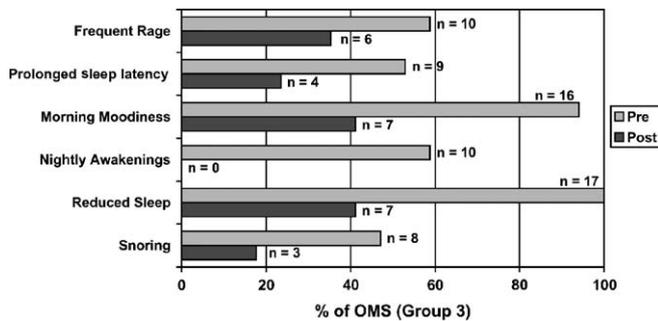


Figure 2. Histogram of the effect of trazodone on the percentage of children with sleep problems, rage, and other behaviors in OMS. “Reduced sleep” was defined as <10 hours/night. “Awakenings” was defined as ≥ 4 /night. “Prolonged sleep latency” denotes sleep latency >30 minutes. Trazodone significantly reduced morning moodiness ($P = .0027$) and snoring ($P = .025$), according to McNemar’s test. Variance was lacking for posttreatment nightly awakenings (0%) and pretreatment reduced sleep (100%), so no statistical test could be used, but the response to treatment was dramatic.

number of night awakenings, rage scores, or percent with ADD/ADHD symptoms. Snoring was not significantly more frequent in those on high-dose ACTH than in those on low-dose ACTH.

Response to Trazodone

Treatment with trazodone significantly reduced the number of children with sleep problems (Figure 2). Trazodone also improved quantitative features of sleep and rage (Table IV). The mean dose was 3.0 ± 0.4 mg/kg/day (range, 1.2 to 6.9 mg/kg/day; median, 2.6 mg/kg/day). The mean duration of trazodone therapy was 1.1 ± 0.2 years (range, 0.08 to 2.4 years; median, 1.0 year).

The effects of trazodone on sleep were not dose-dependent, and trazodone dose did not correlate with the ACTH dose. To further assess the effect of trazodone dose, the children were divided into low-dose ($n = 8$) and high-dose ($n = 9$) groups at the median dose of 2.6 mg/kg. The high-dose subgroup contained significantly more girls ($P = .03$), younger children ($P = .01$), and more severe motor symptoms ($P = .04$) (data not shown), preventing further analysis.

DISCUSSION

This study demonstrates the prevalence of sleep disturbance in children with OMS and these children’s responsiveness to trazodone. The 94% of children with OMS who had difficulty sleeping exceeds the estimated 24% to 43% of children with sleep problems in the general population.¹⁶ Poor sleep quality, caused by sleep fragmentation or sleep deprivation,¹⁷ may increase irritability and behavior problems, and tired children tend to become hyperactive.² Restricting sleep by as little as 1 hour in young children has been associated with significant neurobehavioral decline.¹⁸ The abnormalities in sleep initiation and maintenance in these children with OMS were similar to those reported for depression.¹⁹

Table IV. Effect of trazodone on quantitative features of sleep and rage in group 3

Characteristic	Pretreatment	Posttreatment	<i>P</i> value*
Hours of sleep/night	5.7 ± 0.4	9.8 ± 0.4	.00000025
Number of awakenings	4.1 ± 0.4	0.97 ± 0.26	.00000016
Rage score	3.3 ± 0.5	2.2 ± 0.5	.04

*Paired *t*-test, $n = 17$.

Trazodone was well tolerated, even in toddlers, at the doses prescribed. We are not aware of any previous study of trazodone in this very young population. There has been only a single case report of trazodone for OMS, and sleep was not studied in that case.²⁰ Although those authors reported improvement in the motor signs of OMS, total motor score in our trazodone-treated group did not change significantly.

Another novel observation was that poor sleep contributed to rage attacks and aggressive behavior, which became less frequent during trazodone therapy. Because children with rage had poor sleep and responded to trazodone, we recommend that trazodone be used as a first-line agent for the symptomatic treatment of rage in OMS. Of course, treatment of the primary immune defect should always be the preferred therapy,¹⁵ and when rage does not respond to trazodone, the possibility of an exacerbation of the underlying immunologic abnormality should be considered. Although there have been no previous studies of trazodone for rage, some older children with disruptive behavioral disturbances have responded to trazodone.⁷

Where rage falls within the classification of emotional outbursts in children is not straightforward. Temper tantrums are common between age 18 months (87% of children) and 4 years (59%),²¹ the same age range of OMS onset.¹ The spectrum of behaviors encompassed by tantrums is broad, overlapping in severe cases with what we are calling rage, but tantrums usually are not so extreme, and 75% last less than 5 minutes.²¹ Rage has been defined as “an unpredictable and primitive display of violence that is out of proportion to the provoking incident and often threatens serious self-injury or harm to others.”²² The medical literature contains overlapping terms to describe severe emotional outbursts, including explosive rage, episodic-dyscontrol syndrome, and intermittent explosive disorder (a DSM-IV classification). We find that “rage” is a simple descriptive term that parents can relate to.

Many parents ask whether steroids or ACTH are responsible for the sleep disturbance of OMS. Our data suggest that these agents can contribute to it. ACTH does activate rapid eye movement (REM)-related phasic inhibition during REM sleep.¹² However, irritability and sleeplessness are characteristic features of the OMS prodrome, well before any treatment is initiated. In addition, some parents report that their child’s sleep is much improved on steroid or ACTH

treatment, or that withdrawal from steroid or ACTH therapy is associated with increased sleep problems.

The exact mechanism of trazodone's soporific effect in OMS is unclear because of its multiple potential modes of action, some of which are opposing.⁴ The greatest affinities are for 5-HT receptors, possessing not only agonist-like actions by virtue of inhibiting 5-HT reuptake, but also antagonist properties at 5-HT_{2A/2C} receptors at higher doses. The trazodone metabolite m-CPP is an agonist at 5-HT_{1A} and 5-HT_{1C} receptors and a weak antagonist at 5-HT₂ receptors. However, the sleep disruption and behavioral activation caused by administration of m-CPP alone suggest that the sedative-hypnotic effect of the parent compound is unrelated to m-CPP in humans.²³ Trazodone also has some non-serotonergic properties that may be at play.²⁴

The complexity of sleep physiology and pharmacology implicates multiple neurotransmitters (ie, serotonin, norepinephrine, dopamine, γ -aminobutyric acid, adenosine, acetylcholine)^{4,25} and brain regions (ie, dorsal raphe nuclei, locus ceruleus, dorsal pontine tegmentum, hypothalamus, thalamus, preoptic/basal forebrain, and superchiasmatic nucleus).²⁶ Because opsoclonus and myoclonus appear to be brainstem-mediated in OMS,²⁷ the 3 major projection pathways (serotonergic, noradrenergic, and cholinergic) emanating from the brainstem and involved in sleep physiology may be most relevant. However, primitive emotions, such as rage, are increased in certain childhood disorders of the cerebellum,²⁸ a site involved in OMS.²⁷

Trazodone therapy significantly reduced snoring. Loss of upper airway muscle tone contributes to obstructive sleep apnea/hypopnea, and a 5-HT deficiency state has been suggested.²⁹ The involved muscles, innervated by the hypoglossal nerve, are under serotonergic control, and 5-HT₂ receptor antagonists (including trazodone) can reduce sleep apnea/hypopnea. Although sleep apnea may precipitate daytime inattention, learning difficulties, and possibly hyperactivity, emotional symptoms, and bad conduct,³⁰ it seems unlikely that it is a major contributor to the problems seen in our patients, given its relatively low frequency and lack of relation to reduced sleep. Moreover, adenotonsillar enlargement, the most common cause of childhood sleep apnea,³¹ would not be helped by trazodone therapy.

The therapeutic advantage of trazodone over antidepressant agents for sleep disturbance is that trazodone does not suppress REM sleep and increases deep sleep,³² which is thought to be important to restorative sleep. This highly lipophilic heterocyclic compound, exhibiting linear kinetics, is relatively safe in overdosage,⁴ which is an important safety issue for young children. It produces the well-known sleep alterations of classical sedative amitriptyline-type antidepressants with fewer side effects.³² Children old enough to discern and communicate did not complain of dry mouth or dizziness. Priapism, a rare but serious potential side effect, was not an issue.

Based on how well trazodone is tolerated, we suggest using higher doses as needed in children with more severe rage who have no predisposing risk factors. The dose-equivalent

high-dose range used in adults is about 5 to 8 mg/kg/day. Trazodone doses used in pediatric studies have ranged from 1 to 6 mg/kg/day.^{6,7} Although the relative risks are low, we would not recommend using trazodone in children with OMS who have active seizure activity³³ or ACTH- or steroid-induced cardiac problems.⁴

REFERENCES

1. Tate ED, Allison TJ, Pranzatelli MR, Verhulst SJ. Neuroepidemiologic trends in 105 U.S. cases of pediatric opsoclonus-myoclonus. *J Pediatric Oncol Nurs* 2005;22:8-19.
2. Boyle J, Cropley M. Children's sleep: problems and solutions. *J Fam Health Care* 2004;14:61-3.
3. Tate ED, Pranzatelli MR, Huang Y-Y, Kaplan R. An innovative approach to the problem of sedating children with opsoclonus-myoclonus syndrome: effect on myoclonus and CSF monoamine metabolites. *Ann Neurol* 1994;36:543-4.
4. Haria M, Fitton A, McTavish D. Trazodone: a review of its pharmacology, therapeutic use in depression and therapeutic potential in other disorders. *Drugs Aging* 1994;4:331-55.
5. Mashiko H, Niwa S, Kumashiro H, Kaneko Y, Suzuki S, Numata Y, et al. Effect of trazodone in a single dose before bedtime for sleep disorders accompanied by a depressive state: a dose-finding study with no concomitant use of hypnotic agent. *Psychiatry Clin Neurosci* 1999;53:193-4.
6. Battistella PA, Ruffilli R, Cernetti R, Pettenazzo A, Baldin L, Bertoli S, et al. A placebo-controlled crossover trial using trazodone in pediatric migraine. *Headache* 1993;33:36-9.
7. Zubieta JK, Alessi NE. Acute and chronic administration of trazodone in the treatment of disruptive behavior disorders in children. *J Clin Psychopharmacol* 1992;12:346-51.
8. Levi G, Sogos C. Depressive disorder in pre-adolescence: comorbidity or different clinical subtypes? (A pharmacological contribution). *Isr J Psychiatry Relat Sci* 1997;34:187-94.
9. Balon R. Sleep terror disorder and insomnia treated with trazodone: a case report. *Ann Clin Psychiatry* 1994;6:161-3.
10. Pranzatelli MR, Huang Y-Y, Tate E, Stanley M, Noetzel MJ, Gospe SM, et al. Cerebrospinal fluid 5-hydroxyindoleacetic acid and homovanillic acid in the pediatric opsoclonus-myoclonus syndrome. *Ann Neurol* 1995;37:189-97.
11. Kruesi MJP, Rapoport JL, Hamburger S, Hibbs E, Potter WZ. Cerebrospinal fluid monoamine metabolites, aggression and impulsivity in disruptive behavior disorders of children and adolescents. *Arch Gen Psychiatry* 1990;47:419-26.
12. Kohyama J, Shimohira M, Tanuma N, Hasegawa T, Iwakawa Y. ACTH activates rapid eye movement-related phasic inhibition during REM sleep in patients with infantile spasms. *Acta Neurol Scand* 2000;100:145-52.
13. Pranzatelli MR, Huang Y-Y, Tate E, Goldstein DS, Holmes CS, Goldstein EM, et al. Effect of high-dose corticotropin on cerebrospinal fluid monoaminergic neurotransmitters or metabolites in corticotropin-responsive pediatric opsoclonus-myoclonus. *Mov Disord* 1998;13:522-8.
14. O'Brien LM, Holbrook CR, Mervis CB, Klaus CJ, Bruner JL, Raffield TJ, et al. Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention deficit/hyperactivity disorder. *Pediatrics* 2003;111:554-63.
15. Pranzatelli MR, Travelstead A, Tate ED, Allison TJ, Moticka EJ, Franz DN, et al. B- and T-cell markers in opsoclonus-myoclonus: immunophenotyping of CSF and blood lymphocytes. *Neurology* 2004;62:1526-32.
16. Stores G, Wiggs L. Clinical services for sleep disorders. *Arch Dis Child* 1998;79:495-7.
17. Bonnet MH, Arand DL. Clinical effects of sleep fragmentation versus sleep deprivation. *Sleep Med Rev* 2003;7:297-310.
18. Sadeh A, Gruber R, Raviv A. The effects of sleep restriction and extension on school-age children: what a difference an hour makes. *Child Dev* 2003;74:444-55.

19. Saletu-Zyhlarz GM, Abu-Bakr MH, Anderer P, Gruber G, Mandl M, Strobl R, et al. Insomnia in depression: differences in objective and subjective sleep and awakening quality to normal controls and acute effect of trazodone. *Prog Neuropsychopharmacol Biol Psychiatry* 2002;26:249-60.
20. Papini M, Pasquinelli A, Filippini A. Steroid-dependent form of Kinsbourne syndrome: successful treatment with trazodone. *Ital J Neurol Sci* 1992;13:369-72.
21. Potegal M, Kosorok MR, Davidson RJ. Temper tantrums in young children, 2: tantrum duration and temporal organization. *J Dev Behav Pediatr* 2003;24:148-54.
22. Mandoki MW, Sumner GS, Matthews-Ferrari K. Evaluation and treatment of rage in children and adolescents. *Child Psychiatry Hum Dev* 1992;22:227-35.
23. Lawlor BA, Newhouse PA, Balkin TJ, Molchan SE, Mellow AM, Murphy DL, et al. A preliminary study of the effects of nighttime administration of the serotonin agonist, m-CPP, on sleep architecture and behavior in healthy volunteers. *Biol Psychiatry* 1991;29:281-6.
24. Ware JC, Pittard JT. Increased deep sleep after trazodone use: a double-blind placebo-controlled study in healthy young adults. *J Clin Psychiatry* 1990;51(suppl):18-22.
25. Ursin R. Serotonin and sleep. *Sleep Med Rev* 2002;6:55-69.
26. Kayama Y, Koyama Y. Control of sleep and wakefulness by brainstem monoaminergic and cholinergic neurons. *Acta Neurochir Suppl* 2003;87:3-6.
27. Pranzatelli MR. The neurobiology of opsoclonus-myoclonus syndrome. *Clin Neuropharmacol* 1992;15:186-228.
28. Riva D, Giorgi C. The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. *Brain* 2000;123:1051-61.
29. Veasey SC. Serotonin agonists and antagonists in obstructive sleep apnea: therapeutic potential. *Am J Respir Med* 2003;2:21-9.
30. Urschitz MS, Eitner S, Guenther A, Eggebrecht E, Wolff J, Urschitz-Duprat PM, et al. Habitual snoring, intermittent hypoxia, and impaired behavior in primary school children. *Pediatrics* 2004;114:1041-8.
31. Hoban TF. Sleep and its disorders in children. *Semin Neurol* 2004;24:327-40.
32. Saletu-Zyhlarz GM, Abu-Bakr MH, Anderer P, Semler B, Decker K, Parapatics S, et al. Insomnia related to dysthymia: polysomnographic and psychometric comparison with normal controls and acute therapeutic trials with trazodone. *Neuropsychobiology* 2001;44:139-49.
33. Pisani F, Spina E, Oteri G. Antidepressant drugs and seizure susceptibility: from in vitro data to clinical practice. *Epilepsia* 1999;40(suppl 10):S48-56.

INLET PATCH: HETEROTOPIC GASTRIC MUCOSA—ANOTHER CONTRIBUTOR TO SUPRAESOPHAGEAL SYMPTOMS?

SUHASINI MACHA, MD, SUSHMA REDDY, MD, RAJA RABAH, MD, RONALD THOMAS, PHD, AND VASUNDHARA TOLIA, MD

Objective To determine prospectively the incidence of an inlet patch (IP) in children requiring esophagogastroduodenoscopy (EGD) and assess the prevalence of presenting symptoms between children with and without an IP.

Study design All patients undergoing EGD in a 2-year period were assessed for the presence of an IP with biopsy confirmation. IP, distal esophagus, and stomach biopsy specimens were blindly reviewed by a pathologist for the presence and degree of inflammation and intestinal metaplasia. Symptoms from children with and without an IP were compared.

Results From 407 EGDs done by a single endoscopist, 24 patients had confirmed IP (incidence of 5.9%). The presence and degree of inflammation were always relatively greater in the columnar mucosa of the IP than in the antral/body gastric mucosa in the same patient ($P = .0027$). Inflammation was similar in the squamous epithelium around the IP and in the distal esophagus ($P = .46$). Two patients had intestinal metaplasia of the IP. The patients with IPs had a higher prevalence of respiratory symptoms than the control group ($P = .03$).

Conclusions Children with IPs may have a higher frequency of respiratory symptoms. Periodic surveillance should be performed in children with intestinal metaplasia of an IP. (*J Pediatr* 2005;147:379-82)

An inlet patch (IP) is a distinct region of ectopic gastric mucosa located in the proximal esophagus.^{1,2} IP has been described in adults as a round/oval shaped, flat, sharply demarcated area from the normal adjacent esophageal mucosa, averaging 20 mm in size. It has been identified in 0.3% to 10% of the adult population undergoing diagnostic endoscopy.³⁻⁷ It is usually seen on the lateral or posterior surface of the proximal esophagus during careful withdrawal of the endoscope, and can easily be missed during a routine procedure.⁶ Esophageal strictures, ulcerations, tracheoesophageal fistula, webs, gastrointestinal bleeding, fatal esophageal bleeding, perforation, and colonization by *Helicobacter pylori* have been reported with IP.⁸⁻¹⁰ Furthermore, IP has been associated with Barrett's esophagus and adenocarcinoma.^{6,7,9}

We performed a prospective study to determine the incidence of IP in children undergoing esophagogastroduodenoscopy (EGD), to study its macroscopic and microscopic characteristics, and to determine its association with clinical symptoms. Gastroesophageal reflux disease (GERD) has been linked to diseases of supraesophageal organs, including otolaryngologic (ie, ear, nose, and throat [ENT]), respiratory, and dental organs.¹¹⁻¹³ Because there is evidence of acid secretion from the IP,¹⁴ we hypothesized that the abnormal, strategic location of the acid-secreting gastric mucosa in the proximal esophagus may contribute to supraesophageal symptoms of GERD in affected children.

METHODS

All patients undergoing EGD by a single endoscopist (VT) for routine indications of persistent abdominal pain, recurrent vomiting, dysphagia, and chronic diarrhea were prospectively assessed for the presence of IP over a 2-year period (January 1, 2001 to December 31, 2002) at Children's Hospital of Michigan. An Olympus GIF-160 video gastroscop (Olympus America, Melville, NY) was used for each procedure.

IP was identified as a discrete, salmon-pink or yellowish type lesion in the proximal esophagus, usually within 5 cm of the cricopharyngeus (Figure 1). It was seen most commonly during slow withdrawal and rotation of the gastroscop during mild inflation. Usually, the IP was well demarcated from the surrounding pearly white normal esophageal mucosa.

From the Departments of Pediatrics and Pathology, Children's Hospital of Michigan, Wayne State University School of Medicine, Detroit, Michigan. Submitted for publication Oct 27, 2004; last revision received Dec 29, 2004; accepted Mar 1, 2005.

Reprint requests: Vasundhara Tolia, MD, Director, Pediatric Gastroenterology, Children's Hospital of Michigan, 3901 Beaubien Boulevard, Detroit, MI 48201-2196. E-mail: vtolia@med.wayne.edu.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.03.002

EGD	Esophagogastroduodenoscopy	GERD	Gastroesophageal reflux disease
ENT	Ear, nose, and throat	IP	Inlet patch

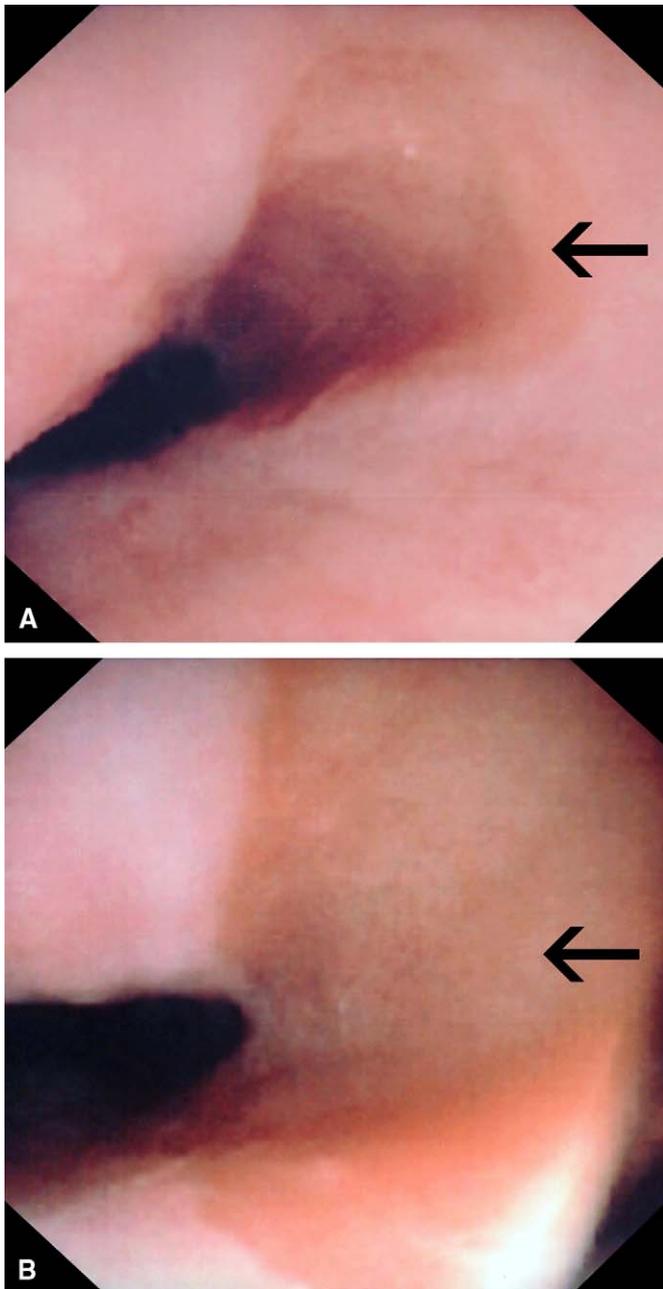


Figure 1. Endoscopic appearance of an IP, seen as a sharply differentiated red area (arrows) from surrounding mucosa.

An additional biopsy specimen was obtained from the patients with suspected IP. All biopsy specimens were blindly reviewed by a single pathologist (RR). The squamous mucosa was examined for changes of reflux esophagitis,¹⁵ and the columnar mucosa was examined for the presence and degree of inflammation and/or intestinal metaplasia according to the modified Sydney classification system.¹⁶

An age-matched control group was randomly selected for review from the rest of the patients undergoing EGD during the same time period. Symptoms related to the gastrointestinal tract (eg, nausea, vomiting, abdominal pain, diarrhea, dysphagia) and supraesophageal symptoms pertaining to respiratory (eg, cough, wheezing, choking/gagging, asthma), or ENT

organs (eg, recurrent otitis media, sinusitis, pharyngitis) were assessed in patients with IP and in a control group. Our institutional review board approved the study design.

Statistical Analysis

Comparison of symptom incidence between the 2 groups was performed using nonparametric Fisher's exact test. Comparisons of continuously scaled variables were performed using a parametric independent samples *t*-test. If assumptions for proper application of the parametric *t*-test (ie, normality and/or homogeneity of variance) were violated, then a nonparametric Mann-Whitney U-test was substituted. Statistical significance was considered achieved at a *P* value $\leq .05$ (2-tailed test). All statistical analyses were performed using SPSS Version 11.5 (SPSS Inc, Chicago, Ill).

RESULTS

A total of 407 EGDs were performed during the study period. IP was suspected in 38 patients and biopsy-confirmed in 24. (for an incidence of 5.9%). In this study group, 12 were male and 12 were female, the mean age was 10 years (range, 1 to 17 years), and the racial/ethnic breakdown was 12 caucasians, 10 African-Americans, and 2 Asian-Americans. Single IP was found in 23 patients; double IP, in 1 patient. The IP averaged 5 mm, as assessed against the span of an open biopsy forceps.

On histology, 21 out of the 24 patients with IP had oxyntic and cardiac mucosa. One contained only cardiac mucosa (Figure 2), and 2 showed intestinal metaplasia suggestive of Barrett's esophagus (Figure 3). The incidence of Barrett's changes in these patients with IP was 8.3% (2/24 patients).

The presence and degree of inflammation were always relatively greater in the columnar mucosa of the IP than in the antral/body gastric mucosa in the same patient (*P* = .0027) (Figure 4). There was no difference in the degree of inflammation in the squamous epithelium adjacent to the IP and that in the distal esophagus (*P* = .46).

Patients with IP demonstrated a higher incidence of respiratory symptoms, specifically cough, wheezing, and asthma, compared with the control group (*P* = .03). There was no significant difference in the incidence of recurrent abdominal pain (*P* = .74), nausea/vomiting (*P* = .53), choking/gagging/dysphagia (*P* = .34), or ENT symptoms (ie, recurrent otitis media, sinusitis, pharyngitis) (*P* = .23) between the 2 groups. Of the 2 patients diagnosed with intestinal metaplasia of the IP, 1 underwent a repeat endoscopy 1 year later with resolution of the intestinal metaplasia and is being followed periodically; the other patient was lost to follow-up.

DISCUSSION

IP has been defined as a rose- or salmon-colored velvety mucosa clearly demarcated from the surrounding pearly gray esophageal mucosa in the proximal esophagus, just below the upper esophageal sphincter. Its surface can be flat, slightly raised, or depressed; it may even resemble a sessile polyp.⁵ IP

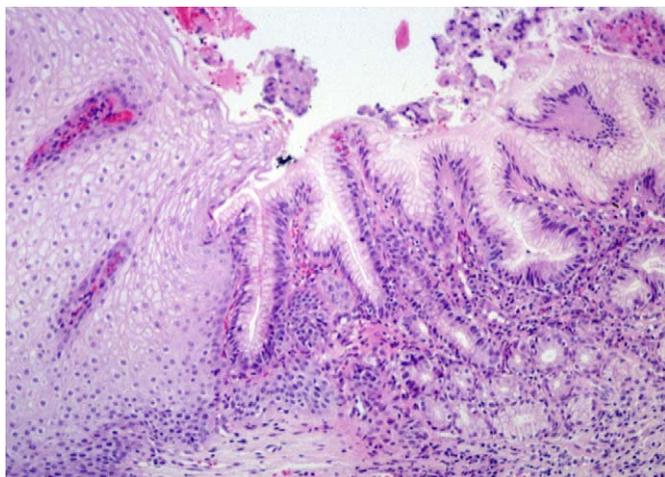


Figure 2. Squamous mucosa on the left side in continuity with the cardiac-type gastric mucosa seen in a proximal esophageal biopsy specimen.

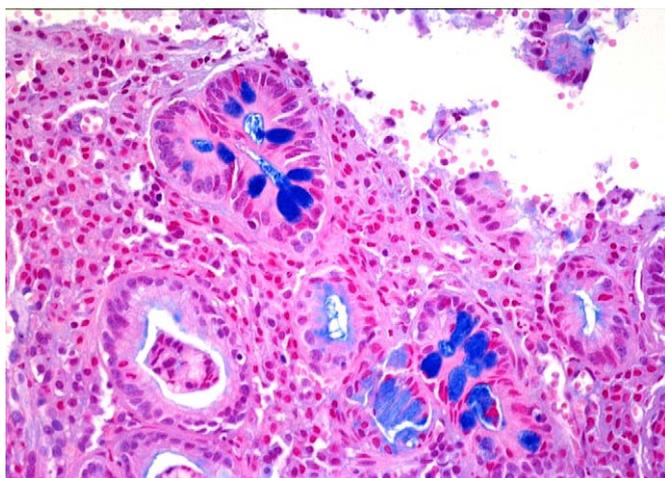


Figure 3. Intestinal metaplasia evident by the presence of goblet cells (arrow) in the columnar mucosa of the IP. (Alcian Blue stain at pH 2.5.)

was first described by Schmidt in 1805 during postmortem examinations.¹⁷ Autopsy studies report an incidence of aberrant gastric mucosa in the esophagus of 4.5% in infants and 11.8% in children.^{1,2} A case report of a child with a circumferential lesion just below the cricopharyngeus containing gastric epithelium with ulceration causing progressive dysphagia and odynophagia has been described.¹

In this study we determined the incidence and symptoms of children with IP detected during endoscopy. IP was suspected in 38 patients, and was confirmed in 24 of these on biopsy. Inaccurate targeting of IP for biopsy or mucosal appearance resembling IP could account for the discrepancy in the numbers between endoscopic suspicion and histologic confirmation.

The upper end of the esophagus harboring IP is the least-inspected area during upper endoscopy. Repeated contractions of the upper esophageal sphincter make a thorough inspection, photography, and biopsy of this area difficult.⁸ It is

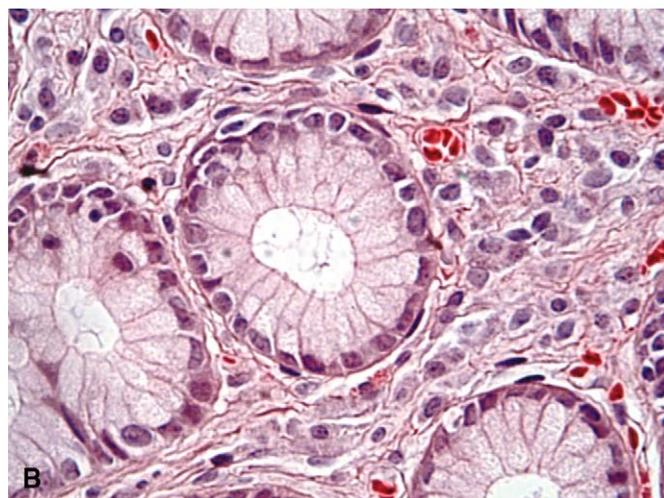
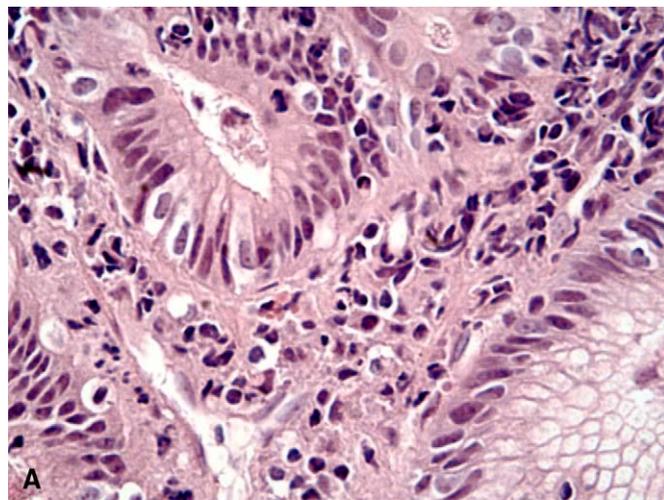


Figure 4. Severe inflammation of the columnar mucosa in the IP (A) compared with the gastric body mucosa (B) in the same patient.

essential that the endoscope be withdrawn slowly at the end of the procedure, to rule out the presence of IP.

Microscopically, IP represents gastric-type mucosa with parietal and chief cells and a variable degree of inflammation.^{7,18} Presence of gastric heterotopic mucosa in the upper esophagus is thought to represent a remnant of gastric mucosa left behind during the descent of the stomach in the first 2 months of embryologic development.^{6,18,19} Another hypothesis is that IP is an acquired lesion with pathogenesis similar to that of Barrett's mucosa in the distal esophagus.⁸

Heterotopic gastric mucosa has been described throughout the gastrointestinal tract, including the tongue, floor of the mouth, submandibular gland, small intestine, pancreas, gallbladder, and Meckel's diverticulum.¹⁰ Although it may appear as a benign incidental finding at EGD, erosions, ulcerations, cystic dilations of the glands, fibrosis, intestinal metaplasia, dysplasia surrounding an adenocarcinoma, and even angiodysplasia have been associated with IP.^{5,20} The presence of intestinal metaplasia suggests that long-term follow-up with periodic surveillance is needed in these patients. In our study, the incidence of Barrett's changes in patients with IP was 8.3% (2/24).

We demonstrated that patients with IP in the pediatric population have a significantly higher incidence of respiratory symptoms, specifically cough, wheezing, and asthma, compared with the control group ($P = .03$); however, the prevalence of gastrointestinal and ENT symptoms was similar in the 2 groups in our study. Although a previous study using pH monitoring in infants had not elicited increased acid reflux at the proximal level with respiratory symptoms,²¹ the findings of the present study support our hypothesis that the proximal location of acid-secreting gastric mucosa in the IP may contribute to supraesophageal symptoms that affect the airway.¹¹ One previous study reported an association of dysphagia, retrosternal pain, and laryngeal symptoms, including cough and dyspnea, with IP in adults.²⁰

The precise mechanism by which reflux causes respiratory or ENT complications remains uncertain. Vagally mediated reflux triggered by acid in the esophagus, leading to heightened bronchial reactivity, a direct axonal reflex, neurogenic inflammation, and microaspiration of gastric acid have been implicated as possible mechanisms.^{12,22} Such stimulation is more likely to occur if acid is present in the proximal esophagus. Whether long-standing inflammation can lead to ENT symptoms remains to be determined.

Incidental identification of IP does not require additional specific treatment unless significant respiratory symptoms are present. These symptoms should be sought by direct questioning if not reported. These lesions must be biopsied for detection of unsuspected findings.

We conclude that although IP is usually considered a benign incidental finding, it could contribute to the increased respiratory symptoms typically associated with GERD. Careful examination of the proximal esophagus during upper endoscopy for evaluation of any metaplastic changes, followed up with periodic surveillance, is recommended. Further prospective studies in children and adults will help further define the role of IP in supraesophageal symptoms.

REFERENCES

- Powell R, Luck S. Cervical esophageal obstruction by ectopic gastric mucosa. *J Pediatr Surg* 1988;23:632-4.
- Rector LE, Connerly MI. Aberrant mucosa in the esophagus in infants and children. *Arch Pathol Lab Med* 1941;31:285-94.
- Maconi G, Pace F, Vago L, Carsana L, Bargiggia S, Porro GB. Prevalence and clinical features of heterotopic gastric mucosa in the upper esophagus. *Eur J Gastroenterol* 2000;12:745-9.
- Tang P, McKinley MJ, Sporrer M, Kahn E. Inlet patch: prevalence, histologic type and association with esophagitis, Barrett's esophagus and antritis. *Arch Pathol Lab Med* 2004;128:444-7.
- Jacobs E, Dehou MF. Heterotopic gastric mucosa in the upper esophagus: a prospective study of 33 cases and review of literature. *Endoscopy* 1997;29:710-5.
- Wang GQ, Dawsey SM, Zhou MH, Lewin KJ. Gastric heterotopia in the upper esophagus (inlet patch) in endoscopic surveys in northern China. *J Clin Gastroenterol* 1994;19:321-4.
- Borhan-Manesh F, Farnum JB. Incidence of heterotopic gastric mucosa in the upper esophagus. *Gut* 1991;32:968-72.
- Ward E, Achem S. Gastric heterotopia in the proximal esophagus complicated by stricture. *Gastrointest Endosc* 2003;57:131-3.
- Sanchez-Pernaute A, Hernando F, Diez-Valladares L, Gonzalez O, Perez Aguirre E, Furio V, et al. Heterotopic gastric mucosa in the upper esophagus ("inlet patch"): a rare cause of esophageal perforation. *Am J Gastroenterol* 1999;94:3047-50.
- Gutierrez O, Akamatsu T, Cardona H, Graham D, El-Zimaity H. *Helicobacter pylori* and heterotopic gastric mucosa in the upper esophagus (the inlet patch). *Am J Gastroenterol* 2003;98:1266-70.
- Tolia V. Gastroesophageal reflux and supraesophageal complications: really true or ballyhoo? *J Pediatr Gastroenterol Nutr* 2002;34:269-73.
- Irwin RS, Zawacki JK. Accurately diagnosing and successfully treating chronic cough due to gastroesophageal reflux can be difficult. *Am J Gastroenterol* 1999;94:3095-8.
- Dahshan A, Patel H, Delaney J, Wuerth A, Thomas R, Tolia V. Gastroesophageal reflux disease and dental erosion in children. *J Pediatr* 2002;140:474-8.
- Galan A, Katzka D, Castell D. Acid secretion from an esophageal inlet patch demonstrated by ambulatory pH monitoring. *Gastroenterology* 1998; 115:1574-6.
- Dahms BB, Rothstein FC. Mucosal biopsy of the esophagus in children. *Perspect Pediatr Pathol* 1987;11:97-123.
- Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis: the updated Sydney system. *Am J Surg Pathol* 1996;20:1161-81.
- Schmidt FA. De mammalium oesophage atque ventriculo. Inaug Dissert, Halle, in off. Bathenea, 1805.
- Cuddihy PJ, Maheshwar A, Griffith H. Symptomatic heterotopic gastric mucosa in the upper esophagus. *J Laryngol Otol* 1998;112:979-81.
- Jabbari M, Goresky CA, Lough J, Yaffe C, Daly D. The inlet patch: heterotopic gastric mucosa in the upper esophagus. *Gastroenterology* 1985; 89:352-6.
- Lauwers GY, Scott GV, Vauthey JN. Adenocarcinoma of the upper esophagus arising in cervical ectopic gastric mucosa: rare evidence of malignant potential of so-called "inlet patch." *Dig Dis Sci* 1998;43:901-7.
- Vijayaratnam V, Simpson P, Lin CH, Tolia V. Role of proximal esophageal acid reflux in infants with respiratory symptoms. *Pediatr Pulmonol* 1999;27:231-5.
- Harding SM, Richter JE. The role of gastroesophageal reflux in chronic cough and asthma. *Chest* 1997;111:1389-402.

HOME NOCTURNAL HEMODIALYSIS IN CHILDREN

DENIS F. GEARY, MB, MRCP(UK), FRCP(C), E. PIVA, RN, J. TYRRELL, RN, M. J. GAJARIA, BSc, CDP, G. PICONE, MSW,
L. E. KEATING, BA, MSc, AND E. A. HARVEY, MD, FRCP(C)

Objective To describe the effect of home nocturnal hemodialysis (NHD) in North American children.

Study design Four teenagers underwent NHD for 8 hours, 6 to 7 nights/week, using either central venous lines or fistulae for periods of 6 to 12 months. Blood flow approximated 200 mL/min, and dialysate flow was 300 mL/min; the dialysate contained potassium and phosphate. The procedure was remotely monitored.

Results The children had unrestricted diets and fluid allowance and did not require phosphate binders. Persistent relative hypotension developed in 2 of 4 children. Weekly Kt/V urea values were consistently >10; other biochemical measures varied. Quality of life and school attendance improved in 3 of 4 children. The workload and reported emotional burden of NHD was substantial. No significant complications occurred. Dialysate losses of calcium, phosphate and carnitine required supplementation. The annual cost per patient was \$64,000 Canadian, which represented a 27% savings compared with thrice weekly in-center hemodialysis.

Conclusions NHD is feasible in selected children, allows free dietary and fluid intake, and improves patient wellbeing. The burden on the family is substantial, and NHD requires support of a dedicated multidisciplinary team. (*J Pediatr* 2005; 147:383-7)

Hemodialysis (HD) was first introduced as a maintenance therapy for children with chronic renal failure in 1968.¹ Approximately a decade later, continuous ambulatory peritoneal dialysis was introduced.² Since then, peritoneal dialysis (PD) has become the most widely used dialysis modality for North American children.³ The use of hemodialysis as a home nocturnal treatment (NHD) was developed for adults in 1994,^{4,5} and the use of this treatment has expanded in the adult renal failure population, in whom it reportedly improves dialysis delivery and patient wellbeing, at reduced cost.⁶⁻¹² We describe our experience with NHD in 4 children at The Hospital for Sick Children in Toronto, including clinical, psychosocial, and economic outcomes.

PATIENTS

Patient 1

Patient 1 was a 13-year-old male with end-stage renal disease caused by focal segmental glomerulosclerosis who started PD at age 4 years, and subsequently underwent bilateral nephrectomy and renal transplantation at age 8. At age 11, because of recurrent disease in the graft and chronic allograft nephropathy, he underwent graft nephrectomy and restarted PD. He had recurrent peritonitis and 2 episodes of pancreatitis, which necessitated a switch to HD. On HD, he remained malnourished, had multiple central venous access clots and infections, was markedly hypertensive and repeatedly fluid overloaded, and was unable to comply with dietary and medication prescriptions. In June 2002, he started NHD.

Patient 2

Focal segmental glomerulosclerosis developed in this 15.5-year-old female patient at age 5 years, and she started maintenance PD 3 years later. In 1996, she received a cadaveric

From the Division of Nephrology, Department of Paediatrics, The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada.

Supported by a grant from the CHANGE foundation.

Submitted for publication Nov 10, 2004; last revision received Apr 7, 2005; accepted Apr 14, 2005.

Reprint requests: Denis F. Geary, MB, MRCP(UK), FRCP(C), Chief, Division of Nephrology, The Hospital for Sick Children, 555 University Ave, Toronto, ON M5G 1X8. E-mail: denis.geary@sickkids.ca.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.04.034

AV	Arteriovenous	NHD	Nocturnal hemodialysis
CVL	Central venous lines	PD	Peritoneal dialysis
HD	Hemodialysis		

renal transplant, which was complicated by recurrence of her original disease, development of seizures and facial palsy, chronic allograft nephropathy, and malnutrition. In 1998, she restarted cycling PD and had a gastrostomy tube inserted for supplemental feeds. She was referred to our hospital in 2003 because of increasing morbidity associated with ultrafiltration failure, despite approximately 20 hours daily of cycling PD. Because of her distance from the hospital, the family elected to start NHD.

Patient 3

This 16-year-old boy developed Wegener's granulomatosis with crescentic glomerulonephritis at age 15 years. He progressed to end-stage renal disease and started PD. The family requested a switch to NHD after 6 months because of peritonitis and severe hypertension.

Patient 4

Hemolytic uremic syndrome developed in this 12.5-year-old girl with end-stage renal disease and severe hypertension at age 3 years, requiring bilateral nephrectomies. In 2001, she underwent a living-donor kidney transplant, but chronic allograft nephropathy and end-stage renal disease developed. Because of geographic location and fears of increasing obesity if she was treated with PD, the family elected to start NHD.

METHODS

The technical considerations, including home renovations, dialysis machines and water purification units, the possible need for water softeners, and the remote monitoring process, were previously reported for our program and for adults.^{13,14}

Vascular access was provided initially with central venous lines (CVL) in all 4 patients and, subsequently, arteriovenous (AV) fistulae in 2 patients. During NHD, central venous lines are held in place with a locking device described by Pierratos.⁷ Access through AV fistulas has been with both single-needle and 2-needle techniques; we used a "buttonhole" technique by repeated insertion of the access needles at the same location to form a needle-track,¹⁵ which facilitated access by the care provider at home. The parent supervisor, patient, or both was taught this technique for access of a fistulae by the teaching nurse.

Dialysate flows of 200 to 300 mL/min were used, with blood flows of 150 to 200 mL/min. Dialysis was provided for approximately 8 hours nightly, 6 to 7 times per week, usually while the patient was sleeping. The dialysate contained potassium at a concentration of 2 to 3 mEq/L. Calcium content of the dialysate was adjusted between 3.0 and 3.5 mEq/L, because chronic negative calcium balance may develop with large ultrafiltration volumes. Phosphate was added to the acid dialysate concentrate as a sodium phosphate (Fleet) enema, which provided a concentration approximating 3 mg/dL.

Staff Requirements

The NHD program was a collaborative effort between the nurses, technologist, social workers, dieticians, and medical staff. The nursing commitment was substantial and demanded expertise in HD and family education. Collaboration with Fresenius Medical Care greatly facilitated the process because of their staff expertise and provision of teaching materials.

Cost Analysis

Estimation of program costs, expressed in Canadian (Cd) dollars, included: home renovations, including plumbing, electrical, cost of water testing, and installation of phone lines, were measured as actual costs and amortized over 1 year. Costs for the 6-week training period were itemized prospectively and amortized over 1 year. Equipment, including dialysis machines, water softeners, reverse osmosis machines, computer hardware, and home centrifuge, were itemized individually and amortized over 5 years. Dialysis disposables/surgical supplies were individually itemized and included as actual costs. Staff costs were prospectively itemized and are presented as the mean for the 4 patients; nursing costs for ongoing patient care were calculated with a nurse-to-patient ratio of 1:8, with training costs extra. Program development costs (including initial supplies, teaching materials, staff time) are provided separately. No costs are included for physicians or medication.

Psychosocial and Clinical Evaluations

Psychosocial evaluations were performed by a social worker (G.P.) on the basis of comments provided by the children, their parents, or both, an analysis of the number of clinic visits for 6 months preceding and subsequently during each 6 months while undergoing NHD, and a record of school attendance.

Quality of life was estimated using the PedsQL version 4.0 generic core scale.¹⁶ This 23-item self-report questionnaire includes 8 items to determine physical functioning; psychosocial functioning is evaluated by 5 questions each related to emotional, social, and school-functioning. Responses to all questions are scored to provide a total of 0 to 100, with higher scores indicating a better health-related quality of life.

A large number of clinical and biochemical tests were monitored to evaluate efficacy of dialysis and clinical well-being, and results are reported in tabular form. Single pool Kt/V urea was estimated with the Daugirdas logarithmic formula.¹⁷ Clinical and biochemical outcomes were collected at baseline and 3, 6, and 12 months. Results are presented in descriptive form, because only 4 patients are included. Comparative statistical analysis is not provided.

The NHD program was initiated for clinical care reasons. However, because data were collected prospectively and there was intent to publish our experience, Research Ethics Board approval was obtained before patients started the program. Also, because these patients are a small group that might be identifiable, written consent was obtained to include the data in the case reports.

RESULTS

Patient Selection

The 4 families who met eligibility criteria agreed to participate in the program and completed the training requirements. No families have been denied access to this program. Clinical and biochemical outcomes are reported at 3 and 6 months for all patients; 12-month data are available for patients 1 and 2. Patient 1 received NHD for 1 year before switching to a hybrid form of dialysis of NHD Sunday to Wednesday nights inclusive, with an in-center HD on Friday for respite purposes. There have been no dropouts from the program, and no patient deaths.

Technical and Vascular Access Evaluations

TECHNICAL. Few technical problems were encountered. Remote monitoring was used for all procedures, but no phone calls to patient homes were required because of a failure to respond to an alarm in timely manner. One family was called when an air detect alarm was noted by the monitor.

VASCULAR ACCESS. Episodes of CVL dysfunction were treated with interdialytic instillation of intraluminal tissue plasminogen activator. One CVL infection (*Staphylococcus aureus*) was documented in patient 1 when he fell in a lake at camp, and 1 tunnel infection was observed in patient 2 (diphtheroid organism). The frequency of these episodes was not considered different than in our general HD population. The use of the "buttonhole" technique to access a fistula repeatedly through the same site was associated with the development of an aneurysm at the site, but to date this has not interfered with its continued use. No line disconnections were reported.

STAFF REQUIREMENTS. Patients and their parents were trained for 6 weeks: 3 in-center 6-hour sessions per week for 5 weeks, followed by 1 week (3-5 sessions) of nights at the hospital, where the parents are required to perform all duties; the nurse is also available overnight. In addition, parents were required to write 7 tests, with a passing grade considered to be >80% for each examination. Ongoing monitoring of safety and efficacy includes remote monitoring, weekly blood tests, and monthly clinic visits.

COST EVALUATION. The costs for development of the NHD program were Cd \$4200 (approximately \$3400 in US dollars). Patient/family training cost averaged Cd \$9000 for the 6 weeks, as aforementioned. The costs of the training are amortized over 1 year and included in the overall annual cost estimate of Cd \$64000.

Psychosocial and Clinical Evaluations

Variability in many of these outcomes is thought to reflect the diversity, complexity, and multiplicity of the problems that were present before initiation of NHD in these patients. Consistent findings among the 4 patients included normal plasma calcium and phosphate values, increased single-

pool Kt/V urea measurements and high β 2-microglobulin levels (Table I; available online at www.jpeds.com). Bone density remained poor in patients 2 and 4, and deteriorated in patients 1 and 3, which suggests the need to avoid sustained negative calcium and phosphate balance. Both free and total plasma carnitine values were below reference range in all patients, until supplemented. The clinical significance of this finding is uncertain, although it might represent a deficiency caused by solute clearance. Many inconsistencies were also observed in outcome measures. The rise in PTH levels in patient 1 between 6 and 12 months could be caused by frequent interruption to his NHD schedule and line function problems during this time (Table I). This patient had a fistula created and transferred to hybrid dialysis after 12 months for respite. Increased CRP levels were also noted in 3 of the 4 patients; the significance of this is unknown.

Information on medications for blood pressure, anemia (erythropoietic therapy), phosphate binders and carnitine supplements are presented in Table II (available online at www.jpeds.com).

Although all the children had unrestricted diets and fluid intakes, weight gain was variable. Requests for accurate documentation of dietary intake were not regularly adhered to, so the effect of frequent dialysis on nutritional state remains unclear. However, for patient 2, who was completely G-tube dependant at the start of NHD, it was documented that her oral intake increased to 25% to 50% of her dietary requirements. Also, when weight loss has occurred, it is unclear whether this is in part caused by increased exercise/activity. Normalized protein catabolic rate was not measured.

Blood pressure control was also variable. Patients 2 and 3, with native kidneys in situ, required anti-hypertensive medication, whereas relative hypotension developed and persisted in patients 1 and 4. These latter 2 anephric children received Midodrine before dialysis to prevent exacerbation of their hypotension.

Quality of life (Table I; online at www.jpeds.com) physical and psychological scores improved in 3 of 4 patients. Patient 1, who had a decreased quality of life score between 6 and 12 months, required respite relief and started hybrid dialysis at 12 months.

School attendance, as a reflection of psychosocial behavior, improved substantially in 3 children, and teacher reports included improved interaction with peers and improved performance overall. Patient 3 had persistent and significant numbers of days missed from school related to complications of his underlying Wegener's granulomatosis and the associated immunosuppressant treatment.

Specific comments from the children and parents included: "Because this program has changed my life completely, by making the quality of my life ten times better..."; "I feel like a normal kid"; "She can't remember the last time she felt so good"; "I used to push her around the block in a wheelchair, and now she is canvassing door-to-door to raise money for her school."

Negative comments about NHD reflected the intensity of the workload and parental anxieties related to the

complexity of care provided at home. The mother of patient 1 was psychologically and emotionally worn out, until respite was provided when a hybrid form of dialysis was instituted. Others described disruption for other family members and difficulty establishing a new routine within the home.

DISCUSSION

This report describes the successful implementation of NHD for children. Although introduced approximately 10 years ago for adults, the only previous pediatric experience with NHD, published in abstract form from Sweden,¹² described 4 children with ages similar to our own patients. They used CVL as blood access, whereas we have also successfully used AV fistulas. Overall, their brief report suggests that outcomes are comparable to our own, and that NHD provides an improvement in patient well-being compared with other dialysis modalities.¹² Consequently, we recommend that this modality be considered for all teenagers, and some younger school-age children starting dialysis.

The success of NHD is perhaps best exemplified by the continuation of the procedure in all patients. No patients have died, although the severity of uremia and its complications when starting NHD was extreme for patients 1 and 2.

The Hemo Study for hemodialysis patients¹⁸ and the ADEMEX Study of peritoneal dialysis patients¹⁹ suggested that increasing the clearance of urea as measured with Kt/V urea, beyond certain limits, does not produce further improvement in patient outcomes. However, we do not believe that the results of these studies are applicable to NHD. Rather, the Hemo Study results suggest that for intermittent therapies, there are limitations to what can be achieved; the Hemo Study can be interpreted to suggest that more frequent dialysis, allowing for less interdialytic accumulation of toxins, may be the only remaining way to improve outcomes for patients undergoing HD. Data in small numbers of patients receiving NHD suggest that long-term survival is improved when compared with conventional dialysis modalities.⁸ As an alternative to NHD, the introduction of short daily dialysis at home may be considered. Short daily dialysis has the advantage that it can be provided during the daylight hours when the family is awake, and therefore remote monitoring will not be required. However, the amount of dialysis provided using a short daily regimen is less than that achieved by overnight dialysis, and because the set-up and tear-down time and supplies needed are the same for each modality, short daily dialysis is less cost-effective.

The introduction of NHD to a patient's home is a huge undertaking. However, the improvement in clinical status, school attendance and performance, which we have noted, and the small but consistent improvement in quality of life reported by our patients suggest that the outcomes justify the psychosocial burden that accompanies NHD. Significant concerns were expressed about the introduction of nocturnal cycling PD to patients' homes.²⁰ The same concerns can be expressed about the introduction of NHD. However, because

most children with end-stage renal disease are now treated with overnight cycling PD,³ it is reasonable to consider that with further experience and familiarity, NHD will become increasingly accepted if the improvements in patient well being that we report are substantiated by others.

Remote monitoring of NHD was provided for all our patients. This provides a safety net and a psychological security blanket for patients and caregivers undertaking NHD. We recommend that some form of monitoring be in place for other patients starting this procedure, despite the fact that home monitoring is no longer recommended for all adult patients.^{8,21} However, it is also important to inform families that remote monitoring may be insufficient if a major dialysis-related complication occurs.

Our overall costs were estimated at Cd \$63,670 per patient annually, which compares favorably with our in-center HD costs, both currently (Cd \$88,000) and a decade ago (Cd \$76,000).²² This represents a savings of 27% for each patient receiving NHD, compared with thrice-weekly in-center HD, and exceeds the savings reported in adult NHD.^{9,10} Although the cost of supplies is double that of conventional HD, savings still result because of the reduction in staff use. The savings are greater in children than adults because the nurse-to-patient ratio in the pediatric HD unit exceeds that of an adult unit. When the patients remain on NHD >1 year, our cost estimates would be lower because we amortized the costs of patient training, and home renovations over 1 year. If the equipment (eg, reverse osmosis and dialysis machines) is used for longer than 5 years, further savings would be realized. Finally, our estimate of appropriate nurse-to-patient ratio of 1:8 was arbitrary. Adult centers report a nurse-to-patient ratio of 1:20 for their home HD programs, but we feel that ratio will not be achievable for children because of the increased psychosocial component of pediatric care.

The possibility that morbidity might result from excess dialysis must be considered for children receiving NHD. Phosphate and calcium losses in the dialysate have been documented,⁸ and supplements of each were added to the dialysate in our patients to prevent hypocalcemia and hypophosphatemia. Calcium deficiency may be compounded by the fact that, unlike patients receiving conventional dialysis, patients receiving NHD do not take calcium-containing phosphate binders. Sustained negative calcium balance, although not documented by us, potentially may adversely affect bones. A deficiency of carnitine, requiring supplementation, was documented in our patients. The potential for carnitine deficiency with frequent dialysis has been addressed in the report of the Carnitine Consensus Conference,²³ although this concern was not mentioned in previous reports of NHD in adults. Prolonged deficiency of carnitine may result in muscle weakness, cardiomyopathy, intradialytic hypotension, and anemia and should be considered in patients receiving NHD who manifest these symptoms.

The authors wish to thank Dr Andreas Pierratos from the Humber River Regional Hospital in Toronto and Michaelene Ourwendyk from Fresenius Medical Care for their assistance in the development of our Home Nocturnal Hemodialysis program.

REFERENCES

1. Fine RN, De Palma JR, Lieberman E, Donnell GN, Gordon A, Maxwell MH. Extended hemodialysis in children with chronic renal failure. *J Pediatr* 1968;73:706-13.
2. Irwin MA, Balfé JW, Hardy B. Continuous ambulatory peritoneal dialysis in pediatrics. *J Am Assoc Nephrol Nurses Tech* 1981;8:11-3.
3. Leonard MB, Donaldson LA, Ho M, Geary DF. A prospective cohort study of incident maintenance dialysis in children: A NAPRTC study. *Kidney Int* 2003;63:744-55.
4. Uldall R, Francouer R, Ouwendyk M, Wallace L, Langos V, Ecclestone A, et al. Simplified nocturnal home hemodialysis (SNHHD): a new approach to renal replacement therapy. *J Am Soc Nephrol* 1994;5:428.
5. Uldall R, Ouwendyk M, Francouer R, Wallace L, Sit W, Vas S, et al. Slow nocturnal home hemodialysis at the Wellesley Hospital. *Adv Ren Replace Ther* 1996;2:133-6.
6. Lockridge RS Jr, Spencer M, Craft V, Pipkin M, Campbell D, McPhatter L, et al. Nocturnal home hemodialysis in North America. *Adv Ren Replace Ther* 2001;8:250-6.
7. Pierratos A. Nocturnal home haemodialysis: an update on a five-year experience. *Nephrol Dial Transplant* 1999;14:2835-40.
8. Pierratos A. Daily nocturnal hemodialysis. *Kidney Int* 2004;65:1975-86.
9. McFarlane PA, Bayoumi AM, Pierratos A, Redelmeier DA. The quality of life and cost utility of home nocturnal and conventional in-center hemodialysis. *Kidney Int* 2003;64:1004-11.
10. Kroeker A, Clark WF, Heidenheim P, Kuenzig L, Rosemary L, Meyeete M, et al. An operating cost comparison between conventional and home quotidian hemodialysis. *Am J Kidney Dis* 2003;42:S49-55.
11. Chan CT, Floras JS, Miller JA, Richardson RM, Pierratos A. Regression of left ventricular hypertrophy after conversion to nocturnal hemodialysis. *Kidney Int* 2002;61:2235-9.
12. Simonsen O. Slow nocturnal dialysis as a rescue treatment for children and young patients with end-stage renal failure. *J Am Soc Nephrol* 2000;11:327A.
13. Geary DF, Piva E, Gajaria M, Tyrrell J, Picone G, Harvey EA. Development of a nocturnal home hemodialysis (NHHD) program for children. *Semin Dial* 2004;17:115-7.
14. Mehrabian S, Morgan D, Schlaepfer C, Kortas C, Lindsay RM. Equipment and water treatment considerations for the provision of quotidian home hemodialysis. *Am J Kidney Dis* 2003;42:S66-70.
15. Twardowski Z. Constant site (buttonhole) method of needle insertion for hemodialysis. *Dial Transplant* 1995;24.
16. Varni JW, Seid M, Rode CA. The PedsQL: Measurement model for the pediatric quality of life inventory. *Med Care* 1999;37:126-39.
17. Daugirdas JT. Second generation logarithmic estimates of single pool variable volume Kt/V: an analysis of error. *J Am Soc Nephrol* 1993;4:1205-13.
18. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, et al. Effect of dialysis dose and membrane flux in maintenance. *New Engl J Med* 2002;347:2010-9.
19. Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol* 2002;13:1307-20.
20. Fine RN. Peritoneal dialysis update. *J Pediatr* 1982;100:1-7.
21. Heidenheim AP, Leitch R, Kortas C, Lindsay RM. Patient monitoring in the London Daily Nocturnal Hemodialysis Study. *Am J Kidney Dis* 2003;42:S61-5.
22. Coyte PC, Young LG, Tipper BL, Mitchell VM, Stoffman PR, Willumsen J, et al. An economic evaluation of hospital-based hemodialysis and home-based peritoneal dialysis for pediatric patients. *Am J Kidney Dis* 1996;27:557-65.
23. Eknoyan G, Latos DL, Lindberg J. Practice recommendations for the use of L-Carnitine in dialysis-related carnitine disorder. *Am J Kidney Dis* 2003;41:868-76.

SLEEP TERRORS IN CHILDHOOD

THORNTON B. A. MASON II, MD, PHD, AND ALLAN I. PACK, MChB, PHD

Sleep terrors are dramatic events that represent a partial arousal state from deep sleep. Over the years, these episodes have also been referred to as *night terrors*, *parvor nocturnus* (in children), and *incubus attacks* (in adults). Sleep terrors are characterized by marked autonomic nervous system activation: tachycardia, tachypnea, tremulousness, mydriasis, and sweating are often present. Facial expressions of terror or intense fear are associated with uncontrollable shouting, screaming, gasps, moans, and agitation.¹ Although the respiratory rate is mildly increased, tidal volume is increased tremendously.² Some semipurposive movements can occur, yet both speech and motor activities are perseverative and confused. The full-blown sleep terror is a fight-flight episode. Although some children with sleep terrors may remain in bed, others may walk or run during attacks. Bodily injury and property damage are possible.³ The duration of sleep terrors is usually brief, often from less than a minute to several minutes; however, some sleep terrors may last as long as a half hour.⁴ Attempts to awaken a child fully during a sleep terror may increase the child's agitation, and the sleep terror may actually be prolonged⁵; indeed there is a "curious paradox" with endogenous arousal coexistent with external unarousability.⁶ Episodes cease rather abruptly,² with the child rapidly returning to a deep sleep.

Although some aspects of the sleep terror may be recalled by the child immediately after an episode, complete amnesia for the event the following morning is typical. In those instances when a child is able to relate some details of the imagery associated with a sleep terror, there is often no detailed storyline or sequence (in distinction to the typical nightmare). The child's descriptions are fragmented and brief. School-aged children may report indistinct recollections of threats (such as monsters, spiders, snakes, etc.) from which they have to escape or defend themselves.⁷ They may speak only of "something" that "is after me" or "that is going to get me." It has been suggested that this perception of threat or attack may underlie the resistance to parental attempts at restraint.⁸

Sleep terrors form part of a larger group of parasomnias. Parasomnias are undesirable movements and behaviors that occur predominantly during sleep and include disordered arousal, partial arousal, and sleep stage transition.¹ The arousal disorders spectrum includes sleep terrors, sleep walking (somnambulism), and confusional arousals (often seen in children, with features common to both sleep walking and sleep terrors). Confusional arousals are marked by mental confusion after arousals and awakenings but do not include the fear or autonomic activation seen in sleep terrors; it should be borne in mind that many parasomnia events previously labeled as sleep terrors in the literature would be classified as confusional arousals on the basis of current classification schema (International Classification of Sleep Disorders).¹ In a landmark study, Broughton⁹ summarized his prior work with Gastaut and their coworkers demonstrating that arousal disorder parasomnias such as sleep terrors and sleep walking occurred during arousal from slow-wave sleep, rather than from rapid eye movement (REM) sleep. He concluded that the slow-wave sleep arousal episode is a normal cyclic event, and that the postarousal state after slow-wave sleep appeared to be the necessary, but not sufficient, condition for confusional sleep disorders to occur. Importantly, "pre-existing constellations of physiological changes predispose a subject to a particular type of attack during the arousal episode."⁹ Moreover, external stimuli delivered in slow-wave sleep may precipitate a sleep terror.¹⁰

EPIDEMIOLOGY

The prevalence of sleep terrors is greater in childhood than in later life, with a peak between ages 5 to 7 years and resolution typically before adolescence.^{11,12} Sleep terrors have been reported to affect approximately 3% of children and <1% of adults.¹³ Prevalence estimates may vary because of different criteria and definitions used, including the frequency of night terrors; in a recent sample of 480 children aged 6 to 11 years, 6.3% had more than 5 sleep terrors ("fearful awakenings") per month, with no gender difference reported.¹⁴ Children have more slow-wave sleep than adults, and therefore sleep architecture differences could set the stage for sleep terror prominence in childhood.

From the Division of Neurology, The Children's Hospital of Philadelphia, the Division of Sleep Medicine, and the Center for Sleep and Respiratory Neurobiology, University of Pennsylvania, Philadelphia.

Supported by an NIH award to Dr. Mason, K23 RR16566-01.

Submitted for publication Nov 30, 2004; last revision received May 11, 2005; accepted Jun 20, 2005.

Reprint requests: Thornton B. A. Mason II, MD, PhD, Division of Neurology, Wood Center 6th Floor, The Children's Hospital of Philadelphia, 34th St and Civic Center Blvd, Philadelphia, PA 19104. E-mail: mason2@email.chop.edu.

J Pediatr 2005;147:388-92.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.06.042

EEG	Electroencephalography	REM	Rapid eye movement
PLMS	Periodic limb movements in sleep	RLS	Restless legs syndrome

RISK FACTORS

Factors that may increase the likelihood of occurrence of sleep terrors in susceptible individuals include acute stress associated with fever¹⁵ or sleep deprivation.¹⁶ If sleep is disrupted from any cause, or if there has been inadequate prior sleep with a consequent stronger drive for restoring adequate slow-wave sleep, then a child may be further predisposed to sleep terrors. Children may, for example, have more frequent sleep terrors when naps are restricted or eliminated entirely. Thus, obtaining a detailed history about amounts of sleep and timing of sleep is a key part of evaluation of children with sleep terrors. If there is an indication that children are chronically sleep deprived, then having the parents take steps to increase the amounts of sleep is an important therapeutic step; sleep could be increased by reinstating a daytime nap, fostering a more regular sleep schedule, or otherwise increasing sleep opportunities or sleep quality. Adults with arousal parasomnias (sleep walking) have been found to have lower slow-wave activity during the first sleep cycle, as well as lower sleep efficiency during the first sleep cycle compared with control subjects.^{17,18} These findings of lower slow-wave activity compared with control subjects are somewhat surprising in view of the role of sleep deprivation facilitating sleep terrors in children through enhanced homeostatic sleep drive (and associated increased pressure for slow-wave sleep). Children with sleep terrors, like adults, may have sleep disturbances detected by electroencephalography (EEG) such as an increase in sleep instability and in microarousals during slow wave sleep that persist independently of frank sleep terror behavior.

Medications that can trigger sleep terrors include neuroleptics, sedative-hypnotics, stimulants, and antihistamines⁶; parents should always be asked about such medication use or exposure as part of the evaluation of sleep terrors. An association between childhood migraine headaches and parasomnias has been reported, possibly with a common underlying disturbance in serotonin levels.^{16,19} Other medical conditions may precipitate arousal parasomnias, such as nocturnal asthma and gastroesophageal reflux.²⁰ Given the dramatic manifestations of sleep terrors, it has been debated whether psychic conflicts or psychopathology may play a role. Any associated psychopathological component is believed to be extremely rare in childhood²¹; in adults, there is controversy, but no close association has been established.²² Nevertheless, the possibility of anxiety at bedtime and during sleep onset should be explored, because such fears may further exacerbate sleep terrors in childhood.

Intrinsic sleep disorders have also been implicated as important factors influencing sleep terrors. Recently, Guilleminault et al⁷ reported in children that sleep-disordered breathing on polysomnography (ie, obstructive sleep apnea) or periodic limb movements in sleep-restless legs syndrome (PLMS-RLS) may trigger sleep terrors (and sleep walking) in childhood, because these parasomnias disappeared after treatment of the sleep-disordered breathing or PLMS-RLS.⁷ In another recent study, examining a community-based cohort of children, those with sleep-disordered breathing experienced more parasomnias

than those without.¹⁴ In adults with sleep terrors and sleep walking, sleep-disordered breathing has also been found to be frequently associated with parasomnia episodes.²³ Thus sleep-disordered breathing needs to be considered as a risk factor for sleep terrors. Overnight polysomnography is recommended for those children who continue to have frequent sleep terrors in spite of efforts to restore adequate sleep or have a history suggesting that the child has obstructive sleep apnea or PLMS.

There has long been evidence of a genetic risk factor for sleep terrors. Hällström²⁴ found support for inheritance in a 3-generation family, possibly consistent with an autosomal dominant disorder. Kales et al²⁵ reported that the prevalence of sleep terrors and sleep walking in first-degree relatives of individuals with sleep terrors was 10-fold greater than in the general population; the authors calculated a 60% increased chance of a child being affected if both parents were affected. Ooki²⁶ in a questionnaire-based study of monozygotic and dizygotic twins found that sleep terrors were under moderate to strong genetic control. Importantly, sleep terrors may co-occur with other parasomnias as a result of shared genetic effects. Hublin et al²⁷ in twin studies found that sleep talking in children and adults co-occurred with sleep walking, nightmares, and bruxism. It should be kept in mind, however, that a shared family environment complicates interpretation of heritability. Moreover, the heritability of sleep terrors could be secondary to other sleep disorders because there is evidence of familial aggregation of RLS²⁸⁻³⁰ and sleep-disordered breathing.³¹⁻³³ Thus other sleep disorders may result in familial sleep terrors indirectly.⁷

DIAGNOSIS

The diagnosis of sleep terrors may be supported in several ways. An adequate medical history is paramount, taken directly or aided by a questionnaire (For examples of screening questionnaires for pediatric sleep see references 34 and 35). A videotape of a typical episode recorded by parents at home may be very helpful to the clinician.³⁶ Sleep diaries can highlight irregularities of sleep/wake schedules and help determine whether episodes are triggered by sleep deprivation. The differential diagnosis of sleep terrors includes nightmares, panic attacks, epileptic events, and cluster headaches (in young children). Nightmares occur within REM sleep and are therefore more prominent in the second half of the night; children arousing from a nightmare usually become fully alert quickly, respond positively to comforting, and may offer a detailed description of dream content after awakening the following morning. Compared to sleep terrors, nightmares are characterized by lower levels of autonomic discharge, vocalization, and mobility, and by less intense apparent anxiety.² Epileptic seizures rarely present as sleep terrors or sleep walking episodes. Seizures are often very short-lived and stereotypic; a patient may or may not have daytime seizures in addition. Patients should be questioned about daytime staring spells that could represent nonconvulsive seizures, as well as paroxysms of repetitive limb movement or of increased muscle

tone. If epilepsy is suspected, because EEG with an expanded montage is so important in establishing the diagnosis of epilepsy, expanded EEG should be performed in patients who have brief, repetitive events (lasting only 1 to 2 minutes or less) with a consistent, predictable sequence from one episode to the next. The relationship between epilepsy and sleep terrors is complex: epilepsy can also produce parasomnias through sleep disruption, although during slow-wave sleep, seizures are uncommon.²⁰ Cluster headaches, while rare in early childhood, may present as paroxysmal arousals followed by agitation.³⁷ On physical examination, features that may contribute to sleep disruption should be sought, including those related to obstructive sleep apnea (eg, tonsillar hypertrophy, micrognathia, macroglossia) or periodic limb movements in sleep (eg, myelopathy, peripheral neuropathy). If an intrinsic sleep disorder such as obstructive sleep apnea or periodic limb movements in sleep is suspected, then overnight polysomnography is clearly indicated.

Overnight polysomnography has proved valuable as a research tool in detailing the physiological events associated with sleep terrors. As noted above, a key association rests with transitions from slow-wave sleep (also known as delta sleep or non-REM sleep stages 3 and 4). Slow-wave sleep occurs predominantly in the initial sleep cycles, that is, early in the night, and sleep terror onset is typically noted in the first third of the night.¹ Indeed, it has been estimated that about two thirds of sleep terrors occur in the first non-REM period. Although a sleep terror attack is initiated out of slow-wave sleep, the EEG during the event appears as light sleep or wakefulness. For example, the EEG may show alpha rhythm. The patient is neither fully asleep when the sleep terror occurs, nor fully awake.³⁸ During the sleep terror attack, there is altered or decreased cortical responsiveness to visual stimuli and an inability to integrate sensory input.^{9,39} In a study of adult patients, maximal heart rate was reached within 15 to 30 seconds from the start of the attack, to rates as high as triple baseline values. The respiratory rate and more so the amplitude increases significantly; this stands in contrast to the REM nightmare, where respiratory rate increases, but the amplitude of respirations may actually decrease.³⁸ Because of both heightened autonomic activity and arousal, skin resistance shows a marked and instantaneous decrease at arousal.³⁸ EEG spectral analysis in adult patients with sleep terrors has demonstrated increased disruptions during sleep with additional frequent, brief nonbehavioral arousals on EEG.³⁹ More studies are needed to characterize the electroencephalographic features of sleep terror arousals, especially in children, but Halász et al⁴⁰ has shown that adult patients with arousal parasomnias have an increased frequency of microarousals preceded by slow wave synchronization (K complexes, bursts of delta waves) compared with control subjects.

MANAGEMENT

Management of sleep terrors may take many forms. Treatment starts with parental reassurance and guidance. Parents should be reassured that sleep terrors occur in many

children and rarely persist into adulthood. A major focus should be placed on relief of sleep debt. A careful history about sleep patterns and duration is key, with evaluation of the night-to-night stability of sleep achieved, periods of relative sleep deprivation, occurrence of recuperative (rebound) sleep, and nap history (frequency, timing, and duration of naps). Sleep hygiene changes should be reviewed and implemented as needed, including advising routine naps for children <4 years age to ensure adequate sleep. Parents of children with sleep terrors and significant sleep onset anxiety issues should help their children focus on safe, comfortable thoughts at bedtime. For those patients who have sleepwalking as a component of sleep terrors, safety concerns should prompt appropriate measures such as securing doors and windows to limit egress, placing mattresses on the floor, using sleeping bags to reduce wandering, and blocking access to stairs and kitchen. Some children have a nightly pattern of sleep terrors, and scheduled awakenings 10 to 15 minutes beforehand have been reported to help ameliorate sleep terrors^{41,42}; we (TM) have not found this intervention to be practical or effective.

For those children who continue to have frequent sleep terrors in spite of efforts to restore adequate sleep, overnight polysomnography is recommended to evaluate for intrinsic sleep disorders. It should be noted that overnight polysomnography is generally not helpful in establishing the diagnosis of sleep terrors because even in individuals with a convincing history of sleep terrors, the likelihood of capturing a typical home sleep terror in the laboratory is low. For example in one study, only 1 of 6 children with a clear history of sleep terrors when monitored in a sleep laboratory for 1 to 4 nights had a sleep terror; in this case, the polysomnographic data demonstrated that the sleep terror arose from slow-wave sleep during the first non-REM sleep period and was associated with typical autonomic activation and behavioral features.³⁸ On the other hand, polysomnography is helpful for identifying triggers for sleep terrors (such as obstructive sleep apnea or PLMS) or for distinguishing sleep terrors from other conditions. If an associated sleep disorder such as sleep-disordered breathing or periodic limb movement disorder is supported by polysomnography, these coexistent conditions need to be treated.⁴³⁻⁴⁵

Generally, medications should be reserved for those rare, protracted, complex cases where an associated sleep disorder has been excluded, where sleep terrors occur repeatedly, and where there is a threat of injury to the patient or to others; medications used with success have included benzodiazepines (clonazepam) and tricyclic antidepressants (imipramine).^{5,6,8,13,46} The effectiveness of benzodiazepines may relate to sedative effects or to decreases in slow-wave sleep. Low doses should be used initially, with upward titration as needed; patients should be monitored for daytime sedation, which may be a prominent issue for medications such as diazepam that have a long half-life. Medications should be given at least 90 minutes before bedtime to achieve effective drug levels in the first part of the night when sleep terrors predominate. A benzodiazepine treatment interval of 3 to 6 weeks may be curative, with resolution of sleep terrors after

discontinuation of the medication.⁸ Recently, results of a randomized, open-label trial of L-5-hydroxytryptophan suggest efficacy in the treatment of sleep terrors.⁴⁷ L-5-hydroxytryptophan is a precursor of serotonin and as such may modify central serotonergic system dysfunction or enhance production of sleep-promoting factors. Referral to a pediatric sleep disorders center would be appropriate whenever polysomnography or pharmacotherapy is being considered.

In conclusion, sleep terrors are common parasomnias that are most prevalent during childhood. There is still much to be learned about the pathophysiology of these episodes of partial arousal from sleep. Usually, sleep terrors can be identified through information provided by parents, and management is straightforward. The management of more complex cases, however, may include the use of diagnostic studies (polysomnography, expanded EEG recordings to evaluate for seizures) and pharmacotherapy.

REFERENCES

1. American Academy of Sleep Medicine. The International Classification of Sleep Disorders, 2nd ed.: Diagnostic and coding manual. Westchester, IL: American Academy of Sleep Medicine, 2005. p. 145-7.
2. Fisher C, Kahn E, Edwards A, Davis DM. A physiological study of nightmares and night terrors, the suppression of stage 4 night terrors with diazepam. *Arch Gen Psychiatr* 1973;28:252-9.
3. Malow BA. Paroxysmal events in sleep. *J Clin Neurophysiol* 2002;19:522-34.
4. Pesikoff RB, Davis PC. Treatment of parvor nocturnus and somnambulism in children. *Am J Psychiatr* 1971;128:134-7.
5. Cooper AJ. Treatment of coexistent night-terrors and somnambulism in adults with imipramine and diazepam. *J Clin Psychiatr* 1987;48:209-10.
6. Mahowald MW. Arousal and sleep-wake transition parasomnias. In: Lee-Chiong TL, Sateia MJ, Carskadon MA, eds. *Sleep medicine*. Philadelphia: Hanley and Belfus; 2002. p. 207-13.
7. Guilleminault C, Palombini L, Pelayo R, Chervin R. Sleepwalking and sleep terrors in prepubertal children: what triggers them? *Pediatrics* 2003;111:e17-25.
8. Rosen GM, Ferber R, Mahowald MW. Evaluation of parasomnias in children. *Child Adolesc Psychiatr Clin N Am* 1996;5:601-16.
9. Broughton RJ. Sleep disorders: disorders of arousal? *Science* 1968;159:1070-8.
10. Broughton RJ. The incubus attack. *Int Psychiatry Clin* 1970;7:188-92.
11. Chokroverty S, Hening WA, Walters AS. An approach to the patient with movement disorders during sleep. In: Chokroverty S, Hening WA, Walters AS, eds. *Sleep and movement disorders*. Philadelphia: Butterworth Heinemann; 2003. p. 201-18.
12. Laberge L, Tremblay RE, Vitaro F, Montplaisir J. Development of parasomnias from childhood to early adolescence. *Pediatrics* 2000;106:67-71.
13. Robinson A, Guilleminault C. Disorders of arousal. In: Chokroverty S, Hening WA, Walters AS, eds. *Sleep and movement disorders*. Philadelphia: Butterworth Heinemann; 2003. p. 265-72.
14. Goodwin JL, Kaemingk KL, Fregosi RF, Rosen GM, Morgan WJ, Smith T, Quan SF. Parasomnias and sleep disordered breathing in Caucasian and Hispanic children—the Tucson children's assessment of sleep apnea study. *BMC Med* 2004;2:14.
15. Kales JD, Kales A, Soldatos CR, Chamberlin K, Martin ED. Sleepwalking and night terrors related to febrile illness. *Am J Psychiatr* 1979;136:1214-5.
16. Owens JA, Millman RP, Spirito A. Sleep terrors in a 5-year-old girl. *Arch Pediatr Adolesc Med* 1999;153:309-12.
17. Gaudreau H, Joncas S, Zadra A, Montplaisir J. Dynamics of slow-wave activity during the NREM sleep of sleepwalkers and control subjects. *Sleep* 2000;23:1-6.
18. Guilleminault C, Poyares D, Abat F, Palombini L. Sleep and wakefulness in somnambulism, a spectral analysis study. *J Psychosom Res* 2001;51:411-6.
19. Barabas G, Ferrari M, Matthews WS. Childhood migraine and somnambulism. *Neurology* 1983;33:948-9.
20. Brown LW. Sleep and epilepsy. *Child Adolesc Psychiatr Clin N Am* 1996;5:701-14.
21. Broughton RJ. NREM parasomnias. In: Kryger MH, Roth T, Dement WC, eds. *Principles and practice of sleep medicine*. Philadelphia: WB Saunders; 2000. p. 693-706.
22. Schenck CH, Mahowald MW. On the reported association of psychopathology with sleep terrors in adults. *Sleep* 2000;23:448-9.
23. Espa F, Dauvilles Y, Ondze B, Billiard M, Besset A. Arousal reactions in sleepwalking and night terrors in adults: the role of respiratory events. *Sleep* 2002;25:871-5.
24. Hällström T. Night terror in adults through three generations. *Acta Psychiatr Scand* 1972;48:350-2.
25. Kales A, Soldatos CR, Bixler EO, Ladda RL, Charney DS, Weber G, Schweitzer PK. Hereditary factors in sleepwalking and night terrors. *Br J Psychiatr* 1980;137:111-8.
26. Ooki S. Statistical genetic analysis of some problem behaviors during sleep in childhood—estimation of genetic and environmental factors influencing multiple health phenomena simultaneously. *Nippon Eiseigaku Zasshi* 2000;55:489-99 [abstract].
27. Hublin C, Kaprio J, Partinen M, Koskenvuo M. Parasomnias: co-occurrence and genetics. *Psychiatr Genet* 2001;11:65-70.
28. Desautels A, Turecki G, Montplaisir J, Sequeira A, Verner A, Rouleau GA. Identification of a major susceptibility locus for restless legs syndrome on chromosome 12q. *Am J Hum Genet* 2001;69:1266-70.
29. Winkelmann J, Muller-Myhsok B, Wittchen HU, Hock B, Prager M, Pfister H, et al. Complex segregation analysis of restless legs syndrome provides evidence for an autosomal dominant mode of inheritance in early age of onset families. *Ann Neurol* 2002;52:297-302.
30. Bonati MT, Ferini-Strambi L, Aridon P, Oldani A, Zucconi M, Casari G. Autosomal dominant restless legs syndrome maps on chromosome 14q. *Brain* 2003;126:1485-92.
31. Redline S, Tishler PV, Schlacter M, Aylor J, Clark K, Graham A. Risk factors for sleep-disordered breathing in children: associations with obesity, race, and respiratory problems. *Am J Respir Crit Care Med* 1999;152:7-32.
32. Morton S, Rosen C, Larkin E, Tishler P, Aylor J, Redline S. Predictors of sleep-disordered breathing in children with a history of tonsillectomy and/or adenoidectomy. *Sleep* 2001;24:823-9.
33. Buxbaum SG, Elston RC, Tishler PV, Redline S. Genetics of the apnea hypopnea index in Caucasians and African Americans. *Genet Epidemiol* 2002;22:243-53.
34. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. *Sleep* 2000;23:1043-51.
35. Archbold KH, Pituch KJ, Panahi Parvis, Chervin RD. Symptoms of sleep disturbances among children at two general pediatric clinics. *J Pediatr* 2002;140:97-102.
36. Mindell JA, Owens JA. Sleep walking and sleep terrors. In: *A clinical guide to pediatric sleep*. Philadelphia: Lippincott Williams & Wilkins; 2003. p. 88-96.
37. Isik U, D'Cruz OF. Cluster headaches simulating parasomnias. *Pediatr Neurol* 2002;27:227-9.
38. Fisher C, Kahn E, Edwards A, Davis D. A psychophysiological study of nightmares and night terrors. *J Nerv Ment Dis* 1973;157:75-98.
39. Espa F, Ondze B, Deglise P, Billiard M, Besset A. Sleep architecture, slow wave activity, and sleep spindles in adult patients with sleep walking and sleep terrors. *Clin Neurophysiol* 2000;111:929-39.
40. Halász P, Ujszászi J, Gáboros J. Are microarousals preceded by electroencephalographic slow wave synchronization precursors of confusional awakenings? *Sleep* 1985;8:231-8.
41. Lask B. Novel and non-toxic treatment for night terrors. *BMJ* 1988;297:592.

42. Lask B. Sleep disorders: "waking treatment" best for night terrors. *BMJ* 1993;306:1477.
43. Section on pediatric pulmonology, subcommittee on obstructive sleep apnea syndrome. American Academy of Pediatrics. Clinical practice guideline: diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 2002;109:704-12.
44. Walters AS, Mandelbaum DE, Lewin DS, Kugler S, England SJ, Miller M. Dopaminergic therapy in children with restless legs/periodic limb movements in sleep and ADHD. *Dopaminergic Therapy Study Group. Pediatr Neurol* 2000;22:182-6.
45. Simakajornboon N, Gozal D, Vlastic V, Mack C, Sharon D, McGinley BM. Periodic limb movements in sleep and iron status in children. *Sleep* 2003;26:735-8.
46. Burstein A, Burstein A. Treatment of night terrors with imipramine. *J Clin Psychiatry* 1983;44:82.
47. Bruni O, Ferri R, Miano S, Verrillo E. L-5-Hydroxytryptophan treatment of sleep terrors in children. *Eur J Pediatr* 2004;163:402-7.

50 Years Ago in *The Journal of Pediatrics*

CONGENITAL SPINAL DERMAL SINUSES

Amador LV, Hankinson J, Bigler JA. *J Pediatr* 1955;47:300-10

Neurosurgeons from Children's Memorial Hospital in Chicago present the case reports of 9 children who represent the spectrum of pathologic and clinical findings collectively referred to as *congenital spinal "dermal sinuses."* The article could be reprinted in its entirety as a contemporary tutorial. This group of embryonic malformations is common, and their presentations and importance are core knowledge requirements for every pediatrician. The embryologic defect occurs early in fetal life when the ectoblast is differentiated into cutaneous and neural ectoderm. As the neural groove closes to form the medullary tube, cutaneous ectodermal cells may also be invaginated, subsequently developing into intraspinal dermoid or epidermoid growths. If mesodermal defect also occurs, spinal dysraphism results, and a tract may connect the skin directly with the spinal canal. Clinically, defects are recognized in 1 of 3 ways: (1) the finding on routine physical examination of a sinus tract on or near the midline from the tip of the spine to the base of the nose; (2) because of the occurrence of bacterial meningitis or recurrent bacterial meningitis, especially caused by unusual organisms; or (3) when compression or traction on the spinal cord occurs and causes motor weakness, nerve root irritation, or autonomic changes and sphincter dysfunction. The finding of pigmentation, hypertrichosis, hemangioma, lipoma, or intermittent sebaceous discharge also can be the external clue to an almost imperceptible sinus tract. The authors provide astute clinical observations, revealing cases, and excellent discussion of anatomy and embryology—all worth the re-reading.

Sarah S. Long, MD
 Section of Infectious Diseases
 St. Christopher's Hospital for Children
 Philadelphia, PA 19134
YMPD1631

10.1016/j.jpeds.2005.05.031

CONTROLLED SLEEP RESTRICTION FOR RHYTHMIC MOVEMENT DISORDER

TAMAR ETZIONI, BSC, NERI KATZ, MD, ELI HERING, MD, SARIT RAVID, MD, AND GIORA PILLAR, MD, PHD

Rhythmic movement disorder is a parasomnia that is difficult to treat. In our study, 3 weeks of controlled sleep restriction with hypnotic administration in the first week resulted in almost complete resolution of the movements in 6 children. This therapeutic success suggests that rhythmic movement disorder results from a voluntary self-soothing behavior. (*J Pediatr* 2005;147:393-5)

Rhythmic movement disorder (RMD) is defined as a group of stereotyped, repetitive movements (RM), involving large muscles, usually of the head and neck (head banging), that typically occur immediately before sleep onset and are sustained into light sleep. Occasionally it may be seen in deep or rapid eye movement sleep.^{1,2} Although several studies reported that RMD may spontaneously alleviate and even disappear with age, it may be important to treat it earlier because it may be harmful and may persist to adulthood.²⁻⁵

Treatment of RMD may be difficult. In some cases benzodiazepines were beneficial,^{4,6} but in other cases they failed.³ In several case reports, antidepressants such as imipramine produced good clinical outcome.³ Behavioral intervention⁷ or hypnosis⁸ has also been suggested, but they have not been sufficiently studied.⁹ Most of these studies reported the effects of short-term treatment, and there are only few data regarding long-term effects.

One potential explanation of the mechanism underlying RMD is that these patients voluntarily generate RM to help them fall asleep. Thus we planned a controlled sleep restriction program, with usage of hypnotics in the first part of the program, to rebuild faith in the ability to fall asleep. We hypothesized that once good sleep initiation is established, RM would reduce in frequency.

METHODS

Six children and adolescents (3 females) aged 7.3 ± 2.9 years (range 3.5 to 12 years), with a diagnosis of RMD (2 of them with a previous treatment failure) were studied. They (or the parents) completed a questionnaire, underwent a 1-week actigraphic study (primarily to objectively determine total sleep time), and commenced a treatment protocol (see below). Parents were asked to observe their children while falling asleep every night during the first month of treatment and quantitatively score the existence of RM (0 = no RM, 1 = rarely RM, 2 = occasional RM, 3 = frequent RM, 4 = continuous intense RM until asleep). Parents scored sleep latency and RM every night during the first month of treatment. Additional assessment took place at 1-year follow-up.

The Actigraph (Mini Monitor Actigraph, Ambulatory Monitoring, New York, NY) is a self-contained microcomputer housed in a $2.5 \times 3.5 \times 0.75$ -inch light-weight case. It is placed on the nondominant hand and translates movements into electrical signals that identify wake or sleep by use of a validated scoring program.¹⁰ The children wore it for 7 consecutive days and nights in their native environment. Actigraphy was obtained before any therapeutic intervention, and the important variables derived from it were sleep latency (the time from "lights out reported by the parents to falling asleep defined by the actigraph), total sleep time (TST, time of actual sleep excluding periods of wakefulness) and sleep efficiency (percentage of TST of total time in bed).

From the Sleep Lab, Meyer Children's Hospital, Rambam Medical Center and Technion-Israel Institute of Technology, and Pediatric Neurology Unit, Meyer Children's Hospital, Rambam Medical Center, Haifa, the Pediatric and Premature Departments, Wolfson Hospital, Holon, and the Pediatric Department, General Health Care, Child Care Center, Tirat Hacarmel, Israel.

Submitted for publication Feb 28, 2005; last revision received May 5, 2005; accepted Jun 22, 2005.

Reprint requests: Giora Pillar, MD, PhD, Sleep Lab, Rambam Medical Center, Haifa 31096, Israel. E-mail: gpillar@tx.technion.ac.il.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.06.045

RM	Repetitive movement	TST	Total sleep time
RMD	Rhythmic movement disorder		

Table. Characteristics and findings of the children

Child	Age (years)	Sex	Previous treatment	Reported HSD (h)	Actigraph SL (min)	Actigraph TST (h)	Actigraph SE (%)
1	5	m	None	11	32	10.2	84
2	12	m	Clonazepam	9	47	7.8	81
3	7	f	None	10.5	11	10	93
4	8	f	Psychological	8.5	36	8.1	86
5	8	m	None	9.5	14	9.8	94
6	3.5	f	None	10	15	9.5	93
Mean ± SD	7.3 ± 2.9			9.8 ± 0.9	25.8 ± 14.6	9.2 ± 1.0	88.5 ± 5.5

Reported HSD, Reported habitual sleep duration (hours); SL, sleep latency (min); SE, sleep efficiency (%).

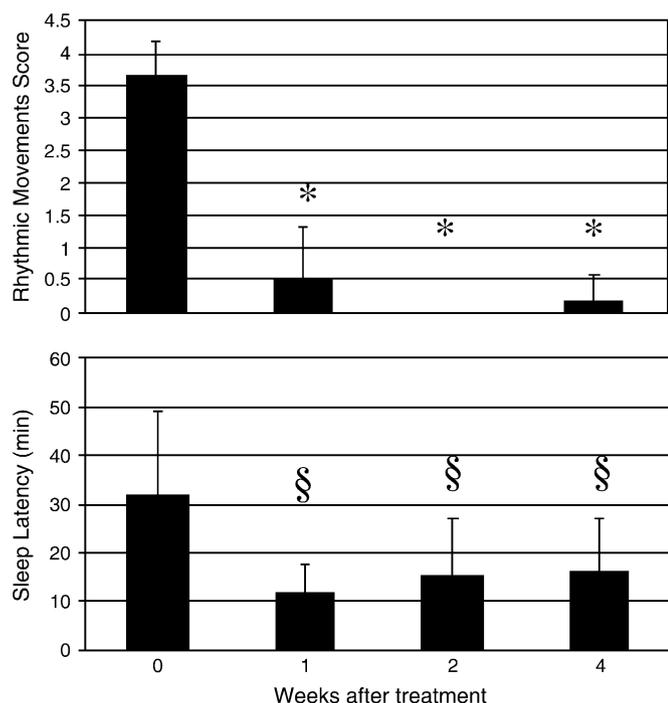


Figure. Rhythmic movement score (upper panel) and sleep latency (lower panel) before treatment (= 0), and at 1, 2, and 4 weeks after treatment protocol. All data are mean ± SD. All changes were significant compared to baseline values (paired *t* test), for RMD score in *P* < .005 level (*), and for sleep latency in *P* < .01 level (§).

Habitual total nocturnal sleep time was determined as the average between the reported and the actigraphic measures. A 3-week sleep restriction regimen was determined for each individual: first week a reduction of 1 hour from nocturnal TST, and administration of chloral-hydrate 0.5 mL/kg before bedtime (no change in nap duration), second week hypnotic was ceased but total nocturnal sleep time was still restricted for 1 hour less than baseline, and third week a gradual return (increment of 10 minutes every night) to the baseline schedule.

RESULTS

Characteristics of the 6 children are presented in the Table. Body weight, number of children in the family or their

place within the family did not have an effect on the existence of RMD or their response to treatment. Two of the children had a previous failure of a therapeutic trial before the current regimen was imposed. Two children had no sleep complaints, whereas 4 reported difficulties in falling asleep, and one of them also reported about frequent awakenings from sleep. Families and children reported a very good compliance with the treatment, with almost no side effects (parents reported bearable nervousness and mild sleepiness or agitation). Both sleep latency and rhythmic movements dramatically improved in all children (Figure), although there was no correlation between them (*r* = 0.1). Although rhythmic movements were completely abolished at 2-week follow-up, at 4 weeks one of the children re-experienced rare RM, which persisted at 1-year follow-up.

DISCUSSION

Our study suggests that the combination of controlled mild sleep deprivation, with usage of hypnotics at treatment initiation, may abolish RM and cure RMD. In addition, the resolution of RMD with primarily sleep deprivation supports the hypothesis that it can be classified as a type of voluntary movement that serves as a self-soothing behavior in the process of falling asleep, rather than as an involuntary movement disorder. Most of these latter movements such as those from epilepsy usually aggravate with sleep deprivation.¹¹

Although usually a self-limiting disorder, we believe RMD should be treated on diagnosis because treatment can prevent secondary social/psychological consequences, physical damage,^{5,8} and persistent into adulthood.^{2-4,12} Hypnotics alone may fail,³ and movements can re-occur after treatment cessation. We do not know whether the treatment should be longer or shorter than our 3-week regimen, which was arbitrarily chosen. Our rationale was to build a mild sleep deprivation protocol for 3 weeks (and not dramatic sleep restriction for shorter period) to allow the child to build confidence in his or her ability to fall asleep without the assistance of the RM. We speculate that this allowed the success to continue long term. The optimal timing and usage of hypnotic treatment will have to be determined on a larger group of children. However, we believe our findings of long-term success in 5 of 6 children,

long after cessation of medication and therapeutic intervention, is an important observation.

REFERENCES

1. Hoban TF. Rhythmic movement disorder in children. *CNS Spectr* 2003;8:135-8.
2. Thorpy MJ, Glovinsky PB. Parasomnias. *Psychiatr Clin North Am* 1987;10:623-39.
3. Alves RS, Aloe F, Silva AB, Tavares SM. Jactatio capitis nocturna with persistence in adulthood. Case report. *Arq Neuropsiquiatr* 1998;56:655-7.
4. Chisholm T, Morehouse RL. Adult headbanging: sleep studies and treatment. *Sleep* 1996;19:343-6.
5. Mackenzie JM. "Headbanging" and fatal subdural haemorrhage. *Lancet* 1991;338:1457-8.
6. Reimao R, Lefevre AB. Evaluation of flurazepam and placebo on sleep disorders in childhood. *Arq Neuropsiquiatr* 1982;40:1-13.
7. Ross RR. Treatment of nocturnal headbanging by behavior modification techniques: a case report. *Behav Res Ther* 1971;9:151-4.
8. Rosenberg C. Elimination of a rhythmic movement disorder with hypnosis—a case report. *Sleep* 1995;18:608-9.
9. Kuhn BR, Elliott AJ. Treatment efficacy in behavioral pediatric sleep medicine. *J Psychosom Res* 2003;54:587-97.
10. Sadeh A, Hauri J, Kripke DF, Lavie P. The role of actigraphy in the evaluation of sleep disorders. *Sleep* 1995;18:288-302.
11. Wills L, Garcia J. Parasomnias: epidemiology and management. *CNS Drugs* 2002;16:803-10.
12. Kohyama J, Matsukura F, Kimura K, Tachibana N. Rhythmic movement disorder: polysomnographic study and summary of reported cases. *Brain Dev* 2002;24:33-8.

CONTINUOUS GLUCOSE MONITORING IN ADOLESCENTS WITH CYSTIC FIBROSIS

CRAIG JEFFERIES, FRACP, MELINDA SOLOMON, MD, KUSIEL PERLMAN, MD, NEIL SWEEZEY, MD, AND DENIS DANEMAN, MD

The presence of cystic fibrosis (CF)-related diabetes was evaluated in 19 adolescents with CF by continuous glucose monitoring system (CGMS) and oral glucose tolerance testing. CGMS confirmed diabetic glucose excursions in 7/19 subjects deemed diabetic on oral glucose tolerance testing. CGMS is a useful tool for detecting hyperglycemia in CF. (*J Pediatr* 2005;147:396-8)

Cystic fibrosis-related diabetes (CFRD) is a common and serious problem in pancreatic-insufficient individuals with CF.¹⁻³ CFRD is associated with both increased mortality and morbidity rates, with a close correlation to both deterioration in lung function and loss of weight.^{4,5} There is often a long, and asymptomatic prediabetic period of up to 4 years before CFRD is detected.⁶

Oral glucose tolerance testing (OGTT) is currently the most sensitive method for detecting CFRD.⁴ However, the continuous glucose monitoring system (CGMS) (Medtronic Minimed, Northridge, CA) is a new tool that is accurate in type 1 diabetes, able to detect more glucose fluctuations and has been validated in nondiabetic adults with CF.^{7,8} CGMS and OGTT were therefore studied in adolescents with CF who had declining nutritional state or lung function.

METHODS

Subjects were recruited consecutively between December 2002 and January 2004 from the Cystic Fibrosis Clinic at the Hospital for Sick Children, Toronto. This clinic has ~300 subjects with CF, with 50% in the subject range and eligible. All subjects were pancreatic insufficient and of either sex; recruitment was aimed at those with unexplained or rapid decline in lung function or nutritional status, supplemental feeds, and any previous blood glucose >7 mmol/L. Exclusion criteria included acutely severely unwell and receiving growth hormone or oral corticosteroid. Ethical approval was obtained from the Research Ethics Board; all parents/guardians and subjects provided written informed consent.

Study Methods

All patients were assessed in the endocrine testing center after an overnight fast; height was measured by stadiometer, weight by electronic scales, and BMI expressed as BMI SD score. One Touch Ultra (One-touch Lifescan, British Columbia, Canada) glucose meter (<10% discrepancy with reference) was provided, 4 tests per day were required, and a minimum of 24 and maximum of 72 hours of CGMS was required. The OGTT was performed using 1.75 g oral glucose/kg. A_{1c} was measured by HPLC (Biorad Variant 2) and glucose by automated analyzer (Bio-Rad, CA).

Statistical Analysis

Graphpad Prism (Aurora, CA) was used for appropriate statistical analysis, a *P* value < .05 was required for significance. Two-hour OGTT glucose values and CGMS excursions were similarly classified as normal if <7.8 mmol/L, impaired 7.8 to 11.1 mmol/L, and diabetic >11.1 mmol/L. All CGMS traces were agreed on by 2 investigators (DD and CJ).

See related articles, p 295, p 302, p 306, p 312, p 316, p 321, p 327, p 332, p 399, and p 402.

From the Divisions of Endocrinology and Respiriology, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.

Submitted for publication Oct 4, 2004; last revision received Mar 30, 2005; accepted May 2, 2005.

Reprint requests: Dr Craig Jefferies, Liggins Institute, University of Auckland, 2-6 Park Ave, Auckland, New Zealand. E-mail: c.jefferies@auckland.ac.nz.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.05.004

A _{1c}	Hemoglobin A _{1c}	CGMS	Continuous glucose monitoring system
BMI	Body mass index	FEV ₁	Forced expiratory volume in 1 second
CF	Cystic fibrosis	G-tube	Gastrostomy tube
CFRD	Cystic fibrosis-related diabetes	OGTT	Oral glucose tolerance test

Table. Glucose and CGMS results

Subject	Fasting glucose (mmol/L)	2-hour glucose (mmol/L)	OGTT result	A _{1c} %	CGMS mean glucose (mmol/l)	Length of recording (hours)	CGMS result
1	6.7	17.5	CFRD	7.7	10.6	60	Diabetic
2	5.7	16.7	CFRD	7.3	10.7	49	Diabetic
3	6.8	13.2	CFRD	6.2	9.4	72	Diabetic
4	6.1	12.1	CFRD	7.3	7.7	45	Diabetic
5	6.6	15.9	CFRD	7.4	7.9	52	Diabetic
6	7.8	15.5	CFRD	6.5	7.0	24	Diabetic
7	6.5	13.9	CFRD	6.2	9.7	48	Diabetic
8	5.9	8.6	IGT	6.3	7.9	61	Impaired
9	4.7	7.9	IGT	5.0	5.1	51	Normal
10	5.2	9.3	IGT	6.1	5	60	Impaired
11	5.5	9.3	IGT	6.3	5.9	36	Impaired
12	5.1	8.3	IGT	6.3	7.1	45	Impaired
13	4.6	10.5	IGT	5.3	5.0	24	Normal
14	4.3	3.9	Normal	6.4	7.1	60	Impaired
15	5.1	3.7	Normal	5.2	6.5	54	Impaired
16	5.1	4.8	Normal	5.8	4.9	46	Normal
17	6.2	5.4	Normal	5.5	7.8	50	Impaired
18	5.5	Incomplete*	Normal	5.7	7.5	56	Diabetic
19	4.7	5.5	Normal	6.2	7.0	48	Normal
Mean (SD)	5.7 (0.9)	9.9 (4.5)		6.3 (0.8)	7.4 (1.8)	50 (12)	

To convert mmol/L to mg/dL, multiply mmol/L by 18.8.

*Subject 18 vomited near the end of the OGTT.

RESULTS

Nineteen (7 male) adolescents were studied at a mean age of 13.9 (2.2) years with a mean forced expiratory volume in 1 second (FEV₁) of 57 (23)% predicted and a BMI SD score of -0.6 (0.9); 6/19 were gastric-tube fed; most were white.

There was no difference between any groups for FEV₁ or BMI SDS ($P > .1$). The A_{1c} was higher in those with CFRD compared with non-CFRD subjects (6.9 ± 0.6 vs 5.5 ± 0.4%, respectively; $P < .01$). Seven subjects had CFRD on OGTT, all were confirmed to have diabetic glucose excursions on CGMS. Five subjects had with a normal OGTT, although only 2 of them had a normal CGMS (Table). Of the 6 subjects with impaired glucose tolerance, 4/6 had a similar result on CGMS, and 2/6 were normal on CGMS.

This study found 7 new cases of CFRD in an estimated ~150 patients; however, they represent a select high-risk group within the overall CF population. Mean CGMS glucose values and A_{1c} correlated significantly ($r^2 = 0.4$, $P < .01$). Overall, 10 subjects were initiated on insulin, with a change in BMI SDS -0.13 for nondiabetic versus 0.3 for CFRD/impaired subjects, $P = .02$ over the next 3 months.

DISCUSSION

The low sensitivity and specificity of fasting glucose and A_{1c} has focused attention on the OGTT as the only reliable test for CFRD.⁹ This is the first study to evaluate the CGMS in CF adolescents with CF at high risk of having disordered

glucose homeostasis and shows that at least it is comparable to OGTT.

Importantly, there were no subjects with CFRD on OGTT that did not have diabetic glucose excursions on CGMS. Similarly the only subject who had a normal OGTT but was diabetic on CGMS most likely had a technically compromised OGTT because he vomited at the end of his glucose test. In subjects with impaired glucose tolerance, CGMS was helpful in either confirming or denying if the impairment was persistent. This study found 7 new cases of CFRD in an estimated ~150 patients; however, they represent a select high-risk group within the overall CF population.

The goal of insulin institution in CFRD has now swung from symptomatic relief of diabetes to preventing further clinical decline, restoring nutritional status, and the long-term aim of decreasing morbidity and mortality rates. CGMS is a potential tool that may improve the detection of CFRD and help to achieve the goals stated above.^{6,9} We conclude that CGMS is a useful tool for detecting hyperglycemia in patients with CF.

We thank S. Carpenter and L. Glabb for their excellent support and assistance, the participants, and their parents/guardians.

REFERENCES

1. Hardin DS, Moran A. Diabetes mellitus in cystic fibrosis. *Endocrinol Metab Clin North Am* 1999;28:787-800.

2. Lanng S. Glucose intolerance in cystic fibrosis patients. *Paediatr Respir Rev* 2001;2:253-9.
3. Solomon M, Wilson D, Corey M, Kalnins D, Zielenski J, Tsui L-C, et al. Glucose intolerance in children with cystic fibrosis. *J Pediatr* 2003;142:128-32.
4. Moran A. Cystic fibrosis-related diabetes: an approach to diagnosis and management. *Pediatr Diabetes* 2000;1:41-8.
5. Koch C, Rainisio M, Madessani U, Harms HK, Hodson ME, Mastella G, et al. Presence of cystic fibrosis-related diabetes mellitus is tightly linked to poor lung function in patients with cystic fibrosis: data from the European Epidemiologic Registry of Cystic Fibrosis. *Pediatr Pulmonol* 2001;32:343-50.
6. Rolon MA, Benali K, Munck A, Navarro J, Clement A, Tubiana-Rufi N, et al. Cystic fibrosis-related diabetes mellitus: clinical impact of prediabetes and effects of insulin therapy. *Acta Paediatr* 2001;90:860-7.
7. Boland E, Monsod T, Delucia M, Brandt CA, Fernando S, Tamborlane WV. Limitations of conventional methods of self-monitoring of blood glucose: lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. *Diabetes Care* 2001;24:1858-62.
8. Dobson L, Sheldon CD, Hattersley AT. Validation of interstitial fluid continuous glucose monitoring in cystic fibrosis. *Diabetes Care* 2003;26:1940-1.
9. Moran A. Diagnosis, screening, and management of cystic fibrosis-related diabetes. *Curr Diab Rep* 2002;2:111-5.

FAILURE OF CONVENTIONAL STRATEGIES TO IMPROVE NUTRITIONAL STATUS IN MALNOURISHED ADOLESCENTS AND ADULTS WITH CYSTIC FIBROSIS

DAINA KALNINS, MSc, RD, MARY COREY, PhD, LYNDIA ELLIS, RN, PAUL B. PENCHARZ, MB, ChB, PhD, FRCPC, ELIZABETH TULLIS, MD, FRCPC, AND PETER R. DURIE, MD, FRCPC

The use of oral dietary supplements was compared with dietary counseling in 13 malnourished patients (3 males, mean age 18.1 years) with cystic fibrosis. Energy intake and nutritional status were evaluated over 3 months. There was no significant change in energy intake or percent ideal body weight in either group. (*J Pediatr* 2005;147:399-401)

Normal growth and weight gain can be achieved in patients with cystic fibrosis (CF).¹ However, a subgroup of patients suffer from malnutrition. Increased energy demands caused by respiratory illness and infection and increased losses caused by vomiting and impaired digestion are some of the causative factors.¹ The purpose of this study was to compare the effects of oral dietary supplements with dietary counseling on energy intake and nutritional status in malnourished adolescents and adults with CF.

METHODS

Patients over 10 years of age with <90% ideal body weight (IBW) or a 5% reduction in percent IBW over a 3-month period were studied. Exclusion criteria included patients with CF-related diabetes, a gastrostomy tube, CF-associated liver disease, a forced expiratory volume in 1 second (FEV₁) < 30%, O₂ dependence, and those already receiving routine supplements.

Before study entry, patients had been counseled on the general diet recommendations for CF.² Subjects were randomized to receive dietary counseling, or a nutritional supplement (Boost Plus, Mead Johnson, Ottawa, Ontario [150 kcal/100 mL; 20% protein, 30% fat, 50% carbohydrate]) with the aim of increasing energy intake by 20% of predicted energy needs over a 3-month period.

Patients completed 72-hour weighed food records at study entry, 1 month, and 3 months. The diet counseling group was asked to increase energy intake by eating high-calorie foods as recommended by the dietitian (DK). Dietary advice was given by phone contact after each set of food records was completed. The supplement group was instructed to take Boost Plus. Compliance was monitored by counting cans remaining at 1 and 3 months.

Height and weight were plotted on the Centers for Disease Control growth curves³ at study entry and 3 months. Ideal body weight was based on weight at the same percentile as height. Percent IBW was calculated by dividing actual body weight by IBW. Pulmonary function tests were performed at entry and 3 months.⁴ Anthropometry and pulmonary function were also evaluated at 6 months. Resting energy expenditure was determined at study entry and 3 months using indirect calorimetry and was used to predict daily energy needs. Fecal fat output⁵ at baseline (or within 1 year of study entry) was divided by fat

See related articles, p 295, p 302, p 306, p 312, p 316, p 321, p 327, p 332, p 396, and p 399.

From the Divisions of Respiratory Medicine, Population Health Sciences, Gastroenterology/Nutrition, and the Research Institute, The Hospital for Sick Children, the Division of Respiratory, St. Michael's Hospital, and the Departments of Pediatrics, Nutritional Sciences, Medicine, and Public Health Sciences, University of Toronto, Toronto, Ontario, Canada.

Supported by Mead Johnson, Canada. Submitted for publication Dec 17, 2004; last revision received May 13, 2005; accepted Jun 20, 2005.

Reprint requests: P. R. Durie, MD, FRCPC, Division of Gastroenterology/Nutrition, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8. E-mail: peter.durie@sickkids.ca.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.06.038

CF	Cystic fibrosis	IBW	Ideal body weight
FEV ₁	Forced expiratory volume in 1 second		

Table. Anthropometry, dietary intake and pulmonary data

	Dietary counseling (n = 6)				Oral supplements (n = 7)			
	Entry	1 mo	3 mos	6 mos	Entry	1 mo	3 mos*	6 mos
Age (yrs)	16.4 ± 6.7	—	—	—	19.5 ± 11.3	—	—	—
Z score wt	-0.8 ± 0.8	—	-0.7 ± 0.6	-0.6 ± 0.9	-1.2 ± 0.5	—	-1.1 ± 0.7	-1.3 ± 0.8
Z score ht	0.2 ± 1.3	—	0.3 ± 1.3	0.4 ± 1.4	-0.2 ± 0.9	—	-0.1 ± 0.9	-0.1 ± 0.8
% IBW	83 ± 10	—	84 ± 13	83 ± 13	86 ± 8	—	85 ± 6	83 ± 6
Intake (kcal/d)	2800 ± 1100	2900 ± 1000	2800 ± 700	—	2400 ± 600	2200 ± 700	2700 ± 700	—
% kcal predicted†	101 ± 36	104 ± 28	99 ± 19	—	92 ± 22	88 ± 27	110 ± 34	—
FEV ₁	62 ± 25	—	63 ± 16	66 ± 13	66 ± 22	—	60 ± 26	62 ± 19

All values expressed as mean ± SD. Data at 6 month follow-up provided; 2 patients continued to use supplements.

*Only 5 patients continued on supplement at 3 months.

†Daily kcal intake expressed as percent of predicted daily energy needs.

intake to determine percent fat malabsorption. If results indicated severe fat malabsorption (ie, 20%), enzyme doses were adjusted using age-based dosing guidelines.⁶

Statistical comparisons were performed using a 2-tailed, 2-sample equal variance *t* test. Differences between means were considered significant at *P* < .05. A repeated measures analysis of variance was performed to assess the energy intakes and anthropometrics. The study was approved by the Research Ethics Board, the Research Institute at The Hospital for Sick Children.

RESULTS

Thirty-six patients were approached to take part in the study; 15 patients agreed to participate, and 13 patients (3 males) completed the study. Reasons for dropping out (one in each group after completing baseline) included feeling unwell and change of mind. All patients were pancreatic insufficient except for one in the supplement group. Twelve patients had tried supplements before. Two patients in the supplement group were no longer taking supplements at 3 months, and their data were included in the final analysis. The supplement group received 21% ± 14% (n = 7) and 28% ± 18% (n = 5) of intake from supplements at 1 and 3 months, respectively. An average of 1.6 cans/day were prescribed, and patients took 1.2 cans/day at 1 month (n = 7) and 1.6 cans/day at 3 months (n = 5).

Repeated measures analysis of variance revealed no differences between the groups in mean change from baseline for percent IBW (*P* = .2) or energy intake (*P* = .8) during the 3-month study period (Table). Follow-up at 6 months also revealed no difference. There was no significant change in FEV₁ in either group. Percent resting energy expenditure in the diet counseling group (n = 6) was 117% ± 13.2% and 121% ± 4%, and in the supplement group (n = 6) it was 123% ± 18% and 123% ± 13% at study entry and at 3 months, respectively (NS). Fat malabsorption was 12.3% ± 3.8% and 16.2% ± 14.5% in the diet counseling group (n = 6) and the supplement group (n = 5), respectively (NS). Two patients in the supplement group did not have a fecal fat analysis; one was

pancreatic sufficient and one failed to complete the fecal fat analysis.

DISCUSSION

Neither oral dietary supplements nor dietary counseling improved nutritional status in this 3-month study. Although only 13 patients participated, a post hoc analysis indicated an 80% power to detect a difference of 6% to 7% IBW, considered to be clinically significant. Regardless of study intervention, increased energy demands caused by chronic infection, decreased appetite, and increased losses were most likely causes resulting in a negative energy balance.¹

Studies in the early 1980s, demonstrating efficacy of dietary counseling and/or supplements, were conducted in patients who had been placed on a low-fat diet before study entry.⁷ These studies were performed at a time when there was a change in philosophy toward restricting fat intake because of the observation that unrestricted dietary fat improved nutritional status and played a significant role in survival of patients with CF.⁸

Recently, one study reported improvement in IBW by 2% with dietary counseling and oral supplements over a 3-month period.⁹ However, it is questionable whether this is clinically significant. Two other studies failed to demonstrate that oral supplements improved nutritional status.^{10,11} Supplements may replace dietary intake and therefore fail to increase total energy intake, as appeared to be the case in our study.

Studies on nocturnal enteral tube feedings have demonstrated improvement in nutritional status.¹² In one study, nutritional status improved significantly after an 12 months period.¹² Patients who do not respond to dietary counseling or oral supplements should be considered as candidates for nocturnal enteral feeding.

In summary, this study raises questions about the efficacy of conventional dietary practices in improving nutritional status in malnourished patients with CF, where more aggressive nutritional rehabilitation may be necessary. A larger scale study is recommended to confirm these results.

REFERENCES

1. Pencharz PB, Durie PR. Pathogenesis of malnutrition in cystic fibrosis, and its treatment. *Clin Nutr* 2000;19:387-94.
2. Ramsey BW, Farrell PM, Pencharz P. Nutritional assessment and management in cystic fibrosis: a consensus report. The Consensus Committee. *Am J Clin Nutr* 1992;55:108-16.
3. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, et al. CDC growth charts: United States. *Adv Data* 2000;1-27.
4. Weng TR, Levison H. Standards of pulmonary function in children. *Am Rev Respir Dis* 1969;99:879-94.
5. Van de Kamer JH, ten Bokkel Huinink H, Weyers HA. Rapid method for the determination of fat in feces. *J Biol Chem* 1949;177:347-55.
6. Borowitz DS, Grand RJ, Durie PR. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. Consensus Committee. *J Pediatr* 1995;127:681-4.
7. Parsons HG, Beaudry P, Dumas A, Pencharz PB. Energy needs and growth in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1983;2:44-9.
8. Corey M, McLaughlin FJ, Williams M, Levison H. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol* 1988;41:583-91.
9. Steinkamp G, Demmelmair H, Ruhl-Bagheri I, von der Hardt H, Koletzko B. Energy supplements rich in linoleic acid improve body weight and essential fatty acid status of cystic fibrosis patients. *J Pediatr Gastroenterol Nutr* 2000;31:418-23.
10. Hanning RM, Blimkie CJ, Bar-Or O, Lands LC, Moss LA, Wilson WM. Relationships among nutritional status and skeletal and respiratory muscle function in cystic fibrosis: does early dietary supplementation make a difference? *Am J Clin Nutr* 1993;57:580-7.
11. Rettammel AL, Marcus MS, Farrell PM, Sondel SA, Kosciak RE, Mischler EH. Oral supplementation with a high-fat, high-energy product improves nutritional status and alters serum lipids in patients with cystic fibrosis. *J Am Diet Assoc* 1995;95:454-9.
12. Vaisman N, Clarke R, Pencharz PB. Nutritional rehabilitation increases resting energy expenditure without affecting protein turnover in patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1991;13:383-90.

OVERWEIGHT AND OBESITY IN Δ F508 HOMOZYGOUS CYSTIC FIBROSIS

DAGMAR KASTNER-COLE, MRCP, COLIN N. A. PALMER, PHD, SIMON A. OGSTON, PHD, ANIL MEHTA, FRCP, AND SOMNATH MUKHOPADHYAY, PHD

Overweight (9%) and obesity (1%) in patients with cystic fibrosis homozygous for the Δ F508 mutation (CF Δ F508) were non-trivial. Children with CF Δ F508, in contrast to the general population, showed a positive association between body mass index and lung function for all body mass index z-scores. (*J Pediatr* 2005;147:402-4)

Counseling and interventions to support weight gain in cystic fibrosis (CF), a condition characterized by malnutrition and increased energy expenditure, constitute an important aspect of clinical management.¹ With such strategies, however, there exists the potential for excessive weight gain in some patients.² In the United Kingdom, there has been a major increase in the prevalence of obesity in the general population,³ but the influence of this factor on the CF population is unknown.

In the general population, overweight and obesity are strongly linked with ischemic heart disease, high blood pressure, and type II diabetes. They also exert a negative effect on forced expiratory volume in 1 second (FEV₁) in children⁴ and adults.⁵ Nutritional status, as measured by body mass index (BMI), exerts a beneficial effect on lung function in the average patient with CF who is likely to be poorly or borderline nourished.⁶ It is not known whether this effect persists in patients with CF who are overweight or obese.

METHODS

We queried the UK CF database in 2002 for height, weight, sex, age, and lung function measures for all patients with CF in the United Kingdom homozygous for the Δ F508 mutation (CF Δ F508). The process of consent and ethics approval for the analysis of this database has recently been described.^{7,8} We used international age-adjusted standards of obesity and overweight for children⁹ expressed as BMI z-scores (≥ 1.40 for overweight and ≥ 2.48 for obesity). BMI values greater than 25 and 30 kg/m², respectively, define overweight and obesity in adults. We plotted normalized FEV₁ against BMI z-scores for children (10 to 18 years) and normalized FEV₁ against BMI values for adults (Figure). Two children with a z-score of less than -4 were excluded from the analysis.

Data were stored and analyzed using SPSS (SPSS Inc, Chicago, IL). Smoothed (Lowess) regression lines were used for the plots assessing effect of BMI on FEV₁. Fifty percent of points fit the curve using the SPSS iterative locally weighted least squares method¹⁰ (Figure). To investigate the relationships further, we used nonlinear regression to compute a segmented straight line with a change in slope at a best point estimate value of x_0 , so that $y = b_0 + b_1z$ for $z \geq z_0$ and $y = b_0 + b_1z + b_2(z - z_0)$ for $z > z_0$.

RESULTS

Three thousand patients (mean age 16.1 years, range 0.8 to 55.7 years) were identified; height and weight were available for 2987 patients (Tables I and II).

The regression lines assessing effect of BMI on FEV₁ showed an apparent change in slope that was particularly marked on the adult data. In children, a significant change in slope occurs around the best point estimate of z-score -1.4 (95% confidence intervals [CI] -2.0 to -0.9) with the slope (improvement in percent predicted FEV₁ per unit z-score)

See related articles, p 295,
p 302, p 306, p 312,
p 316, p 321, p 327,
p 332, p 396, and p 399.

From the Division of Maternal and Child Health Sciences, Institute of Cardiovascular Research and Biomedical Research Centre, and Division of Population Sciences, University of Dundee, Ninewells Hospital, Dundee, Scotland, United Kingdom.

Supported by the University of Dundee, NHS Tayside, Cystic Fibrosis Trust (UK).

Submitted for publication Dec 9, 2004; last revision received Apr 22, 2005; accepted Jun 2, 2005.

Reprint requests: Somnath Mukhopadhyay, Maternal and Child Health Sciences, Ninewells Hospital, Dundee, DD2 1PS, Scotland, United Kingdom. E-mail: s.mukhopadhyay@dundee.ac.uk.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.06.003

BMI	Body mass index	CI	Confidence interval
CF	Cystic fibrosis	FEV ₁	Forced expiratory volume in 1 second
CF Δ F508	Cystic fibrosis homozygous for the Δ F508 mutation		

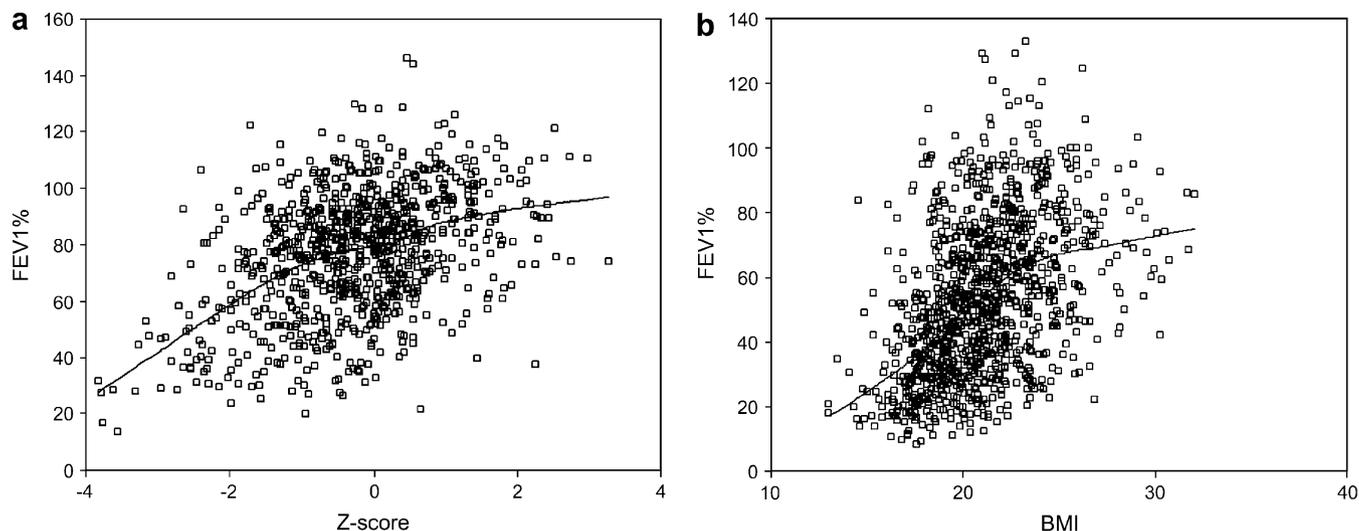


Figure. Scatter plots of FEV₁(as percent predicted) against (a) z-scores for BMI in children (b) BMI in adults with CF. Lowess smoothed curves are displayed for both plots.

Table I. Age-specific distribution of obese and overweight subjects

	Children (0-17.9 years)		Adults (≥ 18 years)		Total (n = 2987)
	Males (n = 994)	Females (n = 875)	Males (n = 627)	Females (n = 491)	
Overweight	79 (7.9%)	89 (10.2%)	80 (12.8%)	26 (5.3%)	274 (9.1%)
Obese	14 (1.4%)	9 (1%)	10 (1.6%)	1 (0.2%)	34 (1.1%)

Table II. Body mass index and lung function in patients with CF

	0-9.9 years		10-17.9 years		≥ 18 years	
	Males (n = 490)	Females (n = 430)	Males (n = 504)	Females (n = 445)	Males (n = 627)	Females (n = 491)
Mean Age (SD)	5.5 (2.7)	5.7 (2.7)	13.9 (2.3)	13.8 (2.3)	26.5 (7.1)	26.3 (7.1)
Mean BMI (SD)	16.3 (1.5)	16.1 (1.6)	18.5 (2.8)	18.8 (2.9)	21.4 (3.3)	20.7 (2.7)
Mean BMI z-score (SD)	0.80 (1.00)	0.00 (0.95)	-0.28 (1.22)	-0.28 (1.08)	-0.81 (1.45)	-0.71 (1.18)
Mean FEV ₁ % (SD)			77.3 (21.0)	75.6 (23.0)	55.9 (25.4)	51.1 (21.7)
			(n = 459)	(n = 416)	(n = 618)	(n = 476)

SD, Standard deviation.

being 17.7% (CI 11.5% to 23.9%) before the point estimate and 6.5% (CI 5.0% to 8.2%) after the point estimate. Thus, in children, lung function shows a positive association with BMI for the entire range of BMI z-scores, although the substantial advantage in the poorly nourished is not sustained beyond a BMI z-score of -1.4 . In adults, a significant change in slope was observed around a threshold BMI of 23.0 kg/m^2 (CI 21.9 to 24.1 kg/m^2), corresponding to a BMI z-score of 0.1 . The slope for FEV₁ against BMI before the threshold was 4.9% (CI 4.1% – 5.7%). The slope after the threshold was 0.7% (CI -0.54% to $+0.86\%$). Thus, in adults with CF, a BMI above 23.0 kg/m^2 could represent a clinical threshold beyond which

there is no significant FEV₁ advantage with a further increase in BMI within the population.

We studied the possibility of a negative relationship between height and BMI. Pearson correlation coefficients were calculated for z scores for height against z scores for BMI for the children and adults with CF. The values are 0.20 and 0.06 , respectively. Thus we did not find a negative relationship between height and BMI in this population.

DISCUSSION

We describe overweight and obesity, and their relationship to FEV₁, in a population of children and young people

with CF. Because large differences in nutritional status are seen between patients with CF who are homozygous for $\Delta F508$ in comparison to those carrying other CF mutations,¹¹ we confined our study to those homozygous for $\Delta F508$, the most common mutation.

The observed prevalence of overweight in CF (2002) is comparable to the prevalence of overweight in the general population 20 years ago.³ The introduction of our modern less active lifestyle associated with changes in eating patterns³ has greatly increased the prevalence of these conditions within the general population, resulting in two thirds of men and half of women in England currently being either overweight or obese.³ This change in lifestyle and eating patterns in the general population could have influenced the BMI status of the population with CF, contributing to the observed prevalence of overweight and obesity. Intensive clinical interventions (caloric supplementation, gastrostomy/nasogastric feeding) and genetic background may also contribute to the development of overweight or obesity in CF. The relative importance of these variables requires further investigation. The near absence of obesity in adult women could be caused by sex-related differences in weight perception and nutritional behavior in adults with CF.¹²

In children, our data suggest a beneficial effect of high BMI on FEV₁ even at BMI z-score levels of 1 to 2. Because a better percent predicted FEV₁ is a recognized surrogate for longer survival in CF, our results do not support calorie restriction in relatively overweight children with CF, as is currently advised for the general pediatric population.³ Caloric counseling may be advisable for young adults with CF and a BMI above 23 kg/m² in view of the absence of a further beneficial effect of BMI on lung function. However, the potentially increased risks of a chronically raised BMI in adulthood (heart disease, high blood pressure and type II diabetes in the general population³) are currently unstudied in CF.

The data on CF patients was kindly provided by the Centre Directors of the UK CF clinics after ethical committee approval and patient consent. We thank M. Fraser, S. Krawczyk, and G. Mehta of the UK CF Database.

REFERENCES

1. Jelalian E, Stark LJ, Reynolds L, Seifer R. Nutritional intervention for weight gain in cystic fibrosis: a meta-analysis. *J Pediatr* 1998;132:486-92.
2. Schwartz MW, Woods SC, Seeley RJ, Barsh GS, Baskin DG, Leibel RL. Is the energy homeostasis system inherently biased towards weight gain? *Diabetes* 2003;52:232-8.
3. Bourn J. Tackling obesity in England. London: Office of the Comptroller and Auditor General (National Audit Office); 2001 15 February 2001. Report No.: HC 220.
4. Lazarus R, Colditz G, Berkey CS, Speizer FE. Effects of body fat on ventilatory function in children and adolescents: cross-sectional findings from a random population sample of school children. *Pediatr Pulmonol* 1997;24:187-94.
5. Canoy D, Luben R, Welch A, Bingham S, Wareham N, Day N, et al. Abdominal obesity and respiratory function in men and women in the EPIC-Norfolk Study, United Kingdom. *Am J Epidemiol* 2004;159:1140-9.
6. Peterson ML, Jacobs DR, Milla CE. Longitudinal changes in growth parameters are correlated with changes in pulmonary function in children with cystic fibrosis. *Pediatrics* 2003;112:588-92.
7. Mehta G, Sims EJ, Culross F, McCormick JD, Mehta A. Potential benefits of the UK Cystic Fibrosis Database. *J Royal Soc Med* 2004;97(suppl 44):60-71.
8. Home page of UK cystic fibrosis database. www.cystic-fibrosis.org.uk/background.htm#dataprotection. Accessed on November 2, 2004.
9. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000;320:1240-3.
10. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. *J Am Statistical Association* 1979;74:829-36.
11. Dray X, Kanaan R, Bienvenu T, Desmazes-Dufeu N, Dusser D, Marteau P, et al. Malnutrition in adults with cystic fibrosis. *Eur J Clin Nutr* 2004;Sep 15 [Epub ahead of print].
12. Walters S. Sex differences in weight perception and nutritional behaviour in adults with cystic fibrosis. *J Hum Nutr Diet* 2001;14:83-91.

CONGENITAL LEFT BRACHIOCEPHALIC VEIN AND SUPERIOR VENA CAVA ANEURYSMS IN AN INFANT



Figure. A, Chest radiography; B and C, venography.

Congenital aneurysms of the mediastinal veins are extremely rare. The case presented involves congenital left brachiocephalic vein and superior vena cava aneurysms associated with respiratory arrest.

A 1-day-old male infant was referred to the neonatal intensive care unit because of respiratory arrest. He was born at 39 weeks' gestation, birth weight was 3610 g, and Apgar score was 9 at 1 minute. The chest radiography (Figure, A) revealed upper mediastinal widening and right pneumothorax. Echocardiography showed no cardiac abnormalities. Chest computed tomography revealed an upper mediastinal mass situated in front of the trachea and pressing it backward toward the spine. At 14 days of age, venography showed huge aneurysms of the left brachiocephalic vein (Figure, B) and superior vena cava (Figure, C). At 22 days of age, an operation was performed to resect the left brachiocephalic vein aneurysm. It was extremely large and bled easily, so resection was discontinued. Instead, a thymectomy, left subclavian vein ligation, and jugular vein ligation were performed, which slightly reduced the size of the aneurysm. At 35 days of age, respiratory support with a ventilator became unnecessary. At 51 days of age, venography showed reduction of the left brachiocephalic vein and a developing collateral vein. At 58 days of age, the patient was discharged from the neonatal intensive care unit.

The cause of venous aneurysms is unknown. They can be congenital in origin or acquired secondary to trauma, inflammation, or degenerative changes in the vascular wall.¹ An association between neck, thoracic venous aneurysms, and cystic hygroma has been described.² Complications of venous aneurysms include venous thrombosis, pulmonary embolism, and rupture.³

Akihisa Nitta, MD
Hiroshi Suzumura, MD
Kenichi Kano, MD
Osamu Arisaka, MD
Department of Pediatrics
Dokkyo University School of Medicine
Mibu, Japan

REFERENCES

1. Shatz IJ, Fine G. Venous aneurysms. *N Engl J Med* 1962;266:1310-2.
2. Joseph AE, Donaldson JS, Reynolds M. Neck and thorax venous aneurysm: association with cystic hygroma. *Radiology* 1989;170:109-12.
3. Schild H, Berg S, Weber W, Schmied W, Steegmuller KW. The venous aneurysm. *Aktuelle Radiol* 1992;2:75-80.

Submitted for publication Jan 5, 2005; accepted Jan 20, 2005.

Reprint requests: Dr A. Nitta, Department of Pediatrics, Dokkyo University School of Medicine, 880 Kitakobayashi, Mibu, Shimotsuga-gun, Tochigi 321-0293, Japan.

J Pediatr 2005;147:405.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.01.039

CLINICAL RESEARCH ABSTRACTS FOR PEDIATRICIANS

EDITOR'S NOTE: Journals reviewed for this issue: *Archives of Disease in Childhood*, *Archives of Pediatrics and Adolescent Medicine*, *British Medical Journal*, *Journal of the American Medical Association*, *Journal of Pediatrics*, *The Lancet*, *New England Journal of Medicine*, *Pediatric Infectious Diseases Journal*, and *Pediatrics*. Gurpreet K. Rana, BSc, MLIS, Taubman Medical Library, University of Michigan, contributed to the review and selection of this month's abstracts.

—John G. Frohna, MD, MPH

Safety and Efficacy of the Nicotine Patch and Gum for the Treatment of Adolescent Tobacco Addiction

Moolchan MT, Robinson ML, Ernst M, Cadet JL, Pickworth WB, Heishman SJ, et al. *Pediatrics* 2005;115:e407-44

Context Despite the belief that nicotine replacement therapy (NRT) would be beneficial in adolescent smokers, few pharmacologic interventions have been evaluated for the treatment of this population.

Objective To determine the safety and efficacy of the nicotine patch and gum for adolescents who want to quit smoking.

Design Double-blind, double-dummy, randomized, three-arm trial with a nicotine patch (21 mg), nicotine gum (2 and 4 mg), or a placebo patch and gum; all participants received cognitive-behavioral group therapy.

Setting Inner-city, outpatient clinic on the East Coast.

Participants Thirteen- to 17-year-old adolescents who smoked ≥ 10 cigarettes per day (CPD), scored ≥ 5 on the Fagerström Test of Nicotine Dependence, and were motivated to quit smoking.

Interventions Twelve weeks of nicotine patch or gum therapy with cognitive-behavioral therapy (CBT), with a follow-up visit at 6 months (3 months after the end of treatment).

Main Outcome Measures Safety was assessed on the basis of adverse event reports for all 3 groups; prolonged abstinence was assessed through self-report and verified with exhaled carbon monoxide (CO) levels of ≤ 6 ppm; and smoking reduction was measured by CPD and thiocyanate concentrations among trial completers.

Results A total of 120 participants were randomized (72% white, 70% female; age: 15.2 ± 1.33 years; smoking: 18.8 ± 8.56 CPD; Fagerström Test of Nicotine Dependence score: 7.04 ± 1.29) from 1999 to 2003. Participants started smoking at 11.2 ± 1.98 years of age and had been smoking daily for 2.66 ± 1.56 years; 75% had at least one current psychiatric

diagnosis. Mean compliance across groups was higher for the patch (mean: 78.4%-82.8%) than for the gum (mean: 38.5%-50.7%). Both the patch and gum were well tolerated, and adverse events were similar to those reported in adult trials. Changes in mean saliva cotinine concentrations throughout treatment were not statistically significant. Intent-to-treat analyses of all randomized participants showed CO-confirmed prolonged abstinence rates of 18% for the active-patch group, 6.5% for the active-gum group, and 2.5% for the placebo group; the difference between the active-patch and placebo arms was statistically significant. There was no significant effect of patch versus gum or gum versus placebo on cessation outcomes. Abstinence rates at the 3-month follow-up assessment were sustained but were not significantly associated with treatment group. Mean smoking rates, but not CO or thiocyanate concentrations, decreased significantly in all three arms but not as a function of treatment group.

Conclusions Nicotine-patch therapy combined with cognitive-behavioral intervention was effective, compared with placebo, for treatment of tobacco dependence among adolescent smokers. Decreases in the numbers of cigarettes smoked appeared to be offset by compensatory smoking. Additional study of nicotine gum, with enhanced instructional support, is needed to assess its efficacy among adolescent smokers.

Comment This important and well-designed study provides evidence for the safety and use of nicotine replacement therapy (NRT), along with group CBT, to help adolescents quit smoking. Moolchan and colleagues conducted one of the only randomized trials with the primary outcome being the safety and efficacy of the nicotine patch and gum on adolescent smoking reduction. The inclusion criteria were appropriately rigorous, as was the sample size calculation that considered the high attrition rates often seen with adolescent smoking cessation trials. Reductions in self-reported smoking were $>80\%$ for all groups by the end of the medication phase, with no differences between groups. The clinical implication of using NRT as a harm reduction method for adolescents is unique and important. Not only would adolescents have less carcinogen exposure, using NRT may also increase the chance that they will quit successfully in the future.

The patch and gum were safe and resulted in significant rates of biochemically confirmed smoking abstinence compared with placebo, with the patch having the highest quit rate. Using the gum on a scheduled basis (eg, every 2 hours) rather than “as needed” may have improved the gum group outcome. It’s important to note that the authors included subjects with comorbid psychiatric conditions taking prescribed medication; this lends support to the safety and use of NRT in this special population. Behavioral counseling is important for smoking cessation, but the group CBT in this study may not be feasible in an outpatient setting. However, incorporating components of CBT over time is practical and may increase effectiveness. As a result of this study, practitioners should feel comfortable prescribing NRT along with behavioral counseling to adolescents with nicotine addiction.

Tahniat S. Syed, MD, MPH
St. Christopher’s Hospital for Children
Philadelphia, PA 19107

Cost-Effectiveness of Conjugate Meningococcal Vaccination Strategies in the United States

Shepard CW, Ortega-Sanchez IR, Scott RD, Rosenstein NE, and the ABCs Team. *Pediatrics* 2005; 115:1220-32

Context The US Food and Drug Administration approved a meningococcal conjugate A/C/Y/W-135 vaccine (MCV-4) for use in persons 11 to 55 years of age in January, 2005; licensure for use in younger age groups is expected in 2 to 4 years.

Objective To evaluate and compare the projected health and economic impact of MCV-4 vaccination of US adolescents, toddlers, and infants.

Design Cost-effectiveness analysis from a societal perspective based on data from Active Bacterial Core Surveillance (ABCs) and other published and unpublished sources. Sensitivity analyses in which key input measures were varied over plausible ranges were performed.

Participants A hypothetical 2003 US population cohort of children 11 years of age and a 2003 US birth cohort.

Interventions: Hypothetical routine vaccination of adolescents (1 dose at 11 years of age), toddlers (1 dose at 1 year of age), and infants (3 doses at 2, 4, and 6 months of age). Each vaccination scenario was compared with a “no-vaccination” scenario.

Main Outcome Measures Meningococcal cases and deaths prevented, cost per case prevented, cost per life-year saved, and cost per quality-adjusted life-year saved.

Results Routine MCV-4 vaccination of US adolescents (11 years of age) would prevent 270 meningococcal cases and 36 deaths in the vaccinated cohort over 22 years, a decrease of 46% in the expected burden of disease. Before program costs are counted, adolescent vaccination would reduce direct disease costs by \$18 million and decrease productivity losses by \$50 million. At a cost per vaccination (average public-

private price per dose plus administration fees) of \$82.50, adolescent vaccination would cost society \$633,000 per meningococcal case prevented and \$121,000 per life-year saved. Key variables influencing results were disease incidence, case-fatality ratio, and cost per vaccination. The cost-effectiveness of toddler vaccination is essentially equivalent to adolescent vaccination, whereas infant vaccination would be much less cost-effective.

Conclusions Routine MCV-4 vaccination of US children would reduce the burden of disease in vaccinated cohorts but at a relatively high net societal cost. The projected cost-effectiveness of adolescent vaccination approaches that of recently adopted childhood vaccines under conditions of above-average meningococcal disease incidence or at a lower cost per vaccination.

Comment The peak incidence of meningococcal disease in the United States occurs during infancy, but the peak fatality rate from meningococcal disease falls during adolescence and young adulthood. The American Academy of Pediatrics and the Centers for Disease Control’s (CDC) Advisory Committee on Immunization Practices have recommended that quadrivalent MCV-4 be administered to adolescents at routine visits for 11- to 12-year-olds, and at visits before high school entry and before living in college dormitories or entering the military for those not previously immunized. The authors, from the CDC, conducted a cost-effectiveness analysis from the societal perspective (accounting for both medical and nonmedical [ie, work loss] costs), comparing an adolescent MCV-4 immunization program with other program options targeted at infants and toddlers. They conclude from their mathematical models that the adolescent strategy is the most cost-effective of these options, at \$121,000 per life-year saved. Such a program would cost almost \$5 million per death averted, and would be expected to save 36 lives over the 22-year time horizon of their study.

As the authors indicate, the cost-effectiveness ratio in excess of \$100,000 per life-year saved compares unfavorably with ratios for other currently recommended childhood vaccines. For example, varicella vaccination and hepatitis B vaccination programs are cost-saving, and vaccination with 7-valent pneumococcal conjugate vaccine has been estimated to cost \$80,000 per life-year saved. Nonetheless, the specter of meningococcal disease may spur providers, parents, and payers to invest in the protection that the MCV-4 vaccine offers, which is superior to that provided by the meningococcal polysaccharide vaccine that preceded it.

In our increasingly cost-constrained healthcare environment, the eventual adoption rates of vaccines such as MCV-4—as well as others such as combined tetanus-diphtheria-acellular pertussis and human papillomavirus vaccines that are currently pending either licensure or review for possible recommendation—will likely depend on their economic costs and benefits, in addition to anticipated health effects and safety. Studies such as this will help multiple stakeholders weigh their options carefully.

Oxycodone vs Placebo in Children with Undifferentiated Abdominal Pain

Kokki H, Lintula H, Vanamo K, Heiskanen M, Eskelinen M. Arch Pediatr Adolesc Med 2005;159:320-5

Context Analgesics for children with acute abdominal pain are often withheld for fear that they might mask physical examination findings and thus might be unsafe. This viewpoint has been challenged recently.

Objectives To evaluate the effects of buccal oxycodone on pain relief, physical examination findings, diagnostic accuracy, and final clinical outcomes in children with acute abdominal pain.

Design Prospective, randomized, double-blind, and placebo-controlled trial between December 2001 and November 2003.

Setting University teaching hospital in Finland.

Participants A total of 104 children 4 to 15 years of age with abdominal pain <7 days' duration were screened, and 63 children with pain scores of 5 or higher on a 10-cm visual analog scale were eligible for the trial.

Interventions Children were randomized to receive buccally either 0.1 mg/kg of oxycodone hydrochloride (n = 32) or the same volume of normal saline (n = 31). The same surgeon described the physical findings and indicated a provisional diagnosis and a provisional disposition before the children received the study medication and at 1 hour and 3.5 hours after initial dosing. Pain scores were recorded at baseline and every 30 minutes for 3.5 hours after the first study drug administration.

Main Outcome Measures Pain intensity difference, presence or absence of abdominal guarding, and diagnostic accuracy.

Results The demographic characteristics, initial pain scores, and physical signs and symptoms were similar between the two groups. Both study drugs were associated with decreasing pain scores. The summed pain intensity difference over 7 observations was significantly greater in the oxycodone group, 22 ± 18 cm, than in the placebo group, 9 ± 12 cm (mean difference 13 cm, with a 95% confidence interval of 2-24 cm; $P = .04$). The diagnostic accuracy increased from 72% to 88% in the oxycodone group and remained at 84% in the placebo group after study drug administration. Laparotomy was performed in 17 patients in the oxycodone group and in 14 patients in the placebo group. Four patients without appendicitis underwent exploratory laparotomy in each group. One patient in the placebo group was initially diagnosed as having nonspecific

abdominal pain, but at 14 hours, she was operated on for appendiceal perforation.

Conclusions Early administration of buccal oxycodone provides a significant pain relief to children with acute abdominal pain, without adversely altering the clinical signs or obscuring the surgical diagnosis.

Comment Most physicians have been taught to withhold pain medication in patients with acute abdominal pain for fear that it may mask worsening symptoms and lead to an adverse clinical outcome. This concern has not been borne out in recent studies with adult patients. Kokki and colleagues have conducted a well-designed, valid, randomized study of buccal oxycodone in children. Both saline placebo and oxycodone resulted in a reduction in pain intensity. The study was powered to detect a difference in the main outcome measure: the summed pain intensity difference (SPID). The SPID is the total of each of the differences in pain ratings from baseline to a specific point in time (every 30 minutes from administration to 3.5 hours later). There was a statistically significant difference in the SPID between the two groups, but this difference was clinically small.¹ Although not adequately powered to look at the potential to miss important adverse outcomes, the study did not find any increased adverse outcomes among those children who were given oxycodone. In fact, the ability to perform a more accurate examination (specifically examining for the presence of guarding) seemed to improve after the analgesic. If that result holds true in larger studies, this could have important implications for children. Finally, as the authors note, one other limitation of the present study is that a surgeon evaluated all children before the study medication was administered. This makes it difficult to generalize these results to children who are initially presenting to an emergency department and who have not yet had a surgical evaluation—another study looking at this group of children would be welcome.

John G. Frohna, MD, MPH
University of Michigan
Ann Arbor, MI 48109

REFERENCE

1. Bowen M, Poehling KA, Gunn VL, Carroll KN, Callahan ST, Arbogast PG, et al. Does the use of oxycodone affect diagnostic accuracy in children with acute abdominal pain? Arch Pediatr Adolesc Med 2005;159:326-8.

ALSO NOTED

The Clinical Significance of Asymptomatic Gross and Microscopic Hematuria in Children

Bergstein J, Leiser J, Andreoli S. Arch Pediatr Adolesc Med 2005;159:353-5

The incidence of asymptomatic hematuria ranges from 0.5% to 2.0% for microscopic, and is unknown for gross hematuria. The authors of this well-done, prospective study attempt to determine the clinical significance of asymptomatic hematuria. Among 342 children with microscopic hematuria, no cause was

The role of small bowel bacterial overgrowth in infantile colic

To the Editor:

Previously in *The Journal of Pediatrics*, small bowel bacterial overgrowth (SBBO) was identified as a cause of abdominal pain and diarrhea in young children.¹ We undertook a pilot study to investigate whether the symptoms of colic can be attributed to SBBO and whether antimicrobial treatment may alleviate the symptoms of colic.

In a randomized, double-blind trial, 8 infants were assigned to a 1-week treatment with metronidazole or placebo in conjunction with breath hydrogen testing and stool tests. Criteria for enrollment included patients who met a standard colic definition: infants between ages 4 weeks to 16 weeks, with crying for more than 3 hours per day, 3 or more days per week for 3 weeks or more, were eligible. All infants had to be term infants (>37 weeks gestation) who were growing normally without congenital defects, excessive vomiting, excessive diarrhea, or evidence of gastrointestinal disease.

After we obtained informed consent, subjects were randomly assigned into 2 groups. One group received metronidazole 10 mg/kg/dose, 3 times daily for 7 days. The second group received a 7-day course of placebo with a similar appearance and taste.

At the start of the trial, the parent completed a baseline evaluation form. A similar form was completed at the end of the treatment week and 1 week after completion of the treatment week. During the treatment, the child's symptoms were evaluated daily with an evaluation form. Parent diaries have been shown to be valid indicators of colic behavior in past studies.² Adverse events were monitored by means of a daily diary. Also, all patients had a stool culture and stool for *Clostridium difficile* toxin evaluation.

In addition, before and after treatment, all subjects underwent a Breath Hydrogen (H₂) test. This required a fasting period of 4 hours before the study. To obtain breath samples, a 5F nasogastric tube tip was placed and taped 1 cm into the nares. With each determination, a minimum of 2 separate samples were obtained via the nasogastric tube. If discrepancies were noted, repeat sampling was performed. After a baseline level was established, an oral glucose load of 1.75 gm/kg was administered. Subsequently, breath H₂ levels were obtained every 15 minutes for 90 minutes. The concentration of H₂ was measured with a model 12i microanalyzer (Quintron Instrument Co, Inc, Milwaukee, Wis), which determines the content of H₂ in parts per million.

The response rate to metronidazole was similar to placebo (Table). In both groups, no definite improvement was

noted during the course of the study. In addition, we examined crying time of each infant. The average crying time for infants among both the treatment group and the control group did not improve during the study. There were no adverse events reported in either study group.

Besides determining whether metronidazole would be helpful for colic symptoms, another goal of the study was to determine whether breath H₂ testing could identify patients who would be most likely to benefit from treatment. In our study, during the first week, 4 of the infants had abnormal breath H₂. After completing treatment, only 2 of the patients had normalization of their breath H₂ during the course of the study. One of these infants, a control patient (subject 6), was "a little better" at both assessment periods; whereas, the study patient with normalization of breath H₂, subject 3, was "a little better" at the first assessment but was "much worse" at the 2-week assessment.

In this limited study, there was no correlation between abnormal breath H₂ results and the likelihood of responding to treatment. In addition, the cohort of patients who did receive metronidazole was not more likely to have an improved breath H₂ on follow-up testing. In fact, one patient in the study group, subject 4, had worsening of his breath H₂. The lack of treatment response and the lack of change of breath H₂ testing was confirmed statistically using Pearson's χ^2 tests and Wilcoxon's signed rank tests.

As in previous studies, our study confirmed high breath H₂ levels in infants with colic.^{3,4} In our study, 50% had an abnormal study result before randomization and 38% after the 1-week intervention. Elevation of breath H₂ in infants is unlikely to be related to lactose intolerance,⁵ but colonic bacteria could cause false-positive breath H₂ test results. Breath H₂ tests are a noninvasive way to measure bacterial overgrowth. The most accurate method, quantitative culturing of the small bowel, is rarely performed because of its invasiveness and expense¹; in addition, there are concerns that this method may miss cases because of sampling error and difficulty culturing anaerobic bacteria.⁶

Previously, there have been no publications regarding the possibility of SBBO as a significant cause of elevated breath H₂ values in infantile colic. However, in otherwise-healthy children SBBO has been identified as a cause of diarrhea, abdominal pain, or both.¹ In adults, SBBO is increasingly recognized as a potential causative factor in irritable bowel syndrome⁶; treatment of SBBO in these patients has been shown to improve the symptoms of irritable bowel syndrome. In this limited trial, metronidazole, when given to patients diagnosed with infantile colic, did not alleviate the symptoms of colic as compared to placebo.

Table. Study results

Subject	BHT - Baseline	Drug	Assess after 1st week	BHT - Follow-up	Assess—2nd week
01	Normal	Flagyl	Much better	Normal	A little better
02	Abnormal	Flagyl	No change	Abnormal	No change
03	Abnormal	Flagyl	A little better	Normal	Much worse
04	Normal	Flagyl	A little better	Abnormal	No change
05	Normal	Flagyl	No change	Normal	No change
06	Abnormal	Placebo	A little better	Normal	A little better
07	Normal	Placebo	No change	Normal	No change
08	Abnormal	Placebo	Much better	Abnormal	Much better

The breath hydrogen results at baseline and after 1 week of therapy are noted in the third and fifth columns respectively. The parental assessments after treatment and 1 week later are noted in the fourth and sixth columns respectively. All 8 subjects had negative stool test results for culture and *Clostridium difficile*.

Jay A. Hochman, MD
Cathy Simms, RN
Children's Center for Digestive Health Care
Atlanta, Ga
YMPD1490
10.1016/j.jpeds.2005.03.015

REFERENCES

1. de Boissieu D, Dhaussain M, Badoual J, et al. Small bowel bacterial overgrowth in children with chronic diarrhea, abdominal pain, or both. *J Pediatr* 1996;128:203-7.
2. Metcalf TJ, Irons TG, Sher LD, Young PC. Simethicone in the treatment of infant colic: a randomized, placebo-controlled, multicenter trial. *Pediatrics* 1994;94:29-34.
3. Moore DJ, Robb TA, Davidson GP. Breath hydrogen response to milk containing lactose in colicky and noncolicky infants. *J Pediatr* 1988;113:979-84.
4. Miller JJ, McVeagh P, Fleet GH, et al. Breath hydrogen excretion in infants with colic. *Arch Dis Child* 1989;64:725-9.
5. Stahlberg MR, Savilahti E. Infantile colic and feeding. *Arch Dis Child* 1986;61:1232-3.
6. Pimentel M, Chow EJ, Lin HC. Normalization of lactose breath testing correlates with symptom improvement in irritable bowel syndrome: a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol* 2003;98:412-9.

Improving care for asthma

To the Editor:

Smith et al¹ report that their attempt at intervention after an acute emergency department visit for asthma did not decrease subsequent such visits or hospitalizations.¹ In discussing options to improve outcome, they focus on providing incentives or help for primary care physicians. Perhaps it is time to recognize the documented benefits of specialty-based programs for asthma. Although all physicians have access to the same medication, outcome from asthma varies greatly among different practitioners. The major component of morbidity from asthma, hospitalization, has not shown signs of decreasing over the past 20 years in spite of widely distributed national guidelines since 1991.² This continuing high hospitalization rate reflects the practice in the general medical community. Although poor urban chil-

dren present a challenge in delivering care for a chronic disease such as asthma, a study in a similar population of Medicaid patients demonstrated substantial decreases in emergency care and hospitalizations from a specialty-based care program.³ Similar results from specialty care have been documented in other reports for both children and adults with asthma.⁴⁻⁶ This reflects more skilled decision-making, closer follow-up with regularly scheduled visits, use of physiological measurements of pulmonary function, and more time and effort spent on patient education than is generally possible in a primary care setting. The resources spent on emergency care and hospitalization for asthma need to be diverted to such specialty-based programs.

Miles Weinberger, MD
Director, Pediatric Allergy & Pulmonary Division
University of Iowa College of Medicine
Iowa City, Iowa
YMPD1491
10.1016/j.jpeds.2005.03.016

REFERENCES

1. Smith SR, Jaffe DM, Fisher EB, Trinkaus KM, Highstein G, Strunk RC. Improving follow-up for children with asthma after an acute emergency department visit. *J Pediatr* 2004;145:772-7.
2. Akinbami LJ, Schoendorf KC. Trends in childhood asthma; prevalence, health care utilization, and mortality. *Pediatrics* 2002;110:315-22.
3. Kelly CS, Morrow AL, Shults J, Nakas N, Strope GL, Adelman RD. Outcomes evaluation of a comprehensive intervention program for asthmatic children enrolled in Medicaid. *Pediatrics* 2000;105:1029-35.
4. Bucknall CE, Robertson C, Moran F, Stevenson RD. Differences in hospital asthma management. *Lancet* 1988;1:748-50.
5. Mayo PH, Richman J, Harris HW. Results of a program to reduce admissions for adult asthma. *Ann Int Med* 1990;112:864-71.
6. Najada A, Abu-Hasan M, Weinberger M. Outcome of Asthma in Children and Adolescents at a Specialty Based Care Program. *Ann Allergy Asthma Immunol* 2001;87:335-43.

To the Editor:

The study by Smith et al¹ in the recent issue of the *Journal* describes a randomized controlled trial to evaluate the effectiveness of telephone asthma coaching and a monetary

incentive to improve post-emergency department (ED) visit follow-up, as well as asthma outcomes over the 6 months after the ED visit. The authors reported an increase of follow-up asthma visits and decreased asthma symptoms in the immediate post-ED visit period (within 15 days). However, there was no increase in subsequent asthma follow-up visits or decrease in ED visits or hospitalizations for the following 6-month period.

Successful asthma self-management includes multiple components, such as correct prescription and proper technique for using rescue and controller asthma medications, appropriate environmental management, and careful monitoring of asthma symptoms. The National Heart, Lung, and Blood Institute (NHLBI) guidelines recommend that clinicians teach patients essential components of self-management and integrate and reinforce patient education into every step of clinical care.²

The intervention described by Smith et al¹ is innovative and adds to our understanding of how to improve post-ED asthma care. However, the study also highlights the importance and responsibility of primary care providers in helping sustain asthma educational efforts initiated in the ED or other settings. Asthma self-management education must be continually reinforced and tailored to the patient's needs. If primary care clinicians are not properly trained to educate families or incorporate NHLBI asthma guidelines into practice, it is unlikely that improved asthma outcomes will be sustained.

Primary care provider education is an important component in implementing NHLBI recommendations. For example, in a randomized controlled trial involving 74 primary care providers and 637 of their patients, Clark et al³ noted that among children who were placed on inhaled corticosteroids during the study period, those children treated by physicians who were trained in asthma education had significantly fewer symptoms and decreased asthma health care use. This finding suggests that the impact of appropriate prescription of anti-inflammatory medications can be significantly enhanced with concurrent patient education from primary care providers.³

Although the intervention described by Smith et al¹ improved patient symptoms for only 15 days, the importance of post-ED follow-up visits should not be disregarded. Directly including primary care providers in post-ED care interventions may be necessary. As noted by the authors, "working with primary care providers to help them provide effective regular care" may help strengthen and sustain the post-ED interventions designed to improve overall asthma care.

Michael D. Cabana, MD, MPH
University of Michigan Health System
Ann Arbor, Michigan
YMPD1492

10.1016/j.jpeds.2005.03.017

REFERENCES

1. Smith SR, Jaffe DM, Fisher EB, Trinkaus KM, Highstein G, Strunk RC. Improving follow-up for children with asthma after an acute emergency department visit. *J Pediatr* 2004;145:772-7.

2. National Heart Lung and Blood Institute. Guidelines for the Diagnosis and Management of Asthma. NIH Publication No. 97-4051.

3. Clark NM, Gong M, Schork MA, Evans D, Roloff D, Hurwitz M, et al. Impact of education for physicians on patient outcomes. *Peds* 1998;101:831-6.

Reply

To the Editor:

We appreciate the interest generated by our study to improve follow-up after acute emergency department (ED) visits for children with asthma. These letters discuss 2 different opinions regarding the best site for regular asthma care once the child is successfully reintegrated into the system of regular care by encouragement from ED staff or coaches.

Dr. Weinberger suggests that asthma care provided by sub-specialists may improve outcomes, such as ED visits and hospital admissions, more than care provided by other practitioners. Several studies show that sub-specialists provide excellent asthma care, and this care can reduce ED and hospital visits.¹⁻³ As Dr. Weinberger points out, sub-specialists are able to devote the entire visit to evaluation of the child's asthma and provide education about asthma for the family. Although the frequency of hospitalizations and ED visits for asthma has decreased slightly over the past few years,⁴ a substantial number of children continue to use these services. Although sub-specialist care is likely to be beneficial for children with asthma, there are not enough sub-specialists to care for all children with asthma, and only those with the most severe disease are really appropriate for referral.

There are also studies that show primary care providers, with appropriate education, can provide regular asthma care that is consistent with the national guideline recommendations.⁵⁻⁷ As Dr Cabana points out, several hurdles must be overcome for primary care providers (PCPs) to meet these expectations. In addition to time and financial barriers, PCPs must also evaluate and provide care for all aspects of health during routine visits. Caring for the whole child and providing all of their health care needs are huge challenges. However, PCPs are in a unique position to incorporate asthma care and teaching with the rest of the child's health care needs. It is important to develop system solutions for PCPs so they have the time and tools to meet these challenges. We agree with Dr Cabana that system solutions need to include linking children seen in acute care settings with their PCPs.

Certainly, sub-specialists should evaluate a child with severe or difficult-to-control asthma. But where should the child with mild persistent or intermittent asthma receive regular asthma care? Perhaps it is not so much the site of care that matters, as much as ensuring that physicians who provide regular care for children with asthma have proper training and resources. Physicians who care for children with asthma need to provide appropriate medications, routine visits, and reinforce educational issues with the children and their families. Clearly more needs to be done to accomplish a regular visit for asthma, with longer-term interventions that ultimately lead to improved home management of asthma and reduced acute care services.

Sharon R. Smith, MD
Connecticut Children's Medical Center
Hartford, Connecticut

Robert C. Strunk, MD
Washington University School of Medicine
St. Louis, Missouri

YMPD1493

10.1016/j.jpeds.2005.03.018

REFERENCES

1. Kelly CS, Morrow AL, Shults J, Nakas N, Strobe GL, Adelman RD. Outcomes evaluation of a comprehensive intervention program for asthmatic children enrolled in Medicaid. *Pediatrics* 2000;105:1029-35.
2. Najada A, Abu-Hasan M, Weinberger M. Outcome of asthma in children and adolescents at a specialty based care program. *Ann Allergy Asthma Immunol* 2001;87:335-43.
3. Zeiger R, Heller S, Melton M, Wald J, Falkoff R, Schatz M. Facilitated referral to asthma specialist reduces relapses in asthma emergency room visits. *J Allergy Clin Immunol* 1991;87:1160-8.
4. Centers for Disease Control and Prevention. Asthma prevalence and control characteristics by race/ethnicity—United States, 2002. *MMWR* 2004; 53:145-8.
5. Lara M, Rosenbaum S, Rachelefsky G, Nicholas W, Moron SC, Emont S, et al. Improving childhood asthma outcomes in the United States: a blueprint for policy action. *Pediatrics* 2002;109:919-30.
6. Brown R, Bratton SL, Cabana MD, Kaciroti N, Clark NM. Physician asthma education program improves outcomes for children of low-income families. *Chest* 2004;126:369-74.
7. Cloutier MM, Wakefield DB, Carlisle PS, Bailit HL, Hall CB. The effect of easy breathing on asthma management and knowledge. *Arch Pediatr Adolesc Med* 2002;156:1045-51.

THE JOURNAL OF PEDIATRICS

Copyright © 2005 by Mosby, Inc.

Information for Readers

Correspondence. Communications regarding original articles and editorial management should be addressed to William F. Balistreri, MD, *The Journal of Pediatrics*, Children's Hospital Medical Center, Sabin Center, 3rd Floor, 3333 Burnet Ave, Cincinnati, OH 45229-3039; telephone 513-636-7140.

Customer service. (orders, claims, online, change of address): Elsevier Periodicals Customer Service, 6277 Sea Harbor Drive, Orlando, FL 32887-4800. Tel: (800) 654-2452 (U.S. and Canada); (407) 345-4000 (outside U.S. and Canada). Fax: (800) 225-6030 (U.S. and Canada); (407) 363-9661 (outside U.S. and Canada). E-mail: elspcs@elsevier.com

Address changes must be submitted four weeks in advance.

Yearly subscription rates. United States and possessions: Individual \$173.00; Institution \$455.00; Student/Resident: \$87.00. All other countries (prices include airspeed delivery): Individual \$213.00; Institution \$496.00; Student/Resident \$109.00. Single Issues \$42.00. To receive student/resident rate, orders must be accompanied by name of affiliated institution, date of term and the signature of program/residency coordinator on institution letterhead. Orders will be billed at the individual rate until proof of status is received. Current prices are in effect for back volumes and back issues.

Further information on this journal is available from the Publisher or from this journal's website (<http://www.elsevier.com/jped>). Information on other Elsevier products is available through Elsevier's website (<http://www.elsevier.com>).

Advertising information. Advertising orders and inquiries can be sent to: **USA, Canada, and South America**, Pat Hampton, Elsevier, 360 Park Avenue South, New York, NY, 10010; phone: 212-633-3181; fax: 212-633-3820. Classified advertising orders and inquiries can be sent to Tracy Peppers, Elsevier Inc., 360 Park Ave South, New York, NY 10010-1710; phone: 212-633-3766; FAX 212-633-3820. **Europe and the rest of the world**, Julie Toop; phone +44 (0) 1865 843016; fax +44 (0) 1865 843976; e-mail media@elsevier.com.

Author inquiries. For inquiries relating to the submission of articles (including electronic submission where available), please visit Elsevier's Author Gateway at <http://authors.elsevier.com>. The Author Gateway also provides the facility to track accepted articles and set up e-mail alerts to inform you of when an article's status has changed, as well as detailed artwork guidelines, copyright information, frequently asked questions, and more. Please see Information for Authors for individual journal. Contact details for questions arising after acceptance of an article, especially those relating to proofs, are provided after registration of an article for publication.

⊗The paper used in this publication meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).

Reprints. For queries about author offprints, e-mail authorsupport@elsevier.com. To order 100 or more reprints for educational, commercial, or promotional use, contact the Commercial Reprints Department, Elsevier Inc., 360 Park Avenue South, New York, NY 10010-1710. Fax: (212) 462-1935; e-mail reprints@elsevier.com. Reprints of single articles available online may be obtained by purchasing Pay-Per-View access for \$30 per article on the journal website, www.us.elsevierhealth.com/jped.

Microform edition available from ProQuest Information and Learning, 300 N Zeeb Rd, Ann Arbor, MI 48106-1346.

© 2005 Mosby, Inc. All rights reserved.

This journal and the individual contributions contained in it are protected under copyright by Mosby, Inc., and the following terms and conditions apply to their use:

Photocopying. Single photocopies of single articles may be made for personal use as allowed by national copyright laws. Permission of the Publisher and payment of a fee is required for all other photocopying, including multiple or systematic copying, copying for advertising or promotional purposes, resale, and all forms of document delivery. Special rates are available for educational institutions that wish to make photocopies for nonprofit educational classroom use.

Permissions may be sought directly from Elsevier's Rights Department in Philadelphia, PA, USA: phone (+1) 215 239 3804, fax (+1) 215 239 3805, e-mail healthpermissions@elsevier.com. Requests may also be completed online via the Elsevier homepage (<http://www.elsevier.com/locate/permissions>).

In the USA, users may clear permissions and make payments through the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, USA; phone: (+1) (978) 7508400, fax: (+1) (978) 7504744, and in the UK through the Copyright Licensing Agency Rapid Clearance Service (CLARCS), 90 Tottenham Court Road, London W1P 0LP, UK; phone: (+44) 20 7631 5555; fax: (+44) 20 7631 5500. Other countries may have a local reprographic rights agency for payments.

Derivative works. Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the Publisher is required for resale or distribution outside the institution.

Permission of the Publisher is required for all other derivative works, including compilations and translations.

Electronic storage or usage. Permission of the Publisher is required to store or use electronically any material contained in this journal, including any article or part of an article.

Except as outlined above, no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior written permission of the Publisher.

Address permissions requests to: Elsevier Rights Department, at the fax and e-mail addresses noted above.

Notice. No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made.

Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made of it by its manufacturer.

September 2005

Pediatrics for the Practitioner - Update 2005, September 22-23, 2005, Johns Hopkins University School of Medicine, Thomas B. Turner Building, Johns Hopkins University School of Medicine, Baltimore, Maryland. This conference is designed for pediatricians, family practitioners, pediatric nurse practitioners and physician assistants involved in providing primary care for infants, children and adolescents. The major focus will be on commonly encountered problems about which current controversies exist and in areas that recently have undergone changes in patient management.

Office of Continuing Medical Education, Johns Hopkins University School of Medicine, Turner 20, 720 Rutland Avenue, Baltimore, Maryland 21205-2195, telephone: (410) 955-2959, fax: (410) 955-0807, e-mail: cmenet@jhmi.edu, Website: <http://www.hopkinscme.net>.

2006 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 periods. **The final month of each registration requires payment of a late fee.** The requirements for online applications may be found on the ABP Website: www.abp.org or may be obtained by contacting the ABP. Additional information including eligibility requirements and registration dates may also be found on the ABP Website.

General Pediatrics Examination:

Examination Date: October 23 and October 24, 2006.

Registration for first-time applicants: December 1, 2005 through May 1, 2006.

Registration for re-registrants: February 15, 2006 through May 31, 2006.

Subspecialty Examinations:**Sports Medicine**

Examination Dates: To be determined by ABFM.

Registration for first-time applicants: September 15, 2005, through December 15, 2005.

Registration for re-registrants: December 15, 2005, through March 15, 2006.

Pediatric Cardiology - Examination Date: August 16, 2006.

Pediatric Critical Care Medicine - Examination Date: August 18, 2006.

Pediatric Pulmonology - Examination Date: August 17, 2006.

Registration for first-time applicants: September 15, 2005, through December 15, 2005.

Registration for re-registrants: December 15, 2005, through March 15, 2006.

Pediatric Rheumatology - Examination Date: November 10, 2006.

Developmental-Behavioral Pediatrics - Examination Date: November 15, 2006.

Pediatric Emergency Medicine - Examination Date: November 16, 2006.

Pediatric Hematology-Oncology - Examination Date: November 17, 2006.

Transplant Hepatology - Examination Date: To be determined by ABIM.

Medical Toxicology - Examination Date: November 14, 2006.

Registration for first-time applicants: February 1, 2006, through May 3, 2006.

Registration for re-registrants: March 16, 2006, through June 16, 2006.